DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125409/0 **BLA APPROVAL**

Genentech, Inc.
Attention: Josephine Ing
Sr. Scientist, Regulatory Affairs
1 DNA Way
South San Francisco, CA 94080-4990

Dear Ms. Ing:

Please refer to your Biologics License Application (BLA) dated December 6, 2011, received December 8, 2011, submitted under section 351 of the Public Health Service Act for Perjeta (pertuzumab).

We acknowledge receipt of your amendments dated December 6, 2011; January 6, 18, and 23; February 1, 3, 10, 27, and 28; March 1, 8, 9, 12, 15, 16, 21 (3), 22 , and 28; April 2, 3, 9 (2), 10, 12, 16, 19, 23, 26, and 30; May 1, 2, 4 (2), 8, 10 (3), 11 (3), 14 (3), 16 (3), 17 (3), 18, 21 (2), 22, 23, 25, 29, and 31; June 4, 5, and 8 (e-mail), 2012.

We have approved your BLA for pertuzumab effective this date, pursuant to the conditions set forth in this letter. You are hereby authorized to introduce, or deliver for introduction into interstate commerce, pertuzumab under your existing Department of Health and Human Services U.S. License No. 1048, as further described below. Pertuzumab is indicated for use in combination with trastuzumab and docetaxel for the treatment of patients with HER2-positive metastatic breast cancer who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease.

Under this license, you are approved to introduce, or deliver for introduction into interstate commerce, only pertuzumab drug product formulated from drug substance manufactured at Genentech's facility in Vacaville, California, during your 2010 campaign that was not produced from any engineering or failed runs. The final formulated product will be manufactured, filled, labeled, and packaged at Roche Diagnostics GmbH, Mannheim, Germany. You may label your product with the proprietary name Perjeta and will market it in 420 mg per 14 mL single-use vials. You are not licensed to introduce, or deliver for introduction into interstate commerce, any other pertuzumab drug product without the submission and Agency approval of a supplemental BLA for such marketing.

Your application for pertuzumab was not referred to an FDA advisory committee because the Agency did not believe that outside expertise was necessary; there were no controversial clinical issues that would benefit from advisory committee discussion.

The dating period for pertuzumab drug product shall be 24 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 pertuzumab drug substance shall be 24 months from the date of manufacture 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 substance and drug product under 21 CFR 601.12.

You are not currently required to submit samples of future lots of pertuzumab and each kit component 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 your compliance with 21 CFR 610.1, which provides that you shall not release any lot of licensed product prior to completion of tests for conformity with applicable standards.

Any changes in the manufacturing, testing, packaging, or labeling of pertuzumab, or in the manufacturing facilities, will require the submission of information to your biologics license application for our review and written approval, consistent with 21 CFR 601.12.

We are approving this application for use as recommended in the enclosed agreed-upon labeling text.

POSTMARKETING REQUIREMENTS AND COMMITMENTS

Below we have set forth a summary of the postmarketing requirements and commitments associated with this approval. Further details of these requirements and commitments will be communicated in a separate letter; Genentech has agreed to the postmarking commitments as described more fully in this separate letter.

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.

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 the serious risk of embryo-fetal toxicity.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk.

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

1. Establish a Pregnancy Registry to collect and analyze information for ten years on pregnancy complications and birth outcomes in women with breast cancer exposed to a pertuzumab-containing regimen within 6 months of conception or during pregnancy. Submit yearly

interim reports, which may be included in your annual reports, on the cumulative findings and analyses from the Pregnancy Registry.

The timetable you submitted on May 16, 2012, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	06/2012
Final Protocol Submission:	08/2012
Interim Report #1:	08/2013
Interim Report #2:	08/2014
Interim Report #3:	08/2015
Interim Report #4	08/2016
Interim Report #5	08/2017
Interim Report #6	08/2018
Interim Report #7	08/2019
Interim Report #8	08/2020
Interim Report #9	08/2021
Interim Report #10	08/2022
Study Completion:	08/2022
Final Report Submission:	08/2023

Submit the protocols to your IND 009900, with a cross-reference letter to this BLA. Submit the interim and final reports 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 601.70 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 601.70 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 601.70. 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.

POSTMARKETING COMMITMENTS

POSTMARKETING COMMITMENTS NOT SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of the following postmarketing commitments:

2. Provide a plan for responding to potential pertuzumab shortages.

   The timetable you submitted by e-mail on June 8, 2012, states that you will complete this plan according to the following schedule:

Draft Plan Submission:	07/2012
Final Plan Submission:	09/2012

3. Conduct a stability study that includes real time and stressed stability testing to assess the stability of the drug substance manufactured from thaws #4 and #6 of the Q1/Q2 2012 pertuzumab campaign. Provide a root cause analysis relating to the cell bank issues. Submit the Final Report as a Prior Approval Supplement (PAS).

   The timetable you submitted by e-mail on June 8, 2012, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	06/2012
Interim Report:	09/2012
Study Completion:	10/2014
Final Report:	12/2014

4. Conduct a process validation study to support manufacture of pertuzumab from the Master Cell Bank. Submit the Final Report as a PAS.

   The timetable you submitted by e-mail on June 8, 2012, states that you will conduct this study according to the following schedule:

Study Completion:	12/2012
Final Report Submission:	02/2013

5. Conduct a process validation study to support manufacture of pertuzumab from a new Working Cell Bank. Submit the Final Report as a PAS.

   The timetable you submitted by e-mail on June 8, 2012, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	04/2013
Study Completion:	09/2014
Final Report Submission:	10/2014

6. Conduct process validation studies to support manufacture of pertuzumab from Working Cell Banks by a modified process. Submit the Final Report as a PAS.

   The timetable you submitted by e-mail on June 8, 2012, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	04/2014
Study Completion:	10/2015
Final Report Submission:	11/2015

7. Conduct stability studies of the Master Cell Bank at more frequent intervals than the currently proposed 10 years. Submit Interim Reports every four years and the Final Report after 20 years.

   The timetable you submitted by e-mail on June 8, 2012, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	09/2012
Interim Report 1:	06/2016
Interim Report 2:	06/2020
Interim Report 3:	06/2024
Interim Report 4:	06/2028
Final Report Submission:	06/2032

8. Reassess release and stability specifications for pertuzumab drug substance and drug product through June 30, 2014. Submit the Final Report as a Changes Being Effected-30 Supplement (CBE-30).

   The timetable you submitted by e-mail on June 8, 2012, states that you will conduct this study according to the following schedule:

Study Completion:	12/2014
Final Report Submission:	03/2015

9. Conduct a study to assess the ability of a non-reduced CE-SDS assay to detect and quantitate pertuzumab fragmentation. Submit the Final Report as a CBE-30.

   The timetable you submitted by e-mail on June 8, 2012, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	09/2012
Study Completion:	07/2013
Final Report Submission:	09/2013

10. Conduct a study to establish a drug substance release specification to control for antibody-dependent cellular cytotoxicity (ADCC) activity of pertuzumab. Submit the Final Report as a PAS.

    The timetable you submitted by e-mail on June 8, 2012, states that you will conduct this study according to the following schedule:

Study Completion:	02/2013
Final Report Submission:	03/2013

11. Conduct a study using end of production cells from commercial scale manufacturing that tests for *in vivo* adventitious viruses and genetic consistency. Submit the Final Report as a PAS.

    The timetable you submitted by e-mail on June 8, 2012, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	08/2012
Study Completion:	12/2012
Final Report Submission:	02/2013

12. Re-qualify the bioburden test for the bulk drug substance and in-process bioburden samples. Submit the Final Report as a Changes Being Effected-0 Supplement (CBE-0).

    The timetable you submitted by e-mail on June 8, 2012, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	06/2012
Study Completion:	07/2012
Final Report Submission:	12/2012

13. Revalidate the hold time for non-sterile cell culture media. Submit the Final Report as CBE-30.

    The timetable you submitted by e-mail on June 8, 2012, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	04/2013
Study Completion:	08/2013
Final Report Submission:	12/2013

14. Conduct a comprehensive risk assessment regarding the microbial control of the cell culture process and generate an action plan based on the assessment. Submit the Final Report as CBE-30.

The timetable you submitted by e-mail on June 8, 2012, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	09/2012
Final Report Submission:	03/2013

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of the following additional postmarketing commitments:

15. Conduct a clinical trial to test whether the addition of hormonal therapy increases the efficacy of pertuzumab-based therapy in the hormone receptor-positive, HER2-positive metastatic breast cancer population. Study MO27775 (PERTAIN) as designed will be completed to fulfill this post-marketing commitment.

    The timetable you submitted on May 16, 2012, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	08/2012
Trial Completion:	09/2016
Final Report Submission:	03/2017

16. Submit the results of the final overall survival (OS) analysis of trial WO20698/TOC4129g as defined in your protocol Statistical Analysis Plan (SAP).

    The timetable you submitted on May 16, 2012, states that you will conduct this trial according to the following schedule:

Trial Completion:	12/2013
Final Report Submission:	05/2014

For all postmarketing commitments, submit clinical protocols to your IND 009900 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final reports to this BLA. In addition, under 21 CFR 601.70 you should include a status summary of each commitment in your annual progress report of postmarketing studies to this BLA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," or "**Postmarketing Commitment Correspondence**."

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 this application in all pediatric age groups because the necessary studies are impossible or highly impracticable.

REPORTING REQUIREMENTS

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:

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
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 http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm.

You must submit distribution reports under the distribution reporting requirements for licensed biological products (21 CFR 600.81).

You must submit reports of biological product deviations under 21 CFR 600.14. You should promptly 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:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Compliance Risk Management and Surveillance
5901-B Ammendale Road
Beltsville, MD 20705-1266

Biological product deviations, sent by courier or overnight mail, should be addressed to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Compliance Risk Management and Surveillance
10903 New Hampshire Avenue, Bldg. 51, Room 4206
Silver Spring, MD 20903

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 [21 601.14(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 text for the package insert. 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 125409/0**."

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the enclosed carton and immediate container labels as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled "Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)". Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Product Correspondence – Final Printed Carton and Container Labels for approved BLA STN 125409/0**". Approval of this submission by FDA is not required before the labeling is used. Marketing the product(s) with final printed labeling (FPL) that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

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 to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

You must submit final promotional materials, and the package insert, 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 Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

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.

POST-ACTION FEEDBACK MEETING

New molecular entities and new biologics qualify for a post-action feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

If you have any questions, call Amy Tilley, Regulatory Project Manager, at (301) 796-3994.

Sincerely,

{See appended electronic signature page}

Richard Pazdur, M.D.
Director
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURES:
Content of Labeling
Carton and Container Labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RICHARD PAZDUR
06/08/2012