DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125427/0

BLA APPROVAL

Genentech, Inc.
Attention: Erica J. Evans, Ph.D.
Regulatory Program Management
1 DNA Way
South San Francisco, CA 94080-4990

Dear Dr. Evans:

Please refer to your Biologics License Application (BLA) dated August 24, 2012, received August 27, 2012, submitted under section 351(a) of the Public Health Service Act for Kadcyla (ado-trastuzumab emtansine).

We acknowledge receipt of your amendments dated June 12, and 25; July 11 and 31; August 24, and 27; September 12, 18(2), 21, 25(2), 26(2), and 28(2); October 8(2), 9(2), 11(2), 17(2), 18(2), 23(2), 24, 25, 29, 30, and 31; November 1, 2(3), 5, 6, 8(2), 12(3), 13(3), 14(2), 16, 20(2), 26, and 30(2); December 5(2), 6, 7(6), 13, 14, 19, 20, 21(2) and January 2, 3, 4, 7, 11, 15(2), 17(2), 18, 22, 23, 24,(3), 25(3), 28(2), 30(2) and February 5, 6, 7, 8, 12, and 15, 2013.

LICENSING

We have approved your BLA for Kadcyla (ado-trastuzumab emtansine) effective this date. You are hereby authorized to introduce or deliver for introduction into interstate commerce, Kadcyla (ado-trastuzumab emtansine) under your existing Department of Health and Human Services U.S. License No. 1048. Kadcyla (ado-trastuzumab emtansine) is indicated, as a single agent, for the treatment of patients with HER2-positive, metastatic breast cancer who previously received trastuzumab and a taxane, separately or in combination.

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture ado-trastuzumab emtansine bulk drug substance at (b) (4), and ado-trastuzumab emtansine final drug product at (b) (4). Drug product labeling and packaging will be done at Genentech Hillsboro Fill Finish Facility in Hillsboro, Oregon.

You may label your product with the proprietary name, Kadcyla, and will market it as a lyophilized product in two single-use presentations of 100 mg per 15 mL vial and 160 mg per 20 mL vial.

Trastuzumab intermediate will be manufactured at Genentech, Inc., Vacaville, CA and Roche Singapore Technical Operations Pte. Ltd, Singapore. DM1 intermediate will be manufactured at (b) (4)

DATING PERIOD

The dating period for ado-trastuzumab emtansine drug product (160 mg/vial) shall be 36 months from the date of manufacture when stored at 2°C to 8°C. The dating period for ado-trastuzumab emtansine drug product (100 mg/vial) shall be 24 months from the date of manufacture when stored at 2°C to 8°C. The date of manufacture shall be defined as the date of (b) (4) the formulated drug product. The dating period for your trastuzumab intermediate shall be (b) (4) The dating period for your ado-trastuzumab emtansine drug substance shall be (b) (4)

We have approved the stability protocols in your license application for the purpose of extending the expiration dating period of the drug substance and drug product under 21 CFR 601.12. Data supporting extension of the expiration dating period should be submitted to the BLA Annual Report.

Consistent with 21 CFR 601.12, Genentech must inform FDA about each change in the product, production process, quality controls, equipment, facilities, responsible personnel, or labeling established in the approved application.

FDA LOT RELEASE

You are not currently required to submit samples of future lots of ado-trastuzumab emtansine 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.

Any changes in the manufacturing, testing, packaging, or labeling of Kadcyla (ado-trastuzumab emtansine), 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.

APPROVAL & LABELING

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

We note that your February 13, 2013, submission includes final printed labeling (FPL) for your package insert. We have not reviewed this FPL. You are responsible for assuring that the wording in this printed labeling is identical to that of the approved content of labeling in the structured product labeling (SPL) format.

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. Content of labeling must be identical to the enclosed labeling (text for the package insert, text for the patient package insert, Medication Guide). 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.

The SPL will be accessible via publicly available labeling repositories.

In addition, within 14 days of the date of this letter, amend any pending supplement that includes labeling changes for this BLA with content of labeling in SPL format to include the changes approved in this supplement.

CARTON AND IMMEDIATE CONTAINER LABELS

We acknowledge your January 30, 2013, submission containing final printed carton and container labels.

ADVISORY COMMITTEE

Your application for Kadcyla (ado-trastuzumab emtansine) was not referred to an FDA advisory committee because outside expertise was not necessary; there were no controversial issues that would benefit from advisory committee discussion.

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 because necessary studies are impossible or highly impracticable. Breast cancer is on the list of conditions that do not occur in pediatric patients and qualify for a full waiver.

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 signals of serious risks of embryo-fetal toxicity and of increased toxicity due to a variable antibody drug ratio and to identify unexpected serious risks of increased toxicity due to (b) (4) .

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 conduct the following:

1. Establish a Pregnancy Registry to collect and analyze information for 10 years on pregnancy complications and birth outcomes in women with breast cancer exposed to ado-trastuzumab-emtansine 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 February 15, 2013, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	03/13
Final Protocol Submission:	05/13
Interim Report #1:	05/14
Interim Report #2:	05/15
Interim Report #3:	05/16
Interim Report #4:	05/17
Interim Report #5:	05/18
Interim Report #6:	05/19
Interim Report #7:	05/20
Interim Report #8:	05/21
Interim Report #9:	05/22
Study Completion:	05/23
Final Report Submission:	05/24

2. Perform a multivariate characterization study to support the implementation of a (b) (4) during manufacture of T-DM1.

   The timetable you submitted on February 15, 2013, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	03/13
Study Completion:	05/13
Final Report Submission:	06/13

3. Develop and validate an (b) (4) method to use as a drug substance and drug product regulatory method for monitoring the (b) (4) content and propose a specification limit for the (b) (4) content based on clinical and commercial batch data.

   The timetable you submitted on February 15, 2013, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	05/13
Study Completion:	11/13
Final Report Submission:	12/13

4. Provide quarterly reports on the status of any (b) (4) These reports should include, at a minimum, a summary of the root cause analyses, associated corrective actions, and disposition of all affected DM1 batches. Also, provide the disposition of any potentially affected finished product batches using these affected DM1 batches. Submit an interim report documenting that the manufacturing processes have been appropriately controlled at the manufacturing facilities according to Genentech's evaluation. The interim report should include a request for follow-up inspection(s). Submit a final report with a statement concerning the follow-up performed on the (b) (4) issues during the course of the FDA inspection(s), an update on whether there have been any further instances of (b) (4), and a proposal to prevent (b) (4) managed by each site's quality system.

   The timetable you submitted on February 15, 2013, states that you will conduct this study according to the following schedule:

Quarterly Report #1:	05/13
Quarterly Report #2:	08/13
Quarterly Report #3:	11/13
Quarterly Report #4:	02/14
Interim Report:	04/14

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