DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
1401 Rockville Pike
Rockville MD 20852-1448

Our Reference No.: 98-0369

September 25, 1998

Robert L. Garnick, Ph.D.
Genentech, Inc.
1 DNA Way
South San Francisco, CA 94080-4990

Dear Dr. Garnick:

Your biologics license application for Trastuzumab is approved effective this date. Genentech, Inc., South San Francisco, California, is hereby authorized to introduce or deliver for introduction into interstate commerce Trastuzumab under Department of Health and Human Services U.S. License No. 1048.

Trastuzumab is indicated for treatment of patients with metastatic breast cancer whose tumors overexpress the HER2 protein and who have received one or more chemotherapy regimens for their metastatic disease. Trastuzumab in combination with paclitaxel is indicated for treatment of patients with metastatic breast cancer whose tumors overexpress HER2 protein and who have not received chemotherapy for their metastatic disease. In accordance with approved labeling, your product will bear the tradename Herceptin and will be marketed in 440 mg multi-dose vials supplied with Bacteriostatic Water for Injection, USP (containing 1.1% benzyl alcohol).

You are not currently required to submit samples of future lots of Trastuzumab to the Center for Biologics Evaluation and Research (CBER) for release by the Director, CBER, under 21 CFR 610.2. FDA will continue to monitor compliance with 21 CFR 610.1 requiring assay and release of only those lots that meet release specifications.

The dating period for this product shall be 30 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 final formulated product. The bulk antibody may be stored for up to 24 months at -20°C. The dating period for the diluent, Bacteriostatic Water for Injection shall be 24 months. The expiration date for the packaged product, Herceptin plus diluent, shall be dependent on the shortest expiration date of either component. Results of stability studies from the first three production lots should be submitted throughout the dating period on an annual basis.

Any changes in the manufacture, packaging or labeling of the product 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 acknowledge your written commitments of August 7, 1998 and September 22, 1998, and as agreed during discussions on September 25, 1998, which include the following:

1. Within one year of approval, the stability of the reconstituted product stored under the "worst case" conditions will be studied. Results including IEC and the antiproliferative assay will be submitted for review.

2. For the next five lots to be released, the antiproliferative assay will be performed using three replicates of three dilutions, however, the lots will be released as per the actual SOP(Q12333). These additional test results will be submitted for review.

3. To develop and conduct a clinical trial which addresses the impact on progression-free survival and response rate of the addition of Herceptin therapy to chemotherapy as compared with chemotherapy alone in patients with 2+ HER2 (weakly positive) overexpression.

4. To obtain ejection fraction data at baseline and at scheduled periodic monitoring intervals in the following Herceptin breast cancer clinical trials:

    - Carboplatin-Paclitaxel-Herceptin vs Paclitaxel-Herceptin (total n ≅ 200)
    - Weekly Paclitaxel-Herceptin (total n ≅ 100)
    - and selected other large clinical trials

5. To assess the ability of medical history, physical exam, and baseline and on-study monitoring of cardiac function to predict and diminish the risk of Herceptin-induced cardiotoxicity. In patients with early signs of Herceptin-induced cardiotoxicity:

    - To evaluate the advisability of discontinuation of Herceptin
    - To evaluate the safety of continuation or reinstitution of Herceptin therapy.

6. To investigate further the safety and efficacy of Herceptin and the risk factors for cardiotoxicity and adequacy of monitoring for cardiotoxicity in the following settings:

    - In a population who has recently received anthracyclines (e.g., collaborative group adjuvant study of AC x 4 followed by Paclitaxel-Herceptin or Paclitaxel alone x 4) and/or in a population in which Herceptin is administered concurrently with anthracycline therapy (e.g., NCI-sponsored study of Herceptin + Doxil® or Herceptin + prolonged infusion of doxorubicin)

    - In a population not previously treated with anthracyclines (e.g., possible collaborative group adjuvant study of taxane/Herceptin regimen in anthracycline naïve patients)

7. To assess the clinical outcome of patients selected for treatment on the basis of the DAKO test and other HER2 diagnostics in the context of Herceptin clinical trials.

8. To perform formal pharmacokinetic interaction studies by assessing serum concentrations of antibody and of drug in human studies of Herceptin + antineoplastic agents (e.g., paclitaxel, doxorubicin).

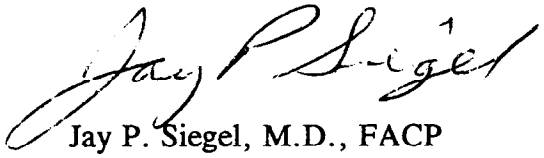
9. To evaluate the use of Herceptin with antimetabolites in a breast cancer clinical trial of cyclophosphamide, methotrexate, and 5-fluorouracil ± Herceptin.

It is requested that adverse experience reports be submitted in accordance with the adverse experience reporting requirements for licensed biological products (21 CFR 600.80) and that distribution reports be submitted as described (21 CFR 600.81). All adverse experience reports should be prominently identified according to 21 CFR 600.80 and be submitted to the Center for Biologics Evaluation and Research, HFM-210, Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852-1448.

Please submit three copies of all final printed labeling at the time of use and include part II of the label transmittal form (FDA Form 2567) with completed implementation information. In addition, you may wish to submit draft copies of the proposed introductory advertising and promotional labeling with an FDA Form 2567 or Form 2253 to the Center for Biologics Evaluation and Research, Advertising and Promotional Labeling Staff, HFM-202, 1401 Rockville Pike, Rockville, MD 20852-1448. Final printed advertising and promotional labeling should be submitted at the time of initial dissemination, accompanied by an FDA Form 2567 or Form 2253.

All promotional claims must be consistent with and not contrary to approved labeling. No comparative promotional claim or claim of superiority over other similar products should be made unless data to support such claims are submitted to and approved by the Center for Biologics Evaluation and Research.

Sincerely yours,



Jay P. Siegel, M.D., FACP
Director
Office of Therapeutics
Research and Review
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