DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-174/S-012

Wyeth Pharmaceuticals Inc.
87 CambridgePark Drive
Cambridge, MA 02140

Attention: Patricia M. Johnson
Associate Director II
Worldwide Regulatory Affairs

Dear Ms. Johnson:

Please refer to your supplemental new drug application (NDA) dated June 13, 2003, received June 16, 2003, and submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Mylotarg ® (gemtuzumab ozogamicin for Injection).

We acknowledge receipt of your submissions dated July 31 and December 9, 2003, February 6 and 26 (3 submissions), March 3, 12, 17, and 31, and April 6 and 12, 2004. We also acknowledge receipt of two electronic mail messages dated April 14, 2004 containing responses to Division information requests that have not yet been submitted in hard copy.

This supplemental new drug application provides for changes to the CLINICAL PHARMACOLOGY, CLINICAL STUDIES, ADVERSE REACTIONS and REFERENCES sections of the package insert based on the integrated clinical data summary entitled "Final Integrated Clinical Data Summary for Single-Agent Phase 2 Studies in Patients with Acute Myeloid Leukemia (AML) in First Relapse (0903B1-201-US/CA, 0903B1-202-EU, 0903B1-203-US/EU). In addition, this supplemental new drug application provided data to address post-marketing commitments noted in our May 17, 2000 letter. Finally, there were editorial changes to the DESCRIPTION, CONTRAINDICATIONS, and HOW SUPPLIED sections of the package insert.

We completed our review of this application, as amended. This application is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text and with the minor editorial revisions listed below.

1. In the CLINICAL STUDIES section, 2nd paragraph, after "In addition to CR, ...platelet recovery $\geq$ 100,000μL." add as a second sentence:

   "Remission status was determined at approximately 28 days after the last dose of Mylotarg."

2. In the PRECAUTIONS, Pediatric Use section, change the word "studied" to "established", so that the text reads:

> "The safety and effectiveness of Mylotarg (gemtuzumab ozogamicin for Injection) in pediatric patients have not been established."

The final printed labeling (FPL) must be identical, and include the minor editorial revisions indicated, to the enclosed labeling text for the package insert. These revisions are terms of the approval of this application.

Please submit the FPL electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – NDA. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 12-174/S-012." Approval of this submission by FDA is not required before the labeling is used.

We received your submissions dated June 11, 2001 and June 13, 2003, reporting on the following postmarketing study commitments.

1. Item 1 (Clinical Pharmacology/Biopharmaceutics): Examine the pharmacokinetic data collected from all trials to explore the possibility that various patient characteristics (demographic, clinical status) affect total and unconjugated calicheamicin pharmacokinetics.

2. Item 2 (Clinical Pharmacology/Biopharmaceutics): Analyze the pharmacokinetic data for total and unconjugated calicheamicin for study 203 and studies 201 and 202 providing a comparison of pharmacokinetics in patients under 60 years and patients 60 years of age or older.

3. Item 3 (Chemistry, Manufacturing and Controls): Provide a detailed description of the test methods used for analyzing the strength and purity of (b)(4) (b)(4)

We have reviewed your submissions and conclude that the above commitments were fulfilled.

The following commitments acknowledged in our May 17, 2000 letter are open:

1. A randomized controlled trial of gemtuzumab ozogamicin, daunorubicin, and cytarabine versus daunorubicin and cytarabine as induction therapy in patients with *de novo* CD33-positive acute myeloid leukemia. This study is designed to demonstrate superior survival in the three-drug (gemtuzumab ozogamicin containing) group. Response rate results can be used as supportive evidence; responses should be defined as CR's or CRp's of at least 4 weeks duration. If the three-drug regimen cannot be designed with acceptable toxicity, a randomized

controlled trial designed to show that survival in patients treated with gemtuzumab ozogamicin and cytarabine is not inferior to survival in patients given daunorubicin and cytarabine should be initiated following discussion with the division. Again, the definition of the supportive secondary end point, response (CR and CRp), should include a pre-specified minimum duration of response of 4 weeks.

2. Item 4 (CMC): Develop a specification for assay of unconjugated antibody.

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. 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, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled "**Postmarketing Study Protocol**", "**Postmarketing Study Final Report**", or "**Postmarketing Study Correspondence**."

We remind you of your April 6 and 14, 2004 agreement to have further discussions with the division regarding the timing for submission of the results of the Prospective Observational Study (POS) of Mylotarg, and a subsequent supplement to the NDA.

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857
Rockville MD 20857

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HFD-410
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Dianne Spillman, Regulatory Project Manager, at (301) 594-5746.

Sincerely,

{See appended electronic signature page}

Richard Pazdur
Director
Division of Oncology Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration

Enclosure

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
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