DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761060/Original #1
BLA 761060/Original #2

BLA APPROVAL

Wyeth Pharmaceuticals Inc., a subsidiary of Pfizer, Inc.
Attention: Brenda W. Kozan
Senior Manager, Worldwide Safety and Regulatory
500 Arcola Road
Collegeville, PA 19426

Dear Ms. Kozan:

Please refer to your Biologics License Application (BLA) dated November 2, 2016, received November 2, 2016, and your amendments, submitted under section 351(a) of the Public Health Service Act for MYLOTARG™ (gemtuzumab ozogamicin), 4.5 mg/vial.

LICENSING

We have approved your BLA for MYLOTARG™ (gemtuzumab ozogamicin), effective this date. You are hereby authorized to introduce or deliver for introduction into interstate commerce, MYLOTARG™, under your existing Department of Health and Human Services U.S. License No. 003. MYLOTARG™ is indicated for the following indications which, for administrative purposes, we have designated as follows:

- BLA 761060/Original #1 - Treatment of newly-diagnosed CD33-positive acute myeloid leukemia in adults.

- BLA 761060/Original #2- Treatment of relapsed or refractory CD33-positive acute myeloid leukemia in adults and in pediatric patients 2 years and older.

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture (b) (4) at (b) (4). Gemtuzumab ozogamicin drug substance and drug product will be manufactured and filled at Wyeth Pharmaceuticals Inc., a subsidiary of Pfizer Inc., Pearl River, NY. Final formulated product will be labeled and packaged at (b) (4) You may label your product with the proprietary name, MYLOTARG™, and will market it in 4.5 mg/vial lyophilized cake or powder for injection.

DATING PERIOD

The dating period for MYLOTARG™ shall be 60 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 your drug substance shall be (b) (4) from the date of manufacture when stored at (b) (4) °C. (b) (4)

FDA LOT RELEASE

You are not currently required to submit samples of future lots of MYLOTARG™ 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 MYLOTARG™, 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.

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). 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.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to carton and immediate container labels submitted on August 1, 2017, 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 — Certain Human*

Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (May 2015, Revision 3). For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved BLA 761060**." Approval of this submission by FDA is not required before the labeling is used.

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.

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 hepatic veno-occlusive disease and hemorrhage with the fractionated dose and schedule of Mylotarg, or to identify an unexpected serious risk of QT prolongation or an unexpected serious risk of anti-drug antibodies.

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 these serious risks.

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

PMR 3266-1 Further characterize the safety and pharmacokinetics of the 3 mg/m^2 day 1, 4, and 7 dose-schedule of Mylotarg as a single agent for treatment of patients with relapsed or refractory CD33-positive acute myelogenous leukemia. Submit a study report and datasets, including an analysis of hemorrhage, complete blood counts, PT, aPTT, and fibrinogen, hepatotoxicity, hepatic veno-occlusive disease (VOD), and the impact of hematopoietic stem cell transplantation pre- or post-Mylotarg on the incidence of VOD. Enroll at least 50 patients.

The timetable you submitted on August 31, 2017, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	03/2018
Final Protocol Submission:	06/2018
Trial Completion:	01/2021
Final Trial Report Submission:	09/2021

PMR 3266-2 Conduct a study to determine the effect of Mylotarg on the QT interval in humans.

The timetable you submitted on August 31, 2017, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	03/2018
Final Protocol Submission:	06/2018
Study Completion:	01/2021
Final Study Report Submission:	09/2021

PMR 3266-3 Submit a validation report for a validated, sensitive, and accurate assay(s) for the detection of binding antibodies to gemtuzumab ozogamicin, including procedures for the accurate detection of binding antibodies to gemtuzumab ozogamicin in the presence of gemtuzumab ozogamicin levels that are expected to be present in the serum or plasma at the time of patient sampling. The assay(s) should be able to detect and confirm binding antibodies directed against both gemtuzumab and the calicheamicin/linker moiety.

The timetable you submitted on August 31, 2017, states that you will conduct this study according to the following schedule:

Final Validation Plan Submission:	09/2017
Final Report Submission:	10/2017

PMR 3266-4 Submit a validation report for a validated, sensitive, and accurate assay for the detection of neutralizing antibodies to gemtuzumab ozogamicin, including procedures for the accurate detection of neutralizing antibodies to gemtuzumab ozogamicin in the presence of gemtuzumab ozogamicin levels that are expected to be present in the serum or plasma at the time of patient sampling.

The timetable you submitted on August 31, 2017, states that you will conduct this study according to the following schedule:

Draft Validation Plan Submission:	04/2018
Final Validation Plan Submission:	06/2018
Final Report Submission:	12/2018

PMR 3266-5 Submit the final report of a study conducted to assess the anti-drug antibody (ADA) response to gemtuzumab ozogamicin with the validated assay developed under PMR 3266-3 and 3266-4.

The timetable you submitted on August 31, 2017, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	03/2018
Final Protocol Submission:	06/2018
Final Study Report Submission:	09/2021

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess a signal of increased hepatic veno-occlusive disease in pediatric patients.

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

PMR 3266-6 Provide data to confirm the safety of gemtuzumab ozogamicin in pediatric patients. Submit an abbreviated study report, including data sets, for Study AAML0531, a randomized trial of approximately 1000 pediatric patients with acute myeloid leukemia evaluating Mylotarg in approximately 500 pediatric patients.

The timetable you submitted on August 31, 2017, states that you will conduct this study according to the following schedule:

Draft Data Analysis Plan Submission:	10/2017
Final Data Analysis Plan Submission:	12/2017
Final Abbreviated Study Report Submission:	05/2018

Submit clinical protocol(s) to your IND 046635 with a cross-reference letter to this BLA. Submit nonclinical and chemistry, manufacturing, and controls protocols and 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 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 SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

PMC 3266-7 Determine the effect of a broad range of concentrations of Mylotarg on the potential to inhibit platelet function by conducting in vitro studies on platelets and megakaryocytes. Assessment methods should include evaluation of effects on platelet aggregation, including GPIb-mediated aggregation. Evaluation should include samples from subjects with and without concomitant conditions associated with platelet dysfunction (e.g., severe renal dysfunction, use of a concomitant anticoagulant, and use of aspirin).

The timetable you submitted on August 31, 2017, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	02/2018
Final Protocol Submission:	03/2018
Study Completion:	03/2019
Final Report Submission:	06/2019

POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

PMC 3266-8 To conduct the bioburden and endotoxin drug substance release method qualifications using two additional batches of drug substance.

The timetable you submitted on August 31, 2017, states that you will conduct this study according to the following schedule:

Study Completion:	05/2018
Final Report Submission:	11/2018

PMC 3266-9 To conduct the sterility and endotoxin drug product release method qualification using two additional batches of drug product.

The timetable you submitted on August 31, 2017, states that you will conduct this study according to the following schedule:

Study Completion:	11/2017
Final Report Submission:	11/2018

PMC 3266-10 Re-evaluate gemtuzumab ozogamicin drug substance and drug product lot release acceptance criteria for appearance, iCE, CGE and cytotoxicity assays based on ≥25 unique combinations of gemtuzumab (b) (4) lots used to manufacture gemtuzumab ozogamicin drug substance and drug product using the commercial manufacturing process and tested using the commercial specification methods. Pfizer will submit the corresponding data, the analytical and statistical plan used to evaluate the specifications, and any proposed changes to the specifications.

The timetable you submitted on August 31, 2017, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	02/2019
Study Completion:	09/2022
Final Report Submission:	04/2023

Submit clinical protocols to your IND 044635 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing 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**."

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

As required under 21 CFR 601.12(f)(4), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. 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.

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.

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

MEDWATCH-TO-MANUFACTURER PROGRAM

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.

If you have any questions, call Kris Kolibab, Senior Regulatory Project Manager, at (240) 402-0277.

Sincerely,

{See appended electronic signature page}

Ann T. Farrell, MD
Director
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE:
Content of Labeling

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

/s/

ANN T FARRELL
09/01/2017