DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761040

BLA APPROVAL

Wyeth Pharmaceuticals, Inc., a subsidiary of Pfizer Inc.
Attention: Alison Russell, PhD
Director, Worldwide Safety and Regulatory
10646 Science Center Drive
San Diego, CA 92121

Dear Dr. Russell:

Please refer to your Biologics License Application (BLA) dated December 20, 2016, received December 20, 2016, and your amendments, submitted under section 351(a) of the Public Health Service Act for BESPONSA™ (inotuzumab ozogamicin), lyophilized (b) (4) powder, 0.9 mg/vial.

We also refer to our approval letter dated August 17, 2017, which contained the following errors: incorrect dosage strength, incorrect manufacturing locations, and PMR 3259-1 listed the incorrect due date for the interim report submission.

This replacement approval letter incorporates the correction of the errors. The effective approval date will remain August 17, 2017, the date of the original approval letter.

LICENSING

We have approved your BLA for BESPONSA™ (inotuzumab ozogamicin) effective this date. You are hereby authorized to introduce or deliver for introduction into interstate commerce, BESPONSA under your existing Department of Health and Human Services U.S. License No. 003. BESPONSA™ is indicated for the treatment of adults with relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL).

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture (b) (4) Drug substance and the final formulated product will be manufactured and filled at Wyeth Pharmaceutical Division of Wyeth Holdings Corp., a subsidiary of Pfizer Inc., Pearl River, NY. Final formulated product will be labeled and packaged at Pharmacia and Upjohn Company, a subsidiary of Pfizer Inc., Kalamazoo, MI. You may label your product with the proprietary name, BESPONSA™, and will market it in 0.9 mg/vial lyophilized (b) (4) powder for i.v. administration: 0.25 mg/mL after reconstitution with 4 mL of sterile WFI.

DATING PERIOD

The dating period for BESPONSA™ 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 your [redacted] drug substance shall be [redacted] months from the date of manufacture when stored at [redacted]°C.

Results of ongoing stability should be submitted throughout the dating period, as they become available, including the results of stability studies from the first [redacted] production lots.

We have approved the stability protocol(s) in your license application for the purpose of extending the expiration dating period of your drug substance **and/or** drug product under 21 CFR 601.12.

FDA LOT RELEASE

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

WAIVER OF HIGHLIGHTS SECTION

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

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 the carton and immediate container labels submitted on July 28, 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 761040**." Approval of this submission by FDA is not required before the labeling is used.

ADVISORY COMMITTEE

Your application for BESPONSA™ was not referred to an FDA advisory committee because the application did not raise significant safety or efficacy issues in the intended population.

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 a known signal of a serious risk of toxicity, including hepatic veno-occlusive disease, transplant related (non-relapse) mortality, and non-transplant related mortality, after hematopoietic stem cell transplantation.

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 study:

PMR 3259-1 Characterize toxicity after hematopoietic stem cell transplantation (HSCT) in adult and pediatric patients who receive inotuzumab ozogamicin. Include hepatic veno-occlusive disease, transplant related mortality (non-relapse mortality), and non-transplant related mortality. Conduct an analysis of registry data (for example the Center for International Blood and Marrow Transplantation Research registry) to evaluate safety at least through day 180 after transplantation. The number of available patients in the database will determine the sample size. Include details of all prior therapies. The minimum duration of the study is to be no less than five years.

The timetable you submitted on August 14, 2017, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	11/2017
Final Protocol Submission:	02/2018
Interim Report Submission:	02/2019
Interim Report Submission:	02/2020
Interim Report Submission:	02/2021
Interim Report Submission:	02/2022
Final Report Submission:	02/2023

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess a known serious risk of hepatic veno-occlusive disease.

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

PMR 3259-2 Conduct a randomized trial of at least 2 dose levels of inotuzumab ozogamicin in patients with relapsed or refractory acute lymphoblastic leukemia who are potential candidates for hematopoietic stem cell transplantation (HSCT) and at high risk for developing veno-occlusive disease (VOD). High risk is defined as patients with prior HSCT, ongoing or prior liver disease, older patients ($\geq$ 55 years), or later salvage line (Salvage $\geq$ 2). Safety parameters will include hepatic VOD, transplant related mortality (non-relapse mortality), and non-transplant related mortality. Descriptive analyses of safety and efficacy (including achievement of minimal residual disease [MRD]-negativity) will be conducted for the intent-to-treat population and the per-protocol population that excludes patients who do not proceed to HSCT. The study will include sufficient clinical pharmacokinetic sampling to analyze the exposure-response relationship for efficacy and safety. Submit the complete clinical study report and datasets.

The timetable you submitted on August 14, 2017 states that you will conduct this trial according to the following schedule:

Draft Protocol Submission:	02/2018
Final Protocol Submission:	05/2018
Trial Completion:	04/2023
Final Report Submission:	11/2023

Submit clinical protocol(s) to your IND 065658 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 NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

PMC 3259-3 Conduct the bioburden and endotoxin test method qualification of inotuzumab ozogamicin drug substance using two additional batches.

The timetable you submitted on August 14, 2017, states that you will conduct this study according to the following schedule:

Final Report Submission:	11/2017

PMC 3259-4 Conduct the sterility and endotoxin test method qualification of inotuzumab ozogamicin drug product using two additional batches.

The timetable you submitted on August 14, 2017, states that you will conduct this study according to the following schedule:

Final Report Submission: 11/2017

PMC 3259-5 Implement bioburden and endotoxin monitoring of the (b) (4) used to manufacture inotuzumab ozogamicin drug product.

The timetable you submitted on August 14, 2017, states that you will conduct this study according to the following schedule:

Implementation: 11/2017

Submit clinical protocols to your IND 065658 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.

POST APPROVAL FEEDBACK MEETING

New molecular entities and new biologics qualify for a post approval 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 Rachel McMullen, Regulatory Project Manager, at (240) 402-4574.

Sincerely,

{See appended electronic signature page}

Richard Pazdur, MD
Director
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/

RICHARD PAZDUR
08/17/2017