DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

Our STN: BL 125518/0

BLA APPROVAL

October 27, 2015

Amgen, Inc.
Attention: Michelle Pernice, Pharm.D.
Senior Manager, Regulatory Affairs
Regional Regulatory Lead
One Amgen Center Drive
Thousand Oaks, CA 91320

Dear Dr. Pernice:

We have approved your biologics license application for talimogene laherparepvec effective this date. You are hereby authorized to introduce, or deliver for introduction into interstate commerce, talimogene laherparepvec under your existing Department of Health and Human Services U.S. License No. 1080. Talimogene laherparepvec is indicated for local treatment of unresectable cutaneous, subcutaneous, and nodal lesions in patients with melanoma recurrent after initial surgery.

The review of this product was associated with the following National Clinical Trial (NCT) number(s): 00769704, 01368276, 00289016, 01740297, 02014441, 02147951, 00402025, and 01161498.

Under this authorization, you are approved to manufacture talimogene laherparepvec at your facility in Woburn, Massachusetts. You may label your product with the proprietary name IMLYGIC and will market it in 2 milliliter single use cyclic olefin polymer vials containing 1 milliliter extractable volume at concentrations of 10^6 plaque forming units (PFU) per milliliter and 10^8 PFU per milliliter.

The dating period for talimogene laherparepvec shall be 48 months from the date of manufacture when stored at -70 to -90°C. The date of manufacture shall be defined as the date of filling into final containers. The dating period for your drug substance shall be [redacted]

Please submit final container samples of the drug product together with protocols showing results of all applicable tests. You may not distribute any lots of product until you receive a notification of release from the Director, Center for Biologics Evaluation and Research (CBER).

You must submit information to your biologics license application for our review and written approval under 21 CFR 601.12 for any changes in, including but not limited to, the

manufacturing, testing, packaging or labeling of talimogene laherparepvec, or in the manufacturing facilities.

You must submit reports of biological product deviations under 21 CFR 600.14. You should identify and investigate all manufacturing deviations promptly, 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 the Director, Office of Compliance and Biologics Quality, at the following address:

Food and Drug Administration
Center for Biologics Evaluation and Research
Document Control Center
10903 New Hampshire Ave.
WO71-G112
Silver Spring, MD 20993-0002

Under 21 CFR Part 208, we have determined that this product poses a serious and significant public health concern requiring the distribution of a Medication Guide. Talimogene laherparepvec is a product for which patient labeling could help prevent serious adverse effects and inform the patient of serious risks relative to benefit that could affect their decisions to use, or continue to use, the product. Therefore, a Medication Guide is necessary for safe and effective use of this product and FDA hereby approves the draft Medication Guide you submitted on October 5, 2015. Please note that:

- Under 21 CFR 201.57 (c)(18) this Medication Guide must be reprinted at the end of the package insert;

- Under 21 CFR 208 you are responsible for ensuring that this Medication Guide is available for distribution to every patient who is dispensed a prescription for this product;

- The final printed Medication Guide distributed to patients must conform to all conditions described in 21 CFR 208.20, including a minimum of 10 point text; and

- You are responsible for ensuring that the label of each container or package includes a prominent and conspicuous instruction to authorized dispensers to provide a Medication Guide to each patient to whom the drug is dispensed, and states how the Medication Guide is provided.

Under 21 CFR 201.57(c)(18), patient labeling must be reprinted at the end of the package insert. We request that the text of information distributed to patients be printed in a minimum of 10-point font.

Please provide your final content of labeling in Structured Product Labeling (SPL) format and include the carton and container labels. In addition, please submit three original paper copies for carton and container final printed labeling. All final labeling should be submitted as Product

Correspondence to this BLA at the time of use (prior to marketing) and include implementation information on FDA Form 356h.

In addition, please submit the final content of labeling (21 CFR 601.14) in SPL format via the FDA automated drug registration and listing system, (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. 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.

You may submit two draft copies of the proposed introductory advertising and promotional labeling with an FDA Form 2253 to the Advertising and Promotional Labeling Branch at the following address:

Food and Drug Administration
Center for Biologics Evaluation and Research
Document Control Center
10903 New Hampshire Ave.
WO71-G112
Silver Spring, MD 20993-0002

You must submit copies of your final advertisement and promotional labeling at the time of initial dissemination or publication, accompanied by Form FDA 2253 (21 CFR 601.12(f)(4)).

All promotional claims must be consistent with and not contrary to approved labeling. You should not make a comparative promotional claim or claim of superiority over other products unless you have substantial evidence or substantial clinical experience to support such claims (21 CFR 202.1(e)(6)).

ADVERSE EVENT REPORTING

You must submit adverse experience reports in accordance with the adverse experience reporting requirements for licensed biological products (21 CFR 600.80) and you must submit distribution reports as described in 21 CFR 600.81. You also agree to provide expanded adverse experience reporting (in addition to complying with the requirements under 21 CFR 600.80) to FAERS for three years following product licensure as follows: submit all reports of herpetic infection in patients and contacts, with qPCR results when available, as 30-day (monthly) reports, if not previously filed as 15-day expedited reports. You should submit postmarketing adverse experience reports and distribution reports to the Office of Biostatistics and Epidemiology, at the following address:

Food and Drug Administration
Center for Biologics Evaluation and Research
Document Control Center
10903 New Hampshire Ave.
WO71-G112
Silver Spring, MD 20993-0002

Prominently identify all adverse experience reports as described in 21 CFR 600.80.

PEDIATRIC REQUIREMENTS

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 in pediatric patients unless this requirement is waived, deferred, or inapplicable. Because the biological product for this indication has an orphan drug designation, you are exempt from this requirement.

POSTMARKETING REQUIREMENTS UNDER SECTION 505(o)

Section 505(o) 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 (section 505(o)(3)(A), 21 U.S.C. 355(o)(3)(A)).

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 identify an unexpected serious risk of talimogene laherparepvec-associated herpetic infection of non-tumor tissue in patients (primary infection/latency and reactivation) and contacts (transmission/accidental exposure).

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, we have determined that you are required to conduct the following study:

PMR #1:
Conduct a prospective observational cohort study of 920 IMLYGIC-treated patients to characterize the risk of herpetic infection among patients, close contacts, and healthcare providers; each subject will be followed for 5 years after initiating IMLYGIC (study Protocol #20130193).

We acknowledge the timetable you submitted on August 4, 2015, which states that you will conduct this study according to the following schedule:

Final Protocol Submission: April 30, 2016

Study Completion Date: August 31, 2024

Final Report Submission: February 28, 2025

Finally, we have determined that a clinical trial, in addition to the above observational study, will be necessary to identify an unexpected serious risk of talimogene laherparepvec-associated herpetic infection of non-tumor tissue in patients (primary infection/latency and reactivation) and contacts (transmission/accidental exposure).

Therefore, based on appropriate scientific data, we have determined that you are required to conduct the following clinical trial:

PMR #2: Complete the ongoing single-arm trial to evaluate the biodistribution and shedding of IMLYGIC in 60 IMLYGIC-treated subjects (study Protocol #20120324).

We acknowledge the timetable you submitted on August 4, 2015, which states that you will conduct this clinical trial according to the following schedule:

Final Protocol Submission: November 30, 2015

Study Completion Date: September 30, 2016

Final Report Submission: May 31, 2017

Please submit the protocol(s) to your IND 12412, with a cross-reference letter to this BLA 125518 explaining that these protocols were submitted to the IND. Please refer to the sequential number for each study/clinical trial and the submission number as shown in this letter.

If the information in the final study report supports a change in the labeling, the final study report must be submitted as a supplement to this BLA 125518. Supplements in support of labeling changes based on a postmarketing study report may be subject to a user fee. For administrative purposes, all submissions related to these postmarketing studies required under section 505(o) must be submitted to this BLA 125518 and be clearly designated as:

- **Required Postmarketing Protocol under 505(o)**
- **Required Postmarketing Correspondence Under Section 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.

You must describe the status in an annual report on postmarketing studies for this product. Label your annual report as an **Annual Status Report of Postmarketing Study Requirements/Commitments** and submit it to the FDA each year within 60 calendar days of the anniversary date of this letter until all Requirements and Commitments subject to the reporting requirements of section 506B of the FDCA are fulfilled or released. The status report for each study should include:

- the sequential number for each study as shown in this letter;
- information to identify and describe the postmarketing requirement;
- the original milestone schedule for the requirement;
- the revised milestone schedule for the requirement, if appropriate;
- the current status of the requirement (i.e., pending, ongoing, delayed, terminated, or submitted); and,
- an explanation of the status for the study or clinical trial. The explanation should include how the study is progressing in reference to the original projected schedule, including, the patient accrual rate (i.e., number enrolled to date and the total planned enrollment).

As described in 21 CFR 601.70(e), we may publicly disclose information regarding these postmarketing studies on our Web site at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Post-marketingPhaseIVCommitments/default.htm.

We 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.

PDUFA V APPLICANT INTERVIEW

FDA has contracted with Eastern Research Group, Inc. (ERG) to conduct an independent interim and final assessment of the Program for Enhanced Review Transparency and Communication for NME NDAs and Original BLAs under PDUFA V ('the Program'). The PDUFA V Commitment Letter states that these assessments will include interviews with applicants following FDA action on applications reviewed in the Program. For this purpose, first-cycle actions include approvals, complete responses, and withdrawals after filing. The purpose of the interview is to better understand applicant experiences with the Program and its ability to improve transparency and communication during FDA review.

ERG will contact you to schedule a PDUFA V applicant interview and provide specifics about the interview process. Your responses during the interview will be confidential with respect to the FDA review team. ERG has signed a non-disclosure agreement and will not disclose any identifying information to anyone outside their project team. They will report only anonymized results and findings in the interim and final assessments. Members of the FDA review team will

be interviewed by ERG separately. While your participation in the interview is voluntary, your feedback will be helpful to these assessments.

Sincerely yours,

Celia M. Witten, Ph.D., M.D.
Director
Office of Cellular, Tissue and Gene Therapies
Center for Biologics Evaluation and Research