FDA U.S. FOOD & DRUG ADMINISTRATION

BLA 761400

BLA ACCELERATED APPROVAL

Regeneron Pharmaceuticals, Inc.
Attention: Danish Iqbal, PhD
Senior Manager, Regulatory Affairs
777 Old Saw Mill River Road
Tarrytown, NY 10591-6707

Dear Dr. Iqbal:

Please refer to your biologics license application (BLA) dated and received December 22, 2023, and your amendments, submitted under section 351(a) of the Public Health Service Act for Lynozyfic (linvoseltamab-gcpt) injection.

We acknowledge receipt of your amendment dated January 10, 2025, which constituted a complete response to our August 20, 2024, action letter.

LICENSING

We have approved your BLA for Lynozyfic (linvoseltamab-gcpt) effective this date. You are hereby authorized to introduce or deliver for introduction into interstate commerce, Lynozyfic under your existing Department of Health and Human Services U.S. License No. 1760. Lynozyfic is indicated for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least four prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody.

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture linvoseltamab-gcpt drug substance at Regeneron Pharmaceuticals, Inc. in Rensselaer, NY. The drug product will be manufactured and filled (b) (4) and labeled and packaged (b) (4) You may label your product with the proprietary name Lynozyfic and will market it in 5 mg/2.5 mL single-dose vial and 200 mg/10 mL single-dose vial.

DATING PERIOD

The dating period for Lynozyfic shall be 18 months from the date of manufacture when stored at 5 ± 3°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) months from the date of manufacture when stored at (b) (4) °C.

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 drug product under 21 CFR 601.12.

FDA LOT RELEASE

You are not currently required to submit samples of future lots of Lynozyfic 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 Lynozyfic, 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 AND LABELING

We have completed our review of this application, as amended. It is approved under accelerated approval pursuant to section 506(c) of the Federal Food, Drug, and Cosmetic Act (FDCA) and 21 CFR 601.41, effective on the date of this letter, for use as recommended in the enclosed agreed-upon approved labeling. This BLA provides for the use of Lynozyfic for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least four prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody.

Marketing of this drug product and related activities must adhere to the substance and procedures of the accelerated approval statutory provisions and regulations.

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 CFR 601.14(b)] in structured product labeling (SPL) format, as described at FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information and Medication Guide). Information on submitting SPL files using eLIST may be found in the draft guidance for industry *SPL Standard for Content of Labeling Technical Qs and As* (October 2009).[2]

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm
[2] When final, this guidance will represent FDA's current thinking on this topic. We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

The SPL will be accessible via publicly available labeling repositories.

We request that the labeling approved today be available on your website within 10 days of receipt of this letter.

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the enclosed carton and container labeling submitted on March 17, 2025, as soon as they are available, but no more than 30 days after they are printed. Please submit these labeling electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (February 2020, Revision 7)*. For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved BLA 761400**." Approval of this submission by FDA is not required before the labeling is used.

ADVISORY COMMITTEE

Your application for linvoseltamab-gcpt was not referred to an FDA advisory committee because the application did not raise significant public health questions on the role of the biologic in the diagnosis, cure, mitigation, treatment, or prevention of a disease.

ACCELERATED APPROVAL REQUIREMENTS

Pursuant to section 506(c) of the FDCA and 21 CFR 601.41, you are required to conduct further adequate and well-controlled clinical trials intended to verify and describe clinical benefit. You are required to conduct such clinical trials with due diligence. If required postmarketing clinical trials fail to verify clinical benefit or are not conducted with due diligence, including with respect to the conditions set forth below, we may withdraw this approval. We remind you of your postmarketing requirement specified in your submission dated June 3, 2025. This requirement is listed below.

4848-1 Complete a randomized clinical trial in patients with relapsed or refractory multiple myeloma. Patients should be randomized to receive linvoseltamab compared to standard therapy for relapsed or refractory multiple myeloma. The primary endpoint should be progression-free survival and key secondary endpoints should include overall response rate and overall survival. The trial should enroll a sufficiently representative study population to allow for generalizability of the result to the U.S. patient population with multiple myeloma.

The timetable you submitted on June 3, 2025, states that you will conduct this trial according to the following schedule:

Final Protocol Submission: 12/2022 (completed)

Trial Completion: 12/2026
Final Report Submission: 06/2027

Submit clinical protocols to your IND 138791 for this product. FDA considers the term final to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.

You must submit reports of the progress of each clinical trial required under section 506(c) (listed above) to this BLA 180 days after the date of approval of this BLA and approximately every 180 days thereafter (see section 506B(a)(2) of the FDCA) (hereinafter "180-day reports").

You are required to submit two 180-day reports per year for each open study or clinical trial required under 506(c). The initial report will be a standalone submission and the subsequent report will be combined with your application's annual status report (ASR) required under section 506B(a)(1) of the FDCA and 21 CFR 601.70. The standalone 180-day report will be due 180 days after the date of approval (with a 60-day grace period). Submit the subsequent 180-day report with your application's ASR. Submit both of these 180-day reports each year until the final report for the corresponding study or clinical trial is submitted[3].

Your 180-day reports must include the information listed in 21 CFR 601.70(b). FDA recommends that you use FORM FDA 3989, *PMR/PMC Annual Status Report for Drugs and Biologics,* to submit your 180-day reports.[4]

180-day reports must be clearly designated "**BLA 761400 180-Day AA PMR Progress Report**."

FDA will consider the submission of your application's ASR under section 506B(a)(1) and 21 CFR 601.70, in addition to the submission of reports 180 days after the date of approval each year (subject to a 60-day grace period), to satisfy the periodic reporting requirement under section 506B(a)(2).

Submit final reports to this BLA as a supplemental application. For administrative purposes, the cover page of all submissions relating to this postmarketing requirement must be clearly designated "**Subpart E Postmarketing Requirement(s)**."

[3] You are required to submit information related to your confirmatory trial as part of your annual reporting requirement under section 506B(a)(1) until the FDA notifies you, in writing, that the Agency concurs that the study requirement has been fulfilled or that the study either is no longer feasible or would no longer provide useful information.
[4] FORM FDA 3989, along with instructions for completing this form, is available on the FDA Forms web page at https://www.fda.gov/about-fda/reports-manuals-forms/forms.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), 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 COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitment:

4848-2 Develop and validate an SE-UPLC method with adequate resolving power to separate the intact linvoseltamab from known product-related impurities (aggregates and fragments).

The timetable you submitted on June 3, 2025, states that you will conduct this study according to the following schedule:

Final Report Submission: 07/2025

Submit clinical protocols to your IND 138791 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/subjects 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**."

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the FDCA authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS), if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks.

In accordance with section 505-1 of FDCA, we have determined that a REMS is necessary for Lynozyfic (linvoseltamab-gcpt) to ensure the benefits of the drug outweigh

the risks of Cytokine Release Syndrome (CRS) and neurologic toxicity, including Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS).

Your proposed REMS must also include the following:

Communication Plan: We have determined that a communication plan targeted to healthcare providers who are likely to prescribe Lynozyfic (linvoseltamab-gcpt) will support implementation of the elements of your REMS. The communication plan provides for the dissemination of information about CRS and neurologic toxicity, including ICANS, as well as requirements for prescriber certification and pharmacy or healthcare setting certification.

The communication plan must include, at minimum, the following:

- REMS Letter to Healthcare Providers and Professional Societies
- REMS Fact Sheet
- Dissemination of the REMS Letters and REMS Factsheet through field-based sales and medical representatives

Elements to assure safe use: Pursuant to 505-1(f)(1), we have also determined that Lynozyfic (linvoseltamab-gcpt) can be approved only if elements necessary to assure safe use are required as part of the REMS to mitigate the risks of CRS and neurologic toxicity, including ICANS, listed in the labeling of the drug.

Your REMS includes the following elements to mitigate these risks:

- Healthcare providers have particular experience or training, or are specially certified
- Pharmacies and health care settings that dispense the drug are specially certified

Implementation System: The REMS must include an implementation system to monitor, evaluate, and work to improve the implementation of the elements to assure safe use (outlined above) that require pharmacies and health care settings that dispense the drug be specially certified.

Your proposed REMS, submitted on February 7, 2025, amended and appended to this letter, is approved.

The REMS consists of a communication plan, elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS.

Your REMS must be fully operational before you introduce Lynozyfic (linvoseltamab-gcpt) into interstate commerce.

The REMS assessment plan must include, but is not limited to, the following:

For each metric, provide the two previous, current, and cumulative reporting periods (where applicable) unless otherwise noted.

Program Outreach and Communication Plan

1. REMS communication plan activities (provide data for the 12-month and 24-month assessments only):
    a. Sources of the distribution lists for healthcare providers
    b. Number and percentage of healthcare providers targeted, stratified by specialty, if known
    c. Number and percentage of Healthcare Provider REMS Letters sent to healthcare providers, via email, USPS mail, and the dates the letters were sent
        i. For letters sent via email, the number and percentage of letters successfully delivered, opened, and unopened
            1) The number and percentage of letters sent via mail because the emailed letter was undeliverable, unopened, or the email was unknown
        ii. For the letters sent by USPS mail, the number and percentage of letters successfully delivered and returned as undeliverable
    d. Number of REMS Letters disseminated to targeted healthcare providers by field-based sales and medical representatives during the 12 months after Lynozyfic was commercially distributed
    e. Number and name of the professional societies that were sent the Professional Society REMS Letter
    f. Number of REMS Fact Sheets disseminated to targeted healthcare providers by field-based sales and medical representatives during the 12 months after Lynozyfic was commercially distributed
    g. Date and name of the professional meetings attended and corresponding information on the REMS materials displayed

Program Implementation and Operations

2. Program Implementation (provide data at the 12-month assessment only):
    a. Date of first commercial availability of Lynozyfic
    b. Date the REMS Website went live
        i. Number of total visits and unique visits to the REMS Website
        ii. Number and type of Lynozyfic REMS materials accessed (i.e., downloaded)
    c. Date the REMS Coordinating Center was fully operational
    d. Date prescribers and pharmacies and healthcare settings were able to complete the REMS certification process (online, by fax, or by email)
    e. Date of the first prescriber certification

   f. Date of the first pharmacy and healthcare setting certification

3. REMS Certification and Enrollment Statistics
   a. Healthcare Providers
      i. Number of newly certified healthcare providers and the number and percentage of active (i.e., who have prescribed Lynozyfic at least once during the reporting period) healthcare providers stratified by:
         1) Credentials (e.g., Doctor of Medicine, Doctor of Osteopathic Medicine, Nurse Practitioner, Physician Assistant, Other). If “other” accounts for >10% of respondents for credentials, provide the most common credentials identified.
         2) Specialty (e.g., Oncology, Hematology, Hematology/Oncology, Other). If “other” accounts for >10% of respondents for specialties, provide the most common specialties identified.
         3) Geographic region as defined by the US Census
         4) Method of enrollment (e.g., online, email, fax) for newly certified healthcare providers only
      ii. Number of incomplete prescriber enrollments, and summary of reported reason(s) for not completing
   b. Pharmacies and Healthcare Settings
      i. Number of newly certified pharmacies and healthcare settings and the number and percentage of active (i.e., who have dispensed or ordered the drug at least once during the reporting period) pharmacies and healthcare settings stratified by:
         1) Type of pharmacy and healthcare setting (e.g., Inpatient Hospital Pharmacy, Outpatient Hospital Pharmacy, Oncology Infusion Center, Community Oncology Physician Office, Specialty Pharmacy, Other). If “other” accounts for >10% of respondents for type, provide the most common type(s) identified.
         2) Geographic region as defined by the US Census
         3) Method of enrollment (e.g., online, email, fax) for newly certified pharmacies and healthcare settings only
      ii. Number of incomplete pharmacy and healthcare setting enrollments, and summary of reported reason(s) for not completing
   c. Wholesalers-Distributors
      i. Number of wholesalers-distributors contracted to ship and number of active (i.e., have shipped) wholesalers-distributors
4. Utilization Data
   a. Number of vials sent to certified pharmacies and healthcare settings, stratified by type of pharmacy and healthcare setting
   b. Number and percentage of prescribers for whom REMS dispense authorizations (RDAs) were generated for first prescriptions, stratified by

medical specialty (e.g., Oncology) and prescriber credentials (e.g., Doctor of Medicine)

c. Number of RDAs for first prescriptions stratified by pharmacy and healthcare setting type

5. REMS Compliance
    a. Audits
        i. A copy of the audit plan
        ii. Report of audit findings for each participant
        iii. Number of audits expected, and the number of audits performed
        iv. Documentation of completion of training for relevant staff
        v. Documentation of processes and procedures in place for complying with the Lynozyfic REMS
        vi. Verification for each audited pharmacy and healthcare setting that the designated Authorized Representative remains the same. If different, include the number of new Authorized Representatives
        vii. Number and type of deficiencies (e.g., critical, major, minor findings) noted for each group of audited participants as a percentage of audited participants
        viii. Confirmation of documentation of completion of training for relevant staff after audit findings indicated training was necessary
        ix. A comparison of the findings to findings of previous audits and an assessment of whether any trends are observed
    b. A copy of the Noncompliance Plan, which addresses the criteria for noncompliance for each participant (healthcare provider, pharmacy and healthcare settings and wholesaler-distributor), actions taken to address noncompliance for each event, and under what circumstances a participant would be suspended or decertified from the REMS
        i. For those with deficiencies noted, report the number that successfully completed a Corrective and Preventive Actions (CAPA) plan within the timeframes specified in the Noncompliance Plan
        ii. For any that did not complete the CAPA within the timeframe specified in the Noncompliance Plan, describe actions taken
        iii. Number of instances of noncompliance accompanied by a description of each instance and the reason for the occurrence (if provided). For each instance of noncompliance, report the following information:
            1) Unique ID(s) of the participant(s) associated with the noncompliance event or deviation to enable tracking over time
            2) Source of the noncompliance data
            3) Results of root cause analysis
            4) Action(s) that were taken in response

iv. Pharmacies and Healthcare Settings
    1) Number of pharmacies and healthcare settings for which noncompliance with the Lynozyfic REMS is detected (numerator) divided by all pharmacies and healthcare settings dispensing Lynozyfic (denominator)
    2) Number and description of pharmacies and healthcare settings that dispensed Lynozyfic when the prescriber was not certified, and any corrective and preventative actions taken to prevent future occurrences
    3) Number of non-certified pharmacies and healthcare settings that dispensed Lynozyfic (numerator) divided by all pharmacies and healthcare settings that dispensed Lynozyfic (denominator)
    4) Number of prescriptions dispensed by non-certified pharmacies and healthcare settings (numerator) divided by all Lynozyfic dispenses (denominator) and the actions taken to prevent future occurrences
    5) Summary of audit findings and any action taken and outcome of actions to prevent future occurrences
    6) Summary of findings for monitoring conducted during the reporting period, including any CAPA

v. Wholesalers-Distributors
    1) Number and description of non-certified pharmacies and healthcare settings that were shipped Lynozyfic, and the number of these that subsequently became certified
    2) The number of authorized wholesalers-distributors for which noncompliance with the REMS is detected (numerator) divided by the number of contracted wholesalers-distributors (denominator)
    3) The number and type of wholesalers-distributors not contracted with Regeneron Pharmaceuticals, Inc. that shipped Lynozyfic, the number of incidents for each, actions taken to remove Lynozyfic from these entities, and actions taken to prevent future occurrences and outcome of such actions
    4) The number of contracted wholesalers-distributors suspended and/or unauthorized to distribute for noncompliance with REMS requirements and reasons for such actions, and actions taken to prevent distribution or removal of Lynozyfic from these entities

c. Any other Lynozyfic REMS noncompliance, source of report and resulting CAPA

d. Number and percentage of dispensed first prescriptions that were authorized by the REMS prior to dispense out of all first dispenses. If < 100% provide the reason(s) and actions taken to remediate. REMS authorization for dispense requires both the prescriber and the pharmacy/healthcare setting be certified.
e. Number of RDAs for first prescriptions rejected, stratified by:
    i. Reasons and number of denials (numerator) divided by all denials (denominator)
        1) Healthcare provider not certified
        2) Pharmacy or Healthcare Setting not certified
        3) Other reasons for denial not categorized above
f. Number of all subsequent prescriptions dispensed that were prescribed by a healthcare provider not certified
    i. Source of how information obtained (e.g., spontaneous report, audits, REMS Coordinating Center, etc.)
g. Number of all subsequent prescriptions dispensed by a pharmacy or healthcare setting not certified
    i. Source of how information obtained (e.g., spontaneous report, audits, REMS Coordinating Center, etc.)

6. REMS Coordinating Center Report
    a. Number of contacts by participant type (patient/caregiver, certified prescriber, pharmacy and healthcare setting Authorized Representative or staff, other healthcare provider, wholesaler/distributor, other)
    b. Summary of the reasons for the call(s) by participant type. Limit the summary to the top five reasons for calls by participant group
    c. Description of each call, including participant credentials, that may indicate an issue with product access due to the REMS, REMS burden, or adverse event
    d. If the summary reason for the call(s) indicates an adverse event related to Cytokine Release Syndrome (CRS) or neurologic toxicity, including Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS) include details and the outcome of the call(s)
    e. Provide an assessment for any reports to the REMS Coordinating Center indicating a burden to the healthcare system or barrier(s) to patient access. Include in the assessment whether the burden or access issue is attributable to the REMS, insurance, healthcare availability, other
    f. Summary of frequently asked questions (FAQ) by participant credentials type. Limit the summary to the top five FAQs for calls by participant group
    g. Summary of any noncompliance that is identified through the REMS Coordinating Center contacts, source of report and resulting CAPA
    h. Summary of CAPAs resulting from issues identified

   i. Percentage of calls to the REMS Coordinating Center that were answered within 20 minutes
   j. The shortest wait time for a call to be answered, the longest wait time for a call to be answered and the median time for a call to be answered
   k. Percentage of calls to the REMS Coordinating Center where the caller abandoned the call before the call was answered
   l. The shortest wait time at which a call was abandoned, the longest wait time before the call was abandoned and the median wait time for a call to be abandoned

Knowledge

7. Knowledge Assessment
   a. Number of completed healthcare provider Knowledge Assessments, including the method of completion
   b. Summary statistics, including mean number of attempts, score, and range of scores and number of attempts to successfully complete the Knowledge Assessment
   c. Summary of most frequently missed questions on the Knowledge Assessment
   d. A summary of potential comprehension or perception issues identified with the Knowledge Assessment
8. Periodic Knowledge Survey of Certified Prescribers (beginning with the 12-month REMS Assessment Report and thereafter with each assessment report)

   A Knowledge Survey will be conducted with random samples of healthcare providers who prescribe Lynozyfic
   a. Evaluation of understanding of the risks of CRS and neurologic toxicity, including ICANS with Lynozyfic and mitigation strategies of the Lynozyfic REMS as well as compliance with the mitigation strategies
   b. An evaluation of prescriber's knowledge on the importance of monitoring patients for signs and symptoms of CRS and neurologic toxicity, including ICANS
   c. Provide the proportion of prescriber survey respondents that demonstrated knowledge of the importance of monitoring patients for signs and symptoms of CRS and neurologic toxicity, including ICANS

Health Outcomes and/or Surrogates of Health Outcomes

9. A summary analysis of all reported cases of CRS and neurologic toxicity, including ICANS, stratified by source of report (e.g., spontaneous)
   a. Include the following stratifications by grade/severity in the analysis
      i. Step-up dosing was initiated in the hospital setting. (For those reports that indicate initiation outside of the hospital setting provide the setting if known)
      ii. Pre-medication was administered

Overall Assessment of REMS Effectiveness

10. The requirements for assessments of an approved REMS under section 505-1(g)(3) include with respect to each goal included in the strategy, an assessment of the extent to which the approved strategy, including each element of the strategy, is meeting the goal or whether one or more such goals or such elements should be modified.

If the information provided in an assessment is insufficient to allow FDA to determine whether the REMS is meeting its goals or whether the REMS must be modified, FDA may require the submission of a new assessment plan that contains the metrics and/or methods necessary to make such a determination. Therefore, FDA strongly recommends obtaining FDA feedback on the details of your proposed assessment plan to ensure its success. To that end, we recommend that methodological approaches, study protocols, other analysis plans and assessment approaches used to assess a REMS program be submitted for FDA review as follows:

i. Submit your proposed audit plan and non-compliance plan for FDA review within 60 days of this letter.

ii. Submit your proposed protocol for the knowledge survey for FDA review within 90 days of this letter.

Prominently identify the submission containing the assessment instruments and methodology with the following wording in bold capital letters at the top of the first page of the submission:

> **BLA 761400 REMS ASSESSMENT METHODOLOGY**
> (insert concise description of content in bold capital letters, e.g.,
> **ASSESSMENT METHODOLOGY, PROTOCOL, SURVEY METHODOLOGIES, AUDIT PLAN, DRUG USE STUDY**)

We remind you that in addition to the REMS assessments submitted according to the timetable in the approved REMS, you must include an adequate rationale to support a proposed REMS modification for the addition, modification, or removal of any goal or element of the REMS, as described in section 505-1(g)(4) of the FDCA.

We also remind you that you must submit a REMS assessment when you submit a supplemental application for a new indication for use as described in section 505-1(g)(2)(A). This assessment should include:

a) An evaluation of how the benefit-risk profile will or will not change with the new indication.

b) A determination of the implications of a change in the benefit-risk profile for the current REMS.

c) *If the new, proposed indication for use introduces unexpected risks*: A description of those risks and an evaluation of whether those risks can be appropriately managed with the currently approved REMS.

d) *If a REMS assessment was submitted in the 18 months prior to submission of the supplemental application for a new indication for use*: A statement about whether the REMS was meeting its goals at the time of the last assessment and if any modifications of the REMS have been proposed since that assessment.

e) *If a REMS assessment has not been submitted in the 18 months prior to submission of the supplemental application for a new indication for use:* Provision of as many of the currently listed assessment plan items as is feasible.

f) *If you propose a REMS modification based on a change in the benefit-risk profile or because of the new indication of use, submit an adequate rationale to support the modification, including*: Provision of the reason(s) why the proposed REMS modification is necessary, the potential effect on the serious risk(s) for which the REMS was required, on patient access to the drug, and/or on the burden on the health care delivery system; and other appropriate evidence or data to support the proposed change. Additionally, include any changes to the assessment plan necessary to assess the proposed modified REMS. *If you are not proposing a REMS modification*, provide a rationale for why the REMS does not need to be modified.

Prominently identify any submission containing the REMS assessments or proposed modifications of the REMS with the following wording in bold capital letters at the top of the first page of the submission as appropriate:

BLA 761400 REMS ASSESSMENT

or

NEW SUPPLEMENT FOR BLA 761400/S-000
CHANGES BEING EFFECTED IN 30 DAYS
PROPOSED MINOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR BLA 761400/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED MAJOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR BLA 761400/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABELING CHANGES SUBMITTED IN SUPPLEMENT XXX

or

NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR BLA 761400/S-000
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)

Should you choose to submit a REMS revision, prominently identify the submission containing the REMS revisions with the following wording in bold capital letters at the top of the first page of the submission:

REMS REVISION FOR BLA 761400

To facilitate review of your submission, we request that you submit your proposed modified REMS and other REMS-related materials in Microsoft Word format. If certain documents, such as enrollment forms, are only in PDF format, they may be submitted as such, but the preference is to include as many as possible in Word format.

SUBMISSION OF REMS DOCUMENT IN SPL FORMAT

As soon as possible, but no later than 14 days from the date of this letter, submit the REMS document in Structured Product Labeling (SPL) format using the FDA automated drug registration and listing system (eLIST). Content of the REMS document must be identical to the approved REMS document. The SPL will be publicly available.

Information on submitting REMS in SPL format may be found in the guidance for industry *Providing Regulatory Submission in Electronic Format – Content of the Risk Evaluation and Mitigation Strategies Document Using Structured Product Labeling*.

For additional information on submitting REMS in SPL format, please email FDAREMSwebsite@fda.hhs.gov.

PROMOTIONAL MATERIALS

Under 21 CFR 601.45, you are required to submit, during the application pre-approval review period, all promotional materials, including promotional labeling and advertisements, that you intend to use in the first 120 days following marketing approval (i.e., your launch campaign). If you have not already met this requirement, you must immediately contact the Office of Prescription Drug Promotion (OPDP) at (301) 796-1200. Please ask to speak to a regulatory project manager or the appropriate

reviewer to discuss this issue.

As further required by 21 CFR 601.45, submit all promotional materials that you intend to use after the 120 days following marketing approval (i.e., your post-launch materials) at least 30 days before the intended time of initial dissemination of labeling or initial publication of the advertisement. We ask that each submission include a detailed cover letter together with three copies each of the promotional materials, annotated references, and approved Prescribing Information, Medication Guide, and Patient Package Insert (as applicable).

For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format-Promotional Labeling and Advertising Materials for Human Prescription Drugs*.[5]

REPORTING REQUIREMENTS

You must submit adverse experience reports under the adverse experience reporting requirements for licensed biological products (21 CFR 600.80).

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 4207
Silver Spring, MD 20903

[5] https://www.fda.gov/media/128163/download

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, please contact me via email at ashlee.bow@fda.hhs.gov or 301-796-6716.

Sincerely,

{See appended electronic signature page}

R. Angelo de Claro, MD
Deputy Office Director (Acting)
Office of Oncologic Diseases
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Content of Labeling
    - Prescribing Information
    - Medication Guide
- Carton and Container Labeling
- REMS

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/s/

ROMEO A DE CLARO
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