BLA 761388

BLA APPROVAL

Genentech, Inc.
Attention: Ruchi Gupta
Regulatory Program Management
1 DNA Way
South San Francisco, CA 94080

Dear Ruchi Gupta:

Please refer to your biologics license application (BLA) dated June 19, 2023, received June 20, 2023, and your amendments, submitted under section 351(a) of the Public Health Service Act for Piasky (crovalimab-akkz) injection for intravenous or subcutaneous use.

LICENSING

We have approved your BLA for Piasky (crovalimab-akkz) effective this date. You are hereby authorized to introduce or deliver for introduction into interstate commerce Piasky under your existing Department of Health and Human Services U.S. License No. 1048. Piasky is indicated for treatment of adult and pediatric patients 13 years and older with paroxysmal nocturnal hemoglobinura (PNH) and body weight of at least 40 kg.

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture crovalimab-akkz drug substance at (b) (4) The final formulated drug product will be manufactured and filled at Genentech, Inc., South San Francisco, CA, and (b) (4) , and labeled and packaged at (b) (4) You may label your product with the proprietary name, Piasky, and market it in 340 mg/2 mL (170 mg/mL) solution in a single-dose 2 mL glass vial.

DATING PERIOD

The dating period for Piasky shall be 36 months from the date of manufacture when stored at 2° to 8 °C. This dating period may include up to 7 days at maximum of 30 °C protected from light. 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.

FDA LOT RELEASE

You are not currently required to submit samples of future lots of Piasky 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 Piasky, or in the manufacturing facilities, will require the submission of information to your BLA 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.

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.[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 guidance for industry *SPL Standard for Content of Labeling Technical Qs and As (October 2009)*.[2]

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, 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 *SPL Standard for Content of Labeling Technical Qs & As.* For administrative purposes, designate this submission "**Final Printed Carton and**

[1] See http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm
[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

Container Labeling for approved BLA 761388" Approval of this submission by FDA is not required before the labeling is used.

ADVISORY COMMITTEE

Your application for Piasky was not referred to an FDA advisory committee because this biologic is not the first in its class for the treatment of PNH and the application did not raise efficacy, safety, or public health questions requiring advice from external experts.

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 REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the Federal Food, Drug, and Cosmetics 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 serious risk of meningococcal infections, infusion related reactions, and hypersensitivity reactions including type III hypersensitivity reactions; and an unexpected serious risk of adverse safety outcomes in pregnant women and infants exposed to Piasky in-utero.

Furthermore, the active postmarket risk identification and analysis system as available 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:

4647-1 Establish a registry to characterize the long-term safety of Piasky (crovalimab-akkz) in adult and pediatric patients 13 years and older with paroxysmal nocturnal hemoglobinuria (PNH) with up to 5 years of follow-up. Yearly safety follow-up data should include a summary of major safety

findings including meningococcal infections and other infections with encapsulated bacteria, infusion and injection site related reactions, hypersensitivity reactions including type III hypersensitivity reactions, and axonal peripheral neuropathy, including multifocal mononeuropathy.

The timetable you submitted on June 11, 2024, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	12/2024
Final Protocol Submission:	04/2025
Interim Report #1:	10/2026
Interim Report #2:	10/2027
Interim Report #3:	10/2028
Interim Report #4:	10/2029
Interim Report #5:	10/2030
Interim Report #6:	10/2031
Study Completion:	06/2032
Final Report Submission:	12/2032

4647-2 Conduct a worldwide descriptive study that collects prospective and retrospective data in women exposed to Piasky (crovalimab-akkz) during pregnancy to assess the risk of pregnancy and maternal complications, and adverse effects on the developing fetus, neonate, and infant. Assess infant outcomes through at least the first year of life. The registry should also collect adverse event data for lactating women and infants exposed to crovalimab through breastfeeding to assess for any potential risks to the infant from breastfeeding. The minimum number of patients will be specified in the protocol.

The timetable you submitted on June 11, 2024, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	12/2024
Final Protocol Submission:	04/2025
Interim Report Submission:	10/2028
Study Completion:	06/2032
Final Report Submission:	12/2032

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.[3]

Submit clinical protocol(s) to your IND 131343 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).**

Submission of the protocol(s) for required postmarketing observational studies to your IND is for purposes of administrative tracking only. These studies do not constitute clinical investigations pursuant to 21 CFR 312.3(b) and therefore are not subject to the IND requirements under 21 CFR part 312.

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(a)(1) 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(a)(1) 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:

4647-3 Complete Study BO42161 (COMMODORE 1), “A Phase 3, Randomized, Open-Label, Active-Controlled, Multicenter Study Evaluating the Safety, Pharmacokinetics, Pharmacodynamics, and Efficacy of Crovalimab

[3] See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (October 2019).* https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

Versus Eculizumab in Patients with Paroxysmal Nocturnal Hemoglobinuria (PNH) Currently Treated with Complement Inhibitors".

The timetable you submitted on May 2, 2024, states that you will conduct this study according to the following schedule:

Trial Completion: 08/2027
Final Report Submission: 02/2028

4647-4 Complete Study BO42162 (COMMODORE 2), "A Phase 3, Randomized, Open-Label, Active-Controlled, Multicenter Study Evaluating the Efficacy and Safety of Crovalimab Versus Eculizumab in Patients with Paroxysmal Nocturnal Hemoglobinuria (PNH) Not Previously Treated with Complement Inhibitors".

The timetable you submitted on May 2, 2024, states that you will conduct this study according to the following schedule:

Trial Completion: 08/2027
Final Report Submission: 02/2028

4647-5 Complete Study BP39144 (COMPOSER), "An Adaptive Phase 1/2 Study to Assess Safety, Efficacy, Pharmacokinetics and Pharmacodynamics of RO7112689 in Healthy Volunteers and Patients with Paroxysmal Nocturnal Hemoglobinuria (PNH)".

The timetable you submitted on May 2, 2024, states that you will conduct this study according to the following schedule:

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

4647-6 Develop and validate a competitive ligand binding neutralizing antibody (NAb) assay with adequate sensitivity and drug tolerance to test inhibition of crovalimab-akkz. This NAb assay will be used to test available confirmed anti-drug antibody positive samples from banked and ongoing clinical studies. Provide a final validation report detailing the performance of the NAb assay.

The timetable you submitted on May 2, 2024, states that you will conduct this study according to the following schedule:

Final Validation Report Submission: 06/2026

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 Piasky (crovalimab-akkz) to ensure the benefits of the drug outweigh the risk of serious meningococcal infections.

Your proposed REMS must also include the following:

Elements to assure safe use: Pursuant to section 505-1(f)(1), we have determined that Piasky (crovalimab-akkz) can be approved only if elements necessary to assure safe use are required as part of the REMS to mitigate the risk of serious meningococcal infections 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, practitioners, or health care settings that dispense the drug are specially certified
- The drug is dispensed to patients with evidence or other documentation of safe-use conditions

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 that dispense the drug be specially certified and the drug be dispensed to patients with documentation of safe use conditions.

Your proposed REMS, submitted on June 19, 2023, amended and appended to this letter, is approved.

The REMS consists of 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 Piasky (crovalimab-akkz) into interstate commerce.

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

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

Program Outreach and Communication

1. REMS communication activities
   Activities related to the distribution of the REMS Letter: Vaccination Reminder Letter to health care providers (HCPs) who are certified to prescribe Piasky will be assessed, and the following metrics will be reported:
   a. Sources for the distribution lists for certified HCPs
   b. Number of certified HCPs targeted
   c. Number of REMS letters sent by date and method of distribution
      i. Number and proportion of emails successfully delivered, opened, and unopened
      ii. Number and proportion of faxes successfully delivered

Program Implementation and Operations

2. REMS implementation (For the first REMS Assessment only)
   a. Date of first commercial distribution of Piasky
   b. Date of Piasky REMS launch
   c. Date when the Piasky website became live and fully operational
   d. Date when the certification process for prescribing HCPs and pharmacies became active
   e. Date when wholesaler-distributors were authorized to distribute the drug (i.e., first order placed)
   f. Date when the REMS Coordinating Center was established and fully operational

3. REMS Certification and Enrollment Statistics
   a. Health care provider (HCP) certification
      i. Numbers certified: total, newly certified, and active (i.e., prescribed Piasky at least once during the reporting period), stratified by credentials (e.g., Doctor of Medicine, Doctor of Osteopathic Medicine, Advanced Practice Registered Nurse, Physician Assistant, Other), medical specialty (e.g., Hematology/Oncology, Immunology, Internal medicine, Nephrology, Neurology, Rheumatology, and Other), and geographic region (as defined by US Census)
      ii. Method of certification (e.g., fax or online)
      iii. Number of HCPs who prescribed but were unable to become certified, accompanied by a summary of the reason(s) why they were unable to be certified.
   b. Pharmacy certification
      i. Numbers certified: total, newly certified, and active (i.e., dispensed Piasky at least once during the reporting period), stratified by geographic region (as defined by US Census)

ii. Method of certification (e.g., fax)
iii. Number of pharmacies that dispensed Piasky but were unable to become certified, accompanied by a summary of the reason(s) why they were unable to become certified.

c. Wholesaler-distributors that distribute Piasky
   i. Numbers and identity of each wholesaler-distributor authorized to distribute Piasky: total and active (i.e. distributed Piasky at least once during the reporting period)

d. Patient Statistics
   i. The number and percentage of new patients treated with Piasky
   ii. The number of unique patients treated with Piasky stratified by sex, age, and geographic region (as defined by US Census)

4. Piasky Utilization Data
   a. Number of Piasky shipments sent to pharmacies, overall, and stratified by quantity per shipment, and by geographic region (as defined by US Census)
   b. For certified pharmacies, the number of prescriptions dispensed stratified by:
      i. Prescriber specialty, degree/credential, and geographic region
      ii. Patient demographics (e.g., age, sex), and geographic region (as defined by the US Census)
      iii. Whether the prescription was new or a refill reported as a total across all pharmacies
   c. The number and percentage (%) of Piasky dispenses corresponding to prescriptions written by REMS certified HCPs

5. REMS compliance
   a. A summary report of non-compliance identified, associated corrective and preventive action (CAPA) plans, and the status of CAPA plans. Provide a summary of non-compliance identified, including, but not limited to:
      i. A copy of the non-compliance plan, including the criteria for determination of non-compliance for prescribers, pharmacies, and wholesalers, actions that will be taken to address non-compliance for each case, and a description of events that would lead to suspension or decertification from the REMS.
      ii. Number of instances of non-compliance accompanied by a description of each instance and the reason for the occurrence (if provided). For each instance of non-compliance, the following information will be reported:
         a) The unique identification (ID) of the stakeholder(s) associated with the non-compliance event to enable tracking over time

b) The source of the non-compliance data
c) The results of root cause analysis
d) The action(s) taken in response to non-compliance

iii. The number and percentage of prescribers who prescribed and pharmacies that dispensed Piasky but were not certified HCPs
   a) The specific reasons why prescribers were not certified at the time of prescribing (e.g., emergency use), and whether these prescribers subsequently became certified

iv. The number and percentage of pharmacies who obtained Piasky that were not certified
   a) The specific reasons for the drug distributions to pharmacies that were not certified

v. The number of pharmacies who became decertified, accompanied by a summary of reasons for decertification

6. Audits: Summary of audit activities including but not limited to:
   a. A copy of the audit plan used for pharmacies and wholesalers-distributors
   b. Number of audits expected, and the number performed for each stakeholder type
   c. Number and category of audit observations, stratified by category
   d. Unique ID for each stakeholder that had observations to track observations by stakeholder over time
   e. Any corrective actions or preventative measures implemented due to audit observations
      i. For stakeholders with audit observations, the number of stakeholders that successfully completed a corrective and preventative action (CAPA) by the due date.
      ii. For any stakeholders that did not complete a CAPA by the due date, any additional actions taken
   f. Summary report of documented processes and procedures for complying with the REMS requirements including how certified pharmacies obtain patient vaccination status from HCPs
   g. Documentation of completion of training for relevant staff.
   h. Verification that at each audited pharmacy, a designated Authorized Representative is certified, and certification is up to date. If the Authorized Representative changes, include the number of new Authorized Representatives and verification of the pharmacy's recertification.
7. REMS Infrastructure and Performance
   a. REMS website
      i. Number of total visits and unique visits to the REMS website
      ii. For each type of REMS material, the number downloaded or printed
   b. REMS Coordinating Center

i. Number of contacts by stakeholder type (e.g., patient/caregiver, HCP, pharmacy) and reason (e.g., certification question)
ii. Details of any complaint(s) received and whether they indicate potential issues with the Piasky REMS burden or patient access
iii. Details of any corrective actions implemented due to identified issues

Safe Use Behaviors

8. Safe Use Behaviors
    a. Methods used to determine whether or not patients received meningococcal vaccinations in accordance with the most current Advisory Committee on Immunization Practices (ACIP) recommendations for meningococcal vaccination in patients receiving a complement inhibitor. Include the type of vaccine (including serogroups targeted by the vaccine), dosing (i.e., first vaccine dose, second vaccine dose, and booster doses), and timing of the vaccinations, when the information is provided.
    b. Data on the number of and percentage of new patients treated with Piasky who received meningococcal vaccination(s) out of the total number of new patients who received Piasky. Of those who received meningococcal vaccination(s), provide the number and percentage who:
        i. Received vaccination(s) in accordance with the most current ACIP recommendations for meningococcal vaccination in patients receiving a complement inhibitor stratified by vaccine administered
        ii. Did not receive vaccination(s) in accordance with the most current ACIP recommendations for meningococcal vaccination in patients receiving a complement inhibitor stratified by vaccine administered
        iii. Did not have all the information necessary for determining compliance with the most current ACIP recommendations for meningococcal vaccination in patients receiving a complement inhibitor
    c. Data on the number and percentage of new patients treated with Piasky who did not receive meningococcal vaccination(s) out of the total number of patients who received Piasky.
    d. Data on whether the patient received antibacterial drug prophylaxis, and a summary analysis of the timing of antibacterial drug prophylaxis in relation to the dosing of Piasky (if available).
    e. If any of the above information is missing, the reasons why this information is missing such as:
        i. Healthcare provider records do not include this information
        ii. Healthcare provider declined to provide this information
        iii. Pharmacy unable to get healthcare provider to respond to queries
    f. The number and percentage of patients dispensed Piasky who received at least one dose of meningococcal vaccines (against all of the following

serogroups: A, C, W, Y, and B) according to the most current ACIP recommendations in patients receiving a complement inhibitor and antibacterial drug prophylaxis, if needed, before the first dispense.

g. The number and percentage of new patients treated with Piasky who completed or were up to date with meningococcal vaccinations (against all of the following serogroups: A, C, W, Y, and B) per the most current ACIP recommendations in patients receiving a complement inhibitor at the time of first dose.
h. For patients who were not initially up to date with meningococcal vaccines when starting treatment, report the number and percentage who, up to 6 months after the first dose:
    i. Completed meningococcal vaccines
    ii. Did not complete meningococcal vaccines but received antibacterial drug prophylaxis
    iii. Vaccination status was unknown after completed follow-up attempts

Health Outcomes and/or Surrogates of Health Outcomes

9. Summary of cases of meningococcal infections in patients receiving Piasky
    a. For US cases:
        i. In the most recent periodic safety report (e.g., Periodic Safety Update Report, Periodic Benefit Risk Evaluation Report) submitted to the Piasky biologics license application with a link to that report identified
        ii. Cumulative listing of all cases of meningococcal infections from approval to include cases identified during the current reporting period
    b. For each US case, provide the following information:
        i. MedWatch or other case report number
        ii. Date of event and date of report to FDA
        iii. Patient age, race, and gender
        iv. Indication for Piasky treatment
        v. Meningococcal vaccination status, including:
            a) The specific vaccines;
            b) The date(s) they were administered including first vaccine dose, second vaccine dose, and booster doses
            c) Timing in relation to Piasky administration (i.e., the dates or duration that a patient received Piasky in relation to the meningococcal vaccine(s)).
            d) Conclusions as to whether the vaccinations were received in accordance with the ACIP guidelines; and references to the specific versions of the ACIP guidelines that were in effect at the time the infections occurred
            e) Source of the vaccine information when available. For information that is not available, the number and type

(patient, prescriber, etc) of outreach attempts made to obtain the information for each case. Also, if the information is not available, provide a narrative explaining why the information is unavailable for each reported case.

vi. Whether the patient was administered any prophylactic antibiotics and if so: the specific antibiotics, antibiotic regimen (dose/frequency), route of administration, duration, and timing relative to Piasky treatment
vii. Summary of clinical course and the outcome; specifically report whether the patient:
    a) Was admitted to an intensive care unit;
    b) Experienced any organ system failure, such as (but not limited to) requiring mechanical ventilation or medication (vasopressors) to support blood pressure;
    c) Died
viii. The length of time between onset of symptoms and when the patient presented for medical evaluation (if available)
ix. Causative meningococcal serotype
x. Whether the Patient Safety Card was presented during the process of the patient seeking treatment

c. For each non-US case, provide the following information:
    i. Case report number
    ii. Patient age and gender
    iii. Indication for Piasky treatment
    iv. Meningococcal vaccination status if known
    v. Outcome
    vi. If associated with any clinical trials
d. Meningococcal infection rate (per year and cumulatively)
    i. Among patients who received Piasky in the US and worldwide, the number of reported cases of meningococcal infection per 100,000 patient-years of post-marketing exposure to Piasky; reporting rate will be summarized cumulatively since the approval of Piasky and also by year and relevant age subgroup (≤18 years, 19–55 years, and >55 years).

Knowledge

10. Starting with the 18-month reporting period and annually thereafter, an assessment of prescribing health care providers (HCPs) and patient understanding of the following:
    a. Patients are vaccinated against meningococcal infections caused by *Neisseria meningitidis* serogroups A, C, W, Y, and B prior to starting therapy according to the current ACIP recommendations for patients receiving complement inhibitors and receive antibacterial drug prophylaxis if needed

b. Patients are aware of early signs and symptoms of meningococcal infection and the need for immediate medical evaluation
c. Prescribers are aware of early signs and symptoms of meningococcal infection and the need for immediate medical evaluation.

Overall Assessment of REMS Effectiveness

11. The requirements for assessments of an approved REMS under section 505-1(g)(3) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355-1) 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 surveys 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 761388 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 761388 REMS ASSESSMENT

or

NEW SUPPLEMENT FOR BLA 761388
CHANGES BEING EFFECTED IN 30 DAYS
PROPOSED MINOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR BLA 761388
PRIOR APPROVAL SUPPLEMENT
PROPOSED MAJOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR BLA 761388
PRIOR APPROVAL SUPPLEMENT
PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABELING CHANGES SUBMITTED IN SUPPLEMENT XXX

or

NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR BLA 761388
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 761388

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 Submissions 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

You may request advisory comments on proposed introductory advertising and promotional labeling. 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*.[4]

You must submit final promotional materials and Prescribing Information, accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at FDA.gov.[5] Information and Instructions for completing the form can be found at FDA.gov.[6]

REPORTING REQUIREMENTS

You must submit adverse experience reports under the adverse experience reporting requirements at 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 at 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

[4] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[6] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

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

REQUESTED ENHANCED PHARMACOVIGILANCE

1) We request that for Piasky you submit all serious and non-serious domestic and foreign cases of axonal peripheral neuropathy, including multifocal mononeuropathy as 15-day "Alert reports" (described under 21 CFR 600.80(c)(1)).

2) We request that you provide a separate narrative summary including analysis of axonal peripheral neuropathy, including multifocal mononeuropathy reported with the use of Piasky as part of your required periodic safety reports [e.g., periodic adverse experience report (PAER) required under 21 CFR 600.80(c)(2)], quarterly during the first 3 years post-approval and annually thereafter, through the 5th year following the initial U.S. approval date.

   Your analysis should include interval and cumulative data relative to the date of approval of Piasky for all serious and non-serious domestic and foreign cases of axonal peripheral neuropathy, including multifocal mononeuropathy with the use of Piasky. Your analysis should provide an assessment of causality, with documentation of indication (including all labeled and off-label use), temporal association, duration of therapy, associated signs and symptoms, confounders, underlying risk factors, treatment given for the event, outcome, and dechallenge/rechallenge.

POST APPROVAL FEEDBACK MEETING

New biological products 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, contact Rolanda Bailey, Regulatory Project Manager, at (240) 402-5631 or email at Rolanda.Bailey@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Hylton V. Joffe, MD, MMSc
Director
Office of Cardiology, Hematology,
Endocrinology, and Nephrology
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURES:

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

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

HYLTON V JOFFE
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