NDA 215014

**NDA APPROVAL**

Apellis Pharmaceuticals, Inc.
Attention: Mary Geissler
Senior Director, Regulatory Affairs
100 Fifth Avenue, 3rd Floor
Waltham, MA 02451

Dear Ms. Geissler:

Please refer to your new drug application (NDA) dated and received September 14, 2021, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Empaveli (pegcetacoplan) injection.

This new drug application provides for the use of Empaveli (pegcetacoplan) injection for the treatment of adult patients with paroxysmal nocturnal hemoglobinuria (PNH).

## 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 the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (Prescribing Information, Instructions for Use, and Medication Guide) as well as annual reportable changes not included in the enclosed labeling. 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.*[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.

[1] 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 https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

## 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 *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*. For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved NDA 215014**." Approval of this submission by FDA is not required before the labeling is used.

## DATING PERIOD

Based on the stability data submitted to date, the expiry dating period for Empaveli (pegcetacoplan) injection shall be 12 months from the date of manufacture when stored at 2 to 8°C.

## ADVISORY COMMITTEE

Your application for Empaveli (pegcetacoplan) was not referred to an FDA advisory committee because the application did not raise significant public health questions on the role of the drug in the diagnosis, cure, mitigation, treatment, or prevention of the disease. Outside expertise was not deemed necessary as there were no significant or controversial issues that would have benefitted from advisory committee discussion.

## 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 in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

## POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess a signal of a serious theoretical risk of autoimmune disease development in patients who receive Empaveli (pegcetacoplan).

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 study:

4047-1 Establish a registry to characterize the long-term safety of pegcetacoplan in adult patients with paroxysmal nocturnal hemoglobinuria (PNH), including patients who are treatment naïve, with at least 5 years of follow-up. Submit yearly safety follow-up data and a summary of the major safety findings for all patients, including the development or worsening of autoimmune diseases such as systemic lupus erythematosus (SLE), and all serious infections with encapsulated bacteria. The final study report should include an integrated safety dataset and patient level data, including data on pegcetacoplan dosing, meningococcal and pneumococcal vaccination status, and concomitant medications.

The timetable you submitted on March 29, 2021, states that you will conduct this study according to the following schedule:

| | |
|---|---|
| Interim Report #1: | 03/2023 |
| Interim Report #2: | 03/2024 |
| Interim Report #3: | 03/2025 |
| Interim Report #4: | 03/2026 |
| Interim Report #5: | 03/2027 |
| Interim Report #6: | 03/2028 |
| Study Completion: | 01/2029 |
| Final Report Submission: | 07/2029 |

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess a known serious risk of increased susceptibility to serious infections caused by encapsulated bacteria in patients who receive Empaveli (pegcetacoplan).

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

4047-2 Complete Study APL2-302, “A Phase 3, Randomized, Multicenter, Open-label, Active-comparator Controlled Study to Evaluate the Efficacy and Safety of Pegcetacoplan in Patients with Paroxysmal Nocturnal

Hemoglobinuria (PNH).” Include an updated summary of safety, efficacy analyses, and datasets at the time of final clinical study report submission.

The timetable you submitted on March 29, 2021, states that you will conduct this study according to the following schedule:

Final Report Submission: 09/2021

4047-3 Complete Study APL2-307, “An Open-label, Nonrandomized, Multicenter Extension Study to Evaluate the Long-Term Safety and Efficacy of Pegcetacoplan in the Treatment of Paroxysmal Nocturnal Hemoglobinuria (PNH)." Include an updated summary of safety, efficacy analyses, and datasets at the time of final clinical study report submission.

The timetable you submitted on March 29, 2021, states that you will conduct this study according to the following schedule:

Interim Report: 06/2022
Trial Completion: 08/2025
Final Report Submission: 02/2026

4047-4 Complete Study APL2-308, “A Phase 3, Randomized, Multicenter, Open-Label, Controlled Study to Evaluate the Efficacy and Safety of Pegcetacoplan in Patients with Paroxysmal Nocturnal Hemoglobinuria (PNH).” Include an updated summary of safety, efficacy analyses, and datasets at the time of final clinical study report submission.

The timetable you submitted on March 29, 2021, states that you will conduct this study according to the following schedule:

Trial Completion: 10/2021
Final Report Submission: 04/2022

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 123087 with a cross-reference letter to this NDA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final report(s) to your NDA. 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).**

[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.

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 or FDA's regulations under 21 CFR parts 50 (Protection of Human Subjects) and 56 (Institutional Review Boards).

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 report periodically 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 314.81(b)(2)(vii), requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) 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 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

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

We remind you of your postmarketing commitments:

4047-5 Develop a sensitive assay to detect and monitor the presence and titer of antibodies that bind the active moiety of pegcetacoplan. The assay should be capable of detecting neutralizing anti-pegcetacoplan antibodies (ADA) in the presence of pegcetacoplan levels that are expected to be present in serum at the time of patient sampling. The final report should include development and validation data to support use of the assay.

The timetable you submitted on May 10, 2021, states that you will conduct this study according to the following schedule:

Draft Protocol Submission: 07/2021
Final Protocol Submission: 11/2021
Final Report Submission: 05/2023

4047-6 Develop and validate a sensitive assay to evaluate the neutralizing activity of anti-pegcetacoplan antibodies (ADA) detected in patient samples. The assay should be capable of detecting neutralizing ADA in the presence of pegcetacoplan levels that are expected to be present in serum at the time

of patient sampling. The final report should include development and validation data to support use of the assay.

The timetable you submitted on May 10, 2021, states that you will conduct this study according to the following schedule:

Draft Protocol Submission: 07/2021
Final Protocol Submission: 11/2021
Final Report Submission: 05/2023

4047-7 Use the sensitive assays developed under PMCs 4047-5 and 4047-6 to establish the incidence, titer and neutralizing activity of antibodies to pegcetacoplan in patient samples from studies APL2-302, APL2-307, and APL2-308. Establish whether there is an impact of antibodies on safety and efficacy of pegcetacoplan. Submit datasets at the time of final report submission.

The timetable you submitted on May 10, 2021, states that you will conduct this study according to the following schedule:

Draft Protocol Submission: 07/2023
Final Protocol Submission: 11/2023
Final Report Submission: 08/2026

A final submitted protocol is one that the FDA has reviewed and commented upon, and you have revised as needed to meet the goal of the study or clinical trial. Submit clinical protocols to your IND 123087 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. 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, the number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," **or** "**Postmarketing Commitment Correspondence**."

## RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the Food, Drug, and Cosmetic Act (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 Empaveli (pegcetacoplan) to ensure the benefits of the drug outweigh the risk of serious and life threatening infections caused by encapsulated bacteria.

Your proposed REMS must also include the following:

**Elements to assure safe use:** Pursuant to 505-1(f)(1), we have also determined that Empaveli (pegcetacoplan) can be approved only if elements necessary to assure safe use are required as part of the REMS to mitigate the risks of morbidity associated with serious infections caused by encapsulated bacteria 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: practitioners who prescribe Empaveli and pharmacies that dispense Empaveli must be specially certified, and the drug be dispensed to patients with documentation of safe use conditions.

Your proposed REMS, submitted on September 14, 2020, 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 Empaveli (pegcetacoplan) into interstate commerce.

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

**Program Implementation and Operations:**

1. REMS Program Implementation (6-month and 1-year assessments only)

    a. Date of first commercial distribution of Empaveli

b. Date of Empaveli REMS program launch

c. Date when the Empaveli REMS website became live and fully operational

d. Date when healthcare providers who can prescribe could become certified in the Empaveli REMS

e. Date when pharmacies could become certified in the Empaveli REMS

f. Date when distributors/wholesalers were authorized to dispense and distribute the drug (i.e., first order placed)

g. Date when the REMS Coordinating Center was established and fully operational

2. REMS Certification and Enrollment Statistics (provide for each reporting period and cumulatively)

   a. Healthcare provider (HCP) certification

      i. Numbers certified: total, newly certified, and active (prescribed Empaveli at least once during the reporting period), stratified by credentials (e.g., MD, DO, NP, PA, other), medical specialty, and geographic region (as defined by US Census)

      ii. Method of certification

      iii. Number of healthcare providers who prescribed but were unable to become certified, accompanied by a summary of the reason(s) why they were unable to be certified

      iv. A key performance indicator is enrollment of prescribers of Empaveli. The target for this key performance indicator is that: 98% of Empaveli prescriptions that are dispensed will be written by enrolled prescribers during each REMS assessment period.

   b. Pharmacy certification

      i. Identity and numbers of each pharmacy certified: total and newly enrolled and active (dispensed Empaveli at least once during the reporting period stratified by pharmacy type, e.g., hospital, specialty)

      ii. Method of certification

      iii. Number of pharmacies that were unable to become certified, accompanied by a summary of the reason(s) why they were unable to be certified

   c. Wholesaler/Distributors

      i. Numbers contracted: total and newly contracted, and active (distributed Empaveli at least once during the reporting period)

3. Empaveli Utilization Data (provide for each reporting period and cumulatively)

a. For certified network specialty pharmacies, the number of prescriptions dispensed by stratified by:
    i. Prescriber specialty, degree/credentials, and geographic region.
    ii. Patient demographics (e.g., age, gender), and geographic region (as defined by US Census)
b. For wholesaler/distributors, the number of vials sold

4. REMS Compliance (beginning with the 1-year assessment report and for each reporting period thereafter)

a. A summary report of non-compliance identified, associated corrective and preventive action (CAPA) plans, and the status of CAPA plans including, but not limited to:

i. A copy of the non-compliance plan, including the criteria for non-compliance for prescribers facilitated by certified network specialty pharmacies, actions taken to address non-compliance for each case, and which events will lead to suspension or decertification from the REMS

ii. The number of instances of noncompliance accompanied by a description of each instance and the reason for the occurrence (if provided). For each instance of non-compliance, report the following information:

1) The unique ID(s) of the stakeholder(s) associated with the noncompliance event or deviation to enable tracking over time

2) The source of the noncompliance data

3) The results of root cause analysis

4) The action(s) taken in response to noncompliance

iii. Number and percent of prescribers who prescribed Empaveli but not certified as identified by the certified network specialty pharmacy

iv. Specific reasons why prescribers were not certified at the time of prescribing (i.e., emergency use, etc.), and whether these prescribers subsequently became certified.

b. Audits: Summary of audit activities including but not limited to:
    i. A copy of the audit plan used for each audited stakeholder

    ii. The number of audits expected, and the number of audits performed for each stakeholder

    iii. The number and types of deficiencies noted

iv. A unique ID for each stakeholder that had deviations to track deviations by stakeholder over time.

v. Documentation of completion of training for relevant staff

vi. A summary report of documented processes and procedures for complying with the REMS requirements including how certified network specialty pharmacies obtain patient vaccination status from HCPs

vii. Verification that at each audited stakeholder's site, the designated authorized representative is up to date. If not, include the number of new authorized representatives and verification of the site's recertification.

viii. Describe any corrective actions taken for any non-compliance identified during the audits as well as any preventative measures that were developed from uncovering these non-compliance events.

For those with deficiencies noted, report the number that successfully completed a corrective and preventive action (CAPA) plan within one month of the audit.

For any that did not complete the CAPA within one month of the audit, describe additional actions taken.

5. REMS Infrastructure and Performance (provide for each reporting period and cumulatively)

a. REMS Website

i. Number of visits and unique visits to the REMS website

ii. Number of REMS materials downloaded or printed for each material

b. REMS Coordinating Center Report

i. Number of contacts by stakeholder type (patient/caregiver, healthcare provider, etc.)

ii. A table summarizing the reasons for calls (e.g., enrollment question) by stakeholder type

iii. If the reason for the call(s) indicates a complaint, provide details on the nature of the complaint(s) and whether they indicate potential REMS burden or patient access issues

iv. A summary report of corrective actions resulting from issues identified

**Safe Use Behaviors**

6. Safe Use Behaviors (provide for each reporting period and cumulatively)

a. Information captured by pharmacies regarding the number and percent of patients who were vaccinated against encapsulated bacteria (*Streptococcus pneumoniae, Neisseria meningitidis* types A, C, W, Y and B and *Haemophilus influenzae* Type B). This information is to include, for each vaccination type:

   i. The bacteria serotype targeted (if applicable)

   ii. The timing of the vaccination in relation to the dosing of Empaveli (if available)

   iii. The dates when vaccine administration occurred (i.e., *Haemophilus influenzae, Streptococcus pneumoniae, Neisseria meningitidis*) (if available)

   iv. The dosing (if a vaccination requires a second dose, whether the second dose occurred or is pending)

   v. An assessment of whether the patient was vaccinated as per the Centers for Disease Control and Prevention (CDC) Advisory Committee on Immunization Practices (ACIP) recommendations

   vi. Whether the patient received prophylactic antibiotics, and timing of antibiotics in relation to the dosing of Empaveli (if available)

   vii. If any of the above information is missing, the reasons why this information is missing such as:
      1. HCP records do not include this information
      2. HCP declined to provide information
      3. HCP did not respond to Pharmacy queries

      Include a narrative describing the vaccines that were not administered (i.e., *Haemophilus influenzae, Streptococcus pneumoniae, Neisseria meningitidis* serotype)

**Health Outcomes and/or Surrogates of Health Outcomes**

7. Summary of cases of meningococcal, streptococcal, or haemophilus infections in patients receiving Empaveli (provide for each reporting period and cumulatively)

   a. For US cases include:

      i. A summary of all cases included in the most recent Periodic Safety Update Report (PSUR) submitted to the Empaveli NDA with a link to that PSUR identified

      ii. A cumulative listing of all cases of encapsulated bacteria 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 report and date of report to FDA
iii. Patient age and gender
iv. Indication for Empaveli treatment
v. Encapsulated bacteria vaccination status, to include the specific vaccines; the dates they were administered; your conclusions as to whether the vaccinations complied with the ACIP guidelines; and references to the specific versions of the ACIP guidelines that were in effect at the time the infections occurred
vi. Whether or not the patient received any prophylactic antibiotics and if so:
    1. The specific antibiotic(s), antibiotic regimen (dose/frequency), and route(s) of administration
    2. The duration of the antibiotic treatment
    3. The timing of the course of the antibiotics in relation to Empaveli treatment
vii. Summary of clinical course and the outcome; specifically report whether the patient:
    1. Was admitted to an intensive care unit
    2. Experienced any organ system failure, such as (but not limited to) requiring mechanical ventilation or medication (vasopressors) to support blood pressure
    3. Died
viii. Causative encapsulated bacteria organism and serotype
ix. Whether the Patient Wallet 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 Empaveli treatment
    iv. Encapsulated bacteria vaccination status if known
    v. Outcome

8. Encapsulated Bacteria Infections Rate (provide for each reporting period and cumulatively)
    a. Among patients who received Empaveli in the US and worldwide, the number of reported cases of encapsulated bacteria infection per 100,000 patient-years of post-marketing exposure to Empaveli; summarize the reporting rate cumulatively subsequent to the approval of Empaveli and stratify by year and age subgroup (≤18 years, 19-55 years, and >55 years).

**Knowledge**

9. Provide stakeholder surveys beginning with the 1-year assessment report and for each reporting period thereafter
    a. An assessment of HCP and patient understanding regarding:
        i. the potential risk of infections caused by encapsulated bacteria with Empaveli
        ii. the early signs of invasive encapsulated bacteria infections
        iii. the need for immediate medical evaluation of signs and symptoms consistent with possible encapsulated bacteria infections
10. The requirements for assessments of an approved REMS under section 505-1(g)(3) including 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; and whether one or more such goals or such elements should be modified.

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.

If the assessment instruments and methodology for your REMS assessments are not included in the REMS supporting document, or if you propose changes to the submitted assessment instruments or methodology, you should update the REMS supporting document to include specific assessment instrument and methodology information at least 90 days before the assessments will be conducted. Updates to the REMS supporting document may be included in a new document that references previous REMS supporting document submission(s) for unchanged portions. Alternatively, updates may be made by modifying the complete previous REMS supporting document, with all changes marked and highlighted. 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:

**NDA 215014 REMS ASSESSMENT METHODOLOGY**
**(insert concise description of content in bold capital letters, e.g., ASSESSMENT METHODOLOGY, PROTOCOL, SURVEY METHODOLOGIES, AUDIT PLAN, DRUG USE STUDY)**

An authorized generic drug under this NDA must have an approved REMS prior to marketing. Should you decide to market, sell, or distribute an authorized generic drug under this NDA, contact us to discuss what will be required in the authorized generic drug REMS submission.

We remind you that section 505-1(f)(8) of FDCA prohibits holders of an approved covered application with elements to assure safe use from using any element to block or delay approval of an application under section 505(b)(2) or (j). A violation of this provision in 505-1(f) could result in enforcement action.

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:

**NDA 215014 REMS ASSESSMENT**

**NEW SUPPLEMENT FOR NDA 215014/S-000**
**CHANGES BEING EFFECTED IN 30 DAYS**
**PROPOSED MINOR REMS MODIFICATION**
***or***
**NEW SUPPLEMENT FOR NDA 215014/S-000**
**PRIOR APPROVAL SUPPLEMENT**
**PROPOSED MAJOR REMS MODIFICATION**
***or***
**NEW SUPPLEMENT FOR NDA 215014/S-000**
**PRIOR APPROVAL SUPPLEMENT**
**PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABELING CHANGES SUBMITTED IN SUPPLEMENT 000**
**or**
**NEW SUPPLEMENT (NEW INDICATION FOR USE)**
**FOR NDA 215014/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 NDA 215014**

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

FDA can accept the REMS document in Structured Product Labeling (SPL) format. If you intend to submit the 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 SPL format using the FDA automated drug registration and listing system (eLIST).

For more 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]

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the Prescribing Information, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. 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

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

## POST APPROVAL FEEDBACK MEETING

New molecular entities and 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, call Carleveva Thompson, Regulatory Project Manager, at 301-796-1403.

Sincerely,

*{See appended electronic signature page}*

Ellis Unger, MD
Director
Office of Cardiology, Hematology, Endocrinology, and Nephrology
Center for Drug Evaluation and Research

[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

ENCLOSURES:

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

**U.S. Food and Drug Administration**
Silver Spring, MD 20993
**www.fda.gov**

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**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.**

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/s/

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