CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

761345Orig1s000

Trade Name:	Elrexfio injection
Generic or Proper Name:	elranatamab-bcmm
Sponsor:	Pfizer Inc.
Approval Date:	August 14, 2023
Indication:	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.

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761345Orig1s000

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APPROVAL LETTER

BLA 761345

BLA ACCELERATED APPROVAL

Pfizer Inc.
Attention: Robert Schaum, PhD
Director, Global Regulatory Affairs
445 Eastern Point Road
Gorton, CT 06340

Dear Dr. Schaum:

Please refer to your biologics license application (BLA) dated and received December 19, 2022, and your amendments, submitted under section 351(a) of the Public Health Service Act for Elrexfio (elranatamab-bcmm) injection.

LICENSING

We have approved your BLA for Elrexfio (elranatamab-bcmm) effective this date. You are hereby authorized to introduce or deliver for introduction into interstate commerce, Elrexfio under your existing Department of Health and Human Services U.S. License No. 2001. Elrexfio 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 Elrexfio (elranatamab-bcmm) drug substance at Wyeth BioPharma in Andover, Massachusetts. The final formulated product will be manufactured, filled, labeled, and packaged at Pharmacia & Upjohn Company LLC, Kalamazoo, Michigan. You may label your product with the proprietary name Elrexfio and will market it in 44 mg/1.1 mL single-dose vial and 76 mg/1.9 mL single-dose vial.

DATING PERIOD

The dating period for Elrexfio shall be 18 months from the date of manufacture when stored at 2-8 °C. The date of manufacture shall be defined as the date of final sterile filtration of the formulated drug product. The dating period for your drug substance shall be (b) (4) months from the date of manufacture when stored at (b) (4) °C.

We have approved the stability protocols 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 Elrexfio 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 Elrexfio, 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 Elrexfio 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.

WAIVER OF ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS

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

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 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

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

using eLIST may be found in the draft 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 *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 761345**." Approval of this submission by FDA is not required before the labeling is used.

ADVISORY COMMITTEE

Your application for elranatamab-bcmm 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 a further adequate and well-controlled clinical trial intended to verify and describe clinical benefit. You are required to conduct such a clinical trial with due diligence. If the required postmarketing clinical trial fails to verify clinical benefit or is 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 August 8, 2023. This requirement is listed below.

4476-1 Complete a randomized clinical trial in patients with relapsed or refractory multiple myeloma. Patients should be randomized to receive an elranatamab-based regimen compared to standard therapy for relapsed or refractory multiple myeloma. The primary endpoint should be progression-free survival and secondary endpoints should include overall survival and overall response rate. The trial should enroll sufficient

[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.

numbers of older patients (ages 65-74 years and 75 years and above) to enable an evaluation of elranatamab in a study population that reflects the age of the U.S. population of patients with multiple myeloma.

The timetable you submitted on August 8, 2023, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	10/2023
Trial Completion:	03/2026
Final Report Submission:	09/2026

Submit clinical protocols to your IND 133940 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 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 trial required under 506(c). The initial report will be a standalone submission and the subsequent report will be combined with your annual status report 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 annual status report. Submit both of these 180-day reports annually until the final report for the corresponding study or trial is submitted.

FDA will consider the submission of your annual status report 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).

180-day reports should include:

- date first participant enrolled in each study or trial, if enrollment has started
- anticipated study or trial completion and final report submission dates
- any changes in plans since the last report with rationale for any changes
- the number of participants enrolled to date in each study or trial
- the number of planned participants, per the final protocol

180-day reports, including both the standalone 180-day report submitted 180 days after the date of approval (with 60-day grace period) and the 180-day report submitted with your annual status report, must be clearly designated "**180-Day AA PMR Progress Report**."

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

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 SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitment:

4476-2 Conduct an integrated analysis of data from clinical trials to further characterize the efficacy, pharmacokinetics, pharmacodynamics, and safety of elranatamab among U.S. racial and ethnic minority patients with multiple myeloma. The population should be representative of the U.S. population of patients with multiple myeloma, including racial and ethnic diversity, and allow for interpretation of the results in these populations.

The timetable you submitted on August 8, 2023, states that you will conduct this study according to the following schedule:

Draft Protocol Submission (Analysis Plan):	01/2024
Final Protocol Submission (Analysis Plan):	04/2024
Study Completion:	08/2026
Final Report Submission:	12/2026

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

We remind you of your postmarketing commitment:

4476-3 Conduct a Low Endotoxin Recovery (LER) study at process relevant temperature and duration to ensure that the bacterial endotoxins analytical method for release can reliably detect endotoxin in elranatamab drug product. In case the study shows endotoxin recoveries below 50% at process relevant conditions, develop an alternative endotoxin method to mitigate LER.

The timetable you submitted on August 8, 2023, states that you will conduct this study according to the following schedule:

Final Report Submission: 03/2024

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 133940 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 Elrexfio 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 and care for patients treated with Elrexfio 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 Elrexfio 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 December 19, 2022, 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 Elrexfio 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

1. REMS communication plan activities (provide data for the 1-year and 2-year assessments only):
    a. Sources of the distribution lists for healthcare providers

b. Number of healthcare providers targeted stratified by specialty if known

c. Number of healthcare professional societies targeted, and which healthcare professional societies reported distribution of the REMS letter to their respective members

d. The number of packets of REMS materials sent by date, attempt, and method of distribution

e. The number and percentage of emails successfully delivered, opened, and unopened

f. The number and percentage of mail successfully delivered and returned as undeliverable

g. The number of REMS Fact Sheets distributed to targeted healthcare providers during the 12 months after ELREXFIO is commercially distributed

h. Date and name of the key scientific meetings attended and corresponding information on the REMS materials displayed

Program Implementation and Operations

2. Program Implementation (*provide data at 1 year assessment only):

   a. *Date of first commercial availability of ELREXFIO

   b. Date the REMS Website went live

      i. Number of total visits and unique visits to the REMS Website

      ii. Number and type of ELREXFIO REMS materials downloaded or accessed

   c. *Date the REMS Coordinating Center was fully operational

   d. Date prescribers and pharmacies/healthcare settings were able to complete the REMS certification process (online and by fax)

   e. *Date of the first prescriber certification

   f. *Date of the first pharmacy/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 ELREXFIO 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)
2. Specialty (e.g., Oncology, Hematology, Internal Medicine/Family Medicine, 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, fax, e-mail) 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/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/healthcare settings stratified by:

1. Type of pharmacy/healthcare setting (e.g., Inpatient Hospital Pharmacy, Outpatient Hospital Pharmacy, Oncology Infusion Center, Community Oncology Physician Office, Other). If “other” accounts for > 10% of respondents for type, provide the most common type(s) identified.
2. Geographic region as defined by the U.S. Census
3. Method of enrollment (e.g., online, fax, e-mail) for newly certified pharmacies/healthcare settings only

ii. Number of incomplete pharmacy/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/healthcare settings, stratified by type of pharmacy/healthcare setting

b. Number and percentage of healthcare providers who wrote/ordered prescriptions that were dispensed, stratified by medical specialty (e.g., oncology) and provider credentials (e.g., Doctor of Medicine)

c. Number of dispense authorizations stratified by pharmacy/healthcare setting type

d. Number of REMS Dispense Authorizations (RDAs) 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

e. The percentage of prescriptions dispensed, as authorized by the REMS. REMS authorization for dispense requires both the prescriber and the pharmacy/healthcare setting be certified.

5. REMS Compliance

   a. Audits

      i. A copy of the audit plan

      ii. Report of audit findings for each stakeholder

      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 ELREXFIO REMS

      vi. Verification for each audited stakeholder's site 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, or minor findings) noted for each group of audited stakeholders as a percentage of audited stakeholders

      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 stakeholder (healthcare providers, pharmacies/healthcare settings and wholesalers-distributors), actions taken to address noncompliance for each event, and under what

circumstances a stakeholder 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 stakeholder(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/healthcare settings

1. Number of pharmacies/healthcare settings for which non-compliance with the ELREXFIO REMS is detected (numerator) divided by all pharmacies/healthcare settings dispensing ELREXFIO (denominator)
2. Number and description of pharmacies/healthcare settings that dispensed ELREXFIO to non-certified prescribers, and any corrective and preventative actions taken to prevent future occurrences
3. Number of non-certified pharmacies/healthcare settings that dispensed ELREXFIO (numerator) divided by all pharmacies/healthcare settings that dispensed ELREXFIO
4. Number of prescriptions dispensed by non-certified pharmacies/healthcare settings (numerator) divided by all ELREXFIO prescriptions dispensed (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/healthcare settings that were shipped ELREXFIO, and the number of these that subsequently became certified
2. The number of authorized wholesalers-distributors for which non-compliance 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 Pfizer Inc. that shipped ELREXFIO, the number of incidents for each, actions taken to remove Elrexfio 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 non-compliance with REMS requirements and reasons for such actions, and actions taken to prevent distribution or removal of Elrexfio from these entities

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

6. REMS Coordinating Center Report

a. Number of contacts by stakeholder type (patient/caregiver, certified prescriber, pharmacy/healthcare setting authorized representative or staff, other HCP, wholesaler/distributor, other)

b. Summary of the reasons for the call(s) by stakeholder type. Limit the summary to the top five reasons for calls by stakeholder group

c. Description of each call, including stakeholder 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 CRS or neurologic toxicity including 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, health care availability, other

f. Summary of frequently asked questions (FAQ) by stakeholder credentials type. Limit the summary to the top five FAQs for calls by stakeholder group

g. Summary of any noncompliance that is identified through 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, Attitude, and Behavior (KAB) Survey of Certified Prescribers (beginning with the 1-Year REMS Assessment Report and thereafter with each assessment report)

    A KAB Survey will be conducted with random samples, if the population is large enough to randomize, of healthcare providers who prescribe ELREXFIO

    a. Evaluation of understanding of the risks of CRS and neurologic toxicity including ICANS associated with Elrexfio and mitigation strategies of the ELREXFIO REMS as well as compliance with the mitigation strategies

    b. An evaluation of the prescriber's knowledge on the importance of monitoring for signs and symptoms of CRS and neurologic toxicity including ICANS in patients exposed to ELREXFIO

    c. Provide the proportion of KAB prescriber survey respondents that demonstrated knowledge of the importance of monitoring for signs and

symptoms of CRS and neurologic toxicity including ICANS in patients exposed to ELREXFIO

Health Outcomes and/or Surrogates of Health Outcomes (Safe Use Behaviors)

9. A summary analysis of all reported cases of CRS and neurologic toxicity, including ICANS, stratified by source of report (i.e., spontaneous).
    a. Include the following stratifications by grade/severity in the analysis (if available)
        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 761345 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 761345 REMS ASSESSMENT

or

NEW SUPPLEMENT FOR BLA 761345/S-000
CHANGES BEING EFFECTED IN 30 DAYS
PROPOSED MINOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR BLA 761345/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED MAJOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR BLA 761345/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 761345/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 761345

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*.[3]

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

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

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

POST APPROVAL FEEDBACK MEETING

New molecular entities and new biologics qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

If you have any questions, call Natasha Kormanik, Senior Regulatory Project Manager, at (240) 402-4227.

Sincerely,

{See appended electronic signature page}

Marc R. Theoret, MD
Supervisory Associate Director (Acting)
Office of Oncologic Diseases
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
  - Prescribing Information
  - Patient Package Insert or 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/

MARC R THEORET
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