NDA 221075

ACCELERATED APPROVAL

Bristol-Myers Squibb Company
Attention: Bahar Demirdirek, PhD
Director, Global Regulatory Lead – Oncology
Route 206 and Province Line Road
Princeton, NJ 08543

Dear Dr. Demirdirek:

Please refer to your new drug application (NDA) dated and received December 17, 2025, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Zenbexus (iberdomide) capsules.

This NDA provides for the use of Zenbexus (iberdomide) capsules, in combination with daratumumab and hyaluronidase-fihj and dexamethasone, for the treatment of adult patients with multiple myeloma who have received at least 1 prior line of therapy including a proteasome inhibitor and an immunomodulatory agent.

APPROVAL & 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 314.510, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

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

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit 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 (text for the Prescribing Information and Medication Guide). Information on submitting SPL files using eLIST may be found in guidance for industry *SPL Standard for Content of Labeling Technical Qs and As.*[2]

[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.

The SPL will be accessible via publicly available labeling repositories.

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

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the enclosed carton and container labeling submitted on July 31, 2026, as soon as they are available, but no more than 30 days after they are printed. Please submit these labeling electronically according to 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 221075**." 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 Zenbexus (iberdomide) capsule shall be 36 months from the date of manufacture when stored at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F).

ADVISORY COMMITTEE

Your application for Zenbexus was not referred to an FDA advisory committee because the clinical trial design is acceptable.

ACCELERATED APPROVAL REQUIREMENTS

Pursuant to section 506(c) of the FD&C Act and 21 CFR 314.510, you are required to conduct further adequate and well-controlled clinical trials intended to verify and describe clinical benefit. You are required to conduct such clinical trials with due diligence. If required postmarketing clinical trials fail to verify clinical benefit or are not conducted with due diligence, including with respect to the conditions set forth below, we may withdraw this approval. We remind you of your postmarketing requirement specified in your submission dated August 7, 2026. This requirement is listed below.

5041-1 Complete a randomized controlled trial of iberdomide in combination with daratumumab and hyaluronidase-fihj and dexamethasone compared to daratumumab and hyaluronidase-fihj and dexamethasone and bortezomib in patients with 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 timetable you submitted on August 7, 2026, states that you will conduct this trial according to the following schedule:

Trial Completion:	11/2027
Final Report Submission:	05/2028

Submit clinical protocols to your IND 129254 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 status reports of the progress of each clinical trial required under section 506(c) (listed above) to the NDA 180 days after the date of approval of this NDA and approximately every 180 days thereafter (see section 506B(a)(2) of the FD&C Act) (hereinafter "180-day reports").

You are required to submit two 180-day reports per year for each open study or clinical trial required under section 506(c). The initial report will be a standalone submission and the subsequent report will be combined with your application's annual status report (ASR) required under section 506B(a)(1) of the FD&C Act and 21 CFR 314.81(b)(2). The standalone 180-day report will be due 180 days after the date of approval (with a 60-day grace period). Submit the subsequent 180-day report with your application's ASR. Submit both of these 180-day reports each year until the final report for the corresponding study or clinical trial is submitted.[3]

Your 180-day reports must include the information listed in 21 CFR 314.81(b)(2)(vii)(a). FDA recommends that you use FORM FDA 3989, *PMR/PMC Annual Status Report for Drugs and Biologics,* to submit your 180-day reports.[4]

180-day reports must be clearly designated "**NDA 221075 180-Day AA PMR Progress Report**."

FDA will consider the submission of your application's ASR under section 506B(a)(1) and 21 CFR 314.81(b)(2), 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).

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[3] You are required to submit information related to your confirmatory trial as part of your annual reporting requirement under section 506B(a)(1) until the FDA notifies you, in writing, that the Agency concurs that the study requirement has been fulfilled or that the study either is no longer feasible or would no longer provide useful information.

[4] FORM FDA 3989, along with instructions for completing this form, is available on the FDA Forms web page at https://www.fda.gov/about-fda/reports-manuals-forms/forms.

Submit final reports to this NDA as a supplemental application. For administrative purposes, the cover page of all submissions relating to this postmarketing requirement must be clearly designated "**Subpart H 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 in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for ages 0 to 1 year because necessary studies are impossible or highly impracticable. This is because a diagnosis of relapsed, refractory, or progressive neuroblastoma <1 year of age is very rare.

We are deferring submission of your pediatric study for patients 1 year of age and older for this application because this product is ready for approval for use in adults and the pediatric study has not been completed.

Your deferred pediatric study required by section 505B(a) of the FD&C Act is a required postmarketing study. The status of this postmarketing study must be reported annually according to 21 CFR 314.81 and section 505B(a)(4)(C) of the FD&C Act. This required study is listed below.

5041-2 Complete a molecularly targeted cancer investigation to assess the pharmacokinetics, dosing, safety, and preliminary efficacy of iberdomide in combination with chemoimmunotherapy in pediatric patients 1 year of age and older with relapsed, refractory, or progressive neuroblastoma.

Study Completion: 12/2032
Final Report Submission: 06/2033

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. See guidance for industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act.*

Submit the protocol(s) to your IND 129254, with a cross-reference letter to this NDA. Reports of this required pediatric postmarketing study must be submitted as an NDA or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from this study. When submitting the reports,

please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

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 Zenbexus (iberdomide) to ensure the benefits of the drug outweigh the risk of embryo-fetal toxicity.

Your proposed REMS must also include the following:

Elements to assure safe use: Pursuant to 505-1(f)(1), we have determined that elements to assure safe use are necessary to mitigate the risk of embryo-fetal toxicity listed in the labeling of the drug.

Your REMS includes the following elements to mitigate this risk:

- 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
- Each patient using the drug is subject to certain monitoring
- Each patient using the drug is enrolled in a registry

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, practitioners, or health care settings 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 December 17, 2025, 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 Zenbexus (iberdomide) into interstate commerce.

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

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

REMS Implementation and Operations

1. Program Implementation (for the first assessment only)
    a. REMS launch date
    b. Date of first commercial distribution of Zenbexus
    c. Date when the REMS Call Center was established and fully operational
    d. Date when the REMS materials became available on the REMS Website and via the REMS Call Center
    e. Date when the first wholesaler-distributor was authorized to distribute Zenbexus
    f. Dates participants could enroll online, by email, or by fax:
        i. Prescribers
        ii. Pharmacies
        iii. Patients
    g. Date when the REMS Website went live
2. REMS Certification and Enrollment Statistics
    a. Healthcare Providers
        i. Number and percentage of newly certified healthcare providers, and number and percentage of active healthcare providers (i.e., who have prescribed Zenbexus within the current reporting period) stratified by credentials, medical specialty and geographic region (as defined by US Census)
    b. Pharmacies
        i. Number and percentage of newly certified pharmacies, and number and percentage of active certified pharmacies (i.e., have dispensed Zenbexus within the current reporting period) stratified by geographic region (as defined by US Census)
    c. Patients
        i. Number and percentage of newly enrolled patients, and number and percentage of active patients (i.e., have received Zenbexus within the current reporting period) stratified by geographic region (as defined by US Census) and by patient risk category:
            1) Females who can become pregnant
            2) Females who cannot become pregnant
            3) Males
        ii. Number of patients with a lapse of treatment of 12 months or longer with Zenbexus that re-enrolled in the REMS when treatment resumed
    d. Wholesalers-Distributors
        i. Number and percentage of newly contracted wholesalers-

distributors, and number and percentage of active wholesalers-distributors (i.e., have shipped Zenbexus within the current reporting period)

3. REMS Utilization Data
    a. Number and percentage of unique patients who received Zenbexus, new and total, by patient risk category (i.e., females who can become pregnant, females who cannot become pregnant and males) grouped by the following age ranges (years):
        i. <18
        ii. 18 – ≤ 29
        iii. 30 – ≤ 39
        iv. 40 – ≤ 49
        v. 50 – ≤ 59
        vi. 60 – ≤ 69
        vii. ≥ 70
    b. Number and percentage of prescriptions (first-fills and refills) dispensed for females who can become pregnant, females who cannot become pregnant and males stratified by:
        i. Healthcare Provider Specialty
        ii. Patient age as outlined in 3a above
4. REMS Infrastructure and Performance
    a. REMS Call Center
        i. Number of contacts by participant type (i.e., patients, healthcare providers, pharmacies, wholesalers-distributors, other)
        ii. Summary of reasons for calls (e.g., enrollment question, location of a pharmacy) and by participant (i.e., authorized representative, pharmacy, healthcare provider, patient, other)
        iii. Summary of frequently asked questions (FAQs) by participant type
        iv. Summary report of REMS-related problems identified and resulting corrective actions
        v. Provide an assessment for any reports to the REMS Call Center indicating a burden to the healthcare system or barrier(s) to patient access. Include in the assessment whether the burden or access issue is attributable to the REMS, insurance, healthcare availability, or other issues
    b. REMS Program Website
        i. Number of visits and unique visits to the REMS Program Website
        ii. Number of REMS materials downloaded for each material
5. Pharmacy and Wholesaler-Distributor Audit Summary
    a. Provide a report of audit findings for pharmacies and wholesalers-distributors, including but not limited to:
        i. A copy of the audit plan for each participant
        ii. The number of audits expected, the number of audits conducted, and the number of audits completed
        iii. The number and type of deficiencies (e.g., critical, major, or minor

findings) noted for group of audited participants
iv. For those with deficiencies noted, report the number that successfully completed a corrective and preventive action (CAPA) plan within the timeline specified in the audit plan
v. For any that did not complete the CAPA within the timeframe specified in the audit plan, describe actions taken
vi. Use a unique identifier (ID) for participants that had deviations to track those deviations over time
vii. Confirm documentation of completion of training for relevant staff
viii. Verify the existence of documented processes and procedures for complying with the REMS

6. REMS Compliance
    a. Provide a summary of the noncompliance identified, including but not limited to:
        i. A copy of the Noncompliance Plan, which addresses the criteria for noncompliance for each participant, actions taken to address noncompliance for each event, and under what circumstances a participant would be decertified 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 noncompliance, report the following information:
            1) The unique IDs of the participant(s) associated with the noncompliance event or deviation to enable tracking over time
            2) The source of the noncompliance data
            3) The results of the root-cause analysis
            4) What action(s) were taken in response and whether any follow-up is planned
        iii. Compliance with pregnancy testing
            1) Number and percentage of all females who can become pregnant who have documentation of two negative pregnancy tests on the Patient Enrollment Form before treatment initiation
                a) Include any reported noncompliance that would inform on this indicator (e.g., Zenbexus dispensed to a non-enrolled patient or without a confirmation number to dispense)
            2) Number and percentage of authorization numbers for females who can become pregnant that expired due to the 7-day dispense window not being met and then resulted in a repeat pregnancy test
            3) Number and percentage of authorization numbers for females who can become pregnant that were dispensed with an expired authorization due to the 7-day dispense window

not being met

b. Number and percentage of prescriptions dispensed that were written by noncertified or deactivated prescribers out of total prescriptions dispensed, source of report(s), actions taken to prevent future occurrences, and the outcome of such actions
c. Number and percentage of prescriptions dispensed by noncertified pharmacies out of total prescriptions dispensed, source of report(s), actions taken to prevent future occurrences, and outcome of such actions
d. Number and percentage of prescriptions dispensed to non-enrolled patients out of total prescriptions dispensed, source of report(s), actions taken to prevent future occurrences, and outcome of such actions. Stratify by dispenses to females who can become pregnant, females who cannot become pregnant, and males.
e. Number and percentage of patients who had discontinued treatment for 12 consecutive months or longer and re-enrolled in the REMS out of all patients who had discontinued treatment for 12 consecutive months or longer and resumed treatment
f. Number and percentage of prescriptions dispensed without obtaining a confirmation number out of total prescriptions dispensed, stratified by dispenses to females who can become pregnant, females who cannot become pregnant and males
g. Number and percentage of shipments sent to noncertified pharmacies out of total shipments, source of report(s), actions taken to remove Zenbexus from these pharmacies, actions taken to prevent future occurrences and outcome of such actions
h. Number and percentage of shipments sent by mail to females who can become pregnant that were shipped the same day the confirmation number was obtained out of the total number of shipments for females who can become pregnant. Include:
    i. If Zenbexus was not shipped the same day the confirmation number was obtained provide the source of report(s), actions taken to prevent future occurrences and outcomes of such actions, and any issues identified as a result of the delays or interruption.
    ii. Whether the shipment method used avoided delays or interruption in therapy (i.e., overnight, ground, etc.) provide the source of report(s), actions taken to prevent future occurrences and outcomes of such actions, and any issues identified as a result of the delays or interruption.
    iii. Provide the mean, median, and range of delay time; reasons for delay; and impact to patients.
i. Number and percentage of shipments sent by mail to females who cannot become pregnant and males that were shipped within 24 hours of receiving the confirmation number out of the total number of shipments for females who cannot get pregnant and males. Include:
    i. If Zenbexus was not shipped within 24 hours of receiving the

confirmation number provide the source of report(s), actions taken to prevent future occurrences and outcomes of such actions, and any issues identified as a result of the delays or interruption.

ii. Whether the shipment method used avoided delays or interruption in therapy (i.e., overnight, ground, etc.) provide the source of report(s), actions taken to prevent future occurrences and outcomes of such actions, and any issues identified as a result of the delays or interruption.

iii. Provide the mean, median, and range of delay time; reasons for delay; and impact to patients.

j. Number and percentage of pharmacies who were noncompliant with the REMS requirements (i.e., did not complete monthly counseling for females who can become pregnant or males) out of all active pharmacies

k. Number and percentage of pharmacies that did not provide verification of the authorized representative every year out of all active pharmacies

l. Number and percentage of prescriptions dispensed for females who can become pregnant and males that did not have a completed pharmacy counseling checklist submitted to the REMS for that dispense out of all dispensed prescriptions for females who can become pregnant and males. Stratify by females who can become pregnant and males.

m. The number of certified prescribers and/or pharmacies that have had their certification revoked, including the reasons for such action

n. Number and percentage of prescriptions dispensed of greater than a 28 days' supply for females who can become pregnant and males and a breakdown of reasons for the dispenses (i.e., Dose Adjustments, Inpatient/Outpatient, Lost/Missing/Damaged) out of all prescription dispenses for females who can become pregnant and males. Stratify by females who can become pregnant and males.

o. Number and percentage of dispenses with confirmation to dispense (i.e., that had a pregnancy test before each prescription was dispensed) for females who can become pregnant out of the total number of dispenses with confirmation to dispense plus the number of dispenses without confirmation to dispense for females who can become pregnant

i. Provide an assessment of any factors that may have affected the required pregnancy tests being completed before each prescription dispense for females who can become pregnant. Include a summary of observed trends, barriers to compliance, and any corrective actions taken or planned.

p. Unintended system interruptions and corrective actions taken

q. Other barriers or delays in product dispensing and corrective actions taken

r. For all noncompliance with the REMS requirements, provide source of noncompliance report(s) and any corrective action(s) or resolution(s)

Safe-Use Behaviors

7. Provide an assessment of whether each patient's reproductive status was

assessed to determine who can get pregnant. Include in the assessment:

a. Numerators and denominators for all percentages
b. The number and percentage of patients who had their current reproductive status indicated in their Patient Enrollment Form and the section fully completed (e.g., no missing data) out of all patients enrolled in the REMS for the reporting period. If < 100%, provide the reasoning and actions taken to remediate.
c. The number and percentage of prescriber surveys for females who can become pregnant where the prescriber confirmed that the patient's reproductive potential status remained the same out of all prescriber surveys for females who can become pregnant
d. Any reported noncompliance that would inform on this assessment (e.g., Zenbexus dispensed to a non-enrolled patient or without a confirmation number to dispense)

8. Reproductive Potential Status Changes
    a. Report the following regarding the Change in Reproductive Potential Status Forms, including:
        i. Number of Change in Reproductive Potential Status Forms received, including the number of forms noted as a misclassification
        ii. Number of status changes to a female who can become pregnant, including the rationale for the change as indicated on the Change in Reproductive Potential Status Form. Also, report:
            1) Time between receipt of the Change in Reproductive Potential Status Form and confirmation that pregnancy testing occurred (time reported as a mean and median)
            2) Verification that routine pregnancy tests of all patients who can become pregnant occurred prior to the next dispense following a change in status to a female who can become pregnant
            3) Number of times Zenbexus was dispensed prior to the patient getting their first pregnancy test following the status change to a female who can become pregnant, any resulting adverse events, and corrective actions
        iii. Number of status changes to a female who cannot become pregnant, including rationale for the change as indicated on the Change in Reproductive Potential Status Form
        iv. Number of instances where a prescriber did not report a change or misclassification in the reproductive status of any patient by completing and submitting the Change in Reproductive Potential Status Form within 10 days of becoming aware of the change
        v. Provide most common reasons for reproductive status misclassifications
9. Participant Surveys
    a. Prescriber Surveys
        i. For Females Who Can Become Pregnant: Number and percentage

of prescriber survey responses for females who can become pregnant out of all prescriber survey responses for females who can become pregnant, in a tabulated format:

1) Whether the prescriber documented counseling their patient
2) Whether the pregnancy test was a laboratory based test (e.g., yes or over-the-counter: no)
    a) If no, include the exception reason(s) why a home pregnancy test was used (e.g., illness, other emergency, etc.).
    b) The pregnancy test results (e.g., positive, negative, pending, inconclusive)
3) Number and percentage of exceptions submitted (i.e., to use home pregnancy test) out of the total number of pregnancy tests required, stratified by the exception reason (e.g. illness, other emergency, etc.
    a) Include an overall assessment of the proportion of exceptions out of total tests, and reasons for exceptions, and trends identified

ii. For Males: Number and percentage of prescriber survey responses for males out of all prescriber survey responses for males, in a tabulated format:
    1) Whether the prescriber documented counseling their patient
iii. Provide an overall interpretation of all prescriber survey responses for females who can become pregnant and for males. Include in your analysis an assessment of prescriber compliance with the REMS.

b. Surveys of Females Who Can Become Pregnant
    i. Number and percentage of responses (e.g., yes or no) stratified by each question. Provide in tabulated format.
    ii. Provide an assessment of whether females who can become pregnant agreed to use contraception or abstinence during treatment with Zenbexus based the survey responses for the following questions: In the past 4 weeks, have you had sexual intercourse with a male partner?, Have you been using at least 2 of the recommended forms of birth control?, and On any occasion during the last 4 weeks, have you had sexual intercourse without using 2 forms of birth control? Include numerators and denominators for all percentages in the assessment.
    iii. Provide an overall interpretation of the survey responses including an assessment of REMS compliance among females who can become pregnant.
c. Surveys of Males
    i. Number and percentage of responses (e.g., yes or no) stratified by each question. Provide in tabulated format.
    ii. Provide an assessment of whether males agreed to use

contraception or abstinence during treatment with Zenbexus based on the survey responses for the following questions: In the past 4 weeks, have you had sexual intercourse with a female?, and While taking iberdomide, have you used a latex condom every time you have engaged in sexual activity with a female?. Include numerators and denominators for all percentages in the assessment

iii. Provide an overall interpretation of the survey responses including an assessment of REMS compliance among males.

Health Outcomes and Surrogate of Health Outcomes

10. Pregnancy Cases
    a. An analysis of all cases of pregnancy reported in association with Zenbexus from any source including but not limited to the following:
        i. The number of pregnancy exposures reported and stratified by source of exposure report (i.e., spontaneous report, reported via the REMS, etc.), and stratified by pregnancies among females who can become pregnant vs female partners of males receiving Zenbexus
    b. Pregnancy incidence rate (in person-years) to allow comparison with expected rates in the general population
    c. Pregnancy incidence rate among females who can become pregnant who received at least one dispense of Zenbexus during the reporting period
        i. Number of pregnancies reported among females who can become pregnant during treatment, out of the total number of females who can become pregnant who received at least one dispense of Zenbexus during the reporting period
            1) Provide an assessment of any factors that may have affected the incidence of pregnancies. Include a summary of observed trends in pregnancy rates during treatment, trends across reporting periods, the completeness of pregnancy reporting, any identified gaps in contraceptive counseling or adherence, and any corrective actions taken or planned to minimize pregnancy exposure to Zenbexus.
    d. A cumulative summary of both US and worldwide pregnancy cases should be provided and at a minimum, include the following information:
        i. Event identification number
        ii. Contraceptive methods used
        iii. Outcome for each pregnancy
        iv. Age of patient
    e. Follow-up of outstanding pregnancy reports from the previous assessment reporting period
    f. Root-cause analysis of each reported pregnancy to determine the reason the REMS failed to prevent the pregnancy exposure

Overall Assessment of REMS Effectiveness

11. 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 noncompliance plan for FDA review within 60 days of the date of this letter.
ii. Submit your pregnancy root cause analysis protocol for FDA review within 30 days of the date of this letter.

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

NDA 221075 REMS ASSESSMENT METHODOLOGY PROTOCOL REVIEW (insert concise description of content in bold capital letters, e.g., **SURVEY METHODOLOGIES, AUDIT PLAN, NONCOMPLIANCE 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) of the FDCA. 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.

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 221075 REMS ASSESSMENT

or

NEW SUPPLEMENT FOR NDA 221075/S-000
CHANGES BEING EFFECTED IN 30 DAYS
PROPOSED MINOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR NDA 221075/S-000

PRIOR APPROVAL SUPPLEMENT
PROPOSED MAJOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR NDA 221075/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 NDA 221075/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 221075

To facilitate review of your submission, we request that you submit your proposed modified REMS and other REMS-related materials in Microsoft Word and PDF format. If certain documents, such as enrollment forms, or website screenshots are only in PDF format, they may be submitted as such, but Word and PDF formats are preferred.

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 314.550, 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 314.550, 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 guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format-Promotional Labeling and Advertising Materials for Human Prescription Drugs*.

REPORTING REQUIREMENTS

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

POST APPROVAL FEEDBACK MEETING

New molecular entities 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.

COMPENDIAL STANDARDS

A drug with a name recognized in the official United States Pharmacopeia or official National Formulary (USP-NF) generally must comply with the compendial standards for strength, quality, and purity, unless the difference in strength, quality, or purity is plainly stated on its label (see FD&C Act § 501(b), 21 USC 351(b)). FDA typically cannot share application-specific information contained in submitted regulatory filings with third parties, which includes USP-NF. To help ensure that a drug continues to comply with compendial standards, application holders may work directly with USP-NF to revise

official USP monographs. More information on the USP-NF is available on USP's website[5].

If you have any questions, contact Ashlee Bow, Regulatory Project Manager, at 301-796-6716 or email ashlee.bow@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

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

ENCLOSURE(S):

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

[5] https://www.uspnf.com/