Our STN: BL 125696/0

BLA APPROVAL
January 31, 2020

Aimmune Therapeutics, Inc.
Attention: Louise Peacock
8000 Marina Boulevard
Brisbane, CA 94005-1884

Dear Ms. Peacock:

Please refer to your Biologics License Application (BLA) submitted on December 21, 2018, received on December 21, 2018, under section 351(a) of the Public Health Service Act (PHS Act) for Peanut (*Arachis hypogaea*) Allergen Powder-dnfp.

LICENSING

We are issuing Department of Health and Human Services U.S. License No. 2109 to Aimmune Therapeutics, Inc., Brisbane, CA, under the provisions of section 351(a) of the PHS Act controlling the manufacture and sale of biological products. The license authorizes you to introduce or deliver for introduction into interstate commerce, those products for which your company has demonstrated compliance with establishment and product standards.

Under this license, you are authorized to manufacture the product Peanut (*Arachis hypogaea*) Allergen Powder-dnfp, which is indicated for the mitigation of allergic reactions, including anaphylaxis, that may occur with accidental exposure to peanut. Peanut (*Arachis hypogaea*) Allergen Powder-dnfp is approved for use in patients with a confirmed diagnosis of peanut allergy. Initial Dose Escalation may be administered to patients aged 4 through 17 years. Up Dosing and Maintenance may be continued in patients 4 years of age and older. Peanut (*Arachis hypogaea*) Allergen Powder-dnfp is to be used in conjunction with a peanut-avoidant diet. Peanut (*Arachis hypogaea*) Allergen Powder-dnfp is not indicated for the emergency treatment of allergic reactions, including anaphylaxis.

The review of this product was associated with the following National Clinical Trial (NCT) numbers: NCT01987817, NCT02198664, NCT02635776, NCT02993107, NCT03126227, NCT03292484, NCT03337542.

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture Peanut (*Arachis hypogaea*) Allergen Powder-dnfp drug substance at (b) (4)

(b) (4). The final formulated product will be manufactured at CoreRx, Inc., 14205 Myerlake Circle, Clearwater, Florida, and filled, labeled and packaged at (b) (4) doing business as (b) (4)

You may label your product with the proprietary name PALFORZIA and market it in 0.5 mg, 1 mg, 10 mg, 20 mg, and 100 mg capsules and 300 mg sachets.

DATING PERIOD

The dating period for Peanut (*Arachis hypogaea*) Allergen Powder-dnfp shall be 24 months in capsules and 18 months in sachets from the date of manufacture when stored at 2 to 8 °C. The date of manufacture shall be defined as the date when the (b) (4) (b) (4) drug substrance. The dating period for your drug substance shall be (b) (4) months when stored at (b) (4)

FDA LOT RELEASE

Please submit protocols showing results of all applicable tests. You may not distribute any lots of product until you receive a notification of release from the Director, Center for Biologics Evaluation and Research (CBER).

BIOLOGICAL PRODUCT DEVIATIONS

You must submit reports of biological product deviations under 21 CFR 600.14. You should identify and investigate all manufacturing deviations promptly, including those associated with processing, testing, packaging, labeling, storage, holding and distribution. If the deviation involves a distributed product, may affect the safety, purity, or potency of the product, and meets the other criteria in the regulation, you must submit a report on Form FDA 3486 to the Director, Office of Compliance and Biologics Quality, at the following address:

Food and Drug Administration
Center for Biologics Evaluation and Research
Document Control Center
10903 New Hampshire Ave.
WO71-G112
Silver Spring, MD 20993-0002

MANUFACTURING CHANGES

You must submit information to your BLA for our review and written approval under 21 CFR 601.12 for any changes in, including but not limited to, the manufacturing, testing, packaging or labeling of Peanut (*Arachis hypogaea*) Allergen Powder-dnfp, or in the manufacturing facilities.

LABELING

Under 21 CFR 201.57(c)(18), patient labeling must be referenced in section 17 PATIENT COUNSELING INFORMATION. Patient labeling must be available and may either be reprinted immediately following the full prescribing information of the package insert or accompany the prescription product labeling.

We hereby approve the draft package insert labeling submitted under amendment 85, dated January 30, 2020 and the draft carton and container labeling submitted under amendment 86, dated January 30, 2020.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, please submit the final content of labeling (21 CFR 601.14) in Structured Product Labeling (SPL) format via the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. 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* at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

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.

PACKAGE AND CONTAINER LABELS

Please electronically submit final printed package and container labels that are identical to the package and container labels submitted on January 30, 2020, according to the guidance for industry *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* at https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm333969.pdf.

All final labeling should be submitted as Product Correspondence to this BLA 125696 at the time of use (prior to marketing) and include implementation information on Form FDA 356h.

ADVERTISING AND PROMOTIONAL LABELING

You may submit two draft copies of the proposed introductory advertising and promotional labeling with Form FDA 2253 to the Advertising and Promotional Labeling Branch at the following address:

Food and Drug Administration
Center for Biologics Evaluation and Research

Document Control Center
10903 New Hampshire Ave.
WO71-G112
Silver Spring, MD 20993-0002

You must submit copies of your final advertising and promotional labeling at the time of initial dissemination or publication, accompanied by Form FDA 2253 (21 CFR 601.12(f)(4)).

All promotional claims must be consistent with and not contrary to approved labeling. You should not make a comparative promotional claim or claim of superiority over other products unless you have substantial evidence or substantial clinical experience to support such claims (21 CFR 202.1(e)(6)).

ADVERSE EVENT REPORTING

You must submit adverse experience reports in accordance with the adverse experience reporting requirements for licensed biological products (21 CFR 600.80) and you must submit distribution reports as described in 21 CFR 600.81. For information on adverse experience reporting, please refer to the guidance for industry *Providing Submissions in Electronic Format —Postmarketing Safety Reports* at https://www.fda.gov/downloads/biologicsbloodvaccines/guidancecomplianceregulatoryinformation/guidances/vaccines/ucm458559.pdf and FDA's Adverse Event reporting System website at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm115894.htm. For information on distribution reporting, please refer to the guidance for industry *Electronic Submission of Lot Distribution Reports* at http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Post-MarketActivities/LotReleases/ucm061966.htm.

PEDIATRIC REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, 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 through < 1 year because necessary studies are impossible or highly impracticable. This is because peanut allergy is not typically diagnosed before the age of 1 year.

We are deferring submission of your pediatric study for ages 1 through < 4 years for this application because this product is ready for approval for use in children 4 through 17 years of age and the pediatric study in children 1 through < 4 years of age has not been completed.

Your deferred pediatric study required under section 505B(a) of the Federal Food, Drug, and Cosmetic Act (FDCA) is a required postmarketing study. The status of this postmarketing study must be reported according to 21 CFR 601.28 and section 505B(a)(4)(C) of the FDCA. In addition, section 506B of the FDCA and 21 CFR 601.70 require you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

Label your annual report as an "**Annual Status Report of Postmarketing Study Requirement/Commitments**" and submit it to the FDA each year within 60 calendar days of the anniversary date of this letter until all Requirements and Commitments subject to the reporting requirements under section 506B of the FDCA are released or fulfilled. This required study is listed below:

1. Deferred pediatric study under PREA for the mitigation of allergic reactions, including anaphylaxis, that may occur with accidental exposure to peanut in pediatric patients ages 1 through < 4 years.

   Final Protocol Submission: October 4, 2018

   Study Completion Date: December 31, 2021

   Final Report Submission: June 30, 2022

Submit final study reports to this BLA 125696. For administrative purposes, all submissions related to this required pediatric postmarketing study must be clearly designated as:

- **Required Pediatric Assessment**

We note that you have fulfilled the pediatric study requirement for ages 4 through 17 years for this application.

POSTMARKETING COMMITMENT SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We acknowledge your written commitment as described in your amendment submissions of November 13, 2019, and November 20, 2019 as outlined below:

2. To establish a pregnancy registry for PALFORZIA to collect, analyze, and report data on pregnancy outcomes and infant outcomes after exposure of PALFORZIA during pregnancy. You will continue enrolling patients until 72 qualifying patients are enrolled or until 5 years after PALFORZIA is commercially available, whichever is first. You will submit annual reports as well as a summary report at the end of the study, after which you will continue enrolling patients in the registry pending CBER review of the report and determination of whether the registry can be discontinued.

   Final Protocol Submission: Feburary 28, 2020

Study Completion: January 1, 2025

Final Report Submission: January 30, 2026

Please submit the clinical protocol to your IND 15463, and a cross-reference letter to this BLA 125696 explaining that this protocol was submitted to the IND.

If the information in the final study report supports a change in the labeling, the final study report must be submitted as a supplement. Please use the following designators to prominently label all submissions, including supplements, relating to these postmarketing study commitments as appropriate:

- **Postmarketing Commitment – Correspondence**
- **Postmarketing Commitment – Final Study Report**
- **Supplement contains Postmarketing Commitment – Final Study Report**

For each postmarketing study subject to the reporting requirements of 21 CFR 601.70, you must describe the status in an annual report on postmarketing studies for this product. Label your annual report as an **Annual Status Report of Postmarketing Requirements/Commitments** and submit it to the FDA each year within 60 calendar days of the anniversary date of this letter until all Requirements and Commitments subject to the reporting requirements of section 506B of the FDCA are fulfilled or released. The status report for each study should include:

- the sequential number for each study as shown in this letter;
- information to identify and describe the postmarketing commitment;
- the original schedule for the commitment;
- the status of the commitment (i.e., pending, ongoing, delayed, terminated, or submitted); and,
- an explanation of the status including, for clinical studies, the patient accrual rate (i.e., number enrolled to date and the total planned enrollment).

As described in 21 CFR 601.70(e), we may publicly disclose information regarding these postmarketing studies on our website at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Post-marketingPhaseIVCommitments/default.htm.

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 [section 505-1(a)].

In accordance with section 505-1 of FDCA, we have determined that a REMS is necessary for Peanut (*Arachis hypogaea*) Allergen Powder-dnfp to ensure the benefits of the drug outweigh the risks of anaphylaxis.

Your proposed REMS must include the following:

Elements to assure safe use: Pursuant to 505-1(f)(1), we have determined that Peanut (*Arachis hypogaea*) Allergen Powder-dnfp can be approved only if elements necessary to assure safe use are required as part of the REMS to mitigate the risk of anaphylaxis listed in the labeling. In addition, we have determined that a Medication Guide is not sufficient to mitigate the serious risks.

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 only in certain health care settings
- 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

Implementation System: The REMS must include an implementation system to monitor and evaluate 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 only in certain health care settings and the drug be dispensed to patients with documentation of safe use conditions.

Your proposed REMS, submitted on January 31, 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 PALFORZIA into interstate commerce.

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

For the purpose of the PALFORZIA REMS, “active” refers to a healthcare provider, healthcare setting, wholesaler/distributor, pharmacy, or patient that has prescribed, administered, distributed, dispensed, or received PALFORZIA during an assessment period.

1. Program Implementation and Operations

    a. Implementation – provide the date for each of the following for the 6-month assessment only:
        i. First Commercial distribution of PALFORZIA

ii. PALFORZIA Website live and fully operational
iii. PALFORZIA call center live and fully operational
iv. Each stakeholder could become certified or enrolled in the PALFORZIA REMS

b. Operation and performance
    i. Call center
        1. Number of contacts by stakeholder type
        2. Summary of reasons for calls by reporter (authorized representative, healthcare setting, patient/caregiver, pharmacy, other)
        3. Summary of REMS-related problems identified and resulting corrective actions
    ii. Enrollment – For each stakeholder, provide the number of newly certified or enrolled and active for each reporting period and cumulatively; stratify by geographic region
        1. Prescribers; further stratify by credentials (e.g., Doctor of Medicine or Osteopathic medicine, Nurse Practitioner, Physician Assistant, Other), and specialty (e.g., pediatric, allergy/immunology, family medicine, other).
        2. Wholesalers and distributors
        3. Healthcare settings: provide number of patients treated at each site, and the time between certification and first order for PALFORZIA for each healthcare site certified during the assessment period
    iii. Utilization
        1. The number of PALFORZIA Initial Dose Escalation prescriptions dispensed
        2. The number of PALFORZIA prescriptions dispensed for each dose level and the average quantity dispensed.
            a. Number of times more than one dose level was dispensed to a patient at the same time.
        3. The number of Office Dose Kits distributed for each dose

2. Knowledge

a. Stakeholder surveys (beginning with the 24-month assessment)
    i. Prescribers' knowledge of the risk of anaphylaxis associated with PALFORZIA, that appropriate administration of Initial Dose Escalation and first dose of each Up-Dosing level must be administered in a healthcare setting equipped to monitor patients and identify and manage anaphylaxis, the need to ensure that patients have injectable epinephrine, the need to counsel patients on continued peanut avoidance, how to recognize the signs and symptoms of anaphylaxis, and to have injectable epinephrine available for immediate use at all times.
    ii. Healthcare settings' knowledge of the risk of anaphylaxis associated with PALFORZIA, and the need to monitor patients for

60 minutes following Initial Dose Escalation and the first dose of each Up-Dosing.

iii. Pharmacies' knowledge of the risk of anaphylaxis associated with PALFORZIA, and the need to ensure that all prescribers and healthcare settings that order PALFORZIA, and all patients dispensed PALFORZIA are enrolled in the PALFORZIA REMS.

iv. Patients' knowledge of the risk of anaphylaxis, associated with PALFORZIA, the need for monitoring after the Initial Dose Escalation and the first dose of each Up-Dosing level, how to recognize the signs and symptoms of anaphylaxis, the need to have injectable epinephrine available for immediate use at all times, and the need for continued dietary peanut avoidance.

3. Safe use behaviors

a. Percentage of patients, source of reports, and outcome of patients who were not observed following Initial Dose Escalation or initial dose of each Up-Dosing level for PALFORZIA.

b. Number of patients who received PALFORZIA who were not enrolled in the REMS (either from a pharmacy or a health care setting).

c. Percentage of patients, source of reports, root cause analysis, and outcome for any enrolled patient who experiences anaphylaxis that did not have access to injectable epinephrine during the event.

d. Percentage and source of report for healthcare settings that have administered PALFORZIA without a certified prescriber or healthcare provider on site.

e. Number, source of report, and outcome for healthcare settings that have administered PALFORZIA that are not equipped to identify and treat anaphylaxis.

f. Shipments of PALFORZIA to non-certified pharmacies and healthcare settings; provide:
   i. Number of shipments of Initial Dose Escalation, Office Dose Kits, and daily dose packs sent to non-certified pharmacies and healthcare settings.
   ii. Location for each shipment (healthcare setting, patient home, other)
   iii. Disposition of shipment and any resulting adverse outcomes.

g. REMS compliance – Provide the PALFORZIA REMS noncompliance plan with the first 6-month REMS assessment; include criteria and actions for noncompliance for each stakeholder including steps you plan to take to decertify stakeholders that are non-compliant with the REMS program requirements.

h. REMS compliance – Provide the PALFORZIA REMS Audit plan for healthcare settings, pharmacies, and wholesalers/distributors with the first 6-month REMS assessment and report the audit findings for each stakeholder:
    i. The number of audits expected, and the number of audits performed.
    ii. The number and types of deficiencies noted for each group of audited stakeholders; include a unique ID for each stakeholder that had deviations to track deviations by stakeholder over time.
        1. For those with deficiencies noted, report the number that successfully completed a corrective and preventive action (CAPA) plan within one month of audit.
        2. For any that did not complete the CAPA within one month of the audit, describe actions taken to prevent future occurrences.
    iii. At a minimum, the audits should evaluate:
        1. Documentation of completion of training for relevant staff.
        2. The existence of documented processes and procedures for complying with the REMS
        3. Verification that in each audited stakeholder's site the designated authorized representative is current. If different, include the number of new authorized representatives and verification of the site's recertification.

4. The requirements, under section 505-1(g)(3) of the Federal Food, Drug, and Cosmetic Act, for assessments of an approved REMS 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.

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 of 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 that 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.
g) *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:

BLA 125696 REMS CORRESPONDENCE
(insert concise description of content in bold capital letters, e.g., UPDATE TO REMS SUPPORTING DOCUMENT - ASSESSMENT METHODOLOGY)

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 125696 REMS ASSESSMENT

or

NEW SUPPLEMENT FOR BLA 125696
CHANGES BEING EFFECTED IN 30 DAYS
PROPOSED MINOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR BLA 125696
PRIOR APPROVAL SUPPLEMENT
PROPOSED MAJOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR BLA 125696
PRIOR APPROVAL SUPPLEMENT
PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABEL CHANGES
SUBMITTED IN SUPPLEMENT XXX

or

NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR BLA 125696 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 125696

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.

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).

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biological products qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm.

POST APPROVAL FEEDBACK MEETING

New biological products qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication

process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, please contact the Regulatory Project Manager for this application.

Sincerely,

Mary A. Malarkey
Director
Office of Compliance and Biologics Quality
Center for Biologics
Evaluation and Research

Marion F. Gruber, PhD
Director
Office of Vaccines Research and
Review
Center for Biologics
Evaluation and Research

Enclosures:
REMS