Our STN: BL 125592/0 **BLA APPROVAL**

Merck Sharp and Dohme Corp.
Attention: Nadine Margaretten, Ph.D.
Associate Director, Worldwide Regulatory Affairs March 1, 2017
126 E. Lincoln Avenue
Rahway, NJ 07065

Dear Dr. Margaretten:

Please refer to your Biologics License Application (BLA) for House Dust Mite (*Dermatophagoides farinae* and *Dermatophagoides pteronyssinus*) Allergen Extract dated February 9, 2016, submitted under section 351(a) of the Public Health Service Act (PHS Act).

We have approved your BLA for House Dust Mite (*Dermatophagoides farinae* and *Dermatophagoides pteronyssinus*) Allergen Extract effective this date. You are hereby authorized to introduce or deliver for introduction into interstate commerce House Dust Mite (*Dermatophagoides farinae* and *Dermatophagoides pteronyssinus*) Allergen Extract under your existing Department of Health and Human Services United States (U.S.) License No. 0002. House Dust Mite (*Dermatophagoides farinae* and *Dermatophagoides pteronyssinus*) Allergen Extract is indicated as immunotherapy for house dust mite (HDM)-induced allergic rhinitis, with or without conjunctivitis, confirmed by *in vitro* testing for IgE antibodies to *Dermatophagoides farinae* or *Dermatophagoides pteronyssinus* house dust mites, or skin testing to licensed house dust mite allergen extracts. House Dust Mite (*Dermatophagoides farinae* and *Dermatophagoides pteronyssinus*) Allergen Extract is approved for use in adults 18 through 65 years of age.

The review of this product was associated with the following National Clinical Trial (NCT) numbers: NCT01700192, NCT01454544, NCT01644617, and NCT01433523.

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture House Dust Mite (*Dermatophagoides farinae* and *Dermatophagoides pteronyssinus*) Allergen Extract drug substance at (b) (4). The final formulated product will be manufactured, filled, labeled and primary packaged at Catalent Pharma Solutions Limited in Wiltshire, United Kingdom. The final product will be secondary packaged at Merck Sharp and Dohme Corp, (b) (4)

You may label your product with the proprietary name ODACTRA and market it as a tablet for sublingual use in 10-tablet aluminum blister package.

ADVISORY COMMITTEE

We did not refer your application to the Allergenic Products Advisory Committee because our review of information submitted in your BLA, including the clinical study design and trial results, did not raise concerns or controversial issues that would have benefited from an advisory committee discussion.

DATING PERIOD

The dating period for House Dust Mite (*Dermatophagoides farinae* and *Dermatophagoides pteronyssinus*) Allergen Extract Tablet for Sublingual Use shall be 36 months from the date of manufacture when stored at 20-25 °C. The date of manufacture shall be defined as the date when the drug substances are added to the excipient.

FDA LOT RELEASE

Please submit final blister packaged drug product together with lot release 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 House Dust Mite (*Dermatophagoides farinae* and *Dermatophagoides pteronyssinus*) Allergen Extract, or in the manufacturing facilities.

LABELING

We hereby approve the draft package insert labeling submitted under amendment 70, dated February 28, 2017 and the draft carton and container labeling submitted under amendment 67, dated February 20, 2017.

Under 21 CFR Part 208, we have determined that this product poses a serious and significant public health concern requiring the distribution of a Medication Guide. ODACTRA is a product for which patient labeling could help prevent serious adverse effects and inform the patient of serious risks relative to benefit that could affect their decisions to use, or continue to use, the product. Therefore, a Medication Guide is necessary for safe and effective use of this product and FDA hereby approves the Medication Guide you submitted on February 28, 2017. Please note that:

- Under 21 CFR 201.57 (c)(18) this Medication Guide must be reprinted at the end of the package insert or accompany the prescription product labeling;

- Under 21 CFR 208 you are responsible for ensuring that this Medication Guide is available for distribution to every patient who is dispensed a prescription for this product;

- The final printed Medication Guide distributed to patients must conform to all conditions described in 21 CFR 208.20, including a minimum of 10 point text; and

- You are responsible for ensuring that the label of each container or package includes a prominent and conspicuous instruction to authorized dispensers to provide a Medication Guide to each patient to whom the drug is dispensed, and states how the Medication Guide is provided.

Please provide your final content of labeling in Structured Product Labeling (SPL) format and include the carton and container labels. In addition, please submit three original paper copies for carton and container final printed labeling. All final labeling should be submitted as Product Correspondence to this BLA 125592 at the time of use (prior to marketing) and include implementation information on Form FDA 356h.

In addition, please submit the final content of labeling (21 CFR 601.14) in 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.

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 http://www.fda.gov/Drugs/DrugSafety/ucm400526.htm and FDA's Adverse Event reporting System website 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 children less than 5 years of age because necessary studies are impossible or highly impracticable. This is because the number of children younger than 5 years of age with allergic rhinitis/rhinoconjunctivitis who have been diagnostically confirmed with sensitivity to house dust mite *Dermatophagoides farinae* or *Dermatophagoides pteronyssinus* is too small.

We are deferring submission of your pediatric studies for ages 5 years through 17 years of age because this product is ready for approval for use in adults and the pediatric studies have not been completed.

Your deferred pediatric studies required under section 505B(a) of the Federal Food, Drug, and Cosmetic Act (FDCA) are required postmarketing studies. The status of these postmarketing studies must be reported according to 21 CFR 601.28 and section 505B(a)(3)(B) 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 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 under section 506B of the FDCA are released or fulfilled. These required studies are listed below:

1. Deferred pediatric study (Study 1) under PREA to evaluate safety and efficacy of ODACTRA in pediatric subjects 5 through 17 years with house dust mite induced allergic rhinitis/rhinoconjunctivitis with or without asthma.

   Final Protocol Submission: October 1, 2017

   Study Completion Date: July 1, 2021

   Final Report Submission: July 1, 2022

2. Deferred pediatric study (Study 2) under PREA to evaluate the safety of ODACTRA in pediatric subjects 5 through 17 years with house dust mite induced allergic rhinitis/rhinoconjunctivitis with or without asthma.

   Final Protocol Submission: October 1, 2017

   Study Completion Date: July 1, 2021

   Final Report Submission: July 1, 2022

Submit the protocols to your Investigational New Drug Application (IND) 15015, with a cross-reference letter to this BLA 125592 explaining that these protocols were submitted to the IND.

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

- **Required Pediatric Assessments**

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We acknowledge your written commitment as described in your submission of February 8, 2017, as outlined below:

3 You commit to conduct a postmarket electronic health record (EHR) study to further describe the safety profile of ODACTRA in marketed use in the United States. The study will enroll all new users of ODACTRA identified through a large integrated electronic health records dataset. The study will aim to accrue 10,000 patients over a 5 year period. The primary objective of the study is to estimate the incidence of serious allergic reactions and eosinophilic esophagitis among patients exposed to ODACTRA. The study will assess the first in-office exposures to ODACTRA and subsequent exposures and outcomes (i.e., serious allergic reactions and eosinophilic esophagitis) to the extent that they are available within the EHR system.

Final protocol submission: August 15, 2017

Study completion: February 28, 2024

Final Report Submission: February 28, 2025

Please submit the clinical protocol to your IND 15015, and a cross-reference letter to this BLA 125592 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. Supplements in support of labeling changes based on a postmarketing study report may be subject to a user fee. 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 Web site at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Post-marketingPhaseIVCommitments/default.htm.

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 yours,

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