DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20852-1448

OUR STN: BL 125478/0

Merck Sharp & Dohme Corp.
Attention: Dr. Scott Greenfeder
126 E. Lincoln Avenue
P.O. Box 2000
Rahway, NJ 07065

Dear Dr. Greenfeder:

We are reviewing your biologics license application (BLA) dated March 11, 2013, for Short Ragweed Pollen Allergen Extract (*Ambrosia artemisiifolia*) (RAGWITEK), Tablet for Sublingual Use, and have determined that the following information is necessary to take complete action. Please promptly submit your written response to the following items so that we may continue evaluating your BLA:

1. Your proposed Pediatric Study Plan (PSP), provided in Module 1.9.2, is inadequate. Your PSP is a request for a partial waiver of the requirement to submit a pediatric assessment for pediatric populations younger than 5 years of age based on the low prevalence of allergenic rhinitis to ragweed pollen during early childhood. In addition, it states a request for a deferral for children 5 < 17 years of age stating your plan to conduct an initial short-term safety evaluation of the product in this age group followed by a study to evaluate efficacy and safety. Please submit a revised PSP that addresses the following:

    a. With regard to your request for a partial waiver for children < 5 years of age, please provide the statutory reason for the partial waiver with supportive documentation (e.g., if you plan to request a waiver because the product does not represent a meaningful therapeutic benefit over existing therapies for persons in this age group and is not likely to be used by a substantial number of persons in this in age group). Please provide a justification for choosing this reason together with available data to support your justification.

    b. With regard to the request for a deferral of submission of assessments for children and adolescents 5 <17 years of age, please provide a concept protocol for each study that you plan to conduct. Each concept protocol should include the proposed objectives, design, age groups, inclusion/exclusion criteria, relevant endpoints, and statistical approach. In addition, please include the dates for Final Protocol Submission, Study Completion, and Final Report Submission.

    We advise you to refer to the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c) and the Draft Guidance for Industry: How to comply with the Pediatric Research Equity Act at

http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM077855.pdf

2. In Module 3.2.P.5.2., "Analytical Procedures (Absence of Specified Microorganisms)," you indicate that tests for specified microorganisms of the drug product will be performed according to (b) (4) and in Module 3.2.P.5.2, "Analytical Procedures (Microbial Enumeration)," you indicate that the examination of non-sterile products is performed according to (b) (4) You provide results in Module 3.2.P.5.4 (Batch Analyses) for microbial enumeration (b) (4) and (b) (4) and results for the absence of specified microorganisms. However, we note your microbiological examination did not include bioburden testing. Please provide the bioburden qualification report for the MK-3641 drug product and include the following test parameters according to the specified bioburden standards:

   a. Suitability of the test method used.

   b. Conformance and recovery of inoculated microorganisms in the presence and absence of drug product. In addition, please include the specific drug product lot numbers used to assess conformance and recovery.

   c. Relevant negative controls as specified in (b) (4)

3. The following toxicological study reports, conducted using Timothy Grass Pollen Allergen Extract (*Phleum pratense*) were submitted in Section 4.2.3.7.7 of your application:

   - 07231 - Report on Serology of Mice Included in Repeated Dose Toxicology
   - 10-042144 - Phleum Pratense Pre- and Post-Natal Development Study in the (b) (4) Mouse by Buccal Cavity Administration
   - 10106 - Report on Serology of Dogs Included in Repeated Dose Toxicology
   - 1-033458 - Phleum Pratense Toxicity Study by Sublingual Tablet Administration to (b) (4) Dogs for 52 Weeks Followed by 8 Weeks off Dose and One Further Week of Treatment
   - 2-032364 - Phleum Pratense Toxicity Study by Buccal Cavity Administration to (b) (4) Mice for 26 Weeks Followed by a 5 Week Recovery Period
   - 2325-2 - Phleum Pratense Grass Extract: (b) (4)
   - 2325-4 - Phleum Pratense Grass Extract:Mutation at the Thymidine Kinase (tk) Locus of Mouse Lymphoma L5178Y Cells (MLA) using the (b) (4)

- 2325-6 - Phleum Pratense Grass Extract: (b) (4)
- 3-024445 - Phleum Pratense Toxicity Study by Buccal Cavity Administration to (b) (4) Mice for 15 Weeks Followed by 4 Weeks Off Dose and One Further Week of Treatment and a 4 Week Recovery Period
- 4-023818 - Phleum Pratense Preliminary Study of Effects on Embryo-Fetal Toxicity in the (b) (4) Mouse by Buccal Cavity Administration
- 5-023911 - Phleum Pratense Single Dose Toxicity Study by Buccal Cavity Administration to (b) (4) Mice with a 14 Day Observation Period
- 6-023930 - Phleum Pratense Single Dose Toxicity Study by Intravenous Administration to (b) (4) Mice with a 14 or 15-Day Observation Period
- 8-033623 - Phleum Pratense Combined Study of Effects on Fertility and Embryo-Fetal Development in the (b) (4) Mouse by Buccal Cavity Administration
- 944-001 - A Subchronic Oral Toxicity Study of Phleum Pratense Grass Extract In Mice
- 944-002 - A Subchronic Oral Toxicity Study of Phleum Pratense Grass Extract In Dogs

Please be aware that these reports will not be reviewed under this application because they were not conducted using Short Ragweed Pollen Allergen Extract (*Ambrosia artemisiifolia*). They will be reviewed under BLA 125473 for Timothy Grass Pollen Allergen Extract (*Phleum pratense*).

We note that these reports were submitted to support draft language for the Pregnancy Category in your proposed package insert. We find it unacceptable to use reproductive data from one pollen to support the reproductive effects of another pollen as pollens from different plant species may be sufficiently different to elicit different toxicological sequelae. Although retrospective information is available regarding the general use of Ragweed Pollen Allergen Extracts, specific information regarding its safety in pregnant women is lacking; therefore, Pregnancy Category C is warranted for your product. In order to support a Pregnancy Category B for your Short Ragweed Pollen Allergen Extract, specific reproductive toxicology studies are required and may be conducted post-licensure.

Please submit your response in a timely manner as an amendment to your BLA so we may continue the review of your application.

If you have any questions, please contact the Regulatory Project Manager, Katie Rivers, M.S. at (301) 796-2640.