Memorandum

Food and Drug Administration
Center for Biologics Evaluation and Research
Office of Compliance and Biologics Quality
Division of Manufacturing and Product Quality

To: **STN 125478 Short Ragweed Pollen Allergen Extract**

From: Deborah Trout, BLA Committee Member, OCBQ/ DMPQ/MRB1 HFM-675

Through: Carolyn Renshaw, Branch Chief, MRB1, DMPQ, OCBQ, HFM-675

Subject: Review of BLA submitted by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., to request approval for MK-3641 Standardized Allergenic Extract, Short Ragweed (*Ambrosia artemisiifolia*) sublingual tablet for oromucosal delivery.

Action Due: April 17, 2014

Recommended Action: Approval provided the 483 responses are acceptable. Review of the responses will be the subject of a separate memo.

Review Narrative

Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., in collaboration with ALK-Abello A/S has developed a novel oral pharmaceutical formulation of the allergen extract from short ragweed pollen (*Ambrosia artemisiifolia*; "common" ragweed) in tablet form (MK-3641) for sublingual administration for the treatment of allergic diseases. The Drug Product is an Allergy Immunotherapy tablet for the treatment of ragweed-pollen induced rhinitis and conjunctivitis in adults (18 years or older), who are sensitized to ragweed.

The MK-3641 tablet is a non-sterile sublingual orally disintegrating tablet for use by the oromucosal route of administration. The drug substance is a (b) (4)

The MK-3641 tablet has been developed utilizing the (b) (4) is the proprietary name for Catalent Pharma Solutions Ltd. (b) (4) orally disintegrating tablets that are

designed to disintegrate rapidly in the mouth without the need of water. Each tablet contains

12 Amb a 1-U of standardized short ragweed pollen extract within a fast dissolving tablet matrix, which is composed of inactive ingredients: gelatin (sourced from fish skin) and mannitol. The gelatin and mannitol meets the compendia requirements of the current(b) (4)

The proposed shelf lives for (b) (4) drug product are both 36 months from the manufacturing date.

The manufacture of the DS occurs at ALK-Abello A/S, Bøge Allé 6-8, Hørsholm, Denmark. This site is a US licensed manufacturing location (US License 1292) that manufactures allergenic extracts for the US and European markets.

The manufacture of the DP occurs at Catalent Pharma Solutions Ltd., Frankland Road, Blagrove, Swindon, Wiltshire, SN5 8RU, United Kingdom. The Catalent site also manufactures approved drug products for the US and European markets.

Drug Substance

The drug substance (DS) is (b) (4) (b) (4)

The manufacture and testing of the DS are performed b (b) (4)

(b) (4)

(b) (4)

(b) (4)

20 pages determined to be no releasable: (b)(4)

(b) (4)

(b) (4)

Drug Product – Catalent Pharma Solutions

Table 9 provides the names, addresses, and responsibilities of the manufacturers of MK-3641 drug product (DP).

Table 9 Manufacturers of MK-3641 Drug Product		
Name and Address of Manufacturer	**Responsibilities**	**US Registration Number/License Number**
Catalent UK Swindon (b) (4) Frankland Road Blagrove, Swindon, Wiltshire, SN5 8RU United Kingdom	Manufacture and primary packaging of tablets, and Testing (Appearance, Disintegration, Microbiological Examination)	US Registration Number 3003812585
(b) (4)		
(b) (4)		

Table 9 Manufacturers of MK-3641 Drug Product		
Name and Address of Manufacturer	**Responsibilities**	**US Registration Number/License Number**
(b) (4)	(b) (4)	(b) (4)

The MK-3641 Drug Product (DP) is a white to off-white circular freeze dried sublingual tablet with a debossed double hexagon detail on base designed to rapidly disintegrate under the tongue. MK-3641 drug product (DP) is a sublingual orally disintegrating tablet indicated for treatment of ragweed pollen allergy. The contact between the relevant allergens and the immune system takes place in the oral cavity; therefore, the allergen content of the formulation should be released as quickly as possible in the oral cavity to ensure maximum exposure before swallowing. Since the allergens are proteins they are sensitive to heat and mechanical stress during processing, therefore the manufacturing process must be gentle in order to avoid degradation. Based upon these considerations, the (b) (4) was determined to be suitable in its formulation properties and manufacturing conditions. The (b) (4) was used for another allergen orally disintegrating tablet: Timothy Grass pollen (*Phleum Pratense*). This product has been approved and marketed as GRAZAX™ exclusively by ALK-Abello in Europe. Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., in collaboration with ALK-Abello, has filed this product in the US (SCH 697243/MK-7243 (Timothy Grass) tablet BLA 125473).

Prior knowledge of the (b) (4) and experience on SCH 697243/MK-7243 (Timothy Grass) tablet was available as the basis of the development of MK-3641 (Ragweed) tablet, from which to establish the initial formulation.

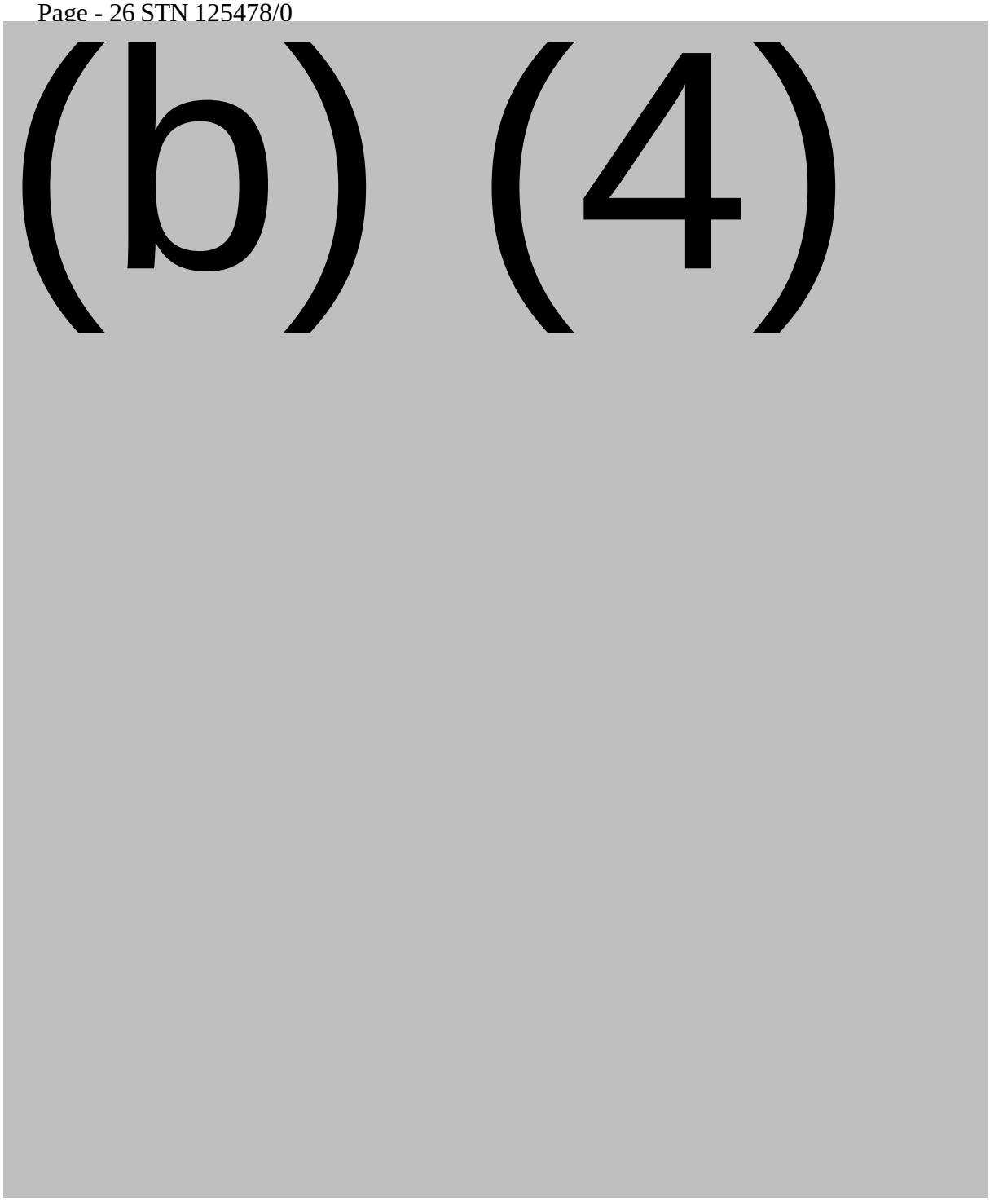
Facilities and Equipment –Drug Product: Ragweed is manufactured on (b) (4). Grass is manufactured on (b) (4) . The Ragweed BLA contains the same information

provided in the Grass BLA for (b) (4) with the exception of Section 1.4.3.4 Summary Of Cleaning Validation for Removal of MK-3641 from Product Contact Equipment.

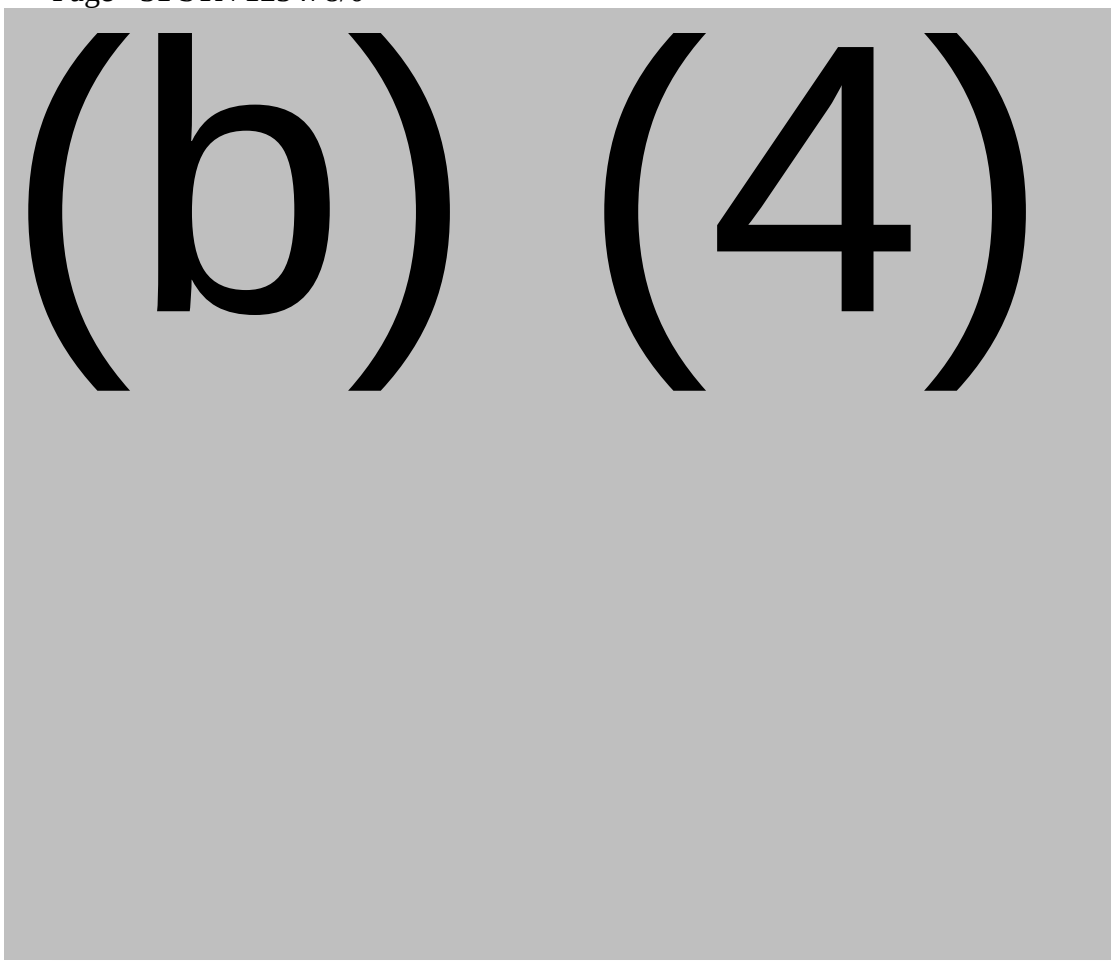
The following is a list of Module 3 Sections for Drug Product that are either identical or very similar between BLA 125,473 (Timothy Grass) and BLA 125,478 (Ragweed).

(b) (4)

4 pages determined to be not releasable: (b)(4)



The manufacturing process flow for the MK-3641 Drug Product is noted below.



Container Closure System Drug Product - Catalent Pharma Solutions

MK-3641 tablets will be packaged in all aluminum blister cards composed of five layer cold formable laminate blister material heat sealed with a paper/foil laminate lidding. The materials selected are the packaging materials of choice for the (b) (4) dosage form. Development work optimized the formulation of SCH 697243/MK-7243 (Timothy Grass) tablet to be compatible with the all-aluminum blister pack. As the base formulations of SCH 697243 (Timothy Grass) tablet and MK-3641 (Ragweed) tablet are identical, the development work is considered applicable for MK-3641 (Ragweed) tablet.

Container integrity testing is performed as a part of the in process testing of the DP. (b) (4) testing is a primary packaging container integrity test by means of (b) (4) . Blisters are (b) (4)

Microbiological Attributes

The MK-3641 drug product (DP) solution prior to and during dosing has been shown to be susceptible to microbial growth. As a result of formulation and process optimization studies, process modifications and controls have been introduced to ensure the microbiological quality of the (b) (4) DP solution and the freeze dried DP. These process parameters include:

- (b) (4)

Drug Product Facilities and Equipment Catalent Pharma Solutions

The MK-3641 DP is manufactured in non-dedicated areas (b) (4) equipment.

General features of the MK-3641 DP manufacturing facilities are provided in Section 3.2.A.1.1 of the BLA. A general layout of the Catalent location was provided in Attachment 1 of Section 3.2.A.1.1. Floor diagrams of the (b) (4) building were provided in Attachment 2, Section 3.2.A.1.1. Additional diagrams were provided in Section 3.2.A.1.1 to show the air flows (pressurizations), the personnel, and materials flows and waste flows, and the flow of the (b) (4)

The rooms used for the manufacture of the MK-3641 DP are (b) (4) areas as is appropriate for the manufacture of a non-sterile solid oral dosage form. (b) (4) is serviced by their own (b) (4)

(b) (4)
area. Equipment is described in Section 3.2.A.1.4 of the BLA.

(b) (4)

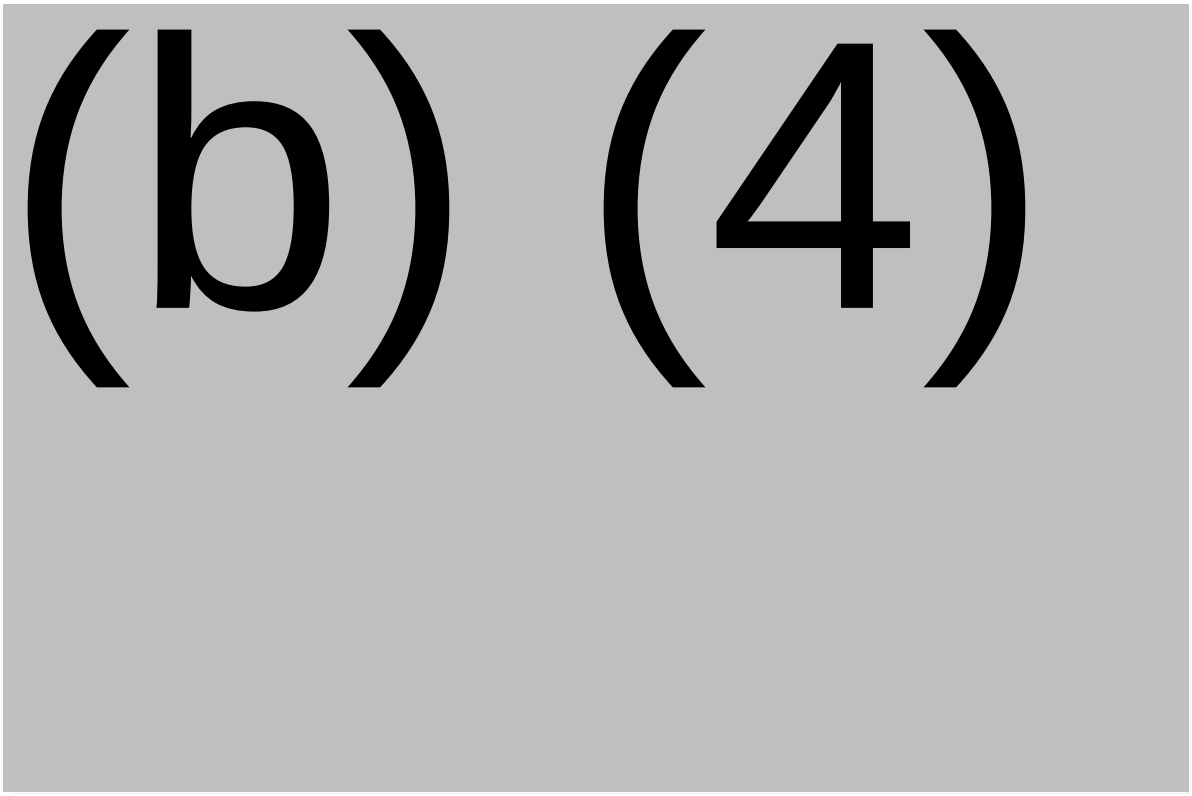
(b) (4)
system was provided in Attachment 1, Section 3.2.A.1.3 of the BLA.

The HVAC systems are monitored on a (b) (4), temperature, and humidity. Production areas for (b) (4) dosage forms are controlled to assure the temperature and humidity are within the required parameters to assure the quality of the DP. After (b) (4)

(b) (4) No particulate monitoring is required for these areas since these are (b) (4) .

Environmental monitoring in the MK-3641 DP production rooms in the (b) (4) building at Catalent will be carried out as follows. Validated EMS systems are installed on (b) (4) manufacturing lines. However, temperature and humidity chart recorders remain in use for recording batch information in the event of the failure of the Environmental Monitoring System (EMS) until the EMS is restored. Digital displays on the EMS instruments are used to monitor and record temperature, humidity, and pressure on (b) (4)

The (b) (4) facility is a multi-product facility that manufactures other products as noted in Section 3.2.A.1.1 of the BLA. Manufacture takes place on a campaign basis and procedures are in place to assure adequate space for each operation, and proper room and line clearance procedures to prevent mix ups. Catalent manufactures the following approved products for the US market Zelapar®, Zofran®, Claritin®, Maxalt®, Saphris®, and Zyprexa®. These products (including MK-3641) are all freeze dried tablets, for which the (b) (4) is used.



Equipment Cleaning - Catalent Pharma Solutions

For the MK-3641 process there are two types of equipment that the MK-3641 is in contact with, the (b) (4)

equipment in contact with MK-3641 (i.e., (b) (4), and the dosing systems) are considered validated thereby permitting use of this equipment for other products. The (b) (4) All other equipment is considered non-product contact for MK-3641 and is cleaned as described in this section.

(b) (4)

(b) (4)

Equipment Cleaning Validation - Catalent Pharma Solutions

Catalent cleaning validation for removal of MK-3641 active covered the product contact equipment. This included the (b) (4) . For the (b) (4) that are used for other DP active preparation, validation of the removal of other product actives is also performed to assure no cross contamination of MK-3641 would occur. The assumption is made tha (b) (4) Cross contamination of MK-3641 could occur in the (b) (4) step and would be incorporated into the whole of the succeeding lot. Cross contamination from MK-3641 and other active residuals could also occur in the (b) (4) Again in this case, any contamination will be incorporated into the whole of the succeeding batch. The final product contact step, (b) (4)

It is not possible for drug to be sublimed from the product during (b) (4)

(b) (4) s. Also, any drug which did sublime in this way could not contaminate any subsequent product, as there is no product contact. However, in case that a tablet would (b) (4) a have been quantified. This was done in order to give extra assurance that the cleaning procedures for the (b) (4) represent best possible practice, and to provide further scientific information concerning the process.

For all cleaning validation studies, the primary assessment was a thorough visual inspection of the processing equipment under test. No visual contamination from actives, excipients, dyes or cleaning agents was allowed. (b) (4)

(b) (4)

8 pages determined to be not releasable: (b)(4)

(b) (4)

(b) (4)

Environmental Assessment

Merck is requesting a categorical exclusion from the preparation of an environmental assessment (EA) for the Standardized Allergenic Extract, Short Ragweed (*Ambrosia artemisiifolia*) pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act. Such exclusion is provided in 21 CFR 25.31(c) for an action on a Biologics License Application (BLA) if the substance occurs naturally in the environment, when approval of the application does not significantly alter the concentration or distribution of the substance, its metabolites or degradation products in the environment. No extraordinary circumstances exist that would warrant the preparation of an environmental assessment.