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 125473 Timothy Grass 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-7243 [Standardized Allergenic Extract, Timothy Grass (*Phleum pratense*) Sublingual Tablets 2800 BAU (bioequivalent allergen unit)], a fast-dissolving, sublingual tablet for oromucosal delivery.

Action Due: April 7, 2014

Recommended Action: Resolve all issues identified below, once issues are resolved and all facility pre-license inspections are closed out or waived, I will prepare an approval recommendation memo.

Review Narrative

Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., and ALK-Abello have entered into a partnership to jointly develop the SCH 697243 (Timothy Grass) Tablet for the North American market. The Drug Product is an Allergen Immuno Therapy tablet for the treatment of rhino conjunctivitis due to grass pollen allergy.

MK-7243 [Standardized Allergenic Extract, Timothy Grass (*Phleum pratense*) Sublingual Tablets 2800 BAU (bioequivalent allergen unit)], is a fast-dissolving, sublingual tablet for oromucosal delivery. A Biologics Licensing Application (BLA) has been submitted in support of the following proposed indication:

MK-7243 is indicated for the disease modifying treatment of diagnosed Timothy and related grass pollen induced allergic rhinitis, with or without conjunctivitis, in adults and children 5 years of age and older.

The MK-7243 tablet is a non-sterile sublingual orally disintegrating tablet (ODT) for use by the oromucosal route of administration. The drug substance (DS) is (b)(4) aqueous (b)(4) purified allergenic extract solution, derived from grass pollen of Timothy Grass (Phleum pratense). The DS is also used in other drug products in Europe and US (subcutaneous Injection or drops for sublingual immunotherapy).

The proper name of the drug substance is Allergenic Extract, Standardized Grass Pollen Extract, Timothy Grass (Phleum pratense),(b) (4) (b)(4) . The DS contains (b)(4) . The MK-7243 tablet contains 2,800 Bioequivalent Allergy Unit (BAU) of the drug substance. The drug substance is a standardized allergen extract from timothy grass pollen (Phleum pratense) sourced from the United States (US). This extract, produced by ALK-Abello A/S, was first marketed in 1982. It has been used in other allergy immunotherapies in Europe (e.g., suspension for subcutaneous injection and tablets or drops for sublingual immunotherapy) and in the US and Canada (for subcutaneous injection).

The MK-7243 tablet has been developed utilizing the (b)(4) is the proprietary name for (b)(4) orally disintegrating tablets that are designed to disintegrate rapidly in the mouth without the need of water. Each tablet contains 2800 BAU of standardized grass 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 USP/NF.

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

The product described in this application is currently marketed under the tradename GRAZAX® in Europe. A Marketing Authorization Application was filed by the Mutual Recognition Procedure in Europe, and ALK-Abello A/S received approval in 2006. ALK-Abello A/S has received regulatory approval in 30 countries (European Union [EU] countries, Norway, Iceland and Switzerland). GRAZAX® is indicated in the EU for the disease-modifying treatment of grass-pollen-induced rhinitis and conjunctivitis in adults and children (5 years or older) with clinically relevant symptoms and diagnosed with a positive skin prick test and/or specific IgE test to timothy grass pollen.

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 UK Swindon Zydis Ltd., Frankland Road, Blagrove, Swindon, Wiltshire, SN5 8RU, United Kingdom. The Catalent site also manufactures approved drug products for the US and European markets.
Both the DS and DP manufacturing facilities are multiuse facilities. The DS manufactured at

ALK-Abello A/S is produced in a dedicated room using dedicated equipment. The DP is manufactured in non-dedicated areas ((b)(4)) using non-dedicated equipment.

Drug Substance

The drug substance (DS) is (b)(4) aqueous (b)(4) purified allergenic extract solution, derived from grass pollen of Timothy Grass (*Phleum pratense*). DS contains (b)(4)

The manufacture and testing of the DS are performed by ALK-Abello A/S, Hørsholm, Denmark, a contract manufacturer for the applicant, Merck Sharp & Dohme, a subsidiary of Merck & Co., Inc.

Table 2 Manufacturers of SCH 697243 Drug Substance

Name and Address of Manufacturer	Responsibilities	US Registration Number/License Number
ALK-Abelló A/S Bøge Allé 6-8 DK-2970 Hørsholm Denmark	Manufacturing, and Testing	US Registration Number (b)(4) US License No. 1292
(b)(4)	(b)(4)	US Registration Number: (b)(4)

The source material used for the production of the DS is grass pollen from Timothy Grass (*Phleum pratense*) cultivated and collected from grasses grown under (b)(4) conditions in the USA, by the (b) (4) ., Grass pollen is collected by (b)(4)

(b)(4)

(b)(4)

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

The original PQ for the (b)(4) purified water system was performed in two parts. The first part was for the (b)(4) . The second part was for the (b)(4) . Performance qualification of the PW generation was performed from November 26, 2001 to December 9, 2001. Performance qualification of the distribution system for (b)(4) was performed from May 22, 2002 to June 4, 2002. The PQ of the (b)(4) was performed and is available on site.
Additional Performance Qualification Studies were executed to address the qualification of the system when changes were made. Each PQ was performed according to an approved protocol, and a final report was prepared that documented the successful completion of each study.

The original performance qualification of the purified water distribution system of (b)(4) met all the acceptance criteria outlined in the protocol. For this PQ study, a (b)(4) period of monitoring of the water was performed. The tests and acceptance criteria are provided in **Table 10**.

(b)(4)

Heating Ventilation and Air Conditioning System – Drug Substance ALK-Abello A/S

The air supply to the manufacturing area for the DS is (b) (4)

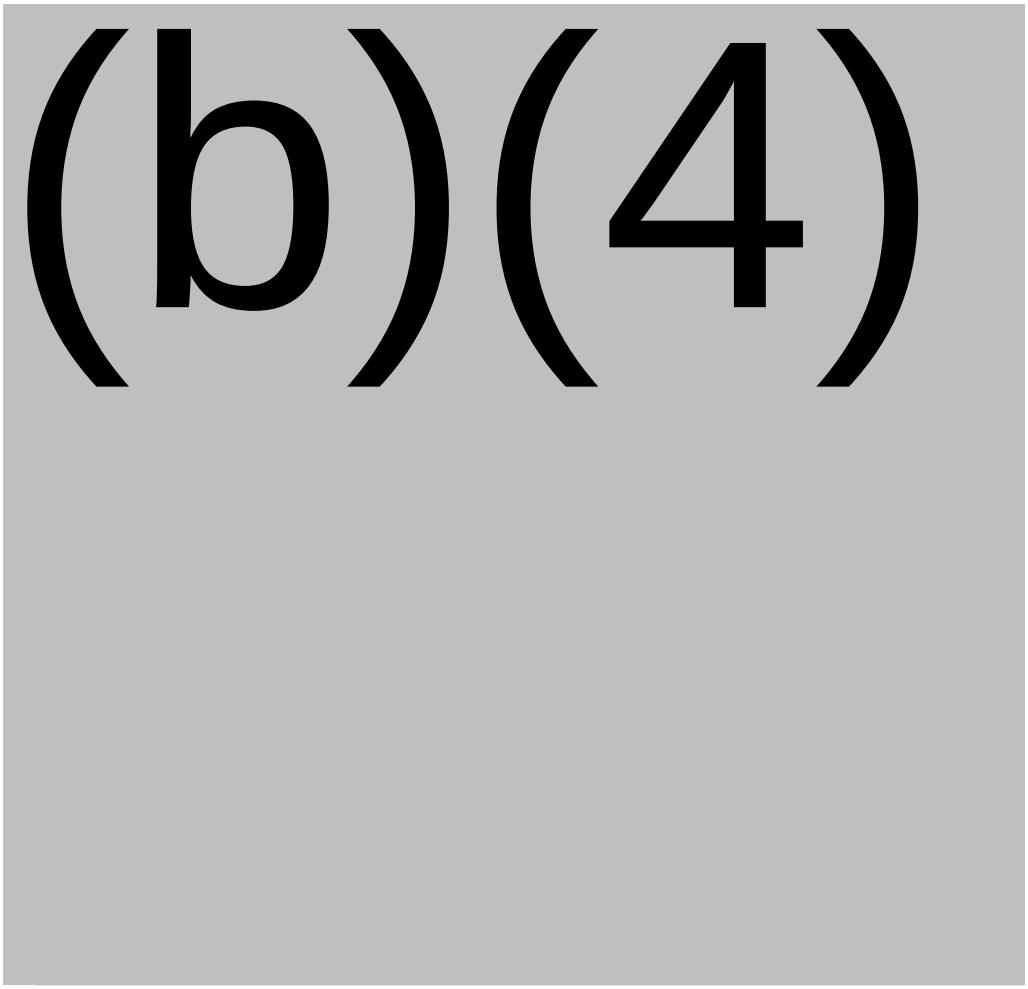
The IQ and OQ were certified as complete and successful. The PQ of air system (b)(4) was performed according to approved protocols. The performance qualification of HVAC System (b)(4) Unit met all the acceptance criteria outlined in the protocol. Airborne non-viable and viable particles were measured in operation to assure compliance with US and European requirements. Pressure differentials were monitored to assure compliance with the requirements and acceptance criteria of the protocols. Re-qualification of the HVAC system is conducted (b)(4) All rooms used in the production of the SCH 697243 DS are monitored routinely for viable and non-viable particulates.

The OQ was performed in March 2002 according to an approved protocol, and two final reports were prepared that documented the successful completion of the OQ. The reports “Operational Qualification Report of Qualification of Air Handling System (b)(4) dated October 2, 2002 and “Re-Qualification of Air Handling System (b)(4) dated January 13, 2003 summarize the results and are on file at ALK. OQ included at rest measurement of (b) (4) ,

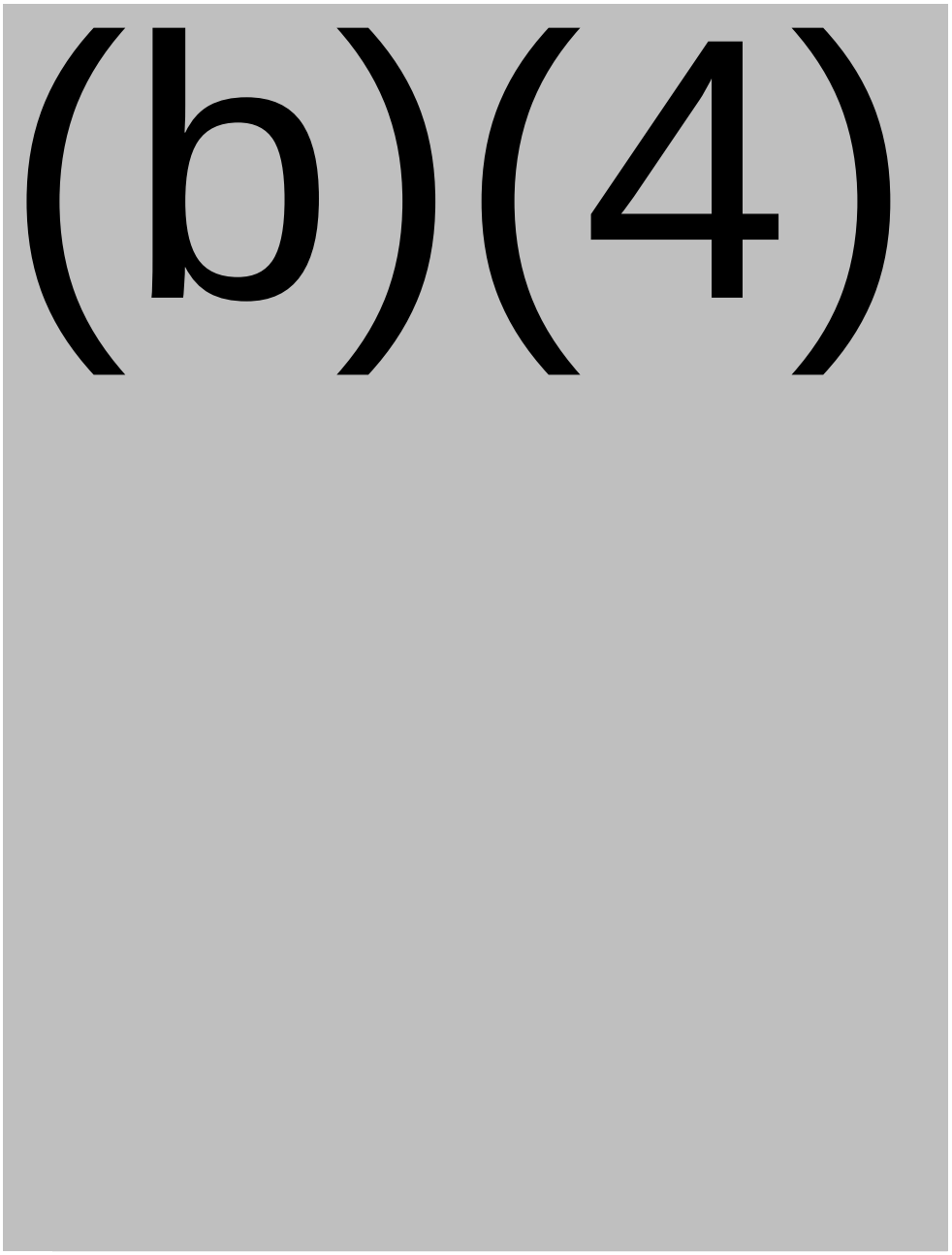
(b) (4) The operational qualification of HVAC system (b)(4) is certified as complete and successful. All deviations were evaluated and closed.

The PQ of the air system (b)(4) took place during the period July 1, 2002 to December 18, 2002. The PQ was performed according to approved protocols, and a final report was prepared that documented the successful completion of the PQ. The report "Performance Qualification of the Ventilation System," Dated January 23, 2003 summarizes the results and is on file at ALK-Abelló A/S. All tests were performed and executed by trained and qualified technical personnel. The performance qualification of HVAC System (b)(4) Unit met all the acceptance criteria outlined in the protocols. The HVAC system PQ took place over a (b)(4) period during which the environmental conditions were tested and monitored as outlined in the following. Airborne non-viable and viable particles were measured in operation to assure compliance with US and European requirements. Pressure differentials were monitored to assure compliance with the requirements and acceptance criteria of the protocols. For non-viable particle monitoring each location was sampled (b)(4) per run and each run was repeated (b)(4) on (b)(4) different days. Upper Confidence Level (UCL) calculations were performed according to (b)(4) . For viable sampling each site was sampled (b)(4) per run and each run was repeated (b)(in a period of a minimum of (b)(4) days. Pressure differentials were monitored for a (b)(4) period.

Additional qualifications of the HVAC have been performed as a result of modifications to the HVAC system. Table 13 outlines the additional studies conducted. In addition, a re-qualification is conducted (b)(4)



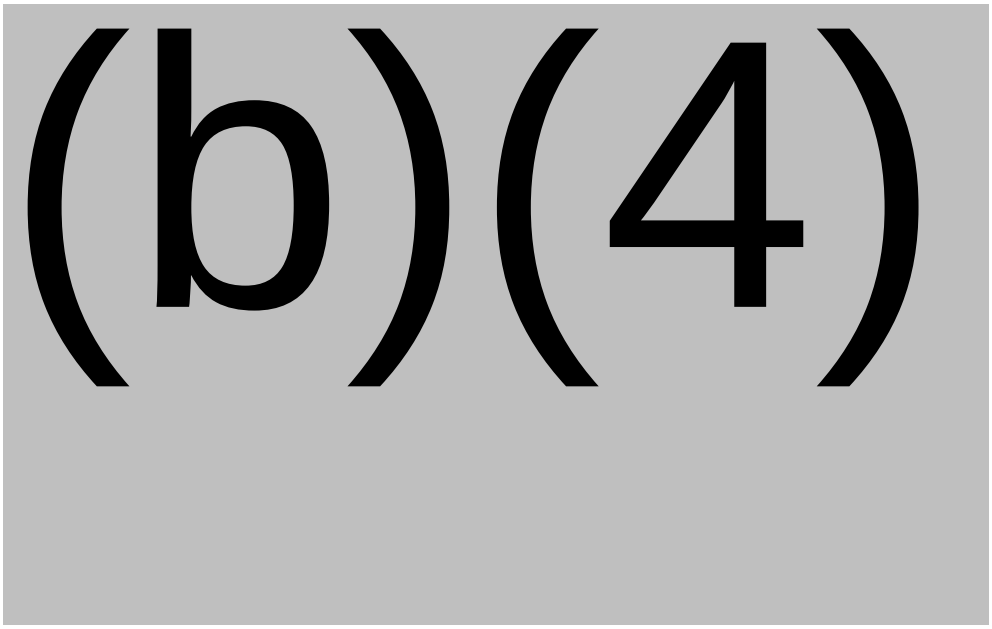
A rebuilding in the DS manufacturing room (room (b)(4)) was performed in 2006 to add a (b)(4). The PQ of this change took place during the period June 6 to June 9, 2006. The PQ was performed according to an approved protocol, and a final report was prepared that documented the successful completion of the PQ. The report "PQ report for re-qualification of premises in Pilot plant dept. (b)(4) after rebuilding of room (b)(4)," dated July 14, 2006 summarizes the results and is on file at ALK-Abello A/S. The performance qualification of HVAC System (b)(4) Unit appeared to meet all the acceptance criteria outlined in the protocols. Results for non-viable and viable particulates are shown in Table 14 and Table 15. Pressure was also monitored during this period and pressure met the acceptance criteria.



Contamination and Cross/Contamination – Drug Substance ALK-Abello A/S

The procedures designed to prevent contamination and cross contamination are described in Section 3.2.A.1.4 of the BLA. Precautions include use of dedicated equipment, cleaning according to written procedures, personnel gowning, and procedural controls. After production of DS with active material, all equipment used in the process is cleaned according to procedures specified for the equipment. Product contact equipment that is used for the manufacture of SCH 697243 DS is dedicated. (b)(4) .

The HVAC system supplying air to room (b)(4) is single pass air and the manufacturing room (b)(4) is maintained at negative pressure to the entry airlock (b)(4). Procedures are also in place to prevent contamination of the DS from the environment. These include controls of materials and personnel flows, materials handling procedures, control of equipment and adequate space in the rooms for the activities taking place, gowning procedures, , and cleaning and disinfection of rooms and areas after use. In addition, the facility is cleaned according to the established written procedures.



(b)(4)

For each sequence, the cleaning parameters are: (b)(4)

(b)(4)

SCH 697243 Commercial Drug Substance Manufacturing Process Validation (b)(4)

This prospective process validation at the (b)(4) scale was performed for the process performed in Room (b)(4) of the commercial facility.

The following three consecutive batches were executed as shown in **Table 11**.

(b)(4)

(b)(4)

(b)(4)

Shipping Validation Drug Substance

A study validating that the shipping procedures are adequate to maintain acceptable temperature requirements for the DS (b) (4) to Catalent UK Swindon Zydis Ltd. in UK was performed using placebo (b)(4) . The acceptance criteria for the shipping validation are outlined as follows:

- (b)(4)

Results indicated that all acceptance criteria were met. The temperature in the containers remained below (b)(4), and the (b) (4) remained (b)(4)

DS will be tested for (b)(4)

Drug Substance Release Specifications

1 page determined to be not releasable: (b)(4)

(b)(4)

(b)(4)

Container Closure Drug Substance

(b)(4)

(b)(4)

Drug Product Facilities and Equipment – Catalent Pharma Solutions

Names, addresses, and responsibilities of the manufacturers of SCH 697243 drug product (DP).

Table 1 Manufacturers of SCH 697243 Drug Product		
Name and Address of Manufacturer	**Responsibilities**	**US Registration Number/License Number**
Catalent UK Swindon Zydis Ltd. 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
ALK-Abelló A/S Bøge Allé 6-8 DK-2970 Hørsholm Denmark	(b)(4)	US Registration Number 3002806343 US License No. 1292
(b)(4)	(b)(4)	US Registration Number (b)(4)
Merck, Sharp & Dohme Corp. (a subsidiary of Merck & Co., Inc.) (b)(4)	(b)(4)	US Registration Number (b)(4) US License No. (b)(4)

The SCH 697243 Drug Product (DP) is a white to off-white circular sublingual tablet, with a de-bossed round detail on base, designed to rapidly disintegrate under the tongue. The tablets are packaged in 10-tablet all aluminum blister packs (trade presentation) composed of a blister film and a lidding foil. The lidding foil has been designed to be peeled back from the blister film to allow the removal of the tablets.

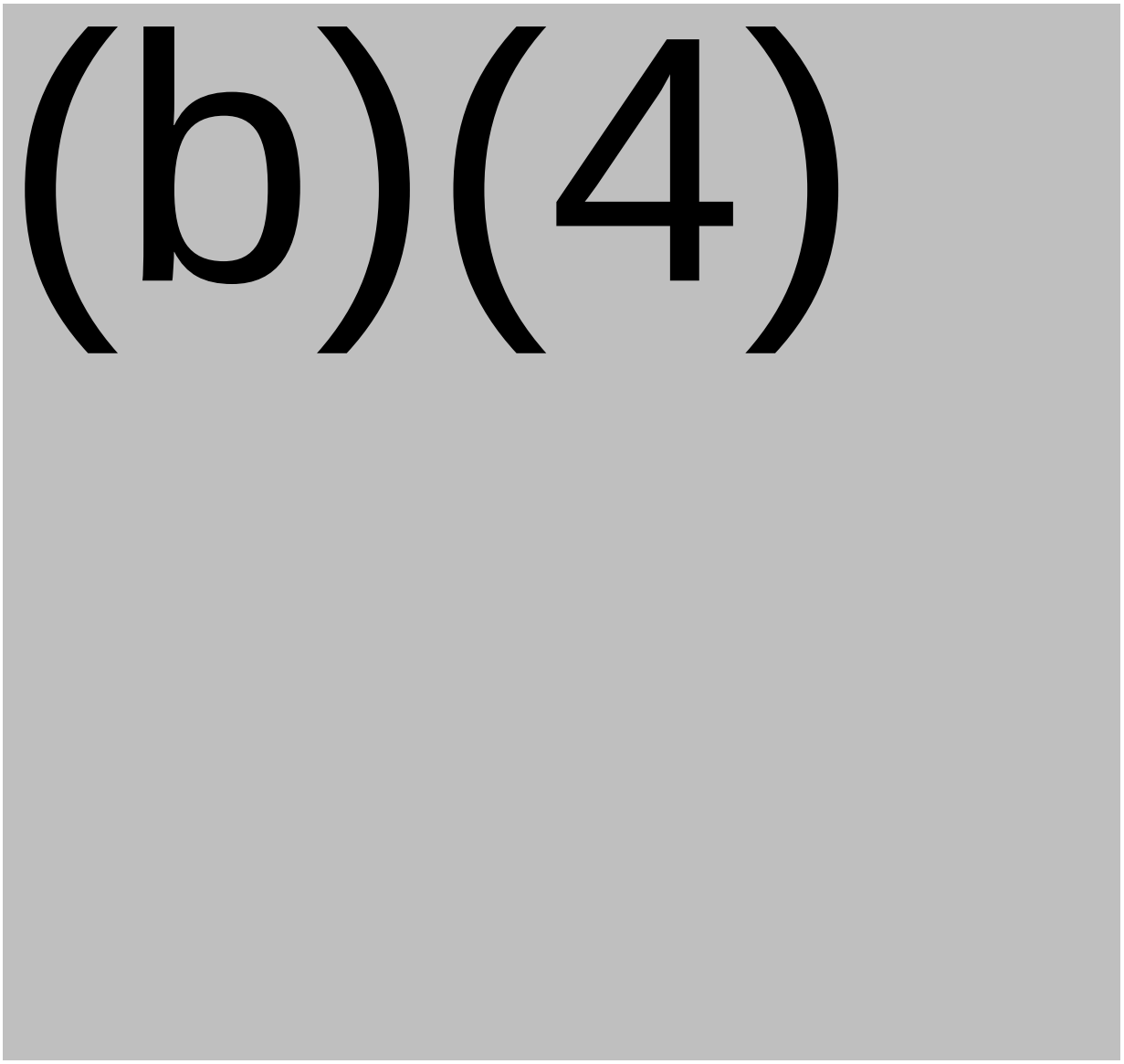
Table 1 provides the batch formula for the drug product (DP), SCH 697243 Tablet, 2800 BAU (bioequivalent allergy unit). DP batches are manufactured at (b)(4) scale per Table 1. Since the DP is formulated based on the potency of the DS, the actual quantity of (b)(4) of Timothy Grass extract (SCH 697243 Drug Substance) varies on a lot to lot basis. The amount of grass pollen extract (b) (4) needed for a (b)(4) batch would typically be (b)(4) . Each bulk (b)(4) DP batch can theoretically produce (b)(4) SCH 697243 sublingual tablets.

Table 1 Quantitative Composition of SCH 697243 Tablet, 2800 BAU

Ingredient	Reference to Quality Standard	Function	Amount per Tablet
SCH 697243 Drug Substance	Standardized in SQ-T to In House Reference Standard	Active ingredient	2800 BAU
(b)(4)			
Gelatin (Fish (b)(4)	(b) (4)	(b)(4)	
Mannitol		(b)(4)	
Sodium Hydroxide			
Purified Water	(b)(4)	Vehicle	(b)(4)
(b)(4)			
(b) (4)			

The manufacturing process flow for the SCH 697243 Drug Product is noted below.

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



Process Validation and/or Evaluation Drug Product

The DP may be performed on either Catalent (b)(4) (see Section 3.2.P.3.3 of the BLA). (b)(4) share the same operating principles, (b)(4) .

(b)(4)

Three consecutive batches were manufactured on (b)(4) (using freeze driers (b)(4) freeze driers (b)(4)). All (b)(4) batches met the validation acceptance criteria including all release and in process testing requirements

The proposed shelf life for the SCH 697243 DP is 36 months from the date of manufacture for storage at USP controlled room temperature in the final DP container. The lots were studied at 25°C (b)(4) °C (b)(4) for up to 36 months.

1 page determined to be not releasable: (b)(4)

(b)(4)

Finished Product Testing Results

Table 1 Release and Shelf Life Specification for SCH 697243 Tablet, 2800 BAU		
Test	**Acceptance Criteria**	**Methods**
Appearance	White to off-white circular freeze dried units with a debossed, round detail on base	Visual Inspection
(b)(4)		
Identity, (b)(4)	(b)(4)	
Identity and Potency, (b)(4)	(b)(4)	
Potency Relative Potency (b)(4)	Conforms to 2800 BAU (b)(4)	Competition ELISA (b)(4)
Water content	(b)(4)	
Microbiological Examination:		
Microbial Enumeration (b)(4)	(b)(4)	
Absence of Specified Microorganisms: (b)(4)	(b)(4)	

Primary Packaging

The tablet count and package size of the blister card is as follows: 1 tablet per cavity, 10 tablets per blister card.

(b)(4)

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The blister forming film consists of (b)(4)

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The lidding foil is composed of a (b)(4)

The secondary packaging does not impact the stability of the product. Secondary packaging for blisters may include re-closeable plastic containers, folding cartons, and inserts or other non-product contact literature or containers.

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)

Drug Product Facilities and Equipment

The SCH 697243 DP is manufactured in non-dedicated areas (b)(4) using non-dedicated equipment.

General features of the SCH 697243 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 SCH 697243 DP are controlled not classified (CNC) areas as is appropriate for the manufacture of a non-sterile solid oral dosage form. Both (b)(4) are serviced by their own dedicated HVAC systems.

Each (b)(4) includes its own (b)(4) . Equipment is described in Section 3.2.A.1.4 of the BLA.

(b)(4)

The manufacturing areas of the (b) (4) building used to manufacture the DP are supplied by (b)(4) different HVAC systems, (b)(4) . A block diagram of each air system was provided in Attachment 1, Section 3.2.A.1.3 of the BLA.

The HVAC systems are monitored on a building monitoring system (BMS) for pressure, 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 freeze drying, the moisture content of the tablets will be affected by the humidity of the environment prior to sealing. No particulate monitoring is required for these areas since these are controlled but not classified areas.

Environmental monitoring in the SCH 697243 DP production rooms in the (b) (4) building at Catalent will be carried out as follows. Validated EMS systems are installed on (b)(4) . However, (b)(4) 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®. (b) (4)

Equipment Cleaning

For the SCH 697243 process there are two types of equipment that the SCH 697243 is in contact with the (b)(4) . Catalent considers all other equipment non-product contact.

(b)(4)

Equipment Cleaning Validation

Catalent cleaning validation for removal of SCH 697243 active covered the product contact equipment. This included the (b)(4) validation of the removal of other product actives is also performed to assure no cross contamination of SCH 697243 would occur. The assumption is made that the (b) (4) since the equipment is in contact with (b)(4) . Cross contamination of SCH 697243 could occur in the (b)(4)

(b)(4)

For all cleaning validation studies, the primary assessment was a thorough visual inspection of the processing equipment under test. No visual contamination from (b)(4) was allowed. Catalent groups equipment into classes considered equivalent for cleaning validation purposes (family approach). Information regarding equipment equivalence is documented in the relevant Operational Qualification summary report for the particular item of equipment. In these cases, cleaning validation is only required for (b)(4) in each group. Once successfully validated, all equivalent items of equipment in a group can be deemed validated. Hence there is no requirement to separately validate each item of equipment in a group for any one particular product.

For the generation of acceptance limits, the value used for the maximum daily intake is defined (b)(4)

Considering that the equipment used and the cleaning methods for that equipment are essentially constant, cleaning validation generally concentrates on the (b)(4)

For removal of drugs, the criterion is as follows: the drug must be removed to a level such that

not more than (b)(4)

The acceptance criterion will be calculated based on (b)(4)

Summary of Cleaning Validation for Removal of SCH 697243 from Product Contact Equipment

Validation of the removal of the SCH 697243 active from the product contact equipment, including the (b)(4) was performed. Swab samples were taken and tested for SCH 697243 active using a (b)(4) assay performed by ALK-Abello A/S. The results for this assay are reported as an (b)(4)

Table 2 summarizes the cleaning validation results.

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

(b)(4)

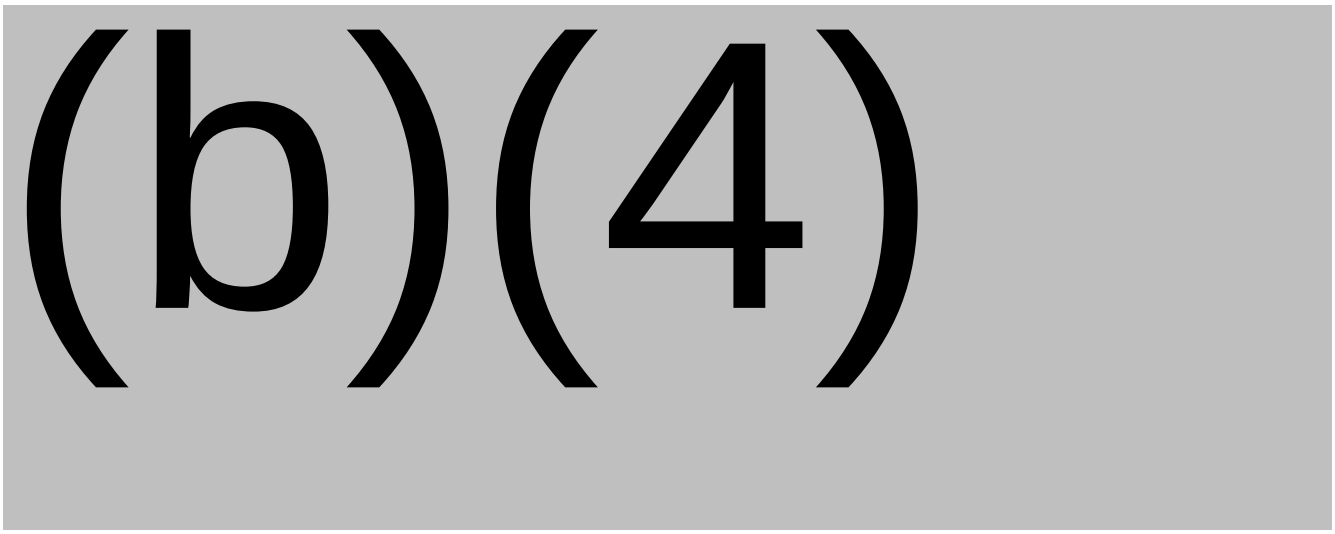
Water System

Purified water (PW) is used during the production of the SCH 697243 Drug Product (DP) for preparing excipients for the DP solution, and cleaning and rinsing of equipment. The PW generated meets the requirements for PW (b)(4).

Freeze Dryers

There are (b)(4) freeze dryers for (b)(4) freeze dryers for (b)(4) (Table 1). Each (b)(4) freeze dryer (b)(4) Each (b)(4) freeze drye (b)(4) . All (b)(4) freeze dryers are of a similar design and operating principle, and use an identical Catalent proprietary control system (supplied by (b)(4)

. All freeze dryers were fully qualified prior to use for the validation of SCH 697243 DP manufacturing process.



1 page determined to be not releasable: (b)(4)

(b)(4)

Environmental Assessment

Merck is requesting a categorical exclusion from the preparation of an environmental assessment (EA) for Timothy Grass (*Phleum pratense*) Extract 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.

The following information requests were identified during the filing review and are the subject of a subsequent addendum review memo.

1. Concerning (b)(4) .

- (b)(4)

2. Please provide your study design and data to support the hold time from the end of (b)(4)

3. You indicate that (b)(4) Tests have been measured for (b) (4) Drug Substance batches. One of the (b) (4) batches failed to meet the acceptance criteria and was rejected (Batch (b)(4)). Please provide the investigation and follow up regarding the reject of Batch (b)(4) .

4. It appears that the (b)(4) Test is only performed on the Drug Substance at release. Please clarify if any in-process (b)(4) is performed for the Drug Substance. If in-process monitoring is not performed please provide a justification and risk assessment for not monitoring (b)(4) during production.

5. Please clarify if a (b)(4) Test is performed on the Drug Substance once it is received at Catalent.

6. Concerning the (b)(4) storage containers (b)(4) used to shipment of Drug Substance.

- Please clarify is these containers are single-use or re-used.

- Are the (b)(4) storage containers (b)(4) received clean, and if so how are they assessed for cleanliness prior to use?

7. Please provide validation data for the (b)(4) assay used to assess integrity of the aluminum blister cards.

8. Please provide data from the lyophilization cycle used for the SCH697243 Drug Product qualification lots that includes: (b)(4) of lyophilization.

9. Please provide complete OQ and PQ protocols and results for freeze driers (b)(4) and freeze driers (b)(4). Please include any testing and data confirming that all (b)(4) freeze dryers are of similar design and operating principle, and detailed explanation of any deviations which occurred during the validation.

10. Please provide the (b)(4) for the SCH 697243 Drug Product.

11. Please provide complete OQ and PQ protocols and results for the following equipment:

- (b)(4)