DEPARTMENT OF HEALTH & HUMAN SERVICES
FDA/CBER/OVRR/DBPAP

Memorandum

Date: March 31, 2014

To: File, STN 125473

From: Taruna Khurana, PhD. Product Reviewer
Laboratory of Immunobiochemistry, OVRR/DBPAP

Through: Ronald L. Rabin, M.D. Chief
Laboratory of Immunobiochemistry, OVRR/DBPAP

Applicant: Merck Sharp and Dohme Corp. U.S. License 0002

Subject: CMC Review and Approval Recommendation Memorandum

Reference: IND13143

Overall conclusion
Based on the CMC review of the original BLA submission and related amendments, I recommend approval of GRASTEK 2800 BAU tablets for the treatment of grass pollen-induced allergic rhinitis or conjunctivitis confirmed by positive skin test or in vitro testing for pollen-specific IgE antibodies for Timothy grass and cross-reactive grass pollens in persons 5 through 65 years of age.

Materials Reviewed
125473/000 Original BLA Modules 2 and 3 (January 25, 2013)
125473/002 (May 3, 2013)
125473/006 (July 19, 2013)
125473/008 (September 20, 2013)
125473/009 (October 23, 2013)
125473/010 t (November 11, 2013)
125473/019 (February 26, 2014)
125473/022 (February 28, 2014)
125473/023 (March 6, 2014)
125473/024 (March 12, 2014)
125473/026 (March 14, 2014)

Summary/Background
On January 25, 2013, Merck Sharp and Dohme Corp. submitted a Biologics License Application (BLA) for Timothy Grass Allergen Extract Tablet for Sublingual use. The Trade name for this product is GRASTEK. GRASTEK is a fast-dissolving, sublingual tablet indicated for sublingual immunotherapy for the treatment of grass pollen-induced allergic rhinitis or conjunctivitis confirmed by positive skin test or in vitro testing for

pollen-specific IgE antibodies for Timothy grass and cross-reactive grass pollens in persons 5 through 65 years of age. Each tablet contains 2,800 Bioequivalent Allergy Units (BAU) of the drug substance, determined by comparison against a CBER reference extract of Timothy grass pollen (*Phleum pratense*).

GRASTEK tablets are circular, white to off-white, with a debossed round detail on one side. The product is marketed under the trade name GRAZAX in Europe since 2006 by ALK-Abello Horsholm, Denmark. The clinical program (safety and efficacy) is discussed in reviews of IND 13143.

The drug substance used in the manufacture of the tablet is standardized Timothy grass pollen extract. SCH697243/MK-7243 is the designated laboratory code name for Timothy grass pollen extract. The drug substance is manufactured at ALK Abello, Denmark. The Drug Product is manufactured at Catalent Swindon, UK. The drug substance is a (b)(4) of Timothy grass pollens in aqueous (b)(4)

Review of source material

3.2.S.2.2 Manufacturing Process/Process Control
The drug substance is manufactured and tested by ALK-Abello A/S, Denmark. The (b)(4) is performed by (b)(4). The source material is supplied by (b)(4). in the U.S.A. The source material is pollen from Timothy grass that is collected from grass (b)(4) conditions in the USA. Grass pollens are mostly collected by (b)(4)

- (b)(4) .
- (b)(4)
-

Pollen lots are released by (b)(4) as per set specification listed in Table 1 below:

(b)(4)

Processing of source material

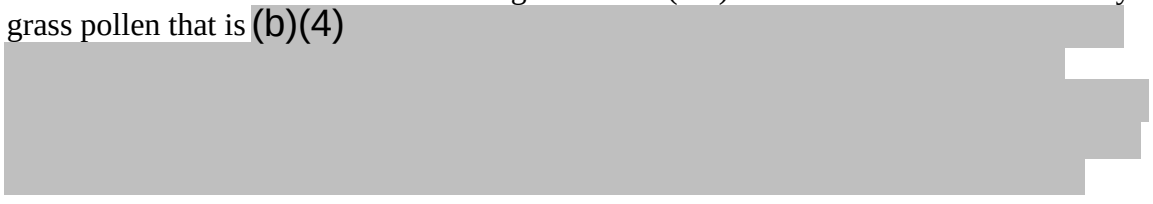
The pollen source material manufacturing process is summarized below.

(b)(4)

(b)(4)

Review of Drug Substance

As indicated earlier the GRASTEK drug substance (DS) is manufactured from Timothy grass pollen that is (b)(4)



3.2.S.2.2 Description of Manufacturing Process
The manufacturing and testing of the DS are performed at the ALK-Abelló A/S, Hørsholm, Denmark facility which is a commercial cGMP facility. The commercial

manufacturing batch size for the DS is (b)(4). The DS manufacturing steps are performed under appropriate levels of cGMP controls. The manufacturing steps and controlled parameters are summarized as follows:

(b)(4)

3.2.S.2.3 Control of Materials

(b)(4)

3.2.S.2.4 Control of Critical Steps and Intermediates

Manufacturing process parameters are evaluated for criticality. Various ranges were examined to determine the proven acceptable ranges (PAR). A study was performed to evaluate the parameters that could influence the quality of the DS, and from this study (b)(4) parameters were designated as critical. The rest were designated and controlled as non critical parameters.

- (b)(4)

- (b)(4)

The effects of various parameters on the quality of the DS were analyzed using the following methods:

- (b)(4)

(b)(4)

3.2.S.2.5 Process Validation and Evaluation

During process validation and evaluation (b) (4) commercial scale batches of the DS ((b)(4)) were manufactured in (b)(4) at ALK Abello A/S's commercial scale facility using equipment and qualified and trained personnel intended for a commercial manufacturing process. These process validation batches were not further processed into DP. Instead, (b) (4) additional DS batches (b) (4) were manufactured after the initial DS process validation lots and these (b) (4) batches were processed into clinical DP lots for use in the P08067 Phase 3 clinical study.

ALK validated the DS process in May/June 2005 before the European launch of GRAZAX. (b)(4) DS lots manufactured from August 2007 to October 2008 were used in the manufacture of the drug products lots prepared in support this BLA. These (b)(4) DS batches, which were produced prior to US process validation, batches met the US release specifications that are tighter than EU specifications for most of the quantitative tests. These batches were manufactured using the same manufacturing process and same test methods were used for analysis.

During the process validation studies, the following various parameters were verified that could affect the product quality:

- (b)(4)

DS samples were analyzed using these parameters. All validation batches met the acceptance criteria.

(b)(4)

Analytical results for three validation batches met the release specifications.

(b)(4)

3.2.S.2.6 Manufacturing process development

The manufacturing process for the DS includes (b)(4) . Various adjustments and changes that were made during process development are summarized as follows:

1. (b)(4)

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

The DS is a (b)(4)

3.2 S.4 Control of Drug Substance

The release and shelf life specifications for the final drug substance are listed in Table 3 below.

Table 2 – Release and Shelf Specifications for the GRASTEK Drug Substance

Test	Acceptance Criteria	Methods
(b)(4)		

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

The batch analysis results for (b)(4) DS batches consisting of clinical and commercial European Union (EU) batches and 3 process validation batches were provided. The DS release specifications were established based on data from (b)(4) clinical and commercial EU batches including clinical Phase 3 batches.

Developmental and clinical batches of the DS were analyzed using (b)(4)

(b)(4) for the developmental batches were reported. All the batches met the acceptance criteria.

(b)(4) commercial US DS batches manufactured under full cGMP between April 2011 and May 2013 met all of the established acceptance criteria.

3.2.S.4.5 Justification of Specifications

(b)(4)

(b)(4)

3.2.S.7 Stability

Three batches of the DS (Batches (b)(4)) were placed under stability study on June 2005. The batches were manufactured using (b)(4) process scale at ALK-Abello A/S facility, Horsholm, Denmark. The batches were stored at (b)(4) . Over a period of (b)(4) stability samples were tested for:

- (b)(4)

The batches were stored for at (b)(4) . Samples were tested at every (b)(4)

All of the (b)(4) tests results obtained for the (b)(4) of the stability study remained within specifications. (b)(4)

(b)(4)

Review of Drug Product

The drug Product (DP) is a white to off-white circular sublingual tablet, with a debossed round detail. The tablet is designed to rapidly disintegrate under the tongue (<10 sec). Each tablet contains 2800 Bioequivalent Allergy Units (BAU) of Timothy Grass extract, which is equivalent to 75,000 SQ-T. The potency of the tablet in BAU is determined using FDA competition ELISA assay relative to FDA reference material of standardized Timothy grass. The tablet formulation consists of (b) (4) of DS dispersed within the fast dissolving matrix of Gelatin and Mannitol. The tablet is manufactured using (b)(4) by Catalent Pharma Solutions, Swindon, UK. Final formulation of the tablet is indicated in section 3.2.P.2.2.

3.2.P.2.2 Pharmaceutical Development

For manufacturing of the DP the DS is shipped in (b) (4) from ALK-Abello, Denmark to Catalent, Swindon, UK (b)(4) (b) (4) fish gelatin are added for (b)(4) . Mannitol is included in the formulation for (b)(4) is used during production as a vehicle for the DS and the excipients. Sodium hydroxide is used to (b)(4)

Formulation Development

Formulation development of the GRASTEK was completed in (b)(4) :

- (b)(4)

(b)(4)

(b)(4)

GRASTEK final formulation

Ingredients	Final Formulation
Timothy grass pollen extract	75,000 SQ-T (equivalent to 2800 BAU)
Fish Gelatin, (b)(4)	(b)(4)
(b)(4) (b)(4)	(b)(4)
Mannitol	(b)(4)
Sodium Hydroxide	(b)(4)
(b)(4)	(b)(4)
(b)(4)	(b)(4)

(b)(4) (b)(4)

Manufacturing Process Development-
Manufacturing of the DP takes place in (b)(4) as follows:

- (b)(4)

(b)(4)

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

(b)(4)

3.2.P.3 Drug Product Manufacturing Process

The commercial manufacturing scale for a DP batch is (b)(4). For each commercial scale batch of the DP typically (b)(4) DS (b)(4) is used. Each bulk of DP batch produces (b)(4) tablets of 2800 BAU each.

Description of manufacturing process and process control-

The manufacturing is performed (b)(4)

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

(b)(4)

3.2.P.3.4 Control of Critical Steps and Intermediates

The set points and acceptable ranges of critical parameters were determined during manufacturing process developmental studies.

(b)(4)

Various in-process tests are in place to achieve acceptable quality of the finished DP. The tests are as follows:

- (b)(4)

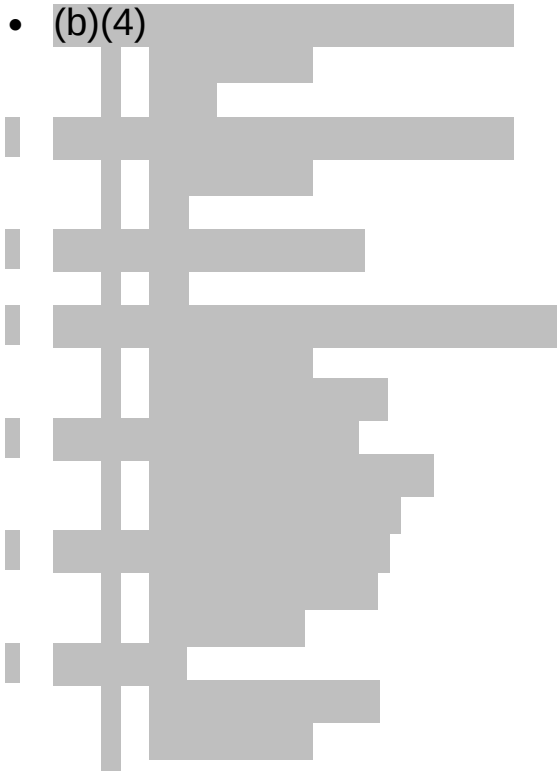
3.2.P.3.5 Process Validation and Evaluation

(b)(4) DP batches manufactured in 2009 and 2010 were evaluated during process validation. The DS for these batches were manufactured at a (b)(4) scale on (b)(4) using the commercial process at ALK/Abello A/S. (b)(4) share the same operating principles. The (b)(4) used are manufactured by the same

supplier, of the same design, materials of construction, and work on the same operating principles.

The following critical process parameters for manufacturing steps were verified for all process validation batches:

- (b)(4)



The critical in process controls were measured in all the PV batches. The (b)(4) . Process validation batches met the acceptance criteria of additional tests performed during (b)(4) , and freeze drying

All the batches complied with the (b)(4) test.

All the batches complied with the acceptable ranges or values of all critical process parameters. The validation batches also met the acceptance criteria of release and shelf life specifications.

(b)(4) The results were acceptable.

3.2.P.4 Control of Excipient

Mannitol, (b)(4) , sodium hydroxide and gelatin are tested as per (b) (4) requirements. The (b)(4) of gelatin (b) (4) are

monitored as a routine QC testing. The in-house specification for (b)(4) and for (b)(4) fish gelatin the (b)(4).

3.2.P.5 Control of Drug Product

Drug product release and shelf life specifications for 2800 BAU tablet is indicated in table below.

Table 3: GRASTEK sublingual tablet specifications

Test	**Acceptance Criteria**	**Methods**
Appearance	White to off-white circular freeze dried units with a debossed, round detail on base	Visual Inspection
Disintegration	≤10 seconds	(b)(
Identity, Protein profile	(b)(4)	(b)(4)
Identity and Potency, (b)(4)	(b)(	(b)(4)
Potency Relative Potency (b)(4)	Conforms to 2800 BAU (b)	Competition ELISA(b)(4)
Water content	(b)(4)	(b)(4)
Microbial Enumeration • (b)(4) • (b)(4)	(b)(4) (b)(4)	(b)(
Absence of Specified Microorganisms: • (b)(4)	(b)(4)	(b)(

(b)(4)

For a full description of analytical procedures please refer to section 3.2.P.5.3, validation of analytical procedures. We requested that the firm include a (b)(4) test to

(b)(4)

3.2.P.5.3 Validation of Analytical Procedures

The firm provided validation data in support of the following analytical procedures:

- Disintegration Test (b)(4)
- Identity (b)(4)
- Potency (CBER-ELISA)
- (b) (4) (b)(4)
- (b) (4) (b)(4)
- Microbiological quality (b)(4)
- Water content (b)(4)

Validation of disintegration-

(b)(4)

Validation of the CBER ELISA-

The validation of the FDA competition ELISA was performed as per FDA Docket #94N-0012 (1993 CBER Laboratory Methods Manual). Precision, specificity, linearity, and accuracy results of the tested batches met the acceptance criteria (b) (4) . For further discussion regarding the FDA competition ELISA please refer to section 3.2.P.5.6.

(b)(4)

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

(b)(4)

Validation of water content-
The water content in the tablet is measured using (b)(4) The method is found suitable for its intended use.

3.2.P.5.4 Batch Analysis
Total of (b)(4) batches including clinical, commercial and three process validation batches were used for establishing specifications for the DP. FDA competition ELISA data was provided for (b)(4) clinical batches and all batches met the specification of 2800 BAU with a relative potency ranging from (b)(4) . All the clinical batches were tested for appearance, identity, water content and disintegration and met the acceptance criteria for these assays. The batches also met with the acceptance criteria of (b)(4) . All the batches tested for microbial limits were within acceptable limits for (b)(4) and absence for specified organisms such as (b)(4) was demonstrated.

3.2.P.5.6 Justification of Specifications
The justification for the methods selected for establishing the GRASTEK DP release specification and acceptance limits established for quality control provided in the BLA are adequate. The methods with justification of specifications are summarized below:

Appearance - Physical state and color of DP are determined by visual inspection. The test is performed during release at Catalent Pharma Solutions and during stability testing of DP at ALK-Abello A/S. The acceptance criteria at release and shelf life are white to off-white, circular freeze dried units with a debossed, round detail on one end. The color of the DP is based on the color of DS that is used for DP manufacturing.

Identity ((b)(4)

Identity and Potency by (b)(4)

(b)(4)

Potency by (b)(4)

Potency by FDA competition ELISA-. Results from stability studies demonstrated compliance with the FDA acceptance criteria for up to 36 months of storage at 25°C/(b)(4) . Analysis indicated no upward or downward trend during the storage period. The proposed acceptance criterion conforms to 2800 BAU. The release and shelf life specifications remain the same. The relative potency of the DP is determined in accordance with current FDA competition ELISA method described in FDA Docket # 94N-0012 (b) (4) . The FDA reference extract and reference serum pool are used in this assay and relative potency of the tablet is determined in comparison to the FDA reference extract. The results are reported in BAU. The acceptance criteria for a valid test reference and control are-

- (b)(4)

If the above criteria are met by reference and samples, the relative potency of the samples is calculated. (b)(4)

The FDA reference is (b)(4)

Product sample is prepared using (b)(4) instead of (b)(4) . On September 16, 2013 through a CMC Information Request FDA requested that per the current FDA competition ELISA procedure the wash solution should be PBS containing 0.05% Tween-20. The firm was requested to align their wash and dilution buffer composition to comply with FDA's current method of competition ELISA. On September 30, 2013 the firm responded that they would align the composition of the wash buffer per FDA's current method. The firm also indicated that throughout the development of the GRASTEK drug product under IND 13143 (b)(4)

(b)(4) was used as the wash and dilution buffer. This method was validated and used as the release method for clinical trial materials, process validation and launch lots, as well as, ongoing stability studies. The firm proposed to align the wash and dilution buffer post-approval immediately following the launch batches.

October 23, 2013 in response to CMC information request #34 the firm indicated that they have initiated studies to align the wash and dilution as per the current FDA competition ELISA procedure for testing of the Timothy Grass Pollen Allergen Extract drug product post approval. An experiment was performed using a commercial scale DP batch. (b) (4) ELISA plates were run with the procedure using (b) (4) and (b) (4) ELISA plates were run with the aligned wash and dilution buffer per current FDA procedure using PBS containing 0.05% Tween-20. This initial experiment showed no significant difference in the results after changing buffers as reflected by the relative potency values. The data were provided for review. The firm indicated that the revised assay will be implemented after the completion of validation using (b)(4) batches (b)(4) times each on (b) (4) plates. The firm will complete this study post approval.

The relative potency data for (b)(4) ELISA runs using (b)(4) were (b)(4) The relative potency data for (b)(4) ELISA runs using PBS with 0.05% Tween 20 were (b)(4). The system suitability requirements, sample requirements and slope values were also comparable for both the conditions. The reference, control and sample curves were parallel and similar for both methods. CBER accepted the proposal.

Water content- (b)(4) method is used for determining moisture or water content that depends on (b)(4)

Disintegration time-A modified (b)(4) method is used for disintegration testing of the DP. Merck's proposal of using disintegration test for the release and stability study was accepted by the Agency on October 29, 2008. Disintegration time for the tablet is ≤10 seconds.

(b)(4)

(b)(4)

3.2.P.6 Reference Standards or Materials
The firm has used its own IHR for the (b) (4) assays. FDA reference is used only for FDA competition ELISA for relative potency measurement.

3.2.P.8 Drug Product Stability
Merck proposed a shelf life of 36 months from the date of manufacture of the DP for storage at 20-25°C with excursion permitted to 15°C-30°C. The proposed shelf life of 36 months is based on data from three primary stability batches (Batches (b)(4)) produced using the commercial process at the commercial scale (b)(4) on (b)(4) The studies were configured as follows:
1. 36 months under normal storage conditions of 25°C (b) (4) /(b)(4)
2. (b) (4) under accelerated storage conditions of (b) (4)

An additional (b)(4) of stability data for three PV batches from (b)(4) (Batches (b)(4)) and (b)(4) (Batches (b)(4)) upon storage at 25°C(b) (4)(b)(4) were also

provided. On October 22, 2013 the firm provided 36 months stability data for all PV batches.

The stability studies were conducted as per (b)(4) . One commercial batch (Batch(b)(4)) was also tested for (b)(4) The data supports 36 months of shelf life of GRASTEK when stored at recommended storage conditions.

Testing intervals were dependent on the length of the study and the stability parameter being studied. Therefore, not all tests were performed at every time point. Parameters assessed were:

- Appearance
- Disintegration
- Identity ((b)(4))
- Potency ((b)(4)
- Potency ((b)(4))
- Water content
- Microbiological Quality

(b)(4)

Long term and accelerated stability data met all specifications and were found to be acceptable.

Appearance-No change in the appearance of tablets was observed at any of the stability time points and stability conditions tested. The color of the tablets complied with the acceptance criterion. During stability testing at (b)(4) a few tablets had an atypical appearance (shrunken). The problem was found to be with the sealing plates that were not flat enough and led to ingress of moisture in the pack and shrunken tablets. The plates were repaired and all the blister packs of these stability batches were visually re-inspected.

Identity test (b)(4)

.

(b)(4)

During the stability studies, a new in-house reference standard (b) (4)) was implemented at the 6 month and 36 month time points and at 15 month time point for the (b)(4) process validation batches. To enable accurate trending throughout the stability study and to identify true changes in the stability profile throughout the shelf-

life, a correlation factor is used. The new IHR is qualified using(b) (4)

Relative Potency (FDA competition ELISA) - All results complied with acceptance criteria and no meaningful trends were observed over the storage period at either storage condition. Lower relative potency results were observed for PV stability batches at 36 months. Data generated for the FDA competition ELISA were re-examined and invalidated as potency of two GRASTEK batches (Batch (b)(4)) were below the acceptance criteria ((b)(4)). During the firm's investigation they found that the root cause was a specific lot of detection antibody and the results generated using that lot of detection antibody were invalidated. The samples were re-evaluated at (b)(4) using another lot of qualified detection antibody and the results were found to be similar to relative potency results before 36 months indicating no trend. Two corrective and preventive actions (CAPA) were initiated as preventive measure for acceptable performance of detection antibody.

Water Content by (b)(4) - Water content complied with acceptance criteria for DP batches stored at the long-term storage condition (25°C/(b)(4)) and at the accelerated storage condition ((b)(4)). The slight increase in water content observed at various time points was still within the acceptance limit of (b)(4).

Disintegration- All the tablets disintegrated within 10 seconds with an average of 1-2 seconds.

Microbiology-Result for the microbial enumeration ((b)(4))) and absence of specified microorganisms complied with the acceptance criteria.

(b)(4)

Samples are tested for appearance, disintegration, water content, competition ELISA, (b)(4) . All samples met the acceptance criteria.

3.2. R Regional Information

3.2.R.1.S Executed batch record – An executed batch record was provided for one PV batch of the DS ((b)(4)). The batch was manufactured at commercial scale ((b)(4)) using commercial process.

3.2.R.1.P Executed batch record – An executed batch record is provided for one PV batch of the DP ((b)(4)). The batch was manufactured at commercial scale ((b)(4)) at the commercial site by intended commercial process.

3.2.R.3 Methods validation package - (b)(4) representative sample kits containing the GRASTEK DS and DP Tablet at 2800 BAUs and all reference standards were prepared

for CBER use if required. Details of validation of all analytical methods used were provided in the BLA and are discussed elsewhere in this memo.

CMC Product Information Request (IR)

Primary CMC product issues and findings identified during the review of the original BLA submissions were transmitted to the firm on September 16, 2013 as an Information Request. The responses received from the firm on October 23, 2013 are in italics, Final outcome of the IR responses are noted in bold.

3.2.S.2.2- Description of Manufacturing Process/Process Control

1. Section 2.0, Processing of source material- (b)(4)

   (b)(4)

   Response is acceptable.

2. Section 2.0, Processing of source material- (b)(4)

   .

   (b)(4)

   Response is acceptable.

3. Section 2.0, Processing of source material- (b)(4)

lots until final product, and method for assigning expiration date to the final pooled lot.

(b)(4)

Response is acceptable.

3.2.S.2.3- Control of Materials

4. We note that the pollen is tested (b)(4) for (b)(4) However, it is not clear from your descriptions if more than one batch or lot of pollen may be harvested from a field in a year. Please clarify. If more than one batch or lot is harvested from a field in a year, then we request that each individual harvest be tested for (b)(4) . In addition, please specify which methods, compendial or otherwise, are used for testing these materials.

(b)(4)

lots were tested in 2013 however test results were not provided. Additional CMC IR communicated on March, 2014

5. In section 2.3, (b)(4) testing of source pollen- you provided testing data for (b)(4) for pollen batches harvested between 2003

and 2007. Please provide the same information and data for the pollen batches harvested after 2007.

Merck- Table 9 and Table 10 included in BLA STN 125473/000, Section 3.2.S.2.3 Control of Materials and provided below have been updated to include (b)(4) *for batches harvested from 2003-2012.*
(b)(4)

Response is acceptable.

6. Attachment 1 of this section is a representative Certificate of Analysis (CoA) from source material vendor (b)(4). We note that no expiration date is indicated on the CoA. Please explain why no expiration date is provided on the CoA and specify if an expiration date is assigned to the pollen source materials. In addition, please indicate if stability studies are performed in support of the expiration date and provide any available data.

Merck-The CoA included is a standard template used by (b)(4) *for all pollen source materials and therefore does not include the expiration date. The expiration date for Timothy pollen is* (b)(4) *from the manufacturing day (the date when pollen is* (b)(4) *The* (b)(4) *expiration date is based on real time stability study initiated by* (b)(4) *on three source material batches upon storage in* (b)(4)
Response is acceptable.

7. Please provide the SOPs for the tests indicated in CoA provided by (b)(4)

(b)(4)

Response is acceptable. SOPs used for testing Timothy source materials are provided.

8. We note that per your description; ALK Abello A/S accepts source materials from (b)(4) (b) (4) based in part on the CoA and in part on some in-house testing. ALK Abello A/S should have a vendor auditing program in place, especially if results are accepted by CoA. Please provide a description of ALK Abello A/S' vendor qualification program and specify if on-site auditing is performed.

Merck- ALK Abelló A/S has a procedure in place for qualifying and approving suppliers of incoming materials. The procedure covers the process of initial qualification and ongoing surveillance of both external suppliers and internal suppliers (sites within the ALK Group). Initial vendor qualification includes categorizing vendors using a risk based approach, which determines the requirements for having agreements in place as well as the surveillance including audits. (b)(4) *. was approved according to the current procedure in December 2011. A technical agreement is in place between ALK-Abelló A/S and* (b) (4) *. including terms for handling e.g. deviations and changes. Onsite auditing is performed every* (b)(4) *(the most recent performed in June 2013). In addition, yearly Quality Management Review according to* (b)(4) *is performed.*
Response is acceptable.

9. Please explain the process used by ALK Abello to track raw materials from receipt through the quarantine, release and storage process. In addition, if an automated system is used, please provide an overview of this system.

(b)(4)

Response is acceptable.

10. In Section 3.0- you indicate that a (b)(4) is evaluated based on certificate of analysis from supplier. Please provide a CoA for the (b)(4)

Merck- CoA from supplier for (b)(4) *is provided.*
CoA from supplier (b)(4) **is provided. The information is partial English. This is acceptable.**

3.2.S.2.4- Control of Critical Steps and Intermediates

11. Table 1 in section 1.0 lists all of the operating parameters and process controls for the DS manufacturing process. (b)(4) are considered as critical steps through the entire manufacturing process of the DS. We do not agree with your classification of most of the operating parameters of the DS production process as "non-critical". Further discussion on these classifications will be necessary.

Merck-Section 3.2.S.2.4.1has a list of all operating parameters that were evaluated over a probable operating range to determine the effect on the critical quality attributes (CQA).(b)(4) *demonstrated an impact and were assigned critical process parameters (CPP). The remainings were assigned as non-critical process parameters. The definition for defining these parameters under two categories is also provided. Classification is based on risk based evaluation of parameters controllability and potential impact on DS quality. All the parameters listed in BLA (critical and non-critical) are monitored and controlled during DS manufacturing process.*
All the parameters (b)(4) **) tested at various PARs are listed. Response is acceptable.**

12. (b)(4) Please explain.

(b)(4)

Response is acceptable.

3.2.S.2.5- Process Validation and Evaluation

13. Please address the following with respect to the values listed in Table 5, Validation Results Process Parameter Conformance SCH 697243 (batches (b)(4)):

    a. The Proven Acceptable Range (PAR) for the(b) (4) Please provide validation data supporting the PAR for this step.

b. The PAR for (b) (4) Please provide validation data supporting the PAR for this step.

c. (b)(4) Please provide validation data supporting the (b)(4) .

d. The PAR for (b) (4) Please provide validation data supporting the PAR for this step.

Merck- The three process validation batches (batches (b)(4)) were manufactured under normal operating conditions with process parameters targeted at set points. The Proven Acceptable Ranges (PAR) for the process parameters were established prior to the execution of the process validation as part of the preceding process design phase based on development data.

(b)(4)

(b)(4)

Reviewer: All the responses are acceptable

14. Please provide SOPs for the preparation, qualification, control and storage conditions for your in-house reference materials (IHR's). In addition, please indicate what the expiration date is for your IHR materials.

Merck: The SOPs for the preparation, qualification, control and storage conditions for the in-house reference material (IHR) are provided in Attachment 1 through Attachment 13. Flow diagram for manufacturing of IHR is also included.
The firm has provided SOPs for IHR preparation in Danish. A Flow diagram for the manufacturing process of IHR is also included. All the SOPs are listed in a table with condensed information about the content of SOPs that are provided in Danish. The SOP for the qualification, control and storage conditions for the IHR is also provided. The IHR is controlled by comparing current and new batch of IHR in accordance with SOP 14-07-022. The current shelf life of the IHR is (b)(4) **.**

3.2.S.2.6- Manufacturing Process Development

15. (b)(4)

Please provide the validation studies supporting this (b)(4) .

Merck: Prior to process validation studies, development data was generated to support the suggested (b)(4) *for this step. The data from the process development studies supporting the* (b)(4) *is provided in the response to Comment 13b.*
Reviewer: Response is acceptable.

16. Please provide process validation studies and resulting data for the (b)(4) step.

(b)(4)

The process validation data are provided in Section 3.2.S.2.5.1.5-Tables 5, 6, and 7.

Based on the reported data the proven acceptable ranges for evaluated parameters are acceptable.

17. You indicate that an analytical study was conducted to compare the (b) (4) of DS. Analytical tests were performed in support of this study. Please provide the analytical testing data from this comparative testing; (b)(4) .

(b)(4)

All the quantitative results were comparable. Response is acceptable.

3.2 S.4- Control of Drug Substance

18. Please specify how often you (b)(4)

(b)(4)

Response is acceptable.

19. Please provide specifications for the (b)(4)

(b)(4)

Response is not sufficient. (b)(4)

20. In section 3.2.S.4.2, (b)(4), Figure 1 is a typical result from IHR batch (b) (4) Please provide the figure for the DS sample for comparison.

Merck: The (b)(4) *figures from the current IHR* (b) (4) *and the DS batch* (b) (4) *are included for comparison.*
(b) (4) **are noticed for IHR and DS. Response is acceptable.**

21. (b)(4)

SOPs are provided in Danish. However, the steps involved (b)(4) **are translated and summarized in English. This is acceptable.**

22. (b) (4)

(b) (4)
please provide supporting data.

(b) (4)

Response is acceptable.

23. In Section 10.0, Reporting results, we note that (b)(4)
. Please explain.

(b)(4)

Response is acceptable.

3.2.S.4.3- Validation of Analytical Procedures

24. (b)(4)
". Please provide this guide for review.

Merck: Guide for (b)(4) *are provided (14-30-D015-d).*
Review of the guide indicates criteria for approval. This is acceptable.

3.2.S.4.4- Batch Analysis

25. We note that different types of batch numbers are used for the DS. For example, in Table 3 ((b)(4)
Batches of SCH 697243 Drug Substance) a batch is designated as (b)(4) while another batch is designated as (b)(4) . Please explain why different batch numbers are used.

Merck: (b) (4)
.

This is acceptable.

3.2.S.7- Stability

26. You have proposed not to include (b)(4) . Please explain your rationale for excluding these tests.

(b)(4)

Response is acceptable.

3.2.P.2.3- Manufacturing Process Development

27. In Table 1 we note that either (b)(4) Please specify which process you intend to use for (b)(4) for commercial scale production batches.

(b)(4)

Response is acceptable.

28. Please provide the procedure used for (b)(4) of DS.

(b)(4)

Response is acceptable.

29. In table 14, Effect of Freeze Drying Conditions on Dried Tablets, we note that frozen and dried tablets from batch (b)(4) (active) were not tested for moisture content, and that tablets from freeze dryer loads (b)(4) were not tested for appearance. Please explain why this batch was not tested as intended.

Merck: Batch (b)(4) was manufactured as part of the scale up manufacture of tablet on (b)(4) Loads (b)(4) were dried as part of a freeze drying study to range and confirm the freeze drying conditions. Loads (b)(4) were used to optimize the cycle with respect to (b)(4) was performed on these loads. All testing was performed as intended according to the protocol. We acknowledge the error in Table 14 in Section 3.2.P.2.3 Manufacturing Process Development. In addition to drying defects and appearance, moisture content of samples from (b)(4) in the freeze dryer was tested on Loads (b)(4) . Data are provided in table.
Moisture content for all three loads sampled from (b)(4) is within acceptance criteria of (b)(4). Response is acceptable.

3.2.P.3.5 Process validation and /or evaluation

30. In table 4 you indicate that process validation batches comply with the (b)(4) , however you have not provided any supporting data. Please provide the (b)(4) data for all of process validation batches.

Merck: The (b)(4) data for the (b)(4) process validation batches are provided.
(b)(4) for all (b)(4) process validation batches are with in acceptance criteria and close to (b)(4) target (b)(4) of (b)(4) . Response is acceptable.

31. In table 5- the moisture content of all of the process validation batches is well below (b)(4). Please consider modifying your release and shelf life specification for moisture content based on water content data from your process validation batches.

Merck: Statistical analysis (p=0.99, 99% CI) for the moisture content data of the (b)(4) clinical and EU batches supports moisture content limit of (b)(4) at release. In addition, moisture content results obtained for batches manufactured post drug product process validation were up to (b)(4) and consistent with the moisture content results obtained from (b)(4) drug product batches. During long term storage there is possibility of (b)(4) increase in water content. No negative effect on product quality is observed. In addition, a (b)(4) study on drug product showed tablets with moisture content of (b)(4) complied with the acceptance criteria for immunochemical and physical tests. Therefore, the proposed shelf life moisture content limit of (b)(4) is appropriate for the drug product.

Scatter plot of release data for moisture content for (b)(4) clinical and EU commercial batches and (b)(4) additional process validation batches are included in the response. The proposed release specification of (b)(4) is considered appropriate from the data collected from (b)(4) batches. During

storage an increase of up to (b)(4) is expected and this increase in water content does not have any negative effect on product quality.
Response is acceptable.

3.2.P.4 Control of excipient

32. In Appendix 1 Certification for gelatin from (b)(4) has been provided but your gelatin is obtained from (b)(4) . Please provide certification for gelatin from (b)(4) .

Merck: (b)(4) *is the manufacturer of gelatin and* (b)(4) *is the distributor of the* (b)(4) .
This relationship is further described in the attached letter from (b)(4)
Response is acceptable.

33. Please provide Certificates of Analysis for both mannitol and sodium hydroxide.

Merck: Certificate of Analyses provided for mannitol and sodium hydroxide.
Response is acceptable.

3.2.P.5.2 Analytical procedures

34. In your interpretation of the method for the FDA ELISA, Section 4.0 reagents, you use (b)(4) is as a wash and dilution buffer. Per the current FDA competition ELISA procedures; the wash solution should be PBS containing 0.05% Tween-20. Please align your wash and dilution buffer composition to comply with the FDA standard method of competition ELISA.

Merck: Throughout the development of drug product (b)(4) *as wash and dilution buffer is used. The current FDA competition ELISA procedure in which PBS containing 0.05% Tween-20 is specified as a wash and dilution buffer was provided during a correspondence. Studies are initiated to align the wash and dilution buffers per current FDA procedure for testing the Timothy Grass Pollen Allergen Extract drug product post approval. An experiment was performed using a commercial scale DP batch.* (b) (4) *ELISA plates were run with the procedure as described in BLA STN 125473/0 Module 3 Section 3.2.P.5.2.4 (FDA docket No. 94N-0012) using* (b) (4) *and two ELISA plates were run with the aligned wash and dilution buffer per current FDA procedure using PBS containing 0.05% Tween-20. This initial experiment showed no significant difference in the results after changing buffers as reflected by the relative potency values. The system suitability requirements, sample requirements and slope values are shown in Table 2. In addition, the reference, control and sample curves were parallel and similar for both methods. The raw data for the* (b)(4) *ELISA plates including the curves are provided in Attachment1.*

The relative potency data obtained from comparative study aligned well. Sponsor indicates that the revised assay will be implemented after the completion of validation using (b)(4) different batches (b)(4) times each on (b)(4) different plates. Response is acceptable.

35. For the (b)(4) by (b)(4) you use (b)(4) . Please indicate why you use (b)(4) and describe your method (b)(4) .

(b)(4) .

Response is acceptable

3.2.P.5.3 Validation of Analytical Procedures

36. For validation of the CBER ELISA method you have only included a summary of the validation parameters. Please provide complete data from the batches that were tested during validation of this assay. Please specify which versions of the CBER ELISA method and optimization methods are used.

Merck: The CBER ELISA is performed in accordance with the FDA docket No. 94N-0012 "Methods of the Allergenics Products Testing Laboratory (October 1993)" and the same was used for the validation and optimization of coating extract, serum pool and conjugate. The FDA Competition ELISA: Phleum pratense Validation Report No. 16-07-DO239-d is provided. The raw data for each analytical run are provided. Since the raw data reports are in Danish, a general introduction of the report is explained in English). The specificity data (ELISA-09-001) is also included
(b)(4) **batches each of (b)(4) and drug product were tested for validation of CBER ELISA analytical procedure. The acceptance criteria for the validation given in the FDA document 94N-0012 were all fulfilled.**

3.2.P.5.4 Batch Analysis

37. We note that different types of batch numbers are used for DP batches. For example in Table 1 of this section the batch numbers indicated are (b)(4) . Please explain the difference in these numbers.

(b) (4)

Response is acceptable.

3.2.P.5.6 Justification of Specifications

38. Please provide information on the modifications you added to (b)(4) during disintegration testing.

Merck: (b)(4) *minor modifications are added to* (b)(4) *. The test is initiated with the* (b)(4) *disintegration apparatus* (b)(4) *for rapid disintegration of this product.*
Response is acceptable.

3.2.P.8 Stability

39. You used three PV batches from (b)(4) for your stability studies. In this sequence, batch number (b)(4) is missing. Please specify the outcome of the missing batch.

Merck: (b) (4)

Response is acceptable.

40. Section 2, Batch Information – you indicate in the Table 1 footnote that a second accelerated stability study was performed to include FDA ELISA assay since it was inadvertently not performed in the original study. Please explain why the FDA ELISA assay was not performed during first accelerated stability study that was initiated on all three batches ((b)(4)) on June 4, 2008.

Merck: Three batches (b)(4) **were released according to the EU specification in 2008 that did not include the FDA ELISA. The FDA ELISA was scheduled to be analyzed, at time zero and at the 6 month time point as an additional test according to the stability protocol. Due to a communication/human error, the FDA ELISA was not analyzed at time zero, but was only performed at the 6 month time point. Therefore, the accelerated study was repeated including time points for 0, 3 and 6 months.**
Response is acceptable.

41. You propose not to include microbiological examination for specified microorganisms in your future stability protocol. You have not provided sufficient information to assess whether this proposal is acceptable. Please provide your rationale for not including this test during stability studies.

Merck: Stability result supports absence of microbial growth for a period of up to 36 months. Absence of specified microorganism is confirmed at release, the presence of these organisms is not expected to change over time, Therefore, we propose to perform (b)(4) *in accordance with* (b)(4) *for the post-approval stability program.*
The proposal is not acceptable and firm has been notified to include the absence of specified microorganisms test at Time Zero and at the end of shelf-life study.

42. Please provide 36 month stability data for PV batches stored under real time conditions.

Merck: The 36 month stability data for PV batches (b)(4) *stored at real time conditions of 25°C* (b)(4) *are provided. All of the stability results for the* (b)(4) *PV batches comply with the acceptance criteria. Relative potency results of the ELISA competition assay at 36 months were lower than the previous time point, but were within acceptance criteria (*(b)(4) *) and conform to 2800 BAU.*
Samples from PV batches were examined at (b)(4) **using qualified lot of detection antibody. The data for relative potency assures that the product does not lose potency during storage over a period of 36 months. Response is acceptable**

3.2. R Regional Information

43. The CoA from Catalent Pharma Solutions lists the date of manufacture as December 14, 2009 and the expiration date as 11, 2013. Please comment on the following:

a. The indicated expiration date of "11, 2013" is incomplete. This is not a complete expiration date. Please explain why there is not a complete expiration date on the CoA.
b. Based on your proposed expiration dating of 36 months, the expiration date should be in 2012 not 2013 as indicated in the CoA. Please comment.
c. Please indicate which firm is responsible for assigning the expiration date to the blister pack.
d. Please explain how you define the Date of Manufacture. This is the date from which the expiration should be calculated.

Merck: The Certificate of Analysis included in BLA STN125473 is for an EU approved commercial batch (Grazax™). Batch no. (b)(4) *was released by*

ALK- Abelló for commercial use in the EU market where a 48 month shelf life is approved, however, the expiry date recorded on the CoA is 47 months based on the assignment of expiry date using the MM-YYYY format.
For the US market the proposed shelf life is 36months and the expiration date is 35 months from the date of manufacture using a MMM (month) YYYY (year) format.
The expiry date is assigned by Catalent Pharma Solutions in accordance with the Merck approved documentation for expiry date assignation.
The Date of Manufacture for the drug product is defined as (b)(4) .

Response is acceptable.

On March10, 2014 an additional information request was communicated to the sponsor through email. The responses received from the firm on March 14, 2014 are in italics below, Final outcome of the IR responses are noted in bold.

CMC IR#4 - (b)(4) testing of (b)(4) - In table 1 of your response you indicate that in 2013 (b) (4) pollen lots were tested for (b)(4) . Please provide the test results for these (b) (4) pollen lots.

(b)(4)

Response is acceptable.

CMC IR#19 - (b)(4)

.

(b)(4)

This is acceptable. An inspection follow-up memo was written to ensure that the (b)(4) studies have been initiated as requested.

CMC IR#39 - Alignment of FDA competition ELISA - You indicate that the revised ELISA will be implemented after the completion of validation using (b)(4) different batches (b)(4) times each on (b)(4) different plates. Please submit a draft Post Marketing Commitment by email for our review and comment. In your PMC you should specify your proposal for the validation, a time frame for collection of data on these lots, and a time frame for submission of the data for our review.

Merck: Merck commits to implement the revised ELISA after the completion of validation. The validation will be performed according to FDA Docket # 94N-0012 using PBS containing 0.05% Tween-20 as the wash and dilution buffer, with the following prerequisites:

- (b) (4)

according to FDA Docket # 94N-0012.

The acceptance criteria are based on FDA Docket# 94N-0012. The validation data for these batches will be collected during April and May 2014. The data will be submitted to CBER.

Response is acceptable.

CMC IR#41 - Absence of specified organism testing for the post approval stability program – We request that you consider adding the absence of specified organism test to your future on-going stability protocols. You responded that the "results obtained from the stability program demonstrated that the formulation of the freeze dried tablet does not support microbial growth, showing that acceptable microbial quality has been demonstrated up to 36 months. As absence of specified microorganisms is confirmed at release, the presence of specified organisms is not expected to change over time. Therefore, the applicant proposes to perform only the Microbial Enumeration test (b)(4) in accordance with (b)(4)

for the post-approval stability program." We do not agree with your proposal at this time. Please include the absence of specified microorganisms test at Time Zero and at the end of your shelf-life study.

Merck: The test for the absence of specified microorganisms has been added at Time Zero and at the end of the proposed shelf-life of 36 months to the post approval stability program. Table containing Post approval stability test schedule is amended

This is acceptable.