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

Memorandum

Date: April 16, 2014

To: File, STN 125478

From: Taruna Khurana, Ph.D. 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 Memorandum

Reference: IND 12970

Overall conclusion
Based on the CMC review of the original BLA submission and related amendments, I recommend approval of RAGWITEK 12 Amb a 1 U tablets for the treatment of short ragweed pollen-induced allergic rhinitis or conjunctivitis confirmed by positive skin test or *in vitro* testing for pollen-specific IgE for short ragweed antibodies in persons 18 through 65 years of age.

Materials Reviewed
125478/00 Original BLA Modules 2 and 3 (March 11, 2013)
125478/02 (May 10, 2013)
125478/03 (May 21, 2013)
125478/06 (July 22, 2013)
125478/08 (October 29, 2013)
125478/09 (December 6, 2013)
125478/010 (December 09, 2013)
125478/012 (December 18, 2013)
125478/014 (January 14, 2014)
125478/015 (February 4, 2014)
125478/017 (February 18, 2014)
125478/020 (March 5, 2014)
125478/021 (March 6, 2014)
125478/025 (March 26, 2014)
125478/028 (April 7, 2014)
125478/033 (April 11, 2014)
Summary/Background

On March 11, 2013, Merck Sharp and Dohme Corp., a subsidiary of Merck& Co., Inc, submitted a Biologics License Application (BLA) for Short Ragweed Pollen Allergen Extract Tablet for Sublingual Use. The Trade name for this product is RAGWITEK. RAGWITEK is a sublingual tablet indicated for the treatment of short ragweed pollen induced allergic rhinitis, with or without conjunctivitis, confirmed by positive skin test or in vitro testing for pollen specific IgE antibodies for short ragweed pollen in persons 18 to 65 years of age. The clinical development program (safety and efficacy) for this product is discussed in reviews of IND 12970.

Each tablet contains 12 Amb a 1 U of allergen extract of short ragweed pollen (*Ambrosia artemissifolia*). The drug substance (DS) used in manufacturing of the tablet consists of (b) (4)

RAGWITEK is a white to off white, circular tablet with a debossed double hexagon on one side. The Drug Product (DP) is manufactured at Catalent Pharma Solutions, Swindon, UK. The potency of the tablet is determined in terms of major allergen Amb a 1 that is measured by (b) (4) assay.

Review of Source Material

3.2.S.2.2 Manufacturing Process/Process Control

The DS is manufactured and (b) (4)

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

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

(b) (4)

Review of Drug Product

The DP is a white to off-white circular sublingual tablet with a double hexagon debossed on one side. The tablet is designed for disintegration of approximately <10 seconds when placed under the tongue. Each tablet contains 12 Amb a 1 U of Short Ragweed pollen extract. The potency of the tablet is measured in Amb a 1Unit using the (b) (4) relative to the CBER reference material of standardized Short Ragweed. The tablet formulation consists of (b) (4) Gelatin and Mannitol. The tablet is manufactured using (b) (4) 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 (b) (4) under a validated procedure from (b) (4) Catalent, Swindon, UK. (b) (4) fish gelatin (b) (4) The fish gelatin is a (b) (4) component of the DP and is controlled for quality. Mannitol is included in the formulation for tablet (b) (4) . Sodium hydroxide is used to (b) (4) during the DP manufacturing process.

Formulation Development
Formulation development of RAGWITEK was completed in following stages:

- (b) (4)
  .

The formulation for Ragweed tablet is identical to that of the Timothy Grass tablet (GRASTEK) except for the (b) (4) . The proposed Ragweed tablet formulation was expected to exhibit very

similar physical characteristics to the existing Timothy grass formulation. Hence, a (b) (4) formulation development program was undertaken.

(b) (4)

RAGWITEK final formulation

Ingredients	Final Formulation
Short Ragweed pollen extract	12 Amb a 1-Unit
Fish Gelatin, (b) (4)	(b) (4)
(b) (4)	(b) (4)
Mannitol	(b) (4)
Sodium Hydroxide	(b) (4)
Purified water	(b) (4)
(b) (4)	

Formulation verification study- Based on Phase II/III clinical trials the 12 Amb a 1 U strength was selected as the final tablet strength. However, at the time of development the formulation verification was conducted at the highest strength of (b) (4) were prepared for the formulation verification study. Various parameters were assessed to evaluate the robustness of the final formulation. The study demonstrated that the proposed formulation met all the acceptance criteria and was suitable for commercial scale production of the tablets.

Optimization of formulation during process development studies-The formulation was further tested at (b) (4) and at (b) (4) From these studies the (b) (4) .

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

- (b) (4)

The (b) (4) process development was conducted at (b) (4)

roduction capacity. (b) (4) formulation is used at all the lines

(b) (4) process development-
The manufacturing process, process parameters and in-process controls for the RAGWITEK tablets are based on information gained from Timothy grass tablet manufacturing (STN 125473). The critical process parameters that could affect quality of the tablets are 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 (b) (4) . The DP is manufactured by Catalent Pharma Solution, Swindon, UK for Merck Sharp and Dohme Corp. The (b) (4) Catalent is responsible for primary packaging of the tablets and for testing (appearance, disintegration and microbiological examination).

(b) (4)

Description of manufacturing process and process control-

(b) (4)

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

(b) (4)

3.2.P.5 Control of Drug Product-

Drug Product release and shelf life specifications for 12 Amb a 1 U tablet are indicated in table below.

Table 4: RAGWITEK sublingual tablet release specifications

Test	Acceptance Criteria	Methods
Appearance	White to off-white circular freeze-dried tablets with a double hexagon de-boss	Appearance
Identity (b) (4)	(b) (4)	(b) (4)
Disintegration[b]	≤10 seconds	(b) (4)
Water content	(b) (4)	(b) (4)
Identity/Potency (b) (4)	(b) (4)	(b) (4)
Potency (b) (4)	(b) (4)	(b) (4)
Uniformity of dosage units[a]	(b) (4)	(b) (4)
Microbial Enumeration (b) (4)	(b) (4) (b) (4)	(b)
Test for Specified Microorganisms: (b) (4)		

(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 demonstrate the homogeneity of tablets across a batch as a routine release test for the finished product (see section 3.2.P.5.6 of this memo for further discussion).

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 (b) (4)
- (b) (4)
- Microbiological quality (b) (4)
- Water content (b) (4)

Validation of disintegration - The disintegration test is performed as described in (b) (4) .

(b) (4)

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

(b) (4)

3.2.P.5.6 Justification of specifications

The justification for the methods selected for establishing the RAGWITEK 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, color and debossing of DP are determined by visual inspection. The test is performed at Catalent Pharma Solutions during release (b) (4) during stability testing of DP. The acceptance criteria at release and shelf life are white to off-white, circular freeze dried units with double hexagon debossed. The color of the DP is based on the color of DS that is used for DP manufacturing.

Identity (b) (4)

Potency by (b) (4)

Water content (b) (4)

Disintegration time - (b) (4) Merck's proposal of using disintegration test for the release and stability study was accepted by the Agency on October 29, 2008. The acceptance criterion for disintegration time is ≤10 seconds.

(b) (4) - The drug product for RAGWITEK is a freeze-dried aqueous solution containing dry matter from the pollen extract (approximately (b) (4), mannitol (b) (4) and fish gelatin (b) (4). The tablets are manufactured from a (b) (4) which

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

(b) (4)

(b) (4)

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 the data from (b) (4) The studies were configured as follows:

1. 36 months under long term storage conditions of 25°C (b) (4)
2. (b) (4)

Additional stability data for (b) (4) upon storage for 36 months at 25°C (b) (4) were also provided. The acceptance criteria for appearance, major (b) (4), water content, disintegration and microbial examination (b) (4) were met.

Three (b) (4) batches (Batches (b) (4)) were also placed under stability at 25°C (b) (4) for 36 months. This is an ongoing study and 12 months data provided. All acceptance criteria were met.

The stability studies were conducted according to the ICH guideline Q5C. The stability studies were performed on commercial scale batches packed in the container/closure

system intended for storage. Batch (b) (4) was tested for (b) (4) as well. The data supports 36 months of shelf life of RAGWITEK 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
- Water content
- (b) (4)
- Microbial examination

(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

(b) (4) All reported results complied with acceptance criteria and no meaningful trends were observed in any of the studies.

During the stability studies, a (b) (4) was implemented at (b) (4) 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 was used. New results for (b) (4) and potency obtained remained within acceptance criteria.

Water Content by (b) (4) - The water content results complied with acceptance criteria for the batches at the long-term storage condition (25°C/(b) (4) and at the (b) (4). The (b) (4) water content noticed at various time points was within acceptance criterion of (b) (4)

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

Microbiology - Results for the microbial enumeration (b) (4) and absence of specified microorganisms tested at initial time point complied with the acceptance criteria. This test has not been performed on Process Validation batches and commercial scale batches placed under stability study at real time and accelerated storage conditions. Merck also proposed of not including microbiological examination for specified microorganisms as future stability protocol. We requested the firm add this test in future stability at the minimum at T0 and at the end of the stability period and the firm agreed on adding this test.

(b) (4)

3.2. R Regional Information-

3.2.R.1.S Executed batch record - An executed batch production record from ALK-Abello was provided for (b) (4) The batch was manufactured at (b) (4) using the (b) (4) process.

3.2.R.1.P Executed batch record - An executed batch record was provided for (b) (4) The batch was manufactured at (b) (4) . Information included in the batch record is complete and satisfactory.

3.2.R.3 Methods validation package - Per 21 CFR 314.50 (e) four representative sample kits containing the RAGWITEK DS and DP Tablet at 12 Amb a 1 U and all the 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 November 8, 2013 as an Information Request. The responses received from the firm on December 18, 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. (b) (4)

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

materials are given the status "Quality Inspection" (QI), which means that it is in quarantine in SAP, and therefore cannot be issued for production. The raw material is analyzed by QA units and release once the batch passes all the release specifications. When a new production is planned, a process order (PO) is created in SAP. The PO links to a bill of material (BOM) which contains all the raw materials used in the production. The manufacturing unit (API Production) retrieves the raw materials physically from storage for production. SAP tracks the inventory level of each raw material and when the level of a raw material reaches a predefined minimum level the raw material is ordered from the approved external raw material supplier.
This response is acceptable.

3.2.S.2.4-ControlofCriticalStepsandIntermediates

12. Table 1 in Section 1.0 lists all of the operating parameters and process controls for the DS manufacturing process. Only the (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 may be necessary. Please re-evaluate and resubmit the critical parameters.

    Response: All relevant process parameters are indicated in manufacturing process development section in original submission. As a part of process design phase, each of the process parameters was assessed over a probable operating range and evaluated or potential impact of drug substance. Only (b) (4) *demonstrated impact and listed as critical steps. Additional data is provided in support. The approach used to classify the process parameters as critical / non-critical is based on existing Quality Systems coupled with the PDA Journal of Pharmaceutical Science and Technology: Technical Report No. 42 Process Validation of Protein Manufacturing. Most of the process parameters even indicated as non critical are monitored and controlled for each batch during the DS processing. Deviation is raised if any parameter exceeds set operating range.*
    The firm has provided set points, proven acceptable ranged and control measures for all the parameters of DS manufacturing process. This response is acceptable.

3.2.S.2.5 - Process Validation and Evaluation

13. Please provide data obtained from the process design phase that were used for defining proven acceptable ranges indicated in Table 5- Process Performance Qualification (PPQ) Results Process Parameters Conformance.

    Response: Summary of data used to define the proven acceptable range (PAR) for the parameters for (b) (4) *is provided.*

This response is acceptable.

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

(b) (4)

This response is acceptable.

3.2.S.2.6 - Manufacturing Process Development

(b) (4)

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

(b) (4)

3.2.P.4 - Control of Excipient

35. Please provide Certificates of Analysis for mannitol, sodium hydroxide, and Gelatin.

    Response: Certificates of Analyses for mannitol, sodium hydroxide, and gelatin are included.
    This response is acceptable.

3.2.P.5.4 - Batch Analysis

36. (b) (4)

3.2.P.8 - Stability

37. Three commercial scale batches (b) (4) were used for your stability studies. In this sequence, batch number (b) (4) is missing. Please specify the outcome of the missing batch.

(b) (4)

included in the stability sections, as Ragweed tablet 12 Amb a 1-U was selected as the final dose strength.
This response is acceptable.

38. Section 3.2.P.8.2, Post Approval Stability protocol/stability commitment, Table 1- We note that the identity test and test for absence of specified microorganisms is not included in post approval stability protocol. You have not provided sufficient information to assess whether this is acceptable. Please provide your rationale for not including these tests on stability.

(b) (4)

39. (b) (4)

40. (b) (4)

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

(b) (4)

3.2.P.3 Drug Product Manufacturing Process

The (b) (4) . The DP is manufactured by Catalent Pharma Solution, Swindon, UK for Merck Sharp and Dohme Corp. The (b) (4) Catalent is responsible for primary packaging of the tablets and for testing (appearance, disintegration and microbiological examination).

(b) (4)

Description of manufacturing process and process control-

(b) (4)

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(b) (4)

3.2.P.5 Control of Drug Product-

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Test	Acceptance Criteria	Methods
Appearance	White to off-white circular freeze-dried tablets with a double hexagon de-boss	Appearance
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Water content	(b) (4)	(b) (4)
Identity/Potency (b) (4)	(b) (4)	(b) (4)
Potency (b) (4)	(b) (4)	(b) (4)
Uniformity of dosage units[a]	(b) (4)	(b) (4)
Microbial Enumeration (b) (4)	(b) (4) (b) (4)	(b)
Test for Specified Microorganisms: (b) (4)		

(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 demonstrate the homogeneity of tablets across a batch as a routine release test for the finished product (see section 3.2.P.5.6 of this memo for further discussion).

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 (b) (4)
- (b) (4)
- Microbiological quality (b) (4)
- Water content (b) (4)

Validation of disintegration - The disintegration test is performed as described in (b) (4) .

(b) (4)

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

(b) (4)

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Identity (b) (4)

Potency by (b) (4)

Water content (b) (4)

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(b) (4)

(b) (4)

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- Disintegration
- Water content
- (b) (4)
- Microbial examination

(b) (4)

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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

(b) (4) All reported results complied with acceptance criteria and no meaningful trends were observed in any of the studies.

During the stability studies, a (b) (4) was implemented at (b) (4) 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 was used. New results for (b) (4) and potency obtained remained within acceptance criteria.

Water Content by (b) (4) - The water content results complied with acceptance criteria for the batches at the long-term storage condition (25°C/(b) (4) and at the (b) (4). The (b) (4) water content noticed at various time points was within acceptance criterion of (b) (4)

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

Microbiology - Results for the microbial enumeration (b) (4) and absence of specified microorganisms tested at initial time point complied with the acceptance criteria. This test has not been performed on Process Validation batches and commercial scale batches placed under stability study at real time and accelerated storage conditions. Merck also proposed of not including microbiological examination for specified microorganisms as future stability protocol. We requested the firm add this test in future stability at the minimum at T0 and at the end of the stability period and the firm agreed on adding this test.

(b) (4)

3.2. R Regional Information-

3.2.R.1.S Executed batch record - An executed batch production record from ALK-Abello was provided for (b) (4) The batch was manufactured at (b) (4) using the (b) (4) process.

3.2.R.1.P Executed batch record - An executed batch record was provided for (b) (4) The batch was manufactured at (b) (4) . Information included in the batch record is complete and satisfactory.

3.2.R.3 Methods validation package - Per 21 CFR 314.50 (e) four representative sample kits containing the RAGWITEK DS and DP Tablet at 12 Amb a 1 U and all the 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 November 8, 2013 as an Information Request. The responses received from the firm on December 18, 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. (b) (4)

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

materials are given the status "Quality Inspection" (QI), which means that it is in quarantine in SAP, and therefore cannot be issued for production. The raw material is analyzed by QA units and release once the batch passes all the release specifications. When a new production is planned, a process order (PO) is created in SAP. The PO links to a bill of material (BOM) which contains all the raw materials used in the production. The manufacturing unit (API Production) retrieves the raw materials physically from storage for production. SAP tracks the inventory level of each raw material and when the level of a raw material reaches a predefined minimum level the raw material is ordered from the approved external raw material supplier.
This response is acceptable.

3.2.S.2.4-ControlofCriticalStepsandIntermediates

12. Table 1 in Section 1.0 lists all of the operating parameters and process controls for the DS manufacturing process. Only the (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 may be necessary. Please re-evaluate and resubmit the critical parameters.

    Response: All relevant process parameters are indicated in manufacturing process development section in original submission. As a part of process design phase, each of the process parameters was assessed over a probable operating range and evaluated or potential impact of drug substance. Only (b) (4) *demonstrated impact and listed as critical steps. Additional data is provided in support. The approach used to classify the process parameters as critical / non-critical is based on existing Quality Systems coupled with the PDA Journal of Pharmaceutical Science and Technology: Technical Report No. 42 Process Validation of Protein Manufacturing. Most of the process parameters even indicated as non critical are monitored and controlled for each batch during the DS processing. Deviation is raised if any parameter exceeds set operating range.*
    The firm has provided set points, proven acceptable ranged and control measures for all the parameters of DS manufacturing process. This response is acceptable.

3.2.S.2.5 - Process Validation and Evaluation

13. Please provide data obtained from the process design phase that were used for defining proven acceptable ranges indicated in Table 5- Process Performance Qualification (PPQ) Results Process Parameters Conformance.

    Response: Summary of data used to define the proven acceptable range (PAR) for the parameters for (b) (4) *is provided.*

This response is acceptable.

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

(b) (4)

This response is acceptable.

3.2.S.2.6 - Manufacturing Process Development

(b) (4)

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

(b) (4)

3.2.P.4 - Control of Excipient

35. Please provide Certificates of Analysis for mannitol, sodium hydroxide, and Gelatin.

    Response: Certificates of Analyses for mannitol, sodium hydroxide, and gelatin are included.
    This response is acceptable.

3.2.P.5.4 - Batch Analysis

36. (b) (4)

3.2.P.8 - Stability

37. Three commercial scale batches (b) (4) were used for your stability studies. In this sequence, batch number (b) (4) is missing. Please specify the outcome of the missing batch.

(b) (4)

included in the stability sections, as Ragweed tablet 12 Amb a 1-U was selected as the final dose strength.
This response is acceptable.

38. Section 3.2.P.8.2, Post Approval Stability protocol/stability commitment, Table 1- We note that the identity test and test for absence of specified microorganisms is not included in post approval stability protocol. You have not provided sufficient information to assess whether this is acceptable. Please provide your rationale for not including these tests on stability.

(b) (4)

39. (b) (4)

40. (b) (4)

(b) (4)

41. (b) (4)

42. (b) (4)

(b) (4)

3.2. R - Regional Information

43. Please provide a Certificate of Analysis from Catalent Pharma Solutions for the drug product.

Response: A Certificate of Analysis from Catalent Pharma Solutions UK, Swindon for drug product batch no. (b) (4) *is provided.*

This response is acceptable.

Other

44. Please submit a draft Lot Release Protocol.

Response: The draft Lot Release Protocol is provided.
The draft Lot Release Protocol was reviewed and commented on.

On March 18, 2014 an additional information request was communicated to the firm through email. The responses received on March 26, 2014 are in italics, Final outcome of the IR responses are noted in bold.

(b) (4)

(b) (4)

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