



REVIEW MEMORANDUM

Date: February 03, 2017

To: File, STN 125592/0

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

Subject: CMC Review and Approval Recommendation Memorandum

Cross reference: IND15015, MF (b) (4)

Overall Conclusion

Based on the CMC review of the original BLA submission and the related amendments, I recommend approval of ODACTRA, 12SQ-HDM tablet for the treatment of house dust mite (HDM)-induced allergic rhinitis, with or without conjunctivitis, confirmed by *in vitro* testing for IgE antibodies to *Dermatophagoides farinae* or *Dermatophagoides pteronyssinus* house dust mites, or skin testing to licensed house dust mite allergen extracts. ODACTRA is approved for use in persons 18 to 65 years of age.

Materials Reviewed

125592/0 (February 09, 2016; Original BLA, Product Related Information)

125592/0/001 (February 19, 2016; Proposed proprietary name "ODACTAR")

125592/0/003 (April 7, 2016; Clarification of proper name)

125592/0/004 (April 11, 2016; English translation of (b) (4) and drug substance batch records)

125592/0/005 (May 10, 2016; Blister label)

125592/0/011 (July 1, 2016; (b) (4) reagents and SOP for transfer to LIB)

125592/0/014 (July 19, 2016; Draft Lot Release Protocol)

125592/0/016 (August 5, 2016; Response CMC information request)

125592/0/017 (August 11, 2016; Blister and carton Label)

125592/0/021 (September 14, 2016; Drug substance (b) (4) test method validation)

125592/0/023 (September 12, 2016; Information and questions to CBER regarding BLA and IND (b) (4) from Merck (b) (4))

125592/0/025 (September 30, 2016; Reporting out of specification stability result for drug substance)

125592/0/027 (October 07, 2016; Response CMC information request)

125592/0/031 (October 31, 2016; Update on the investigation of drug substance OOS stability result)

125592/0/033 (November 04, 2016; Word file of draft lot release protocol)

125592/0/034 (November 04, 2016; Response (b) (4) information request)

125592/0/037 (December 02, 2016; Update on the investigation of drug substance OOS result)

125592/0/038 (December 06, 2016; In-house reference material stability)

125592/0/040 (December 15, 2016; Drug Product specification and release test table)

125592/0/041 (December 16, 2016; (b) (4) for fish gelatin, requested by FDA-SRS team for UNII Code assignment)

125592/0/043 (December 22, 2016; (b) (4) assay control chart and tablet information requested by LIB/CBER)

125592/0/044 (January 05, 2017; Word version of updated draft lot release protocol)

125592/0/047 (January 06, 2017; Interim release limits and additional OOS result of the DS)

125592/0/052 (January 20, 2017; Revised lot release protocol)

125592/0/053 (January 20, 2017; (b) (4) and Der 2 content of Drug Product)

125592/0/054 (January 24, 2017; Telecon discussion summary of proposed revised release limits)

Summary/Background

On February 09, 2016 Merck Sharp and Dohme Corp. submitted a Biologics License Application (BLA) for House Dust Mite (*Dermatophagoides farinae* and *Dermatophagoides pteronyssinus*) Allergen Extract Tablet for Sublingual use. The approved trade name for this product is ODACTRA. ODACTRA final drug product (DP) is a fast-dissolving, sublingual tablet indicated for immunotherapy for the treatment of house dust mite-induced allergic rhinitis, with or without conjunctivitis, confirmed by positive skin test or in vitro testing for *Dermatophagoides farinae* or *Dermatophagoides pteronyssinus* IgE antibodies in persons 18 through 65 years of age. Each tablet contains 12 SQ-HDM (b) (4) based on total allergenic potency.

The ODACTRA is a white to off-white circular tablet with a debossed pentagon detail on one side. The drug substances (DSs) used in the manufacture of the final DP tablet are mite (b) (4) extracts of both *Dermatophagoides pteronyssinus* (*Der pte*) and *Dermatophagoides farinae* (*Der far*) house dust mites. The final DS contains (b) (4)

The DSs are manufactured by (b) (4)


The final DP is manufactured at Catalent Swindon, UK using fast dissolving (b) (4). The *Der far* and *Der pte* (b) (4)

and dosed into blister. The potency of the DP is determined by measuring group 1, group 2 allergen content and total allergen activity.

1. Review of Source Material

The drug product (DP) is manufactured from two separate drug substances (DSs). Each DS is an allergen extract derived from two species of cultivated house dust mites (HDM) *Dermatophagoides pteronyssinus* (*Der pte*) and *Dermatophagoides farinae* (*Der far*).

(b) (4)



1.1 Manufacturing Process and Process Control (BLA Section 3.2.S.2.1)

Der pte and *Der far* mite source materials are manufactured and release tested at

(b) (4)


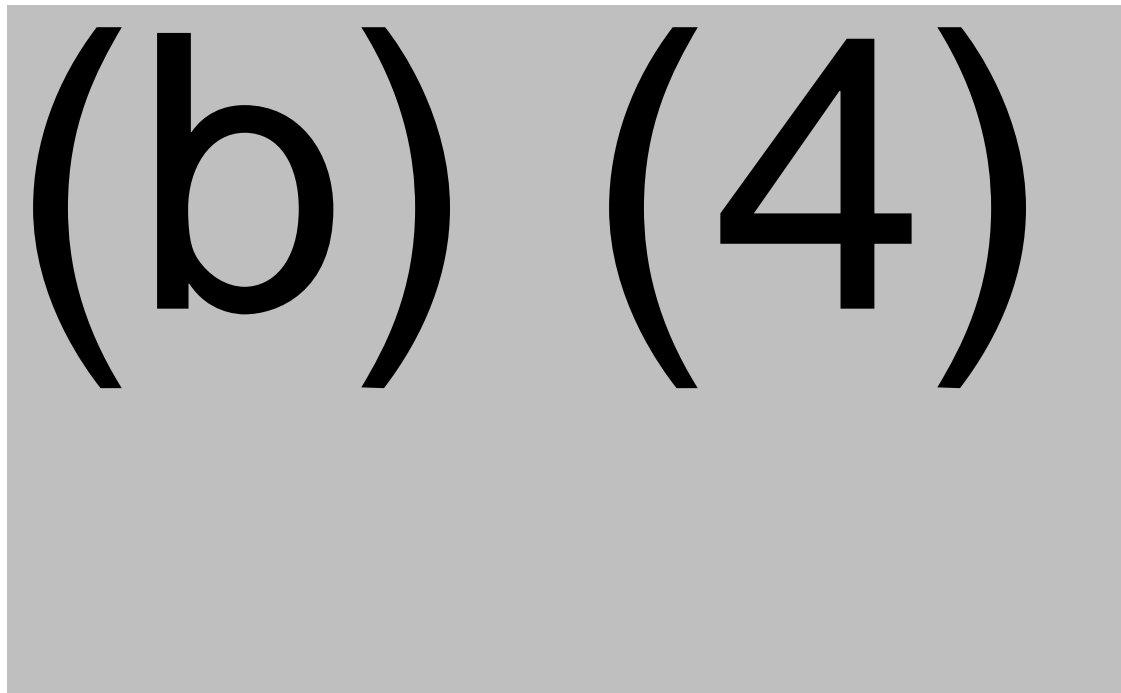


Table 1: Release Specifications for *Der pte* and *Der far* source material^{(b) (4)}



(b) (4)

Table 2: Release Specifications for *Der pte* and *Der far* source material^{(b) (4)}



(b) (4)

(b) (4) [Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

2. Review of Drug Substance

2.1 DS Manufacturing Process (BLA Sections 3.2.S.2.2 and 3.2.S.2.3)

(b) (4) [Redacted]

[Redacted]

[Redacted]

(b) (4)

3.0 Review of Drug Product

The drug Product (DP) is a white to off-white circular tablet with a debossed pentagon detail on one side. The tablet is manufactured using (b) (4). The tablet formulation consists of Der pte and Der far DSs mixed with gelatin and mannitol. The tablet disintegrates in <10 sec when placed under tongue. Each tablet contains 12 SQ-HDM extract. The potency of the tablet is determined using (b) (4) assay against (b) (4) IHR material. The commercial unitage for the tablet is SQ-HDM. SQ is (b) (4) standardization method for quality of the product.

3.1 Pharmaceutical Development (BLA Section 3.2.P.2)

For manufacturing of the DP (b) (4) to Catalent, Swindon, UK. (b) (4) fish gelatin (b) (4) Mannitol is included in the formulation for (b) (4). Purified water is used as vehicle for the (b) (4). Sodium hydroxide is used to (b) (4).

Formulation development of the DP was completed in the following stages:

(b) (4)

- Process performance qualification batches (PPQ) and commercial scale stability batches

Initial formulation of HDM tablet was based on (b) (4) and supported by stability studies. (b) (4) of (b) (4) fish gelatin referred to as (b) (4) used in the optimized formulation. (b) (4) used for formulation development for the DP. A formulation containing (b) (4) was selected as final formulation. Comparable solutions and tablet characteristics were obtained with different lots of gelatin at (b) (4). For formulation verification (b) (4) were manufactured. Manufacturing parameters were tested for robustness of the formulation and progression to pilot scale batches. No affect was observed on (b) (4). Based on the data obtained from these verification batches no further formulation optimizations were considered.

Based on a verification study performed on a (b) (4) DU batch (b) (4) and a 12 DU batch (b) (4) the DS holding time was (b) (4).

Based on development studies (b) (4)

Bench scale batches for (b) (4) DU ((b) (4)) and 12 DU ((b) (4)) were tested for 36 month at 25°C/(b) (4). Appearance and physicochemical, immunochemical results were within acceptance criteria. Based on these data no further changes were implemented.

Tablet formulation

Ingredients	Final Formulation
Dp extract	6 DU
Df extract	6 DU
Fish Gelatin, (b) (4)	(b) (4)
(b) (4)	(b) (4)
Mannitol	(b) (4)
Sodium Hydroxide	(b) (4)
Purified water	(b) (4)
(b) (4)	(b) (4)

Mannitol, purified water, sodium hydroxide and gelatin are tested as per USP/NF (b) (4) requirements. The (b) (4) of gelatin (b) (4) are monitored as a routine QC testing. The in-house specification for (b) (4) fish gelatin (b) (4).

3.2 Drug Product Manufacturing Process Development (BLA Section 3.2.P.3)

The steps in DP manufacturing process are follows;

- Drug (b) (4) preparation

- Blister forming and dosing
- (b) (4)
- Freeze-drying (b) (4)
- Inspection
- Sealing and bulk packing for subsequent secondary packaging

The DP manufacturing facility is a multiuse facility. The DP is manufactured on Line (b) (4). The final commercial scale is (b) (4) resulting in (b) (4) tablets.

Table 4: Clinical trial P001 batches manufactured using Process (b) (4)

Batch	Tablet strength (DU)	Batch size (kg)	Date of manufacturing
1381582	12		(b) (4)
1381583	12		
1424963	12		
1424964	12		
1428378	12		

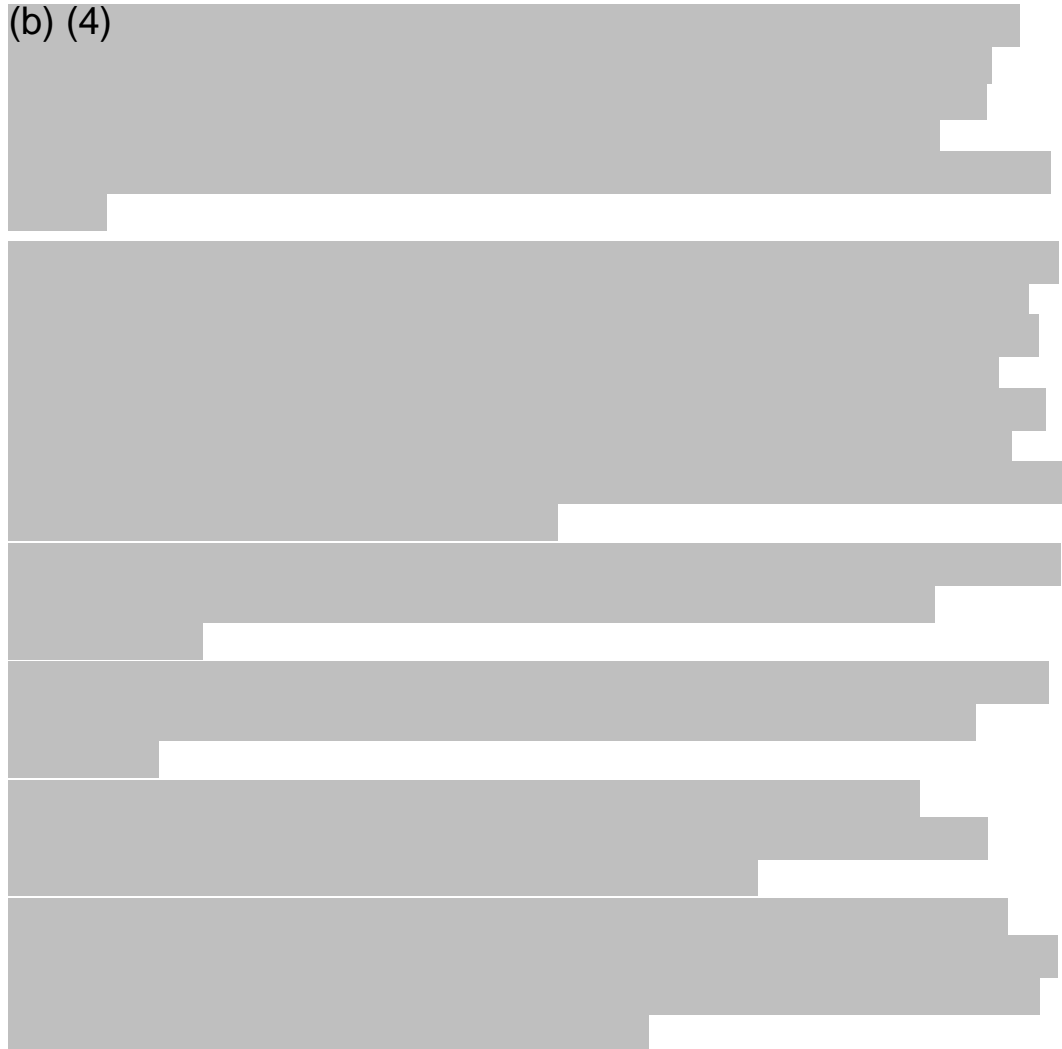
3.2.1 Pilot scale process development

(b) (4)

3.2.2 Scale up to commercial scale

(b) (4)

(b) (4)



A comparability evaluation was conducted between the clinical development batches and tablets manufactured at commercial scale. The evaluation included comparison of the composition and packaging material, process equipment, process parameters and in-process tests, batch release data and stability data.

Batch release data is provided for the clinical trial batches and three commercial scale PPQ batches. The release data for all the batches were within the proposed commercial specifications acceptance criteria as indicated in table 5. The following tests were performed;

- Appearance (AM253)
- Disintegration (AM059)
- Water content (SOP21838)
- (b) (4) (for clinical) (b) (4) (for commercial scale. SOP18309)
- (b) (4) (SOP33199)
- Major Allergen content (b) (4) (SOP18200, SOP18220)
- Microbial enumeration (b) (4) (AM732)
- Absence of specified MOs (AM714)

3.3 Manufacturing Process and Process Controls (BLA Section 3.2.P.3.4)

(b) (4)



3.4 DP Manufacturing Process Validation (BLA Section 3.2.P.3.5)

Three process validation batches were manufactured at (b) (4) commercial scale on Line (b) (4) for manufacturing process performance qualification (PPQ).

- Batch (b) (4) (date of manufacture; (b) (4))
- Batch (b) (4) (date of manufacture; (b) (4))
- Batch (b) (4) (date of manufacture; (b) (4))

The following critical process parameters for the PPQ batches were verified:

- (b) (4)
-
- The list of critical process parameters is redacted. The first item is "(b) (4)". The subsequent items are represented by grey rectangular blocks of varying widths, indicating redacted text. There are approximately 10-12 items in this list.

- (b) (4)

The critical in-process controls were measured for the PPQ batches. (b) (4)

The PPQ batches complied with the (b) (4)

The PPQ batches were tested (b) (4), water content, (b) (4), group 1 and group 2 allergen content, appearance, (b) (4), disintegration, and microbial enumeration. The results are acceptable.

The batches were also tested for (b) (4)

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

3.5 Control of Drug Product (BLA Section 3.2.P.5)

Drug product release and shelf life specifications for the 12 SQ-HDM tablet are indicated in table below.

Table 5: Drug Product Release Specifications

Test	Acceptance Criteria	Methods
Appearance	White to off-white circular freeze dried units with a debossed, pentagon detail on base	Visual Inspection
Disintegration	≤10 seconds	(b) (4)
Potency Allergen Content (Der p 1, Der f 1) Allergen Content (Der 2)	(b) (4) (b) (4)	(b) (4)
(b) (4) Total allergenic activity	(b) (4)	(b) (4)
Water content	(b) (4)	(b) (4)

(b) (4)

[Redacted text block]

3.6.2 Validation of Der p 1 and Der f 1 (b) (4)

(b) (4)

[Redacted text block]

[Redacted text block]

3.6.3 Validation of Der 2 (b) (4)

(b) (4)

[Redacted text block]

[Redacted text block]

3.6.4 Validation of water content (b) (4)

(b) (4)

[Redacted text block]

(b) (4)

3.7 Drug Product Batch Analysis (BLA Section 3.2.P.5.4)

Multiple pilot and commercial scale batches manufactured between 2011 and 2014 were used for establishing specifications for the drug product. The batches were tested for the following parameters as indicated in table 5:

- Appearance
- Disintegration
- Water content
- Total allergen content
- Der f 1 content
- Der p 1 content
- Der 2 content
- (b) (4)
- Specified microorganisms

Three PPQ batches (batch (b) (4), batch (b) (4), and batch (b) (4) manufactured in 2013 at commercial scale (b) (4) were also tested for (b) (4) in addition to the above mentioned tests.

The tested samples met the acceptance criteria of (b) (4) for group 1 and group 2 allergen content, and (b) (4) for total allergenic activity. 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.

3.8 Justification of Specifications (BLA Section 3.2.P.5.6)

The release and end of shelf life specifications for the DP are the same except for the water content limit. The acceptance criteria for the quantitative tests and assays are derived from (b) (4) historical clinical batches manufactured at a pilot scale of (b) (4). The justifications for defined specifications are summarized below;

3.8.1 Appearance: Physical state and color of the DP are determined by visual inspection. The test is performed during release at Catalent Pharma Solutions Ltd. The DP is also tested for color and appearance during stability testing (b) (4). The acceptance criteria at release and shelf life are same; white to off-white, circular freeze dried units with a debossed, pentagon detail on one end.

3.8.2 Disintegration- The tablet disintegrates in less than 10 seconds. The test is performed per (b) (4). All the DP batches complied with the acceptance criteria of ≤ 10 seconds during release testing.

3.8.3 Water content- The acceptance criteria for water content at release is (b) (4).

(b) (4)

3.8.4 Major allergen content (Potency)- (b) (4)

3.8.5 Total Allergenic Activity (Potency) - (b) (4)

3.8.6 (b) (4)

3.9 Lot Release Potency Assay

During the investigational stage of the product the plan was to use the CBER IgE competition ELISA as the final drug product release test. The CBER house dust mite reference materials and CBER human serum pool were provided to the Applicant to qualify the CBER competition ELISA for measuring potency of the drug product. During those tests it was observed that the current CBER human serum pool S8Dpf was not able to assess the potency of the drug product mostly because of the compositional differences observed between the CBER reference materials (*Der pte* and *Der far*) and the final drug product. The product is (b) (4) extracts of two species of the house dust mite. Extensive discussions and exchange of raw data and test reagents occurred between CBER and the Applicant between 2013 and September 2015 to resolve the issue of potency assay. The Applicant provided data showing the inconsistent results obtained for (b) (4) and final drug product batches when the CBER competition ELISA and CBER reference reagents were used for potency testing.

During the Pre-BLA meeting held on September 8, 2015 the Applicant proposed using (b) (4) for assessing the potency of the finished product. CBER agreed with the Applicant's proposal of using (b) (4) assay as the potency assay for the final product provided consistency of (b) (4) and IHR materials are maintained. At that time CBER also suggested the Applicant compare tablet potency to the CBER reference materials. The Agency also requested the Applicant calculate the conversion factor for CBER reference material each time (b) (4) replaces critical reagents, especially the (b) (4) and in-house *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae* reference materials. However, during the review of the BLA it was decided that since the product is compositionally different from CBER's reference material the conversion factor might be misleading and will not provide a clear profile of the product.

3.10 Reference Standards (BLA Section 3.2.P.6)

The reference material used in the (b) (4) assays are prepared by the Applicant. As discussed previously CBER reference standards and CBER lot release tests are not used for this product. For the (b) (4) assay (b) (4)

(b) (4)

(b) (4)

(b) (4)

3.11 Drug Product Container Closure (BLA Section 3.2.P.7)

The final DP is packaged in aluminum blister. The blister is (b) (4) lidding foil. One tablet is packaged in one blister cell and 10 tablets per blister card. Please refer to the DMPQ reviewer's memo for detailed information on the final DP container.

3.12 Drug Product Stability (BLA Section 3.2.P.8)

The Applicant has proposed shelf life of 36 months for the DP when stored at (b) (4) controlled room temperature.

The proposed shelf life of 36 months is based on real time data obtained from formal stability studies of three pilot scale (b) (4) batches (b) (4) manufactured using commercial process Line (b) (4). The study was configured as follows:

- 36 months under normal storage conditions of 25°C (b) (4) (36 months data is acceptable)
- (b) (4) accelerated storage conditions (b) (4) data is acceptable)

The applicant has 36 months stability data from the stability studies conducted on two pilot scale batches manufactured on the commercial line ((b) (4)).

- 36 months under normal storage conditions of 25°C (b) (4)
- (b) (4) under accelerated storage conditions of (b) (4)

One commercial scale batch ((b) (4)) manufactured on the commercial production line was placed for stability on April 15, 2013

- 36 months under normal storage conditions of 25°C (b) (4) (36 months data is available and complied with acceptance criteria)
- (b) (4) under accelerated storage conditions of (b) (4) data is within specifications)

The stability studies for PPQ batches (b) (4) were initiated on April 30, 2014. 28 months of stability data is available for storage conditions of 25°C (b) (4) storage and (b) (4) of stability data is for (b) (4)

(b) (4) pilot scale batch (b) (4) was also tested for (b) (4)

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

Testing intervals were dependent on the length of the study and the parameter assessed.

- Appearance
No change in appearance of the tablets was observed at any of the stability time points and stability conditions
- Disintegration
All the tablets disintegrated within 10 seconds with an average of 3 seconds.
- Group 1 and Group 2 content, Total allergenic activity
All reported results complied with acceptance criteria and no meaningful trends were observed in any of the studies over the stability storage period at either storage condition.
- Water content
Water content complied with the acceptance criteria for DP batches stored (b) (4)

- Microbiological Quality
(b) (4)

5.0 CBER Information Requests and Applicant's Responses

On April 1, 2016 an information request was communicated to the Applicant. The responses received on April 8, 2016 (**amendment 4**) are in italics and the final outcome of the response is in bold.

1. Please provide Standard Operating Procedures (SOPs) for all of the release tests described in Sections 3.2.S.4.2 and 3.2.P.5.2 - Analytical Procedures.

Merck: SOPs for the DS and DP release tests are provided.

Review: The response is acceptable.

2. The Clinical Study Report (CSR) provided for clinical study P001 (Section 5.3.5.1) lists the clinical supplies dispensed to subjects as manufacturing lot numbers; (b) (4). The placebo lots are indicated as (b) (4) (pages 4 and 5 of 637). Please indicate the section of Module 3 that contains the product information regarding the above listed drug product and placebo batches used in study P001.

Merck: (b) (4) designated numbers do not match with Merck assigned numbers for the same lots in the CSR. Section 3.2.P.5.4 is amended to include the corresponding assigned numbers. CoAs are provided for Placebo (b) (4) are included in amendment 4.

Review: This is acceptable.

3. Section 3.2.R (Regional Information) contains drug substance batch records written in (b) (4). Please provide executed batch records for the commercial scale drug substance batches in English.

Merck: English translations of the batch records for the intermediate products and the drug substances are added in Section 3.2.R.

Review: Batch records of (b) (4)

DS (doc (b) (4) are acceptable.

On June 24, 2016 an information request was communicated to the Applicant. The responses received on August 5, 2016 (**amendment 16**) are in italics and final outcome of the response is in bold.

1. Figure 2 has (b) (4) listed as (b) (4). Please clarify the need for performing (b) (4) steps for manufacture of (b) (4)

Merck: (b) (4)

Review: The response is acceptable.

2. Section 3.2.S.2.3. Attachment 1 of this section is a representative Certificate of Analysis (CoA) from (b) (4). We note date of manufacture but no expiration date is indicated on the CoA. Please explain why no expiration date is included on the CoA and specify if an expiration date is assigned to the (b) (4).
Merck: The expiration date is assigned by (b) (4) based on the date of manufacture. Based on real time stability data the expiration date for the (b) (4) SM is (b) (4) from date of manufacture. The data is provided in section 3.2.S.2.3.1.
Review: The data and expiration date are acceptable.
3. Section 3.2.S.2.3- Your proposal of assigning (b) (4) shelf life to the source materials is not acceptable based on (b) (4) data (Tables 8, 9, 10, and 11). Please provide (b) (4) real-time stability data in support of your proposal.
Merck: The proposal for shelf life is revised from (b) (4). The study is in progress and will continue as planned for (b) (4).
Review: The response is acceptable. .
4. Section 3.2.S.2.3- Please identify the reference materials for (b) (4) (b) (4) that are used for comparison of (b) (4) during stability testing. Please provide representative images of (b) (4) comparison tests.
Merck: The reference materials are (b) (4) that are established as a (b) (4). (b) (4) SM are compared with (b) (4). The (b) (4) for each SM are provided.
Review: The (b) (4) are acceptable.
5. Section 3.2.S.2.3- Please indicate the critical steps identified during the production of source materials.
Merck: The critical parameters for both Der pte and Der far SMs are included. The critical parameters are; (b) (4)
Review: The response is acceptable.
6. Section 3.2.S.2.4- Tables 4 and 5, in-process controls for Dermatophagoides pteronyssinus (Dp) and Dermatophagoides farinae (Df) (b) (4), have holding time of (b) (4). Please indicate the exact holding time and provide data in support of the holding time.
Merck: The holding time for (b) (4). The data in support of (b) (4) is provided in section 3.2.S.2.6.7.
Review: The data supports (b) (4) holding time for both intermediates. The response is acceptable.
7. Section 3.2.S.2.4- You indicate that a study was performed to evaluate the parameters that could impact the quality of the drug substance. Please indicate the test methods and data collected to assess the quality of the drug substance in this study.

Merck: The details of process parameters studies and justifications for the defined range are provided in section 3.2.S.2.6.7.

Review: The studies performed to assess process parameters that could impact quality of the DS are acceptable.

8. Section 3.2.S.2.5- You state that the (b) (4) was only performed on Df species as the manufacturing processes are identical for both species and the results of Df (b) (4) are applicable to Dp species. We understand that (b) (4) We suggest that you perform (b) (4) for Dp species as well. Please comment.

Merck: (b) (4)

Review: The justification and clarification provided are acceptable.

9. Section 3.2.S.2.6-During drug substance manufacturing process development the (b) (4) was not tested for (b) (4). Please explain the discrepancy.

Merck: Both (b) (4) has been tested for (b) (4) during DS manufacturing process development. Sections 3.2.S.2.6.7.1.2.2 and 3.2.S.2.6.7.1.2.3 have process parameters studies performed for (b) (4) (b) (4)

Review: The response is acceptable.

10. Section 3.2.S.2.6-In section 3.2.S.2.6.4, Figure 2 ((b) (4)) you indicate that Dp and Df drug substances were (b) (4). Please provide a representative (b) (4).

Merck: The (b) (4) indicated in the figure2 are further clarified.

Review: The response is acceptable.

11. Section 3.2.S.2.6- Please provide detailed information about IHR used during the tests conducted for comparison of the manufacturing process (b) (4) and process (b) (4).

Merck: The IHRs used for the comparability study demonstrating comparability between DS manufacturing process no. (b) (4) and (b) (4) were batch (b) (4) (Der far) and (b) (4) (Der pte). Section 3.2.S.5.5 has table containing specifications for this IHRs.

Review: The response is acceptable.

12. Section 3.2.S.2.6-In figure 5, ((b) (4)) the (b) (4). Please provide (b) (4) with label on the side (b) (4).

Merck: The figure is revised and included.

Review: The revised figure is acceptable.

13. Section 3.2.S.2.6-In section 3.2.S.2.6.6, Table 2, (Overview of Dp)(b) (4)

(b) (4)

(b) (4)

Review: (b) (4)

The response is acceptable.

14. Section 3.2.S.2.6-Figure 8 of (b) (4)

Merck: The requested figure is provided.

Review: The response is acceptable.

15. Section 3.2.S.4.3- The (b) (4) of the drug substance is not validated. Please comment.

Merck: (b) (4)

The established acceptance criterion is included in a table.

Review: The qualification of the (b) (4) for the DSs is acceptable.

16. Section 3.2.S.4.3- Please provide validation data (b) (4) [REDACTED] are included in the submission for review.
- Merck: (b) (4) for the robustness experiments performed for the (b) (4) [REDACTED] procedure are provided. Robustness study was performed and result summary is included.*
- Review: The parameters tested and results obtained as represented in the figures show the robustness of the (b) (4) [REDACTED] and suitability for the intended use.**

17. Section 3.2.S.4.3- The acceptance criteria for %CV of intermediate precision in case of Der (b) (4) [REDACTED]

Merck: The acceptance criteria for both Dp and Df are data driven. The method set up is identical except the IHR which is (b) (4) [REDACTED]. The difference in precision is expected.

Review: The response is acceptable.

18. Section 3.2.S.4.3- Please clearly state the procedure used to validate (b) (4) [REDACTED] for repeatability and intermediate precision in terms of number of operators, instruments, days.

Merck: (b) (4) [REDACTED]

Review: The response is acceptable.

19. Section 3.2.S.4.3-In validation of (b) (4) [REDACTED], Linearity, you have stated that linearity was validated by performing (b) (4) [REDACTED]. Please justify how you defined the acceptance criteria for linearity for both the drug substances based on (b) (4) [REDACTED]

Merck: The Applicant acknowledged lack of clarity. The acceptance criteria for linearity are data driven and are defined based on investigation of (b) (4) [REDACTED] for each DS species during development.

Review: The response is acceptable.

20. Section 3.2.S.5-The date of manufacture for the current Dp IHR (b) (4) [REDACTED] is April 3, 2013 and for Df IHR (b) (4) [REDACTED] it is April 10, 2013. Based on the assigned shelf life of (b) (4) [REDACTED] both these IHRs are currently expired. You state that the (b) (4) [REDACTED] stability study (Study 2) is initiated for these two IHRs. Please provide (b) (4) [REDACTED] stability data for these two commercial scale IHRs.

Merck: (b) (4) [REDACTED] stability data for the confirmatory stability study 2 of commercial scale IHRs is provided. The study was initiated on June 27, 2013. The (b) (4) [REDACTED] data will be provided in December 2016. On December 18, 2015 Der

pte IHR (b) (4) and Der far IHR (b) (4) were replaced with current IHRs Der pte IHR (b) (4) and Der far IHR (b) (4).

Review: The stability data show that IHRs remains stable for (b) (4) when stored at (b) (4) stability data for the Der pte and Der far IHRs was requested. The Applicant provided (b) (4) data for Der pte and Der far commercial scale IHRs in amendment 38. The data are acceptable.

21. Section 3.2.S.5- Please specify the current IHRs for Dp and Df HDM.

Merck: Der pte IHR (b) (4) (date of manufacture May 5, 2015) and Der far IHR (b) (4) (date of manufacture April 7, 2015) are the current IHRs. The specifications with acceptance criteria are provided. IHR section 3.2.S.5.2 of the BLA is updated with additional information such as (b) (4)

Review: The response is acceptable.

22. Section 3.2.S.5- Please provide stability data for the current (b) (4) that was placed for stability testing on June 2014.

Merck: The (b) (4) was placed for stability testing in June 2014 and currently (b) (4) stability data are available. The data is included. Sections 3.2.S.5.1 and 3.2.S.5.7 of the BLA are updated. (b) (4) is no longer the (b) (4) qualified and released for use on the 17th of June 2016.

Review: The results for (b) (4)

23. Section 3.2.S.7-You indicate that during stability studies pilot scale drug substance batches were stored in (b) (4). Please comment whether the storage containers used during this study follow the same specification as the storage containers used for commercial scale batches.

Merck: The DS containers, (b) (4) for normal storage and storage in stability studies are of the same material. The (b) (4) is the only difference.

Review: The response is acceptable.

24. Section 3.2.S.7-Your proposal of (b) (4) shelf life for Dp and Df drug substance batches is not acceptable. The stability data you included in the submission is for (b) (4) for the pilot scale batches. Please provide stability data collected under real-time storage conditions in support of your proposal of (b) (4) shelf life for the DS of both species of house dust mite.

Merck: The applicant acknowledged the comment and proposed a shelf life of (b) (4) for the DS of both species of HDM based on the available stability data. Sections 3.2.S.7.1 and 3.2.S.7.3 are updated with stability summary and stability data respectively.

Review: (b) (4) stability data is provided for the commercial scale batches (Dp DS (b) (4) and Df DS (b) (4); study 2) and (b) (4)

data is available for the three PPQ batches of each species (study 3). The response is acceptable.

On September 12, 2016 an additional information request was communicated to the Applicant through email. The response received from the firm on September 14, 2016 (**amendment 21**) is in italics, final outcome of the response is noted in bold.

1. Please submit the (b) (4) method validation for the drug substance.

Merck: Report 16-07-DO716-b, validation of (b) (4) test in HDM (b) (4) is included.

Review: The validation was performed from April 2010 to March 2011. The (b) (4) from the test samples was within acceptance criterion. The validation report is acceptable. Additional information can be found in DBSQC review memo.

On September 14, 2016 an information request was communicated to the Applicant.. The responses received from the Applicant on October 07, 2016 (**amendment 27**) are in italics and the final outcome of the responses are noted in bold.

1. We notice that (b) (4) is not included as release specification for Der pte and Der far (b) (4) source materials. (b) (4)

The stability data included in the BLA amendment submitted on August 5, 2016 show (b) (4)

can cause (b) (4). Please include (b) (4) as release test for Der pte and Der far (b) (4).

Merck: Agreed to introduce (b) (4) for Der far and Der pte (b) (4) source materials (SMs). Data is currently being collected to define these (b) (4) limits. The limits will be justified based on a minimum of (b) (4) data points for each SM. The limits are expected to be established at the end of 2016.

Review: The response is acceptable.

2. Section 3.2.S.2.6.7, Justification of acceptance criteria and PARs for the commercial scale production process, Table 3 -Process Parameters for the HDM Der far and Der pte (b) (4) indicated as non-critical parameter. (b) (4) outside the range can (b) (4). Please comment and amend the critical parameter table.

Merck: The process parameters and their criticality have been defined using a risk-based approach and were based on an overall scientific evaluation of the data obtained during process parameters studies and process justification studies. (b) (4) during Der pte and Der far (b) (4) were verified based on variation in critical quality attributes (CQAs). Within the tested range of (b) (4) negligible variation was observed and therefore, this parameters is classified as non-critical.

Review: The (b) (4) included in the amendment show negligible variation in CQAs. The response is acceptable.

3. In section 3.2.S.2.6.7 you have (b) (4) [REDACTED]. Please clarify this statement and indicate the outcome of a batch that does not pass the acceptance criteria for (b) (4) [REDACTED].
- Merck: The acceptance criterion for (b) (4) [REDACTED] of the DS is (b) (4) [REDACTED]. All HDM batches to date have complied with this in-process test, indicating that the process is running in a state of good control. However, in the future, if a batch does not comply with the acceptance criterion (b) (4) [REDACTED] a deviation will be initiate according to (b) (4) [REDACTED] procedure. The deviation will identify the root cause, corrective actions, and disposition of the batch. Deviations must be approved by quality assurance.*

Review: The response is acceptable.

4. Please indicate qualification procedure for each new batch of (b) (4) [REDACTED]

Merck: New batches of (b) (4) [REDACTED]

Review: The response is acceptable.

5. Please clearly indicate the method (b) (4) [REDACTED] currently used for determining the total allergenic activity of the (b) (4) [REDACTED] DP batches during release and stability testing.

Merck: For (b) (4) [REDACTED] is performed for DP release and stability testing.

Review: The response is acceptable.

6. Please provide qualification protocol and data for the drug substance (b) (4) [REDACTED]

Merck: Validation Protocol (attachment 1 in amendment 27) and Validation Report are provided in response for (b) (4) [REDACTED] testing of the Der far and Der pte drug substances.

Review: The response is acceptable. The (b) (4) [REDACTED] qualification reports are reviewed by DMPQ reviewer.

7. In section 3.2.P.3 Drug Product Manufacturing Process you have that (b) (4) [REDACTED] is responsible for the storage. Please clarify.

Merck: The drug product is shipped from Catalent Pharma Solutions (b) (4) [REDACTED] secondary packaging at the (b) (4) [REDACTED].

Review: The response is acceptable. The issue was also clarified by Merck during the Pre-Approval Inspection (see EIR of the PAI).

8. Please indicate the amount of drug substance used during commercial scale manufacturing of a drug product batch.
Merck: The range for the amount of drug substance used is (b) (4). The amount for each drug substance is calculated based on (b) (4) of each drug substance batch. Calculation example for DP PPQ batch (b) (4) is provided.
Review: The response is acceptable.
9. In section 3.2.P.5, control of drug product, we notice that drug product batches are not tested for (b) (4). Assessing (b) (4) in comparison to in house reference material is indicative of compositional consistency among the batches and overall quality of the final product. We suggest you include (b) (4) test for the drug product.
Merck: Agreed to implement an assessment of (b) (4) as drug product release specification. The (b) (4) of the drug product will be compared with the IHR. Sections 3.2.P.5.1, 3.2.P.5.2, and 3.2.P.5.3 are updated.
Review: The response is acceptable.
10. Please provide qualification protocol and data for drug product microbial enumeration tests.
Merck: Qualification protocols and reports for (b) (4) tests for DP are provided as attachments (amendment 27).
Review: The reports are reviewed by the DBSQC reviewer. Please refer to that memo for additional information.
11. Please provide 36 month stability data for pilot scale drug product batch (b) (4)
Merck: 36 months stability data is provided for the batch (b) (4). Section 3.2.P.8.1 is updated with stability data and summary.
Review: The response is acceptable.
12. Please provide additional stability data for Process Validation batches and additional commercial scale batch (b) (4). The stability for PPQ batches was initiated on April 30, 2014 and batch (b) (4) was place for stability test on April 15, 2013.
Merck: 36 months stability data for commercial scale batch (b) (4) and 28 months stability data for process validation batches are provided.
Review: The updated stability data is acceptable.
13. Please provide Certificate of Analysis issued by Catalent, UK for the final drug product.
Merck: CoA for PPQ batch (b) (4) is provided (attachment 6 in amendment 27). The final CoA is prepared by (b) (4) and is provided in attachment 7.
Review: The final CoA from (b) (4) that includes the tests performed by Catalent is acceptable. For the future batches CoA will also have (b) (4) as well.
14. Please provide certification for gelatin from the supplier.

Merck: CoAs are provided for (b) (4) gelatin. Catalent also issues a CoA for gelatin after performing additional testing after receipt.

Review: CoAs are acceptable.

15. Please provide Certificates of Analyses for mannitol and sodium hydroxide.

Merck: CoAs are provided.

Review: CoAs are acceptable.

On October 18, 2016 an information request was communicated to the Applicant regarding (b) (4) assay. The summary responses received from the Applicant on November 4, 2016 (**amendment 34**) are in italics and the final outcome of the response is noted in bold.

1. In enclosure 2 submitted in the July 1, 2016 amendment to your BLA we notice DP (b) (4) procedure indicated as “draft”. Please clarify if the procedure is draft or final.

Merck: The attached SOP18309 version 6.0 is the current of the DP (b) (4) analytical procedure. Version 5.0 was a draft version until the validation report was finalized.

Review: The response is acceptable.

2. Please indicate if the (b) (4) assay is completely validated and the validation report submitted on July 1, 2016 is final and not experimental.

Merck: The (b) (4) assay is completely validated and the validation report is final and valid from 07 Aug 2013. The word version of the report was provided as amendment 11 (July 01, 2016). An identical signed PDF version of the report (16-07-DO1020-a) is included in amendment 34 (November 04, 2016).

Review: The response is acceptable.

3. Please indicate the ICH guidelines used for the validation of (b) (4) procedure.

Merck: The (b) (4) procedure was validated in accordance with the principles described in the ICH guideline Q2(R1) “Validation of Analytical Procedures: Text and Methodology”.

Review: The response is acceptable.

4. (b) (4) analytical worksheet 18310-11.0 has (b) (4) HDM DP (b) (4). This reference material is made up of IHR batch (b) (4) and IHR (b) (4). Please indicate the date of manufacture of these IHRs and of these two specify Der p and Der f IHR.

Merck: The DOM of Der far IHR (b) (4) is April 07, 2015 and for Der pte IHR (b) (4) is May 05, 2015.

Review: The response is acceptable.

5. Please provide the procedure for sample reanalysis used during (b) (4) validation.

Merck: During (b) (4) validation for the HDM drug product, (b) (4)

(b) (4)

Review: The response is acceptable.

6. Please provide a list of all the (b) (4) runs performed in the quality lab for the potency test and (b) (4) of the drug product batches with reportable results for (b) (4). Please include all rejected runs in the list and specify the reason for the rejected runs.

Merck: Amendment includes table of all approved analytical runs performed in quality lab indicating (b) (4) in mDU/mL and final reportable result for each sample in % of stated amount. In a separate table there are (b) (4) DP (b) (4) runs for all potency tests performed in quality lab. Out of (b) (4) runs two were rejected (runs 884-2016-435 and 884-2016-461; control sample was outside current control limits).

Review: The response is acceptable.