



Memorandum

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To: File, STN 125592

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Applicant: Merck Sharp & Dohme Corp., U.S License No.0002

Subject: Testing in Support Summary Memorandum

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 the final drug product (DP) is ODACTRA. The ODACTRA final DP is a fast-dissolving tablet manufactured by Catalent (Swindon UK) using (b) (4). The tablet disintegrates in less than 10 seconds when placed under the tongue.

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 DSs are manufactured by (b) (4). The final DP is manufactured by (b) (4) *Der far* and *Der pte* DS (b) (4) dosing into blister packs. The potency of the DP is determined by measuring group 1 and group 2 allergen content and total allergen activity.

Review

The manufacturing process is discussed in detail in the CMC product reviewer's memo for this BLA. A brief summary of the manufacturing process follows:

- **Drug Substance:** (b) (4)
Dermatophagoides pteronyssinus and *Dermatophagoides farinae* (b) (4)

(b) (4)

- **Drug Product:** (b) (4)
(b) (4) dosing and freeze-drying into blister packs.

Each DP tablet contains 12 SQ-HDM (b) (4). The potency of the final DP is based on the standardized amount of allergens from each species. 1 DU in the HDM tablet is the sum of 0.5 DU of *Der f 1* and 0.5 DU of *Der p 1*.

The Applicant manufactured three DP Process Performance Qualification (PPQ) lots at the (b) (4) commercial scale as part of their validation studies. The three PPQ lots ((b) (4)) were not sealed with foils containing FDA approved labeling information. In addition, the lots have an expiration date of March 2017. Due to these factors, the lots were not considered for commercial release.

Lot release results included in the original submission for the 3 PPQ DP lots are provided in Table 1 below.

Table 1: (b) (4) Lot Release Results of Process Performance Qualification Lots

Release Tests	Analytical Procedure	Acceptance Criteria
Appearance	Visual examination	White to off-white circular freeze-dried units with a debossed pentagon detail on base
Disintegration	(b) (4)	<10 seconds
Water content	(b) (4)	(b) (4)
Total allergenic activity (potency)	(b) (4)	(b) (4)
Der f 1 content (potency)	(b) (4)	(b) (4)
Der p 1 content (potency)	(b) (4)	(b) (4)
Der 2 content (potency)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)

(b) (4)

(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Test for specified microorganisms (b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)

The Applicant's potency test method for the ODACTRA DP is the (b) (4) method is a quantitative (b) (4) used to determine the total allergen activity of HDM DP

The (b) (4) method was qualified at CBER. Biologists in the Laboratory of Immunobiochemistry (LIB) qualified the (b) (4) Potency test method using final DP tablets from the PPQ lots between October and December 2016. The method and the data analyses were performed according to the Applicant's procedure, Doc ID: SOP18309-05 "Translation of SOP 18308-5.0. DP (b) (4) Analytical Procedure for HDM Tablets". Critical reagents indicated in Table 2 were provided by the Applicant.

Table 2: Critical reagents received from (b) (4)

(b) (4)	(b) (4)
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The following are steps involved in (b) (4):

- (b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

Summary of the (b) (4) Method and LIB test results:

(b) (4)

(b) (4)

(b) (4)

A 5x5 grid with a 1x1 square at (1,1), a 2x2 square at (2,2), and a 3x3 square at (3,3).

(b) (4) Review Issue:

During review of the Applicant's validation report submitted on July 1, 2016 in amendment 11, the product reviewer and LIB reviewers noted the system suitability criteria of the (b) (4) method was not properly defined and were rejected by the Applicant during multiple validation multiple runs. Additional tracking and trending data was requested and submitted for review. The additional data was reviewed by the product reviewer, LIB, and an assay consult reviewer. The reviewers found the data acceptable as very few assay runs were rejected between 2014 and 2016. The Applicant's validation of the assay with supportive additional data was found acceptable for approval of the BLA.

Testing in Support Rationale

A Lot Testing Plan (LTP) was developed for ODACTRA. The final format of the Lot Release Protocol (LRP) was agreed upon by CBER and the Applicant. All required CBER personnel were involved in the review and development of the LRP and the LRP.

As described previously in this memo, the Applicant manufactured 3 ODACTRA DP PPQ lots. During CBER's qualification of the Applicant's (b) (4) potency test; the 3 PPQ lots were tested multiple times. The LIB potency test results are considered supportive of this BLA. The 3 PPQ lots were not suitable for commercial release due to lack of appropriate labeling and an expiration date in March 2017. The Applicant does not have additional final DP lots or launch lots available for testing. The review committee determined that requesting the Applicant to submit additional samples of the same 3 PPQ lots for further supportive testing was not an efficient use of FDA resources and would not provide additional information. OVR management concurred with this decision. The (b) (4) potency test was the primary test of interest to CBER. Applicant testing results for other product assays were reviewed by

the product reviewer under the Analytical Methods Validation section of the BLA and found acceptable. All assays on the lot release protocol were found suitable for their intended use.

The LRP for DP PPQ lot (b) (4) containing all supportive testing data was reviewed multiple times during development of the LRP and was found acceptable. The 3 PPQ lots cannot be released commercially as previously described. Therefore, the review committee determined that submission of the LRPs for CBER release was not required.

Recommendation

I recommend approval of this BLA.
