

RECORD OF TELEPHONE CONVERSATION

Submission Information

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Review Office	OVRR
Applicant	Merck Sharp & Dohme Corp. / Lic. # 0002
Product	House Dust Mites Allergenic Extract
Trans-BLA Group:	No

Telecon Details

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Author	STEELE, MATTHEW
EDR	No
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FDA Originated?	Yes
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Related PMCs	None
Telecon Summary	CMC IR
FDA Participants	Matt Steele
Applicant Participants	Nadine Maragarettten

Telecon Body:

From: Steele, Matthew
Sent: Friday, June 24, 2016 1:57 PM
To: nadine_margaretten@merck.com
Cc: Sweeney, Colleen; Khurana, Taruna
Subject: STN 125592 IR

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Dear Dr. Margaretten,

Please see the comments we have regarding your Chemistry Manufacturing and Controls. If possible, please reply by the first week in August.

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

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

3.2.S.2.3- Control of Materials

2. Attachment 1 of this section is a representative Certificate of Analysis (CoA) from source material vendor (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) source material.
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.
4. Please identify the reference materials for (b) (4) source materials that are used for comparison of (b) (4) during stability testing. Please provide representative (b) (4) comparison tests.
5. Please indicate the critical steps identified during the production of source materials.

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

6. Tables 4 and 5, in-process controls for *Dermatophagoides pteronyssinus* (Dp) and *Dermatophagoides farinae* (Df) (b) (4) manufacturing, have (b) (4). Please indicate the exact holding time and provide data in support of the holding time.
7. 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.

3.2.S.2.5- Process Validation and Evaluation

8. 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 manufacturing processes are identical however there are subtle differences in the (b) (4) conditions. We suggest that you perform (b) (4) for Dp species as well. Please comment.

3.2.S.2.6- Manufacturing Process Development

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9. During drug substance manufacturing process development the (b) (4) was not tested for (b) (4) unlike the (b) (4) the. Please explain the discrepancy.
10. In section 3.2.S.2.6.4, Figure 2 ((b) (4)) you indicate that Dp and Df drug substances were compared with in-house reference (IHR) but the (b) (4) do not show (b) (4) for IHR. Please provide a representative (b) (4) where reference was (b) (4).
11. Please provide detailed information about IHR used during the tests conducted for comparison of the manufacturing process (b) (4) and process (b) (4).
12. In figure 5, ((b) (4)) the label is (b) (4) all of the (b) (4). Please provide (b) (4).
13. In section 3.2.S.2.6.6, Table 2, (Overview of Dp (b) (4) comparability data) stage (b) (4), you have stated that the commercial scale batch showed a (b) (4) analysis that was not present in the pilot scale. However, in Table 3, an overview of Df (b) (4) comparability data, stage (b) (4) you state that (b) (4) are present in commercial scale and pilot scale. Please explain the appearance of (b) (4) in the Dp (b) (4). Please indicate the (b) (4) and if you observed this (b) (4) during downstream processes for Dp material. Please comment if the presence of this (b) (4) has any impact on the quality of the final Dp drug substance.
14. Figure 8 of (b) (4) in section 3.2.S.2.6.6 for Df DS comparability batches for stage (b) (4) has distorted lower half. Please resubmit this figure or a representative (b) (4) clearly showing the (b) (4).

3.2.S.4.3- Validation of Analytical Procedures

15. The (b) (4) method for (b) (4) of the drug substance is not validated. Please comment.
16. Please provide validation data (b) (4). No (b) (4) of varying conditions are included in the submission for review.
17. The acceptance criteria for %CV of intermediate precision in case of Dp (b) (4) is (b) (4) while for Df it is (b) (4). The result at low, target and high values remained less than (b) (4). Please justify the acceptance criterion of (b) (4) CV for Dp sample (see Table 1 Validation of (b) (4)).
18. Please clearly state the procedure used to validate (b) (4) for repeatability and intermediate precision in terms of number of operators, instruments, days.
19. In validation of (b) (4), you have stated that linearity was validated by performing (b) (4). Please justify how you defined the acceptance criteria for linearity for both the drug substances based on (b) (4).

3.2.S.5-Reference Standards or Materials

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20. The date of manufacture for the current Dp (b) (4) is April 3, 2013 and for Df (b) (4) it is April 10, 2013. Based on the assigned shelf life of (b) (4) both these IHRs are currently expired. You state that the conformational stability study (Study 2) is initiated for these two IHRs. Please provide (b) (4) stability data for these two commercial scale IHRs.
21. Please specify the current IHRs for Dp and Df HDM.
22. Please provide stability data for the current (b) (4) that was placed for stability testing on June 2014.

3.2.S.7- Stability

23. You indicate that during stability studies pilot scale drug substance batches were stored in (b) (4) containers. Please comment whether the storage containers used during this study follow the same specification as the storage containers used for commercial scale batches.
24. 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.

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