

## RECORD OF TELEPHONE CONVERSATION

Submission Type: BLA

Submission ID: 125592

Office: OVRR

Product: House Dust Mite Allergen extract

Applicant: Merck Sharp & Dohme Corp.

Telecon Date/Time: January 18, 2017 12:00 PM

Initiated by FDA? Yes

Telephone Numbers: 301-796-7777 and 1-855-828-1770

Communication Category(ies): Other (Out of specification stability data for the drug substance and Advice on the proposed limits and (b) (4) )

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### **Telecon Summary:**

Discussion of out of specification (OOS) stability data for Der far drug substance and Der f<sup>(b) (4)</sup> proposed limits.

### **FDA Participants:**

Taruna Khurana, Ph.D., Regulatory Project Manager, CMC Reviewer, DVRPA/OVRR

Ron Rabin, M.D., Chief, Laboratory of Immunobiochemistry, DBPAP/OVRR

Capt. Colleen Sweeney, R.N., M.S., Chair, DVRPA/OVRR

LCDR Matthew Steele, Team Leader Regulatory

Jennifer Bridgewater, MPH, Associate Director for Regulatory Policy, DBPAP/OVRR

### **Non-FDA Participants:**

#### Merck

Colleen Godshall, B.S., Assoc. Dir., Regulatory CMC

Mirko Bollen, Ph.D. Assoc. Prin. Scientist, Biologics and Vaccine Formulation

Cathy Hoath, B.S., Director Regulatory CMC


Lisa Kruk, B.S. Director, Quality Operations External Manufacturing

Hendrik Nolte, M.D., Ph.D., Executive Director, Clinical Research

Nadine Margaretten, Ph.D., Director, Regulatory Affairs

Shenouda, Andro, Pharm.D., M.S, Post-Doctoral Fellow, Regulatory Affairs

(b) (4)



(b) (4)

**Telecon Body:**

Prior to the scheduled telecon the Applicant submitted multiple amendments to their BLA STN 125592 reporting the drug substance (DS) Out of Specification (OOS) result for Der f (b) (4) time point followed by investigation of the OOS. The Der f (b) (4) content of the DS is determined by (b) (4). During investigation of the OOS result the Applicant determined that the most probable root cause of the OOS results was the use of a (b) (4).

The BLA amendments included a proposal to use temporary tightened release limits for (b) (4) (b) (4) of the DS and the drug product under a “planned deviation”. These temporary release limits would be applied until the (b) (4) is corrected and the assay is revalidated. After revalidation, the temporary tightened limits would be replaced by the originally proposed wider limits. We did not find the proposal acceptable. We initiated a teleconference with Merck (b) (4) personnel to discuss and clarify their proposal and other issues related to their OOS investigation.

During the telecon we asked the Applicant to explain their proposed plan for redesigning and revalidating the Der f (b) (4) method. The Applicant indicated that they are currently working on redesigning that will be followed by the revalidation of the assay. In the meantime the Applicant plans to have temporary release limits for Der f (b) (4) results. The Applicant also mentioned that they plan to submit amendment containing a redesigned (b) (4) method by end of January 2017. We stated that their proposed use of a “planned deviation” for interim limits that would later be changed was not acceptable. Instead, the applicant should propose specific release limits as an amendment to the BLA based on their investigational findings for the OOS data. After approval of the BLA, the applicant can submit a supplement requesting approval of the originally-proposed release limits based on results of their method validation and additional supportive data. We requested that the Applicant submit an amendment with their proposed release limits for Der f (b) (4) by Monday January 23, 2017 to allow enough time for review before the action due date. The Applicant agreed.

We asked the Applicant to explain the correlation factor assigned to the new in-house reference material (IHR). The Applicant explained that whenever an IHR is replaced during an on-going stability study the (b) (4) the new IHR. The Applicant added that (b) (4) is also part of reference replacement. We asked what the replacement frequency of the IHR was. The Applicant said that currently the turnover is (b) (4), but the next batch of IHR will be a prepared at a larger scale to avoid frequent replacement.

We discussed the role of intermediate precision CV of (b) (4) in relation to the Der f (b) (4) OOS result. The Applicant agreed that (b) (4) CV for intermediate precision is reasonable for an (b) (4) assay and added that the root cause of the OOS is combination of (b) (4) is the major cause of the OOS.

We asked if the (b) (4) redesigning will be implemented for other allergens or only for Der f<sup>(b) (4)</sup>. The Applicant explained that the other allergen methods were fully validated and do not require any modifications. We asked whether validation is for Der f<sup>(b) (4)</sup> only and the Applicant confirmed that it is.

We again reminded the Applicant that the validation data with release limits needs to be submitted as a post-approval supplement and that an amendment with the new proposed limits for BLA approval be submitted by Monday January 23, 2017. There were no further discussion or questions asked and the call ended at 12:40 PM.