Memorandum

Food and Drug Administration
Center for Biologics Evaluation and Research
Office of Compliance and Biologics Quality
Division of Manufacturing and Product Quality

To: **STN 125473 Timothy Grass Pollen Allergen Extract**

From: Deborah Trout, BLA Committee Member, OCBQ/ DMPQ/MRB1 HFM-675

Through: Carolyn Renshaw, Branch Chief, MRB1, DMPQ, OCBQ, HFM-675

Subject: Review of BLA-amendment 125473/0.2 received May 3, 2013

Action Due: April 7, 2014

Recommended Action: Request additional information based on Merck's response to FDA comment 4:

Concerning your response dated May 3, 2013 to our request for information dated April 23, 2013. You did not provide validation data for the (b)(4) assay (IR comment 7) as requested. Please provide method validation to support the use of this assay. Your response should address the following:

- Does your package have adequate (b) (4) characteristics to test using the (b)(4) method?
- Is the (b)(4) standardized? Is (b)(4) added to the mixture? If so, to what concentration.
- What amount of (b)(4) is an operator able to visually see?
- Are you using a positive control (b)(4) and have you challenged the procedure to determine what (b)(4) operators can detect?
- Do you challenge the method regularly to confirm its ability to detect defects?

Merck indicates that FDA comments 1d, 9 and 11 will be provided in a separate amendment.

Review Narrative

FDA Comment 1:
The following comments pertain to the (b)(4) steps designated (b)(4) :

(b)(4)

Merck response 1a:
The critical process parameters (CPP) for the SCH 697243 drug substance are critical input or process operation parameters that should be controlled within a narrow operating range to ensure that the process is in control and that the final drug substance (DS) critical quality attributes (CQA) meet their specification. If there is a high risk of exceeding the proven acceptable range due to the parameter being difficult to control, and/or if the severity of exceeding the proven acceptable range is assessed as high, then the process parameter is deemed critical.

Categorization of the potential critical parameters was therefore based on two major considerations:

1) The parameters impact on drug substance quality and,
2) The assessed ease or difficulty of the control of the parameter

(b)(4)

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

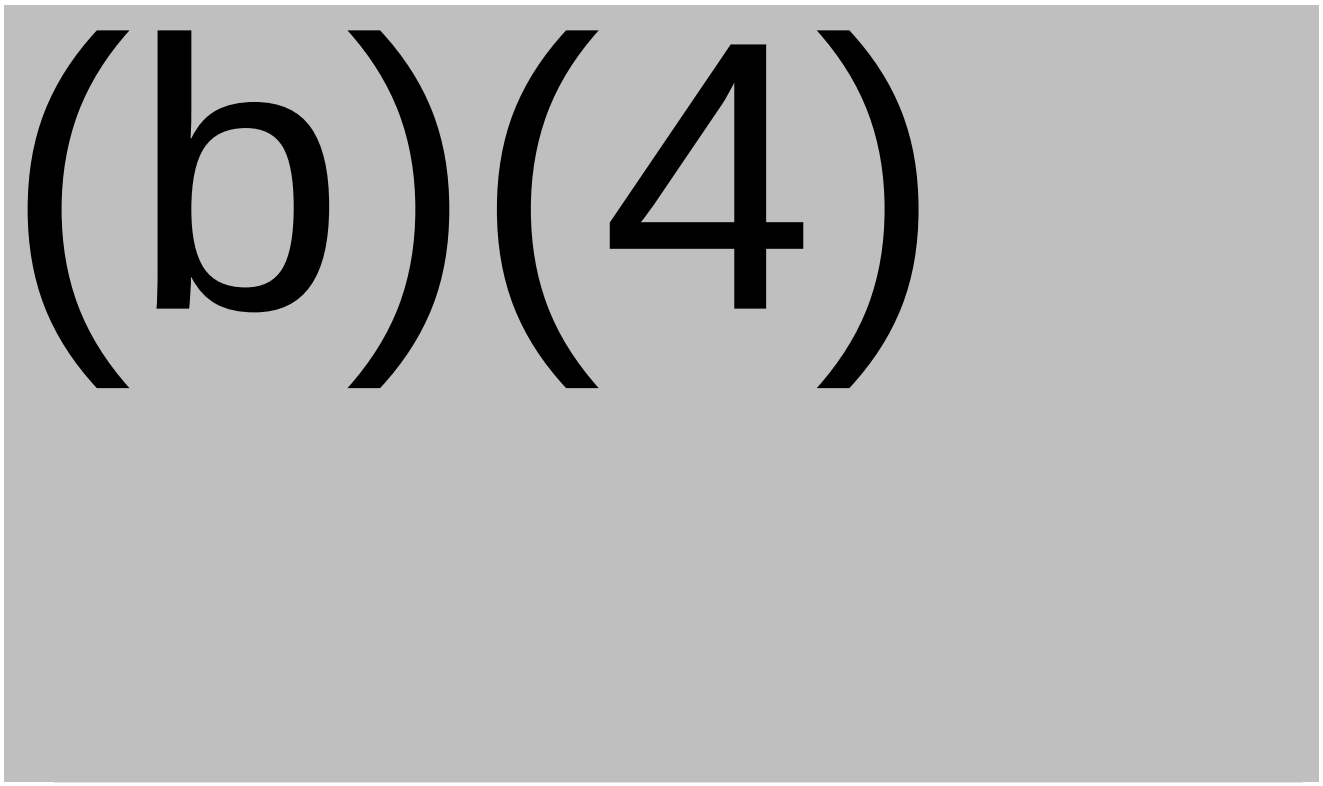
(b)(4)

The firm's response appears acceptable.

Merck Response 1d:
As indicated in an Email to Dr. Juan Lacayo from Scott Greenfeder, Ph.D. on April 23, 2013, the (b)(4) will be provided in the near future in a separate response as additional time is required to scan and prepare the documentation package.

FDA Comment 2:
In section 3.7 of 3.2.S.2.2 DESCRIPTION OF MANUFACTURING PROCESS/PROCESS CONTROLS, you describe an (b)(4) . Please provide your study design and data to support thi (b)(4)

Merck Response 2:
(b)(4)



(b)(4)

The firm's response appears acceptable.

FDA Comment 3:
You indicate that (b)(4) Tests have been measured for (b) (4) Drug Substance batches. One of the (b) (4) batches failed to meet the acceptance criteria and was rejected (Batch (b)(4)). Please provide the investigation and follow up regarding the reject of Batch (b)(4) .

Merck Response 3:
(b)(4) . The investigation was inconclusive in that no assignable cause was identified. A confirmatory retest was performed and the original result was confirmed. The batch was rejected. The (b)(4) test result for this batch is regarded as an isolated incident in that all (b)(4) test results for prior and subsequent batches were within the acceptance criteria.

The firm's response appears acceptable.

FDA Comment 4:

It appears that the (b)(4) Test is only performed on the Drug Substance at release. Please clarify if any in-process (b)(4) is performed for the Drug Substance. If in-process monitoring is not performed please provide a justification and risk assessment for not monitoring (b)(4) during production.

Merck Response 4:
(b)(4)

DS Contamination Control Plan
EM Program: The manufacture of DS is within a Controlled Not Classified facility with an established Environmental Monitoring (EM) program. The EM program for the manufacturing area includes routine sampling at qualified locations for viable air and surface testing and non-viable air testing. The Contamination Control plan includes a sanitization program including the regular use of disinfectants and sporicidal agents. This program effectively monitors resident micro-flora and affirms the continued effectiveness of the systems used to control microbial contamination.

Personnel: The Contamination Control plan includes robust gowning procedures for entrance into the manufacturing facility and includes the use of coveralls, dedicated shoes, and hair and beard covers. All operating personnel are trained in gowning and operational procedures within the controlled environment.

Materials: The Source Material (SM) for the process is harvested Timothy Grass pollen. The SM is a biologic derived from plant origin, and (b)(4)

Equipment Cleaning: Process Equipment cleaning (b) (4) is validated and includes (b)(4) . This operation includes (b)(4)

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

(b)(4)

The firm's justification and data to support not monitoring for (b)(4) ***during production will be assessed during the pre-approval inspection.***

FDA Comment 5:
Please clarify if a (b)(4) Test is performed on the Drug Substance once it is received from the Catalent Pharma Solutions in Swindon, UK.

Merck response 5:
The applicant would like to clarify, that the (b)(4) Test is not performed upon receipt of the SCH 697243 Drug Substance (DS) at Catalent Pharma Solutions in Swindon UK . The DS amount required for each batch of drug product is (b) (4) at ALK-Abello A/S, Denmark (b)(4)

The firm's response appears acceptable based on the information provided in response to FDA Comment 12 noted below.

FDA Comment 6:
Concerning the (b)(4) storage containers (b)(4) used for shipment of the Drug Substance.

a. Please clarify whether these containers are single-use or re-used.
b. Are the (b)(4) storage containers (b)(4) received clean, and if so how are they assessed for cleanliness prior to use?

Merck Response 6:
a. (b)(4) containers, (b)(4) are all single-use items.
b. The (b)(4) containers and (b)(4) are received newly manufactured from the vendor. At the vendor the containers have been (b)(4)

(b)(4)

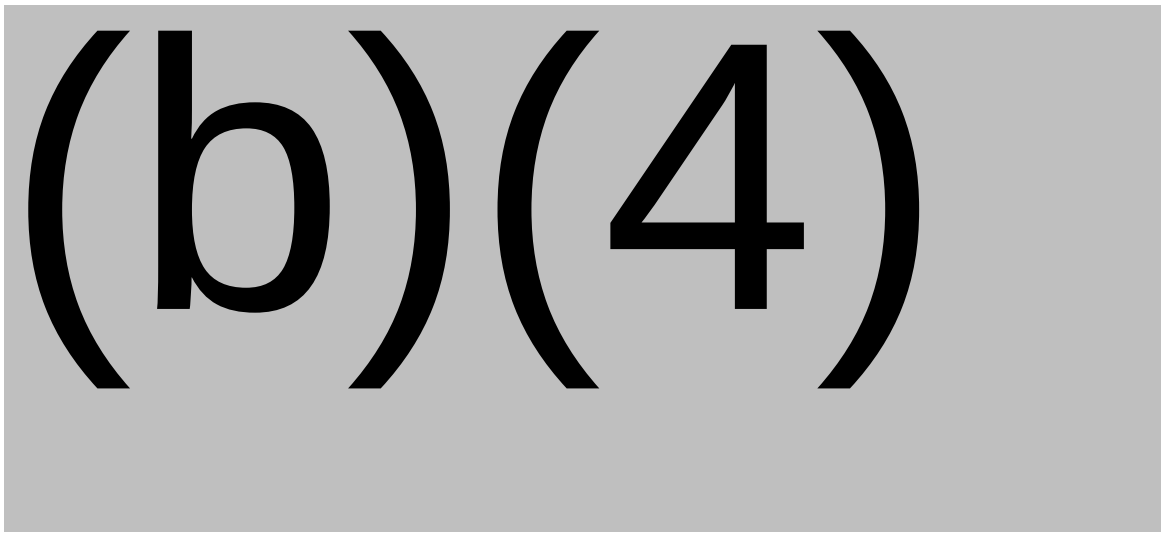
The firm's response appears acceptable.

FDA Comment 7:
Please provide validation data for the (b)(4) assay used to assess integrity of the aluminum blister cards.

Merck Response 7:
The (b)(4) test (b)(4) is an industry standard test method. The (b)(4) test is performed by (b)(4)

(b)(4)

All results comply with the acceptance criteria.



In summary, the (b)(4) as a routine In-Process Control test provides an appropriate level of assurance of seal integrity.

The firm's response is not complete. I need the following relayed to Merck ASAP.

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FDA Comment 8:
Please provide data from the lyophilization cycle used for the SCH 697243 Drug Product qualification lots that includes:(b)(4) of lyophilization.

Merck Response 8:

Freeze drying is performed using a pre-programmed lyophilization cycle. The same product specific drying cycle was used for drying the (b)(4) SCH 697243 Drug Product Process Validation batches referenced in Section 3.2.P.3.5 Process validation. The SCH 697243 lyophilization cycle

(b)(4)

(b)(4)

The firm's response appears acceptable.

FDA Comment 9:
Please provide complete OQ and PQ protocols and results for freeze driers (b)(4) freeze driers (b)(4) . Please include any testing and data confirming that all (b)(4) freeze dryers are of similar design and operating principle, and detailed explanation of any deviations which occurred during the validation.

Merck Response 9:
As indicated in an Email to Dr. Juan Lacayo from Scott Greenfeder, Ph.D. on April 23, 2013, the OQ and PQ Protocols and results for the freeze driers (b)(4) freeze driers (b)(4) will be provided in the near future in a separate response as additional time is required to scan and prepare the documentation package.

FDA Comment 10:
Please provide the (b)(4) for the SCH 697243 Drug Product.

Merck Response 10:
(b)(4)

(b)(4)

Freeze drying is conducted using a product specific drying cycle. Studies performed during product development and process validation show that the drying cycle is robust. Product manufactured using the drying cycle meets the critical quality attributes. This is demonstrated by the results of the finished product testing for the process validation batches. The results are provided below in Table 1-Table 3.

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

(b) (4)

The firm's response appears acceptable.

FDA Comment 11:
Please provide complete OQ and PQ protocols and results for the following equipment:
(b)(4)

Merck Response 11:
As indicated in an Email to Dr. Juan Lacayo from Scott Greenfeder, Ph.D. on April 23, 2013, the OQ and PQ Protocols and results for the (b)(4) will be provided in the near future in a separate response as additional time is required to scan and prepare the documentation package.

FDA Comment 12:
(b)(4)

Merck Response 12:

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