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 125473/0.4 received May 30, 2013

Action Due: April 7, 2014

Recommended Action: Responses provided for items 1d, 9 and 11 appear acceptable. Outstanding issues associated with amendment 2 will be addressed in a separate review memo.

Review Narrative

FDA Comment 1d:
Please provide equipment qualification(s) for the (b)(4) units.

Merck Response 1d:
(b)(4) All equipment qualification activities were completed successfully. All non-conformities (deviations) were documented and closed.

The overall Process Plant qualification approach is described below, and the applicable referenced qualification documents are provided in Attachment 1 through Attachment 6 (sections in Danish have been translated to English and are provided at the end of each OQ and PQ document). All other supporting qualification documentation is available on site at ALK-Abello, Hørsholm Denmark.

Qualification Approach
An overview of all OQ/PQ documentation for the Process Plant (eq. no (b)(4)), which

includes the (b)(4) unit (eq. no (b)(4)) is detailed below.

The full hardcopy qualification documentation package (IQ, OQ, and PQ,) including test plans, raw data and results from the Process Plant qualification activities is available on site at ALK-Abello, Hørsholm, Denmark. The site Qualification documentation is comprised of multiple volumes of data in a combination of English and Danish.

The following equipment qualification documents were provided in the amendment:
Attachment 1: OQ protocol (Doc ID: P13-01-DO322-a)
Attachment 2: OQ Verification of Requirements (Doc ID: P13-01-DO323-a)
Attachment 3: OQ report (Doc ID: P13-02-DO244-a)
Attachment 4: PQ Protocol and Test Scheme, (b)(4) (Doc ID: P13-01-DO396-a)
Attachment 5: PQ Retest Protocol and Test Scheme, (b)(4) (Doc ID: P13-01-DO410-a)
Attachment 6: PQ Report, (b)(4) (Doc ID: P13-02-DO296-a)
Attachment 7: Appendix 1 Summary of the FAT/SAT test plans that are referenced in the OQ for (b)(4) relevant to the (b)(4) unit. (English Translation)

Operational Qualification
The OQ protocol (Doc ID: P13-01-DO322-a), OQ Verification of Requirements (Doc ID: P13-01-DO323-a) and OQ report (Doc ID: P13-02-DO244-a) are provided in Attachment 1, Attachment 2 and Attachment 3. The OQ protocol (Doc ID: P13-01-DO322-a) is the parent document that defines the test plan requirements for the Process Plant OQ per relevant functional requirements defined in the ALK-Abello site User's Requirement Specification (URS). This includes the test plans defined in the OQ Verification Requirements document (Doc ID: P13-01-DO323-a). The OQ Verification of Requirements (Doc ID: P13-01- DO323-a) test plans include steps to confirm that all relevant functional requirements were tested successfully during the execution of Factory Acceptance Test (FAT) and Site Acceptance Test (SAT) test plans. All the FAT and SAT test plans are in Danish and encompass 11 volumes of data. The FAT and SAT test plan requirements relevant to the (b)(4) unit (eq. no (b)(4)) OQ have been translated into English and are summarized in Appendix 1 (Attachment 7). The OQ report (Doc ID: P13-02-DO244-a) is a summary of the results obtained during execution of the OQ protocol and the OQ Verification of Requirements document.

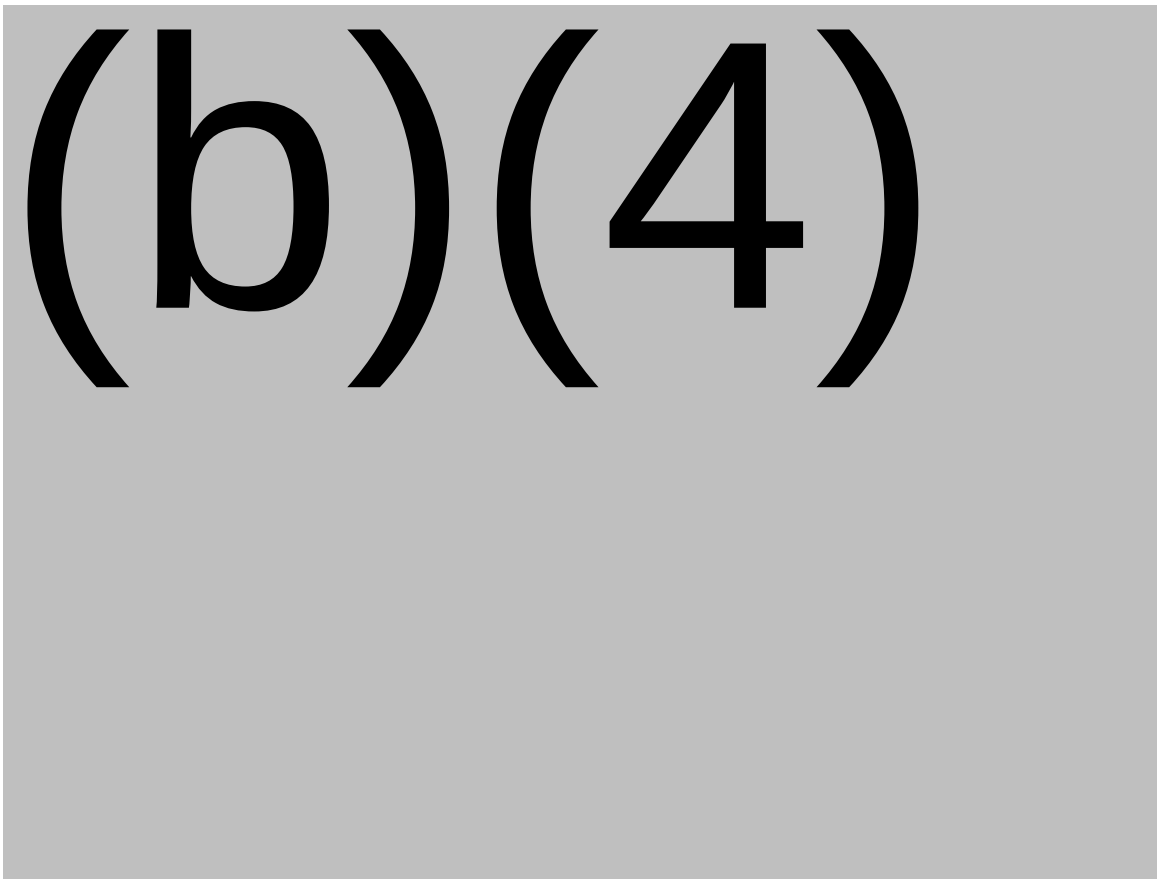
Performance Qualification
The PQ protocol (Doc ID: P13-01-DO396-a), PQ retest protocol (Doc ID: P13-01-DO410-a) and PQ report (Doc ID: P13-02-DO296-a) are provided in Attachment 4, Attachment 5 and Attachment 6. The PQ was performed for the Process Plant as one integrated unit (b)(4) and thus the PQ requirements are the overall requirements for the entire Process Plant (eq. no (b)(4)). The PQ documentation is also a combination of English (protocols and reports) and Danish (test sheets). The PQ retest protocol (Doc ID: P13-01-DO410-a) was completed to address one nonconforming result during execution of the initial PQ. The non-conformity was associated with a (b)(4) which occurred during execution of a process recipe. A nonconformity (deviation) was logged; a CAPA was identified and the retest protocol was

prepared and executed. The retest was completed successfully and the non-conformance (deviation) was closed. All PQ results, including the retest, were summarized in the PQ report (Doc ID: P13-02-DO296-a).

Periodic Equipment Review and Change Control

The processing equipment qualification status is periodically reviewed in accordance with the site Validation Master Plan. In addition, since the time of completion of the qualification, the Process Plant (eq. no (b)(4)) including the (b)(4) unit (eq. no (b)(4)) has been maintained under the site change control system. Equipment and facility qualification impact assessments and applicable requirements are completed as part of site change control. All change controls related to the (b)(4) unit are documented and available at ALK- Abello Hørsholm, Denmark.

PQ Test Plan



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

(b)(4)

Based on the data and information provided in amendment 0.2 and the equipment qualification criteria noted above Merck's responses to address FDA Comment 1d appears acceptable.

FDA Comment 9:
Please provide complete OQ and PQ protocols and results for freeze driers 2(b)(4) and 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:
The OQ and PQ protocols and summary reports for the freeze dryers (b)(4) and freeze dryers (b)(4) are listed in Table 1 and provided in Attachments 1 through 22 of the amendment.

Overview of Equipment Qualification Process at Catalent
At Catalent, when a (b)(4)

(b)(4) . All deviations which occurred during equipment qualification and process validation were investigated and results are included and explained in the summary reports.

Continuous Equipment Qualification
The validated status of (b)(4) is continuously maintained through the use of a change control system by performing impact assessment of any proposed changes to the (b)(4) and through periodic equipment reviews.

Freeze Dryer Design and Operating Principles
Freeze dryers (b)(4) were manufactured (b)(4) the freeze dryers (b)(4) were manufactured (b)(4) . These (b)(4) freeze dryers have been manufactured using the same general design and share the same operating principles and perform against very similar user requirement specifications. Specifically, (b)(4) but their function and performance requirements are identical.

(b)(4)

(b)(4)

Operational Qualification included the following:

Reviewer Note: For brevity purposes results provided below are an example of just one validation run for freeze dryer (b)(4) ***All results (Attachments 1 through 22) were reviewed for accuracy and completeness.***

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

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

(b)(4)

Lyophilization Cycle Study

- Verify the conformity of the lyophilization cycle during each phase. (b)(4) . The cycle must conform to the values and parameters in the recipe.

Actual test results were not provided. The Qualification reports indicate that all recipe parameter and value were successfully met for all lyophilzer studies.

Freeze Drying Process Validation Study: (b)(4) (Conformance Lots)

The process validation of Grazax 75000 SQ-T in (b) (4) All Aluminum Blisters (AAB) was undertaken during January 2010 on (b) (4) at a batch size of (b)(4). Grazax is currently validated for EU and German markets on (b) (4) This validation will support the (b)(4) and will support the BLA for registration of the product to the US market. Three validation batches of Grazax 75000 SQ-T (b)(4) (b) (4) AAB on (b)(4) were manufactured, as detailed in Table 1.

(b)(4)

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

(b)(4)

Freeze Drying Process Validation Study: (b)(4) (Conformance Lots)

The process validation of Grazax 75000 SQ-T (b)(4) (b) (4) AAB on (b)(4) was undertaken during (b)(4) as per validation protocol PR227903. (b)(4) . Grazax 75000 SQ-T will be filed in the US as SCH 697243 (Timothy Grass) 2800 BAU. Three validation batches of Grazax 75000 SQ-T (b)(4) (b) (4) AAB on (b)(4) were manufactured, as detailed in Table 1.

(b)(4)

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

(b)(4)

The firm's response to FDA Comment 9 appears acceptable. The recipe parameters provided in amendment 0.2 appear to be within the ranges verified during OQ studies.

FDA Comment 11:

Please provide complete OQ and PQ protocols and results for the following equipment:

(b)(4)

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

(b)(4)

The firm's response and data submitted for the (b)(4) ***appears acceptable.***

(b)(4)

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

The data and information provided for the (b)(4) ***Systems appears acceptable.***

(b)(4) (b) (4)

(b)(4)

(b)(4)

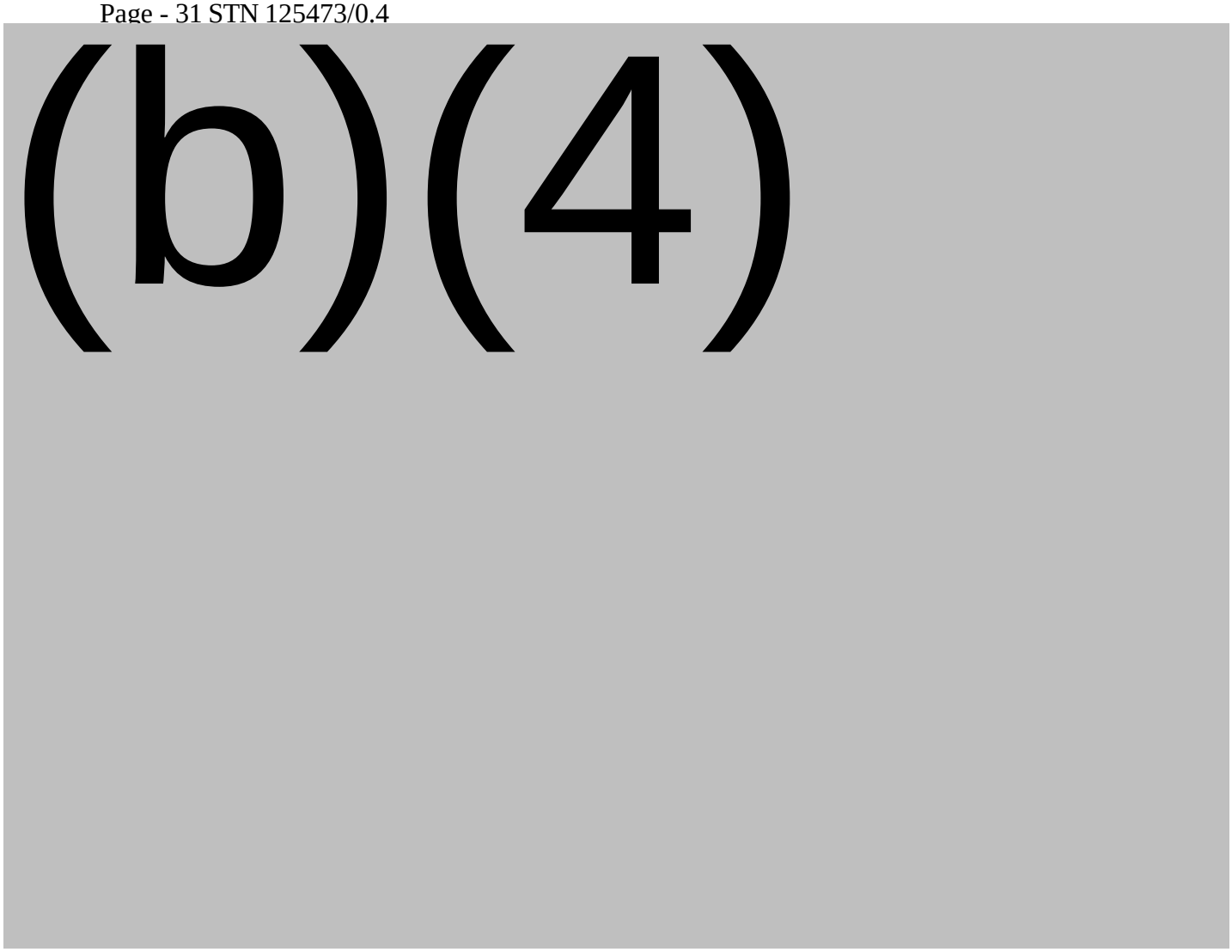
1 page determined to be not releasable: (b)(4)

(b)(4)

The data and information provided for the (b)(4) ***appears acceptable.***

(b)(4)

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



The data and information provided for the (b)(4) ***Systems appears acceptable.*** (b)(4) ***is addressed in a separate amendment.***