



To: Administrative File STN 125586/0

From: Christine Harman, Chemist, CMC facility reviewer, CBER/OCBQ/DMPQ/BI

Through: Carolyn Renshaw, Branch Chief, CBER/OCBQ/DMPQ/B1

Through: John Eltermann, Division Director, CBER/OCBQ/DMPQ

CC: Jean Gildner, RPM, CBER/OTAT/DRPM/RPMBII
Mikhail Ovanesov, (Chairperson), Product Reviewer, CBER/OTAT/DPPT

Applicant: Portola Pharmaceuticals, Inc.

Product: Coagulation Factor Xa (Recombinant), Inactivated (lyophilized)
Trade name: Andexanet alfa

Indication: For patients treated with a direct or indirect fXa inhibitor when reversal of anticoagulation is needed, in situations such as in life-threatening or uncontrolled bleeding, (b) (4) [REDACTED].

Subject: Complete Response Review: Review of the response to the CR letter items 9-12, that pertain to DMPQ issues

Due Date: February 3, 2018

RECOMMENDATION

Based on the review of the responses provided for CR items 9-12 and provided there are no outstanding issues from product office, clinical or other involved offices, approval is recommended with the following inspectional considerations for the next biennial inspection. The inspectional consideration is part of the standard scope of inspection. CBER understands that the consideration may or may not be taken (based on risk and available resources) and is not requesting documentation to be submitted as evidence of completion

- Please review the routine monitoring of (b) (4) [REDACTED] in regards to the (b) (4) [REDACTED] used in the andexanet manufacturing process to ensure there is no upward trending of the presence of spore forming micro-organisms such as (b) (4) [REDACTED].
- Please confirm that a (b) (4) alert limit of (b) (4) [REDACTED] is implemented for (b) (4) [REDACTED] used for (b) (4) [REDACTED] steps in the andexanet manufacturing process.

EXECUTIVE SUMMARY

In 2015, Portola Pharmaceuticals, Inc. submitted an original BLA STN125586/0 for licensure of Andexanet alfa and after an eight month review a Complete Response (CR) letter was issued August 17, 2016. Portola Pharmaceuticals Inc. is submitting a response to the CR letter. The response was received by CBER August 4, 2017 as amendment 76 (eCTD 0077, STN 125586/0). This memo covers the review of the firm’s responses to items 9-12. The review of the response to the other CR letter items is deferred to the appropriate offices/divisions for assessment. During the review of the responses, two Information Requests were issued to the firm. The firm’s response was received as Amendment 80 (eCTD 0081, STN 125586/0) and Amendment 94 (eCTD 0095, STN 125586/0) and found adequate. Based on the review of the responses for 9-12, approval is recommended.

I. CR Response Review narrative

The items contained in the CR letter pertaining to DMPQ issues that are covered in this review include the following:

- 9. The Proven Acceptable Ranges and Normal Operating Ranges for (b) (4) and (b) (4) indicated for the lyophilization cycle parameters used for the FDP manufacturing are not supported by the process validation provided in the BLA. Results of (b) (4) lab-scale experiments were provided in amendment 50 (received 1 Jul 2016); however, there was no justification for how the lab-scale studies support the lyophilization parameters ranges at commercial scale. Please provide a detailed plan to support these ranges at commercial scale.**

Firm Response and Data to Support: The firm provided Pharmaceutical Development Report “Measurement of Equipment Capability for Laboratory and Production Scale Freeze Dryers Relevance of Equipment Capability to the Graphical Design Space for (b) (4)” and provided a narrative in section 3.2.P.2.3.2.2 of the CR response which provides additional details in regards to the lyophilization developmental (DoE) studies not included in the original BLA submission and corresponding amendments. The additional information provided in the report and narrative are summarized as follows:

Pharmaceutical Development Report

This report summarizes the results a comparative study between (b) (4) laboratory scale lyophilizers and (b) (4) full-scale lyophilizers. The lab-scale lyophilizers and full scale lyophilizers were compared in regards to capability comparing (b) (4)

Capability Studies

(b) (4)

[Redacted text block containing multiple lines of information under the 'Capability Studies' section.]

(b) (4)

[Redacted text block]

Narrative in Section 3.2.P.2.3.2.2 Lyophilization Characterization

A more detailed description of previous information provided in past amendments during review of the BLA were provided. In the narrative, the firm indicates that a scale-down model was used to determine the Proven Acceptable Ranges (PARs) for the lyophilization step. This scale down model is supported by the Pharmaceutical Development Technical Report “Measurement of Equipment Capability for Laboratory and Production Scale Freeze Dryers and Relevance of Equipment Capability to the Graphical Design Space for (b) (4)”. The scalability from laboratory lyophilizer to the production lyophilizers was demonstrated using a model formulation containing (b) (4) combined with (b) (4) and the (b) (4)-lab scale and (b) (4) production scale lyophilizers (b) (4) smaller capacity than the other (b) (4) were compared for their (b) (4) capability by measuring the (b) (4) rate they support as a function of (b) (4). Using the laboratory-scale model, the (b) (4) and hold time during (b) (4) were studied in a DoE and modeled against the outputs that include product quality attribute testing (included but not limited to the following: reconstitution time, moisture content, protein concentration and particulate matter, etc.) and process performance attributes (including time of completion of (b) (4), time for completion of (b) (4) and (b) (4) product temperature).

The experimental design involved (b) (4) experimental runs that were used to establish the PARs for (b) (4) and (b) (4) were varied to evaluate the effects on the process and the results were indicated as follows:

(b) (4)

The (b) (4) time ranges as determined by (b) (4) ranged from (b) (4), which is within the (b) (4) hold time of (b) (4). As shown in above table, the product temperature ranged from (b) (4); all of which is below the collapse temperature of (b) (4). It was determined that the (b) (4) did not have a statistically significant effect on the time of completion for (b) (4), although theoretically, these two parameters should have an effect. The following predictive models using the data shown in above table were generated

(b) (4)

Samples from the DoE runs were tested for quality attributes such as (b) (4). All results for all runs were within the specification limits. The results of (b) (4) were indicated as follows:

(b) (4)

Reviewer Comments: The firm did not directly address this CR item given that the firm did not provide an acceptable justification or plan to support the PAR and NOR ranges at commercial scale. The Pharmaceutical Development Report, which the firm claims to support the comparability between the lyophilizers is not adequate in regards to the following:

- The firm indicated that since the capability of the production dryer exceeds that the laboratory scale that this supports the conclusion that any cycle that will run on the laboratory scale should run on the production scale equipment. However, demonstrating capability alone does not*

sufficiently support that the cycles will yield the same result in regards to product quality in that the product may not experience the same “thermal history” in the lab-scale lyophilizer as compared to the production scale lyophilizer. Thus, the firm was issued an IR to address this deficiency.

- The report did not include sufficient details in regards to how the coefficients that include the (b) (4) [redacted] were determined as these coefficients are used to generate the mathematical models which are then used to create the design space
- Figure 4 in the report which compares the capability of the small scale vs. full scale lyophilizers as a function of (b) (4) [redacted] rate vs. (b) (4) [redacted], there were more data points (b) (4) [redacted] provided for the lab-scale lyophilizer as compared to the (b) (4) [redacted] full-scale lyophilizers which only had (b) (4) [redacted] data points. Additionally, there was no data in regards to the (b) (4) [redacted] rate for either of the lyophilizers at the (b) (4) [redacted] which is the maximum end of the range in (b) (4) [redacted] for the PARs.
- There was insufficient detail in regards to the geometry of the lab-scale lyophilizer and production scale lyophilizer

Additionally, the firm did not provide sufficient details in how the predictive models for product temperature were generated and if these models were generated with the consideration of a combined influence of both (b) (4) [redacted] on the product temperature.

An IR was issued to address these deficiencies, please refer to Information Requests and Firm Response section of the memo for details of firm response.

10. In regards to the Container Closure Integrity Testing (CCIT) for stability samples performed by (b) (4) [redacted], which was incomplete, please provide the following:

a. Specific details of the “point of failure” control that was used

Firm Response and Data to Support: The firm indicated that the positive control, performed in every assay, consisted of at least (b) (4) [redacted]. The sample suitability control consists of at least (b) (4) [redacted] test article punctured using a (b) (4) [redacted]-gauge needle. Both the positive control and sample suitability control are put through the (b) (4) [redacted] procedure. Additionally, the firm noted that the CCIT method was validated to detect a point of failure defect as small as (b) (4) [redacted] created by (b) (4) [redacted].

Reviewer Comments: The firm response is adequate.

b. Clarify if visual inspection or (b) (4) [redacted] analysis was performed for product filled vials on stability

Firm Response and Data to Support: The firm indicated that (b) (4) [redacted] analysis is performed on product-filled vials on stability and described the details of the method in as follows:

- (b) (4) [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

Reviewer Comments: The firm response is adequate

c. Provide details, SOPs etc. of the visual inspection process and how operators are qualified to perform visual inspection

Firm Response and Data to Support: The firm indicated that (b) (4) analysis is performed for CCIT and there is no visual inspection performed.

Reviewer Comments: The firm response is adequate

d. Results of the (b) (4) study (in the presence of the product), which was noted in your response to IR item 5 in Amendment 50 (received 01 July 2016), to be conducted at (b) (4)

and stability determined by (b) (4) on Days (b) (4).

Firm Response and Data to Support: The firm provided (b) (4) Report 908047-S01 and summarized the results as follows:

- (b) (4) aliquots of drug product were spiked to (b) (4) of (b) (4) and observed at baseline (b) (4)
- A (b) (4) was observed at all spiking concentrations on (b) (4) and all test method acceptance criteria were met demonstrating the (b) (4) was stable up to (b) (4)

The acceptance criteria and results indicated in the report included the following:

(b) (4)

Reviewer Comments: The firm response is adequate.

11. In regards to CCIT method performed at (b) (4), please provide details, SOPs, etc. in reference to the qualification of the operators that perform (b) (4). Include a description of course 04-01-C001, which was used for the qualification of operators noted in your response to IR item 5 in Amendment 50, received 1 July 2016.

Firm Response and Data to Support: The firm provided a copy of Course 04-01-C001 in addition to the (b) (4) SOPs that were used for the qualification of operators. These documents are summarized as follows:

Course 04-01-C001: This document describes the course for qualifying operators for performing (b) (4) inspections. The steps in the procedure for the qualification process include

- Follow SOPs 04-06-046 and 04-06-047

(b) (4)

Trainees to be qualified are given (b) (4) samples to (b) (4) and the number of containers identified is documented and assessed

(b) (4) SOPs: The SOPs provided include the following:

04-06-046-10 Integrity Challenge for Container/Closure Interfaces Using Vials

04-06-047-10 Integrity Challenge for Syringe/Cartridge/Closure Interfaces

These SOPs describe the procedures and acceptance criteria for testing the container/closure interfaces of various container closure systems. The SOP includes description of the two methods used that include Microbial Challenge and (b) (4) Challenge, in addition to describing the procedures for these methods, the preparation of components for the challenges, investigation of the samples after testing and preparation of the results.

Reviewer Comments: The firm response is adequate.

12. Regarding (b) (4) equipment cleaning validation, please provide the following:

a. Validation data to support the effectiveness of the cleaning of the (b) (4)

Firm Response and Data to Support: The firm provided the following details (described in section 9.2 of 3.2.S.2.5) in regards to the validation of the cleaning effectiveness of the (b) (4)

. The report VAL-30328.02.1 was referenced (not provided in submission):

- Study focused on the additional testing performed for samples not routinely collected during execution of the processing MBRs.
- Samples were taken for (b) (4) during the (b) (4) steps
- Two different test methods were used for evaluation of (b) (4) that include (b) (4) for detection of broader spectrum of microorganisms
- Acceptance Criteria for testing for (b) (4) Validation was indicated as follows:

(b) (4)

- Results were provided as follows:

(b) (4)

(b) (4)

The firm indicated that the lots met all acceptance criteria; however, (b) (4) was detected in some of the samples tested but only exceeded the alert levels and did not exceed the action levels. All (b) (4) results were below the (b) (4) acceptance criteria with the highest result observed at (b) (4).

Additionally, in section 9.1 of 3.2.S.2.5 Process Validation and/or Evaluation, the firm provided information in regards to (b) (4) studies for the (b) (4) and for the 9.1.2 (b) (4), which was the same information provided in the original submission.

(b) (4). For the (b) (4) study for the (b) (4), the firm plans to extend repeated use of a minimum of (b) (4) product runs (referencing protocols VAL-30226-01 and Report VAL-30226-02). The first blank run was executed prior to the initial product run to demonstrate baseline cleaning effectiveness. The final blank run was executed after the final product run to demonstrate cleaning effectiveness at end of determined (b) (4). Intermediate blank runs were executed on an interval of (b) (4) product runs and not more than (b) (4) product runs. Testing and acceptance criteria performed during the study were indicated as follows:

Product Run

(b) (4)

Blank Run

(b) (4)

In addition to this testing, the (b) (4) are trended using statistical process control. The (b) (4) values for the (b) (4) step for product and blank runs must be (b) (4) of original (b) (4) value.

Reviewer Comments: In regards to cleaning validation, the firm referenced the validation report VAL-30328.02.1, but did not include the report in the amendment. Additionally, the firm indicated that (b) (4) was observed with some of the samples reaching the alert level, but that did not exceed the action level. The firm should indicate what the alert levels are and which samples exceeded the alert levels. In regards to the lifetime studies, the firm did not provide sufficient detail for how the (b) (4) are cleaned and stored and routinely monitored. Several protocols and interim reports were referenced but not provided (Protocol VAL-30226-01 and Report VAL-30226-02 (for the (b) (4)) and protocol VAL-30227-01 and report VAL-30227-02). The firm was issued an IR to provide the cleaning validation report VAL-30328.02.1, provide clarification of the alert levels, and to provide details of how the (b) (4) are cleaned and stored and routinely monitored. Please refer to the Information Request section of memo for details of firm response.

b. Validation data to support the cleaning and storage of all (b) (4). In addition, please indicate the frequency in monitoring the (b) (4) during storage.

Firm Response and Data to Support: The firm provided details of small scale (b) (4) studies, in addition to at-scale studies performed for (b) (4) that include (b) (4). These studies include the use of (b) (4) lot of (b) (4) with initial targeted maximum number of (b) (4) cycles with exceptions noted for the at-scale studies for (b) (4) ((b) (4) runs) and (b) (4) ((b) (4) runs). The firm indicated that the (b) (4) studies were completed at both small-scale and manufacturing (at-scale) scale.

All small-scale (b) (4) studies included (b) (4) runs with both product runs and blank runs. Blank runs were performed every (b) (4) run between product runs. The (b) (4) blank run for each of the (b) (4) was performed prior to the (b) (4) product run to demonstrate baseline cleaning effectiveness. There was no monitoring of (b) (4) in the small-scale studies; however, for the blank runs in the small scale studies the (b) (4) was determined by (b) (4) analysis.

For all at-scale studies performed with the (b) (4) the following testing and acceptance criteria was indicated to demonstrate cleaning effectiveness:

(b) (4)

(b) (4)

Similar to the small-scale studies, intermediate blank runs were performed on an interval of (b) (4) product runs. To confirm microbial control of the (b) (4) are taken and analyzed for (b) (4).

Small Scale (b) (4) (referenced protocol (b) (4)-CP-031 and report (b) (4)-CR-031)
Each run included the following process steps for both the small-scale studies and at-scale studies:

(b) (4)

(b) (4)

Results of Small Scale studies for (b) (4): The results for the (b) (4) parameters relating to functionality (product run impurities) that include (b) (4)

were provided for the product runs but acceptance criteria for these parameters were not indicated for the small-scale study.

For the blank product runs (total of (b) (4)), the (b) (4) and (b) (4) were monitored in addition (b) (4) was performed for detecting (b) (4) and the following was indicated:

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

Reviewer Comments: For the (b) (4) observed for Blank Run (b) (4) the firm indicated that (b) (4) may have been caused by contamination of the sample due to handling. The firm supported this rationale in regards to the (b) (4) of Blank Run (b) (4) indicating that the (b) (4) was not observed after Blank Run (b) (4). For the (b) (4) observed in Blank Run (b) (4), the firm again indicated that this was due to sampling handling versus (b) (4); however, this was the last run in the small study and no additional runs were performed. The (b) (4) observed in the last run is not a major issue since the firm did perform the (b) (4) studies at scale, which include (b) (4) monitoring.

At-Scale (b) (4) (referenced protocol VAL-30228-01 and Report VAL-30228-02) Similar to the small-scale studies, every (b) (4) run included a blank run, thus (b) (4) product runs followed by a blank run. The blank runs were performed to measure the (b) (4), which was analyzed by (b) (4). Samples for (b) (4) were taken from in regards to each run (all (b) (4) runs) for the (b) (4).

Results: Results from (b) (4) runs which include (b) (4) intermediate blank runs was provided. The results for the (b) (4) parameters relating to functionality (product run impurities) that include (b) (4)

were provided for product runs were shown to be within the acceptance criteria with the following deviations that were footnoted in Table 3.2.S.2.5-96 Product Runs Impurity Analysis indicated as follows:

- Product Run (b) (4) (Batch No. (b) (4)) - No value for (b) (4), root cause indicated as testing not completed due to lot termination at (b) (4)

- Product Run ^{(b) (4)} (Batch No. (b) (4))- Out of specification for (b) (4) reported as (b) (4) acceptance criteria indicated as (b) (4) ; likely root cause indicated as assay dilution error
- Product Run ^{(b) (4)} (Batch No. (b) (4))- No value for (b) (4)

Reviewer Comments: There were additional footnotes indicating that there was a change in the intermediate process limit for ^{(b) (4)} (changed from (b) (4)) and for (b) (4) (changed from (b) (4)). The new limits were indicated as the acceptance criteria in the table. If applying the older acceptance criteria indicated in the footnotes for ^{(b) (4)} there would be Product Runs that do not meet the acceptance criteria and include the following:

- Run ^{(b) (4)} (Batch No. (b) (4))- Reported value for ^{(b) (4)} indicated as (b) (4) which meets new acceptance criteria of (b) (4) but does not meet old acceptance criteria of ^{(b) (4)}.

This value for ^{(b) (4)} for Run ^{(b) (4)} was not considered a deviation or OOS since the acceptance criteria had been changed. All runs meet new acceptance criteria for (b) (4) . The change in the in-process limit for (b) (4) was discussed with the product office. The product office has had discussions with the firm in regards to these changes of the in-process specifications for ^{(b) (4)}. Please refer to the product office memo for details.

All acceptance criteria were met in regards to (b) (4) for the ^{(b) (4)} product runs (for (b) (4)) with exception to the (b) (4) run. The ^{(b) (4)} run did not require a sample to be taken and the ^{(b) (4)} run a sample was not taken due to operational oversight. The results in regards to (b) (4) for the blank runs were indicated as follows. All results met the acceptance criteria.

(b) (4)

(b) (4)

Small Scale (b) (4) (referenced protocol (b) (4)-CP-032 and report (b) (4)-CR-032)

Each run included the following process steps for both the small-scale studies and at-scale studies:

(b) (4)

Results of Small Scale studies for (b) (4) : The results for the (b) (4) parameters relating to functionality that include (b) (4)

(b) (4) were provided for product runs no acceptance criteria were indicated for the small scale studies. For the blank product runs (total of (b) (4)), (b) (4) was performed for detecting protein carryover and the following was indicated:

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

At-Scale (b) (4) (referenced protocol VAL-30229-01 and Report VAL-30229-02)

Similar to the small-scale studies, every (b) (4) run included a blank run, thus (b) (4) product runs followed by a blank run. The blank runs were performed to measure the (b) (4), which was analyzed by (b) (4). Samples for (b) (4) were taken from in regards to each run (all (b) (4) runs) for the (b) (4).

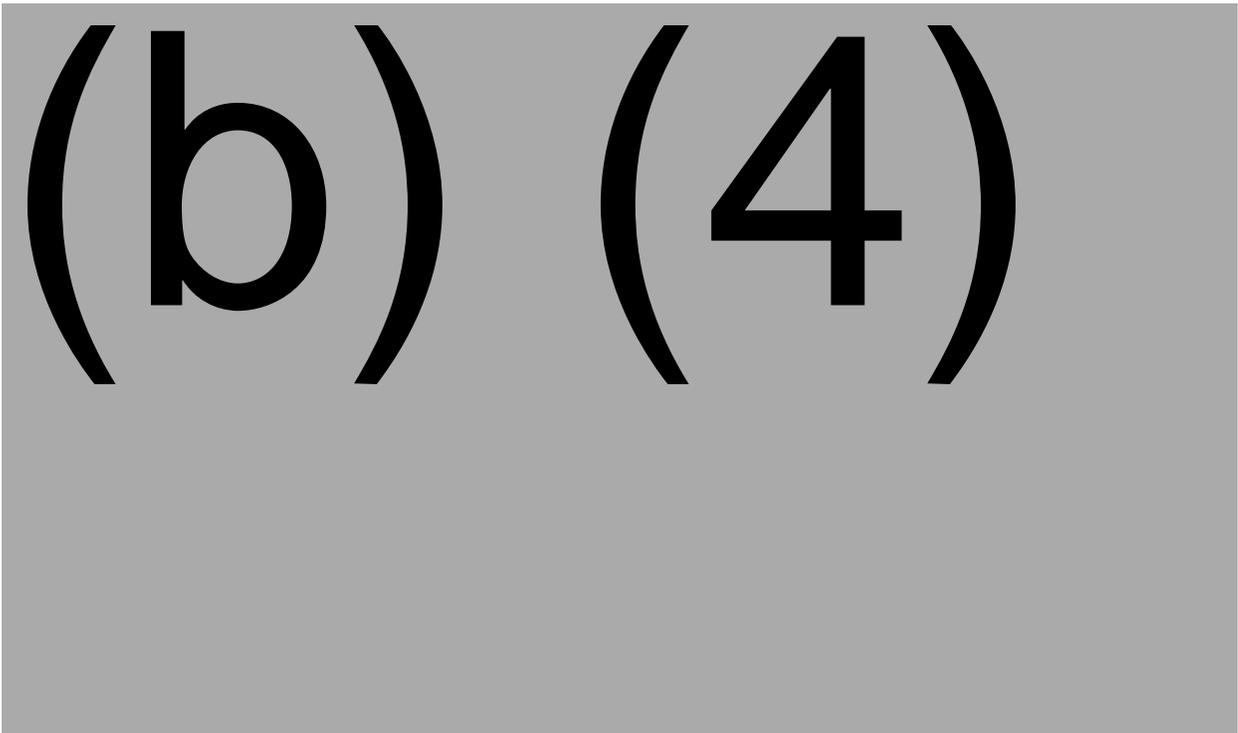
Results: Results from (b) (4) runs which include (b) (4) intermediate blank runs was provided. The results for the (b) (4) parameters relating to functionality (product run impurities) that include (b) (4)

were provided for product runs were shown to be within the acceptance criteria with the following deviations that were footnoted in Table 3.2.S.2.5-104 Product Runs Impurity Analysis indicated as follows:

- (b) (4)
-

Reviewer Comments: As previously indicated for the (b) (4), there was a change in the specification for the (b) (4) in-process limit. This change was discussed with the product office. The product office has had discussions with the firm in regards to these changes of the in-process specifications. Please refer to the product office memo for details.

All acceptance criteria were met in regards to (b) (4) for the (b) (4) product runs ((b) (4)) with exception to the first run as the first run did not require a sample to be taken. The results in regards to (b) (4) for the blank runs were indicated as follows. All results met the acceptance criteria.



(b) (4)

Small Scale (b) (4) (referenced protocol (b) (4)-CP-033 and report (b) (4)-CR-033)
Each run included the following process steps for both the small-scale studies and at-scale studies:

(b) (4)

Results of Small Scale studies for (b) (4) : The results for the (b) (4) parameters relating to functionality that include (b) (4) were provided for product runs and were all shown to be within the acceptance criteria. For the blank product runs (total of (b) (4)), (b) (4) was performed for detecting (b) (4) and the following was indicated:

- (b) (4)

At-Scale (b) (4) (referenced protocol VAL-30230-01 and report VAL-30230-02)
Although the validation protocol indicated a minimum of (b) (4) runs, the (b) (4) of the (b) (4) caused a mechanical failure of the (b) (4) after (b) (4) product cycles. There were visible (b) (4) in

the (b) (4) to meet HETP/Asymmetry specifications. Thus, a total of (b) (4) product runs and (b) (4) blank runs were performed using the same lot of (b) (4). The blank runs were performed to measure the (b) (4), which was analyzed by (b) (4). Samples for (b) (4) were taken from in regards to each run (all (b) (4) runs) for the (b) (4).

Results: Results from (b) (4) runs which include (b) (4) intermediate blank runs and (b) (4) product runs was provided. The results for the (b) (4) parameters relating to functionality (product run impurities) that include (b) (4) were provided for product runs were shown to be within the acceptance criteria with the following deviations that were footnoted in Table 3.2.S.2.5-112 Product Runs Impurity Analysis indicated as follows:

- (b) (4)

Reviewer Comment: *As previously indicated for the (b) (4) and the (b) (4), there was a change in the specification in the (b) (4) in-process limit. This change was discussed with the product office. The product office has had discussions with the firm in regards to these changes to the in-process specification limit. Please refer to the product office memo for details.*

All acceptance criteria were met in regards to (b) (4) for the (b) (4) product runs ((b) (4)) with exception to the first run as the first run did not require a sample to be taken, in addition for product runs (b) (4) were not taken for storage solution. The results in regards to (b) (4) for the blank runs were indicated as follows. All results met the acceptance criteria.

(b) (4)

(b) (4)

Small Scale (b) (4) (referenced protocol (b) (4)-CP-034 and report (b) (4)-CP-034)

Each run included the following process steps for both the small-scale studies and at-scale studies:

(b) (4)

Results of Small Scale studies for (b) (4) : The results for the (b) (4) parameters relating to functionality that include (b) (4) were provided for product runs and were all shown to be within the acceptance criteria. For the blank product runs (total of (b) (4)), (b) (4) was performed for detecting (b) (4) and the following was indicated:

- (b) (4)

At-Scale (b) (4) (referenced protocol VAL-30231-01 and report VAL-30231-02)

For the product runs a minimum of target of (b) (4) runs at-scale was performed. The runs included (b) (4) product runs and (b) (4) blank runs.

Results: Results (b) (4) product runs and (b) (4) blank runs was provided. The results for the (b) (4) parameters relating to functionality (product run impurities) that include (b) (4) were provided for product runs were shown to be within the acceptance criteria with the following deviations that were footnoted in Table 3.2.S.2.5-120 Product Runs Impurity Analysis indicated as follows:

- (b) (4)

The results of (b) (4) product runs for (b) (4) evaluated during (b) (4) were provided and met the acceptance criteria with exception of an (b) (4) result of (b) (4) of (b) (4) samples from (b) (4) different runs. These samples are indicated below:

(b) (4)

These samples were greater than the acceptance criteria. The firm indicated that this was likely due to manipulation of (b) (4) as the (b) (4) was within criteria.

The results evaluated for the blank runs which are performed every (b) (4) cycles were provided and are shown below. The results from the first (b) (4) blank runs met the acceptance criteria; however, the (b) (4) blank run (Lot (b) (4)) failed to meet the (b) (4) acceptance criteria; therefore, the (b) (4) will be limited to (b) (4) cycles since that many cycles were run prior to Blank Run (b) (4) which met the acceptance criteria.

(b) (4)

(b) (4)

Reviewer Comments: The firm provided sufficient data in regards to cleaning to support the number of reuses specified in the (b) (4) studies. However, the final assessment of the allowed number of (b) (4) re-uses in regards to functionality is deferred to the product office.

II. Information Requests and Firm Response

IR#1: The following information request was sent to the firm September 21, 2017 and firm response was received October 6, 2017 as Amendment 80 (eCTD 125886.0081). The responses are indicated below:

1. Please provide the Cleaning Validation Report VAL-30328.02.1.

Firm Response: The firm provided validation report VAL-30238.02.01, "(b) (4) [redacted] Cleaning" and includes the results of (b) (4) [redacted] samples taken from the (b) (4) [redacted] during the (b) (4) [redacted] steps for product (b) (4). The report is summarized as follows:

- Scope of validation protocol was limited to the sampling of (b) (4) [redacted] used in the processes that included: (b) (4) [redacted]
- (b) (4) consecutive executions of the protocol were performed
- Sampling and test method matrix was indicated as follows:

(b) (4)

Two different test methods are used for the testing of (b) (4) [redacted] [redacted] Test for

Additionally, the firm did not indicate if there was an alert limit. The firm should set an alert limit to monitor the process and take appropriate action in controlling the process should the (b) (4) trend towards the acceptance criteria given the wide difference between the acceptance limit for (b) (4) and the process capability. The firm was issued an information request to set an alert limit.

2. You indicated in 3.2.S.2.5 Process Validation and/or Evaluation Section 9.2 (b) (4) Studies that (b) (4) was detected in some of the samples tested, but only present at alert levels. Please provide the alert limit for (b) (4) counts noted during process validation. In addition, please provide information on microbial identification for noted alert limits exceeded.

Firm Response: The firm provided the following information as follows:



Reviewer Comments: (b) (4) and thus considered an objectionable organism. There should be an inspectional consideration for Team Biologics to ensure that the presence of (b) (4) organisms after cleaning of (b) (4) is not an upward trending, re-occurring issue. Please refer to the recommendation section for details of the inspectional follow-up.

3. In 3.2.S.2.5 Process Validation and/or Evaluation sections 9.1 and 9.2 of your CR response, you indicated (b) (4) studies are currently being performed to support (b) (4) uses of the (b) (4) and the (b) (4). Please provide a description of how the (b) (4) are cleaned and stored (including maximum storage time between uses), in addition to how the (b) (4) are routinely monitored (i.e. (b) (4))

Firm Response: The firm provided the following details in regards to the cleaning and storage of the (b) (4):

- (b) (4) (b) (4) **Cleaning Process and Storage**
- (b) (4)

(b) (4)

Reviewer Comments: The firm has adequately addressed this IR, no further action needed.

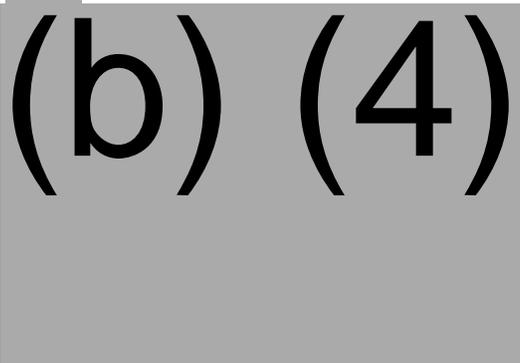
4. In regards to the Pharmaceutical Development Report: “Measurement of Equipment Capability for Laboratory and Production Scale Freeze Dryers Relevance of Equipment Capability to the Graphical Design Space for (b) (4)” provided to support the comparability of the lab-scale lyophilizer to the production scale lyophilizers, please provide and note the following:

- a. Please provide the mathematical details used to determine the relationship between the process variables (i.e. (b) (4)) based on the (b) (4)**

Firm Response: The firm indicated that (b) (4) provided the responses to the IR items that related to the lyophilization studies (IR items 4-6). The responses provided addressed each sub-item specifically. To address sub-item (a), the mathematical details used to construct and model the graphical design space were described. (b) (4) significant parameters that were described include the (b) (4). These (b) (4) parameters determine the relationship between the (b) (4) rate and the (b) (4) for any given (b) (4) as shown by the (b) (4) in the graphical design space for (b) (4) as follows:

Figure 3: Representative Graphical Design Space for (b) (4) - Graph of depicting the design space for (b) (4) based on the relationship between the (b) (4) and (b) (4)

(b) (4)



The firm indicated that a conservative approach was taken basing the calculations on the end of (b) (4) when (b) (4) and the risk to product is greatest. At this point, the (b) (4) . The design space is established by calculating at a (b) (4) . At least (b) (4) points on this curve are calculated and a curve is fit to these data. The result is (b) (4) . This process is repeated for as many shelf temperatures as appropriate. The product (b) (4) are created by choosing a value of product (b) (4) :

(b) (4)

(b) (4)

(b) (4)

(b) (4)

[Redacted text block]

Reviewer Comments: The firm has adequately addressed this IR item. No further action needed.

- b. Please indicate what pre-determined quality targets (i.e., maximum value of product temperature that influence the critical quality attributes that include cake (b) (4)) were used in your development study.**

Firm Response: Predetermined quality attributes evaluated in the andexanet alfa lyophilization scale down model DoE development study were indicated as follows:

(b) (4)

(b) (4)

(b) (4)

Reviewer Comments: The firm has adequately addressed this IR item. No further action needed.

- c. The stated conclusion “ that any cycle that will run on laboratory equipment should run on production scale equipment” based on demonstrating capability in regards to (b) (4) between the lab-scale and productions scale lyophilizers does not sufficiently support that the cycles will yield the same result in regards to product quality in that the product may not experience the same “thermal history” in the lab-scale lyophilizer as compared to the productions scale lyophilizer. This report is deficient in that there is no consideration or supportive data for the effect of scale up on product quality in regards to but not limited to the following:
- i. Effects of variation in (b) (4) in the (b) (4) relating to difference in size and geometry of the freeze-dryer
 - ii. Effects of temperature of (b) (4) even when the same set point is used
 - iii. Effects of variations in the rate of (b) (4)
 - iv. Effect of variations in (b) (4)
 - v. Effect of load configuration differences

Specifically, demonstrating capability of each lyophilizer alone is not sufficient in translating operating conditions between different scales. Please provide details of the scale up correlations in regards to product quality.

Firm Response: The firm indicated that equipment capability curve for the freezer dryer is important in defining the (b) (4) rate that can be supported and noted that the limits of the rate are different for different freezers; however, agreed that that the equipment capability curve alone is not sufficient to assure product quality upon scale up. The firm indicated that there were steps taken to mitigate risk in regards to other variables that included (b) (4). The elements of mitigating risk when using the process design approach to lyophilization cycle development were indicated as follows:

- Design Space is based on conservative approach:
 - (b) (4)
 - (b) (4)
 - (b) (4)
 - (b) (4)
- Laboratory equipment is of the same general design as production equipment such as:
 - (b) (4)
 - (b) (4)
 - (b) (4)
- (b) (4)
- An (b) (4) step was incorporated in the cycle used for andexanet alfa. One difference in the thermal history between the laboratory and production operations is that products tend to (b) (4) in production environment because there is (b) (4). The degree of (b) (4) cannot be controlled using existing technology, thus an (b) (4) step is used for andexanet. The (b) (4) step encourages the (b) (4) in thermal history. This minimizes the differences in (b) (4) rate between the laboratory and production equipment.
- Regarding (b) (4) variation in (b) (4) (including differences in (b) (4)) between the laboratory and production equipment, at the most aggressive (b) (4) rate, (b) (4), at a (b) (4), the (b) (4) variation was (b) (4) and thus do not consider this a significant difference. Experimentally, only a (b) (4) difference was measured between the (b) (4) at a (b) (4) rate of (b) (4). This pressure difference increases by a factor of (b) (4) if the clearance between the (b) (4) decreases from (b) (4) to (b) (4). Given that there is much larger clearance than (b) (4) in the

dryer used for andexanet process, the firm does not consider (b) (4) variation in (b) (4) within the chamber to be a significant source of uncertainty

- Regarding the effects of (b) (4) variations when same set point used, the (b) (4) is monitored both at the (b) (4) and at the (b) (4) from the (b) (4). Additionally, it was noted that it would not be possible for the product temperature to approach the critical product temperature of (b) (4) even when considering possible variances in (b) (4) observed in the process data (*Reviewer Comments: Firm provided (b) (4) temperature overlays of lab scale lyophilizer and of (b) (4) commercial scale lyophilizer runs, very little variance was observed between the (b) (4) temperature and (b) (4) temperature of the (b) (4)*)
- The differences in (b) (4) is not considered a significant risk because the (b) (4) are similar with respect to (b) (4) and selection of (b) (4) is deliberately conservative. (b) (4) generally do not exceed (b) (4).
- In regards to (b) (4) between the (b) (4), the (b) (4) from the (b) (4) to the (b) (4) is greater in the laboratory equipment than in the production because of the (b) (4) of the (b) (4) in laboratory equipment is larger than in a production setting. The door of a laboratory dryer is (b) (4) which has a (b) (4) of about (b) (4). The (b) (4) of the (b) (4) of a laboratory dryer is about (b) (4). There are no measurements of the (b) (4) of (b) (4) of a production dryer, but the values will be smaller because of the (b) (4) in the production equipment, which decreases the (b) (4).
- In regards to load configuration, the only variation in load configuration is the use of (b) (4) with andexanet. In this case, the geometrical relationship between (b) (4) will be the same. The (b) (4), but there would be no risk to product quality arising from the product temperature being any (b) (4).
- Monitoring of scaled-up batches includes a more aggressive sample plan to check for variability in (b) (4) levels. Comparative (b) (4) measurement is a useful process analytical technology that allows determination of the end point of both (b) (4) without the need for temperature monitoring probes in individual vials of product.

Reviewer Comments: The firm adequately address this IR item. No further action needed.

- d. In reference to Table 4: Equipment Capability Curves for Laboratory Scale vs. Production Scale Freeze Dryers, please indicate why the (b) (4) (lab-scale lyophilizer) has more data points than the production scale lyophilizers. It appears from the graph that the (b) (4) rates of the production lyophilizers were monitored at only (b) (4) as**

compared to the lab-scale lyophilizer in which the (b) (4) rates were monitored at numerous (b) (4). Additionally, please indicate why the capability studies in regards to (b) (4) rates did not include monitoring of the (b) (4) set at (b) (4) for the production lyophilizers, which the maximum end of the “Proven Acceptable Range” for the (b) (4) indicated from your DoE studies.

Firm Response: The firm indicated that there are more data points for the (b) (4) freeze dryers for the following reasons:

- The data for the (b) (4) lyophilizer used in Figure 4 of the capability report is (b) (4) data from (b) (4) lyophilizers
- Data shown in Figure 4 is the (b) (4) of a given freezer dryer as a function of (b) (4). The (b) (4) is a linear function thus it is not necessary to include large number of data points to establish the capability curve, thus the limited number of data points used for production lyophilizers is adequate for comparison to the laboratory scale equipment

In regards to a (b) (4) pressure set point was not included in the capability studies, the studies were aimed at documenting equipment capability independently of any specific product or specific freeze dry cycle. The (b) (4) curve is a straight line; thus, it is not considered necessary to include a (b) (4) set point in this type of study.

Reviewer Comments: The firm’s response to this IR item is adequate. No further action needed.

e. Please provide a detailed geometric comparison of the lab-scale lyophilizer and production scale lyophilizers, specifically including details of the (b) (4)

Firm Response: The firm provided a detailed table comparing the make, model and controls between the laboratory scale and production scale lyophilizers. Additionally, the firm included line drawing of the (b) (4) of the (b) (4) and line drawings of the (b) (4) of the (b) (4) freeze dryer. The table providing comparison of the lyophilizer is shown as follows:

Comparison of Laboratory and Production Freeze Dryers



(b) (4)

Reviewer Comments: The ratio of the (b) (4) for the lab-scale lyophilizer and production scale lyophilizer were provided and were indicated to be similar (i.e. (b) (4) for the production scale lyophilizer), thus the (b) (4) capability between the lab-scale

lyophilizer and the small-scale lyophilizer are similar despite the differences in size of the (b) (4) lyophilizers. The firm has adequately addressed this IR item. No further action is needed.

5. In Section 3.2.P.2.3 Manufacturing Process Development (pg. 27) of the CR response, you indicated that a predictive model (Figure 3.2.P.2.3-6) was determined based on the (b) (4) experiments performed at lab-scale. Please provide the details for how these (b) (4) product temperature models were generated and what data points were used. Additionally, please indicate if these models considered the combined influence of both (b) (4) on product temperature or was the influence of each parameter on product temperature only considered separately in your models. Please provide justification for your approach.

Firm Response: The firm indicated that the (b) (4) product temperature models were generated using the entire data set shown in Table 3.2.P.2.3-15 of the BLA Complete Response submission. The model considered the combined effect of both (b) (4) as both parameters together can influence product temperatures. A description of the Process DoE design was summarized as follows:

- (b) (4)
-
-
-

(b) (4)

Evaluation of Product Temperature model were evaluated as follows:

Product Temperature= (b) (4)

The results of an (b) (4) Analysis of the Product Temperature showed a good fit of the factors to the response and the model being statistically significant as indicated by the following plot.

(b) (4)

Based on the model analysis and the p-values determined, the (b) (4) [redacted] were demonstrated to have a significant impact on product temperature. The (b) (4) [redacted] parameters were determined to be statistically insignificant. Thus, the (b) (4) [redacted] parameters were removed from the model. The data set was re-analyzed using the (b) (4) [redacted] parameters as the main effects. Both (b) (4) [redacted] show a significant impact on product temperatures; however, their interaction was shown to be statistically insignificant (see data in table below), thus the interaction was removed from the model.

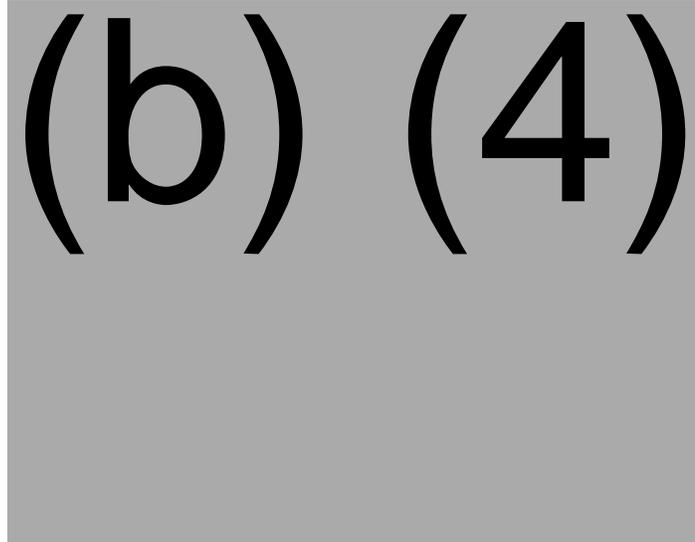
(b) (4)

The following model equation was used to generate the predictive model shown in Figure 3.2.P.2.3.6 of the CR response:

Predicted Product Temperature C= (b) (4)

A response surface based on the model equation above in addition to the product (b) (4) temperature (b) (4) as the limit was provided

Figure 8: Multidimensional response surface- Provides a visualization of the effects of the (b) (4) represented by the array of colors on the product temperature.



Using this model, the PARs were determined where the variations may impact product temperature. Based on this model PAR limits are (b) (4). The proposed PARs for (b) (4) are within the statistically limits.

Reviewer Comments: The firm has adequately addressed this IR item. No further action needed.

6. In Table 3.2.P.3.5-12 Lyophilization Process Parameters and Hold Temperature for the Consistency Lots provided in the original BLA submission (Section 3.2.P.3.5 Process Validation and/or Evaluation), you indicated a low and high value for each parameter including (b) (4) for each of the process validation runs. Please indicate what these low and high values represent in the validation runs for (b) (4).

Firm Response: The firm indicated that the lyophilization cycle is monitored using a System Control and Data Acquisition (SCADA), in which the programmed (b) (4) is controlled at (b) (4) from set point and the programmed (b) (4) is controlled (b) (4) from set point. In-process cycle is performed for each lyophilization cycle. Routine monitoring checks of the cycles critical values ((b) (4)) are recorded in real-time from the SCADA unit. The high and low values documented in Table 3.2.P.3.5-12, Lyophilization Process Parameters and Hold Temperature for Consistency Lots represent the low and

high values that were observed during the in-process cycle monitoring of the validation runs for (b) (4).

Reviewer Comments: The low and high values that were reported in the table are within the programmed limits from set point. The firm has adequately addressed this IR item. No further action needed.

IR#2: The following information request was sent to the firm December 7, 2017 and firm response was received December 14, 2017 as Amendment 94 (eCTD 125886.0095). The responses are indicated below:

- 1. In reference to the data included in validation report VAL-30238.02.01 for the (b) (4) used for (b) (4) processes (provided in IR response received as Amendment 80 Oct 6, 2017), please set an alert limit for (b) (4) at cleaning steps, (b) (4).**

Firm Response: The firm indicated that a (b) (4) alert limit of (b) (4) will be implemented for both (b) (4) for (b) (4). The alert limit will be included in (b) (4) (Harvest Fluid Concentration) and (b) (4) ((b) (4)). The alert limit will be implemented into the manufacturing Quality System for the 2018 manufacturing campaign due to start January 12, 2018 at (b) (4).

Reviewer Comments: The implementation of the alert limit for (b) (4) will be included as an inspectional consideration to confirm the implementation of this limit. Please refer to recommendation section of memo for details. The firm has adequately addressed this IR item.