DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service

Food and Drug Administration
Center for Biologics Evaluation and Research
10903 New Hampshire Ave
Building 71, G112
Silver Spring, MD 20993-0002

To: Administrative File: STN BLA 125586/0

Mikhail Ovanesov, Committee Chair, CBER/OBRR/DHRR
Thomas Maruna, RPM, CBER/OBRR/IO

CC: Review Committee Members

From: Joan Johnson, CMC/Facility Reviewer/Inspector, CBER/OCBQ/DMPQ/B1

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

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

Applicant: Portola Pharmaceuticals, Inc. (Portola) FEI 3004737419

Product: Coagulation Factor Xa (Recombinant), Inactivated, Drug Substance
Established 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) that is administered by injection.

Subject: Primary Review: Review of original BLA for **Andexanet alfa Drug Substance** covering DMPQ related aspects.

Due Date: 17 Aug 2016

Recommendation

Based on the information provided in the original BLA, corresponding amendments, and outstanding inspectional issues, a Complete Response Letter is recommended with the following CR item to be included (for the drug substance part):

1) Regarding drug substance equipment cleaning validation, please provide the following:

   - Data to support the cleaning efficacy of the (b) (4) .
   - Validation data to support the (b) (4) . In addition, please indicate the frequency in (b) (4) .

There are additional CR items in regards to the drug product manufacturing and comparability protocol, which is noted in a separate review memo. This memo only covers review of the drug substance manufacturing. For details, refer to review memo prepared by DMPQ reviewer, Christine Harman, covering the review for drug product manufacturing and comparability protocol.

Executive Summary

Portola Pharmaceuticals submitted original BLA STN125586/0 for licensure of Andexanet alfa, which was received electronically (in eCTD format) by CBER as a rolling BLA. The modules 1, 2 and 4 were received November 6, 2015 (eCTD 0000) and the remaining modules 3 and 5 were received December 18, 2015 as Amendment 1 (eCTD 0001).

This BLA was designated as a Breakthrough Therapy and granted priority review status; therefore, is reviewed under the 8 month review timeframe. **A Comparability Protocol (CP) and associated amendment was also submitted in the BLA for post-approval manufacturing changes to the Drug Substance (on (b) (4)) and Drug Product process. The review of the CP and associated amendment is performed by DMPQ reviewer Christine Harman and included in the Drug Product review memo.**

This review covers the aspects of the BLA submission that are under the purview of DMPQ as per responsibilities outlined in "SOPP 8401.4: Review Responsibilities for CMC Section of Biologic License Applications and Supplements". The review of other aspects of the submission is deferred to the appropriate office/division.

I was assigned as a facility reviewer for the drug substance manufacturing process and inspector in January 2016. For the drug substance manufacturing facility ((b) (4)), CBER performed a PLI inspection as part of the integrated review of this submission. That inspection was performed from (b) (4) .

The following documents were reviewed related to the Andexanet alfa Drug Substance manufactured by (b) (4) located in (b) (4) :

- 2.3. Quality Overall Summary - Introduction
- 2.3.S.1 General Information
- 2.3.S.2 Manufacture ((b) (4))
- 2.3.S.3 Characterization

- 2.3.S.4 Control of Drug Substance
- 2.3.S.6 Container Closure System - overview
- 2.3.S.7 Stability
- 2.3.A.1 Facilities and Equipment – overview
- 2.3.A.2 Adventitious Agents Safety Evaluation
- 3.2.S.1 General Information – Nomenclature, Structure, General Properties
- 3.2.S.2.1 Manufacturers
- 3.2.S.2.2 Manufacturing Process & Controls
- 3.2.S.2.3 Control of Materials
- 3.2.S.2.4 Controls of Critical Steps and Intermediates
- 3.2.S.2.5 Process Validation & Evaluation – (b) (4) Comparability Report, Validation Summary Report for (b) (4) DS Process Performance Qualification on (b) (4), Product Comparison Report for Manufacture on (b) (4)
- 3.2.S2.6 Manufacturing Process Development – Comparability Report for DS at (b) (4) (clinical) vs. 10mg/mL (commercial)
- 3.2.S.3 Characterization – elucidation of structure and impurities
- 3.2.S.4 Control of Drug Substance – Specification, Analytical Procedures and Validation, Batch Analysis and Justification of Specification
- 3.2.S.5 Reference Standards or Materials
- 3.2.S.6 Container Closure System – Suitability and Certification
- 3.2.S.7.1 Stability Summary and Conclusions
- 3.2.S.7.2 Post Approval Stability
- 3.2.S.7.3 Stability Data
- 3.2.A.1 Facilities and Equipment – (b) (4)
- 3.2.A.1 Facilities Floorplan – (b) (4)
- 3.2.A.2 Adventitious Agents Safety Evaluation and Viral Clearance Report
- 3.2.A.3 Excipients
- 3.2.R.1 Regional Information - Executed Batch Records
- 3.2.R.2 Regional Information - Method Validation Package, (b) (4) Validation
- 3.2.R.3 Regional Information – Comparability Protocols ((b) (4) to (b) (4) Lots), (b) (4) Batch Record (Blank),

Review Memo Format

I have provided a summary of information provided in the submission that is under DMPQ purview as outlined in SOPP 8401.4: In general, my Review Assessment / Comments are provided at the end of review sections in a double lined box. Any information requests (IRs) related to review will be included in these boxes in bolded text. A summary of the firm's response to that IR will immediately follow in italicized text. My assessment of the response will immediately follow in a double lined box.

Note: (b) (4) is a contract manufacturer of the drug substance for Portola. In this memo, "(b) (4)" is used when referring to the drug substance manufacturing operations and location.

1. Amendments related to Drug Substance Review

The following IRs was sent to the firm July 1st, 2016 and response was received July 12th, 2016 as Amendment 0048:

- Please provide summary data or report for the andexanet alfa drug substance shipping validation protocol VAL-80003-01.
- Please provide summary data or report for the hold time study performed per Process Hold Time Study Protocol VAL-30234-01.*DMPQ review of IR response: the firm's response is adequate. Detailed review is provided in the section 9 for hold time study and section 17 for shipping validation.*

2. Product Background

Portola's Andexanet alfa is being developed for the urgent reversal of anticoagulation in patients administered either direct or indirect factor Xa (fXa) inhibitors who experience a major bleeding episode (b) (4).

Andexanet alfa is administered as a single bolus administration for an acute event, at a target rate of approximately 30 mg/min (over approximately 15-30 minutes) followed by a 120 minute infusion, with the dose depending on the timing of and the specific fXa inhibitor that the patient previously received: 400 mg bolus plus a 4 mg/min infusion (480 mg) for 880 mg total dose or an 800 mg bolus plus an 8 mg/min infusion (960 mg) for 1760 mg total dose.

Andexanet alfa drug substance (DS) is manufactured at (b) (4) in the production facility Building (b) (4), located in (b) (4). The drug substance is a (b) (4) . The formulated DS is then (b) (4) to use for Drug Product (DP) manufacturing at (b) (4) in (b) (4). There is no additional formulation during the drug product manufacturing process. The final sterile filtration occurs at (b) (4) just before filling.

3. (b) (4) Facility (Drug Substance Manufacturer)

a. Process Overview

(b) (4)

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

b. Facility Overview

The (b) (4) site for the manufacture of Andexanet alfa DS is comprised of (b) (4) buildings consisting of general and administrative office space (Building (b) (4)), GMP testing laboratories, process development services and secondary storage area for (b) (4) and DS product (Building (b) (4)), GMP manufacturing suites and ancillary support utilities (Building (b) (4)), GMP utility, facility maintenance and equipment/parts storage (Building (b) (4)) and GMP warehousing and (b) (4) storage (Building (b) (4)).

Andexanet alfa DS is manufactured in the Production Facility area of Building (b) (4), a large-scale facility (approximately (b) (4)) used for commercial and clinical manufacturing. The (b) (4) manufacturing area consists of the following:

Building (b) (4) also contains the following process support areas:

- Solution preparation suite
- Glass wash area
- (b) (4) load area
- (b) (4) unload/equipment storage area
- Cold room for storage

c. Material, Equipment and Personnel Flow

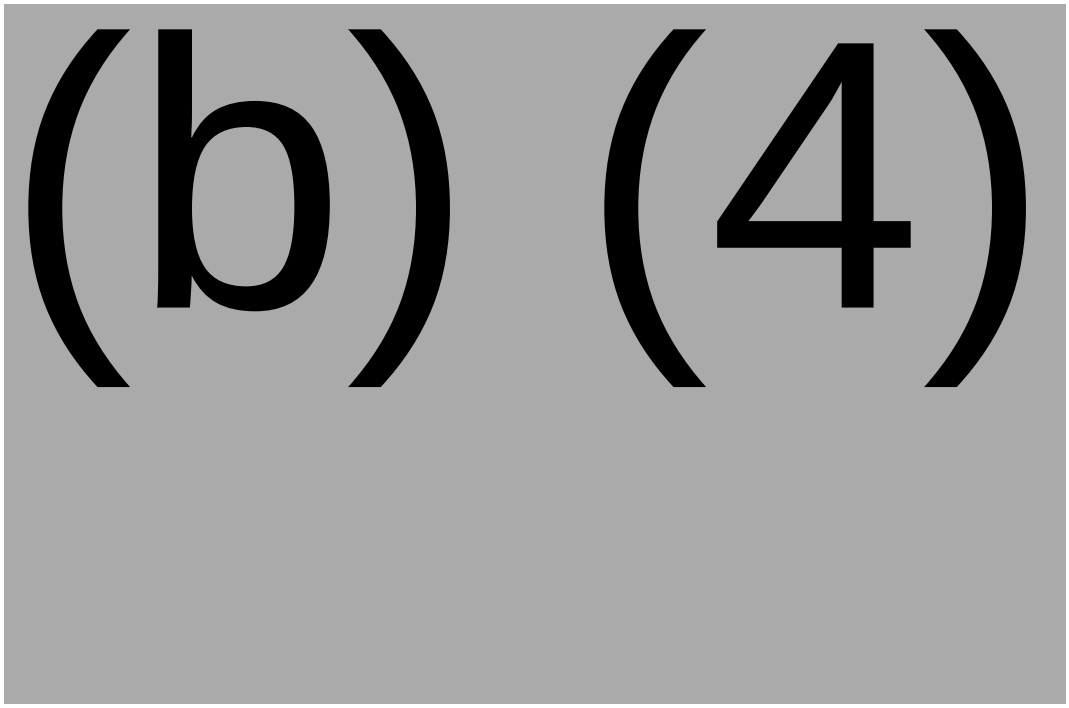
Access to (b) (4) is controlled by key card and limited to authorized personnel only. Personnel entering (b) (4) manufacturing area are gowned according established SOP (GMP-0083). All materials and equipment brought into (b) (4) are wiped down when entering the material airlock and wiped down again when entering production areas. Entry and exit airlocks are equipped with interlocks to allow only one door open at a time. Maximum occupancy for all classified areas is established based on HVAC system qualification.

Personnel enter each production area through designated entry airlock and exit through designated exit airlock in a unidirectional flow. Manufacturing materials and equipment enter the production area through designated material airlock, wiped down, identified with operational status and verified per product campaign. Process intermediates are transferred between production suites in a closed system using either process transfer lines or pass through wall portals for adjoining suites. Procedures describing the flow of personnel, materials, equipment, and waste throughout the manufacturing area in (b) (4) are established and detailed in SOP GMP0265.

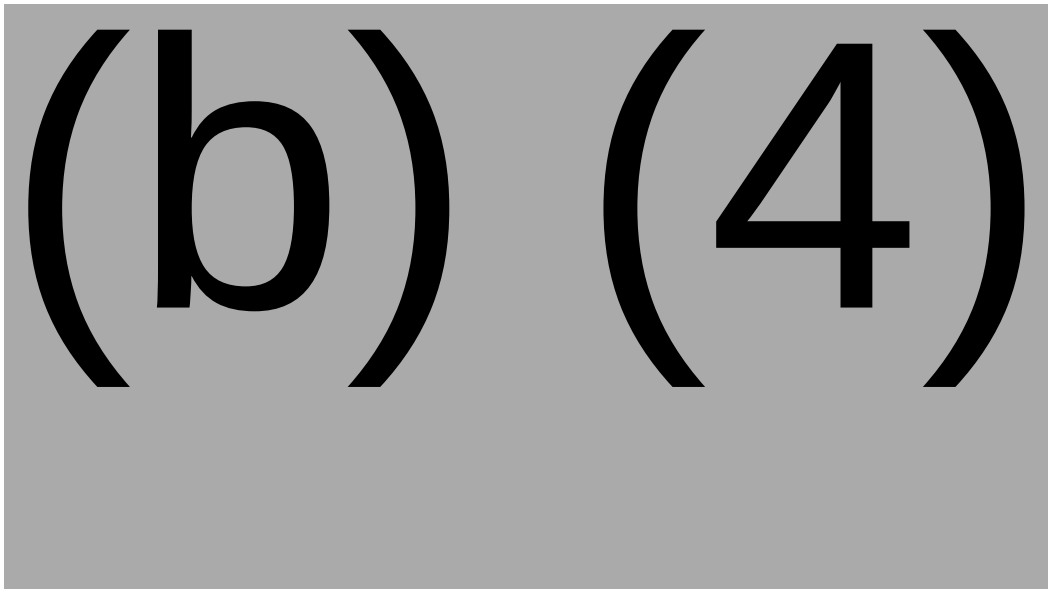
DMPQ Review Comments: Diagrams appear to correspond with the description in the submission. Standard approach to facility design and flow appears evident. No objectionable findings noted.

d. Contamination / Cross Contamination Control

There are (b) (4) other (b) (4) and (b) (4) that are used to produce recombinant products at (b) (4) and they produce either recombinant protein (b) (4) from CHO cell line. A list of (b) (4) drug substance of various recombinant protein (b) (4) manufactured in (b) (4) is provided in the submission and listed below



Factor IX (recombinant coagulation factor, (b) (4)) was the only commercial product approved by FDA in 2014. The following product codes are used for non-US market: (b) (4) . For product (b) (4) , only (b) (4) are performed at (b) (4).



(b) (4) states that no (b) (4) is done onsite. (b) (4) and Drug Substance are manufactured on site. No (b) (4) are manufactured on site.

The Andexanet alfa production cell line is a Chinese Hamster Ovary (CHO) clone that was (b) (4). Production (b) (4) were specifically designed within (b) (4) to accommodate both clinical and commercial manufacturing operations. There are no product dedicated suites in the manufacturing facility.

(b) (4) incorporates the following features to control and prevent cross contamination:

- HVAC, with HEPA filtration and established one way flow of air due to pressure differentials.
- Rooms with pharmaceutical construction grade surfaces, designed to facilitate cleaning.
- Use of a campaign manufacturing schedule.
- Use of qualified disinfectant agents for the control and elimination of microbial contamination.
- Gowning requirements that are specific for each area.
- Controlled access to manufacturing areas.
- Change-over/cleaning procedures.
- Equipment cleaning/sterilization.
- Waste Decontamination

Recombinant proteins manufacture is conducted on a campaign schedule. Product changeover, equipment cleaning and room clearance procedures are in place to avoid mix-ups and cross-contamination. Product is identified at each stage of the production process to avoid mix-up and ensure full traceability.

(b) (4) utilizes validated cleaning and changeover procedures, including testing for residues if appropriate, to control transfer of organisms and product residues between each runas well as between each product campaign. In-process testing is used to monitor process performance. A program of routine environmental monitoring, utilizing air and surface sampling, is in place. Area cleaning is performed according to prescribed schedules, using qualified cleaning agents. Changeover procedures include (b) (4) testing in addition to validated cleaning procedures. Operations in the (b) (4) are separated due to the design of the rooms and HVAC systems. (b) (4) are supplied from the same AHU ((b) (4)) but the air in both rooms is (b) (4) exhausted. All open work is performed in biosafety cabinets. (b) (4) each have a dedicated HVAC unit ((b) (4) for (b) (4)). Operations in the (b) (4) suites are conducted by different personnel if both rooms are in use at the same time.

Personnel are not permitted to move from the (b) (4) area (Purification Suite (b) (4)) to the (b) (4) area (Purification Suite (b) (4)) without exiting and donning fresh gowning. Purification Suite (b) (4) and the Final Fill Suite are treated as a single area in that only one product can be processed in the two rooms at any one time.

e. Viral Segregation and Control of (b) (4)

Facility design and process operations require that an (b) (4) viral reduction step occur in the (b) (4) suite before material can be further processed in Purification (b) (4). The (b) (4) viral reduction step is inactivation of virus by (b) (4) . (b) (4) viral clearance is accomplished in Purification suite (b) (4) via (b) (4) steps). The (b) (4) viral reduction step is (b) (4) . Only material that has been (b) (4) can enter Purification suite (b) (4) and the (b) (4) fill suite.

(b) (4) into process/product solutions is controlled via facility, equipment, and processes designed to maintain low (b) (4) levels during manufacture.

The performance of cleaning methods for equipment is routinely monitored via (b) (4) and testing of (b) (4) samples. (b) (4) analyses are typically performed on (b) (4) samples during qualification of the cleaning method. (b) (4) samples are tested for (b) (4). Each sample ((b) (4)) and sample site has associated alert and action limits for designated equipment and processing steps. Cleaning agents currently utilized at (b) (4) include (b) (4) . (b) (4) is the initial cleaning agent used in (b) (4) , equipment washer cycles and manual cleaning. (b) (4) is used after (b) (4) for (b) (4) and equipment washer cleaning. (b) (4) is used as the terminal cleaning agent for all cleaning. (b) (4) is used to prepare all cleaning solutions and perform equipment rinsing.

(b) (4)

DMPQ Review Comments: Standard practices for prevention of cross-contamination and (b) (4) control appear to be in place. No objectionable finding noted.

f. Facility Cleaning /Sanitization

According to (b) (4), the layout and design of the production areas and equipment permit effective cleaning and decontamination. A cleaning and disinfection program is in place for all classified clean room areas. Cleaning and disinfection of room surfaces and equipment exterior surfaces are performed in accordance with SOPs.

Facility cleaning is performed according to SOP MO-175. Training for operators performing cleaning is documented. The purchase, control, and use of agents used to clean the facility are controlled by (b) (4) material specifications and SOP which specify the concentrations for each of the cleaning agents, and cleaning agents are rotated. Sanitizing agent (b) (4) is used for routine cleaning and sanitizing of the production areas daily. (b) (4) . Additionally, (b) (4) is used for a (b) (4) cleaning procedure that includes cleaning of the ceilings and walls and also performed as part of the product change over procedure.

Sanitizer effectiveness studies have been conducted (VAL-30060-03 approved on 28Jul2015) and the effectiveness of facility cleaning is verified by routine EM. Sites, frequencies, and limits for EM are established based on (b) (4) ISO requirements, type of activity performed in the area, extent of product exposure, and historical data analysis.

Routine Environmental Monitoring (EM) of the production areas is governed by written Procedures and process specific monitoring is performed during upstream and downstream processing operations. There are four room classifications within the Building (b) (4) manufacturing facility: ISO (b) (4), ISO (b) (4), ISO (b) (4), and Controlled non-Classified (CNC). Localized environments are used to provide ISO (b) (4) conditions for Final Fill operations and other process critical manipulations. Alert and action limits for (b) (4) , and personnel monitoring are established and maintained in controlled documents.

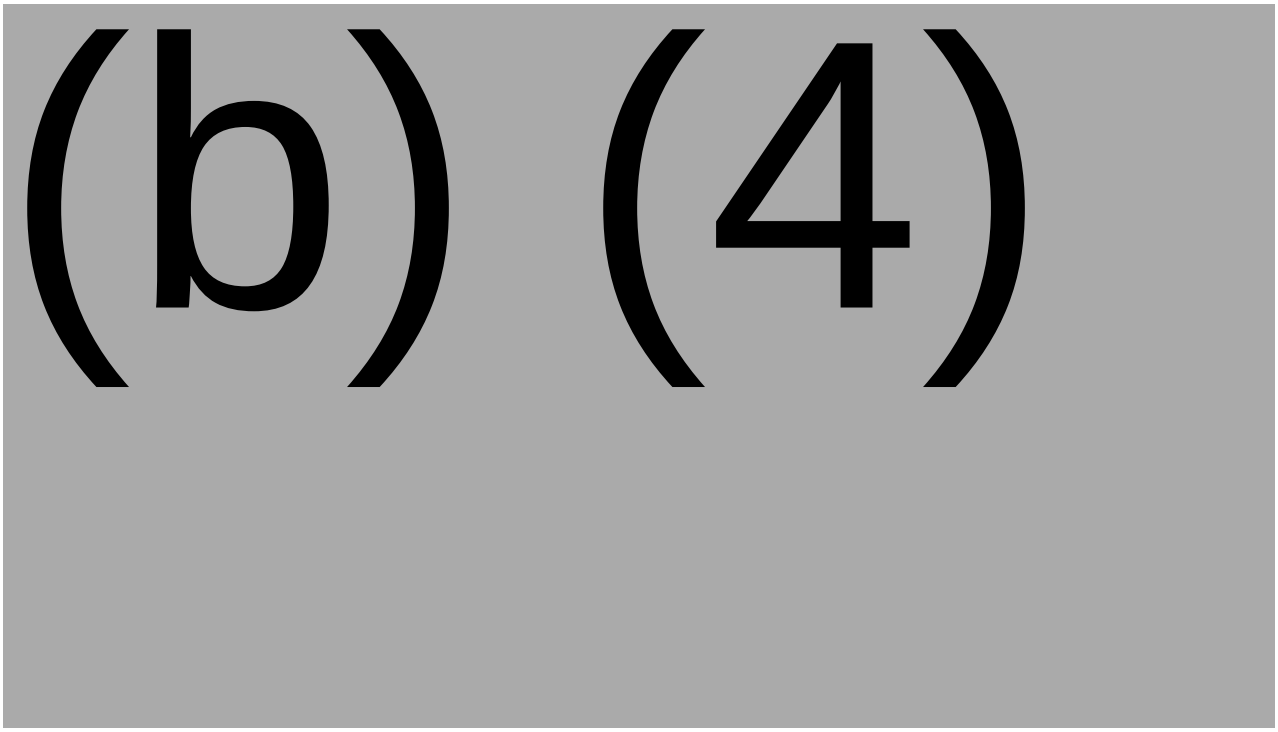
DMPQ Review Comments: Cleaning and disinfection practices appear to be adequate for their intended use. No objectionable finding noted.

g. Direct Impact Utilities

HVAC

The existing HVAC system is modified and one additional HVAC unit is added as part of the (b) (4) expansion project. Clean room classification, air balance, directional air flow is verified as part of the HVAC qualification. The HVAC units are controlled and monitored by the (b) (4) Building Monitoring System (BMS).

HVAC systems that supply the classified areas for Buildings (b) (4) are:



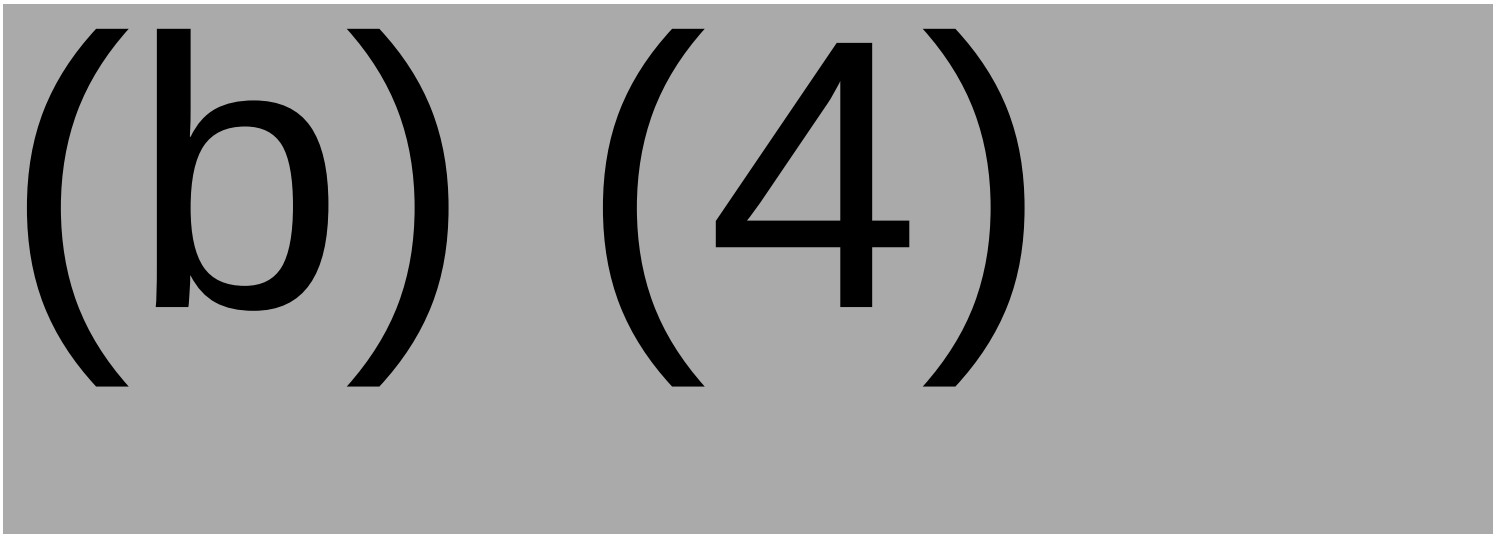
HVAC qualification and control performed for the existing (b) (4) suites and (b) (4) expansion were verified and reviewed during PLI.

EIR summary on HVAC: SOPs and Validations summaries related to HVAC system were reviewed and found to be in control.

Environmental Monitoring (EM)

EM for viable counts in the different clean room production areas and for inoculum preparation area follows the same frequency as for all classified areas at (b) (4) site. Frequency for EM for viable counts and acceptance criteria is as follows:

Room Classification / Zone **Frequency**



Filling of the DS for low (b) (4) products is performed in Class (b) (4) environment (under (b) (4) hood in Rm (b) (4)). Action and Alert levels are established for the different classified areas.

DMPQ Review Comments: Filling of the Final Drug Substance in Class (b) (4) environment appears acceptable for (b) (4) control. (b) (4) is monitored throughout the process and specified in the release of DS. No objectionable findings noted.

Review of EM trending data and Alert and Action Excursion investigations for all manufacturing area was performed during PLI.

EIR Summary on EM monitoring: Trend of mold was identified in (b) (4) operations at beginning of September 2015 and CAPA1800 was initiated to remediate the problem. Refer to EIR section 8.4 for detail.

WFI System

The Existing WFI system is modified to (b) (4) . The (b) (4) to provide WFI for the existing points in (b) (4) . A (b) (4) independent WFI generation and distribution system is installed exclusively to supply the (b) (4) cell culture and harvest suites and (b) (4) .

(b) (4)

(b) (4)

(b) (4)

(b) (4)

EIR Summary on Direct Impact Utility Systems: Qualification documents for WFI system qualification for (b) (4) *use are comprehensive and complete. No excursions for* (b) (4) *system monitoring data from January-March 2016. Process* (b) (4) *requalification for* (b) (4) *was performed as required and acceptable. No objectionable findings noted.*

4. Processing Equipment Overview

(b) (4) states that each piece of critical equipment is qualified for GMP use and a requalification program is in place to ensure equipment remains in a validated state. A major production equipment list is provided below:

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

5. Equipment and Utility Qualification

(b) (4) provided a Validation Plan (VAL-90034-01) for the (b) (4) Facilities, Utilities and Equipment qualification with the submission. The qualification tests (IQ, OQ, PQ) are in accordance to Site SOPs per predefined requirements in qualification protocols. All clean rooms and HVAC-systems are in a qualified state. Cleanrooms and equipment (e.g. HEPA-filter, laminar flows) are requalified regularly in accordance to the Site SOP (based on ISO 14644). For the PQ, all classified clean rooms were monitored for viable particles, airborne particles and surface microbial contaminants for (b) (4) days. Monitoring of the clean rooms for PQ occurred during normal production activity, "in operation" (dynamic) conditions.

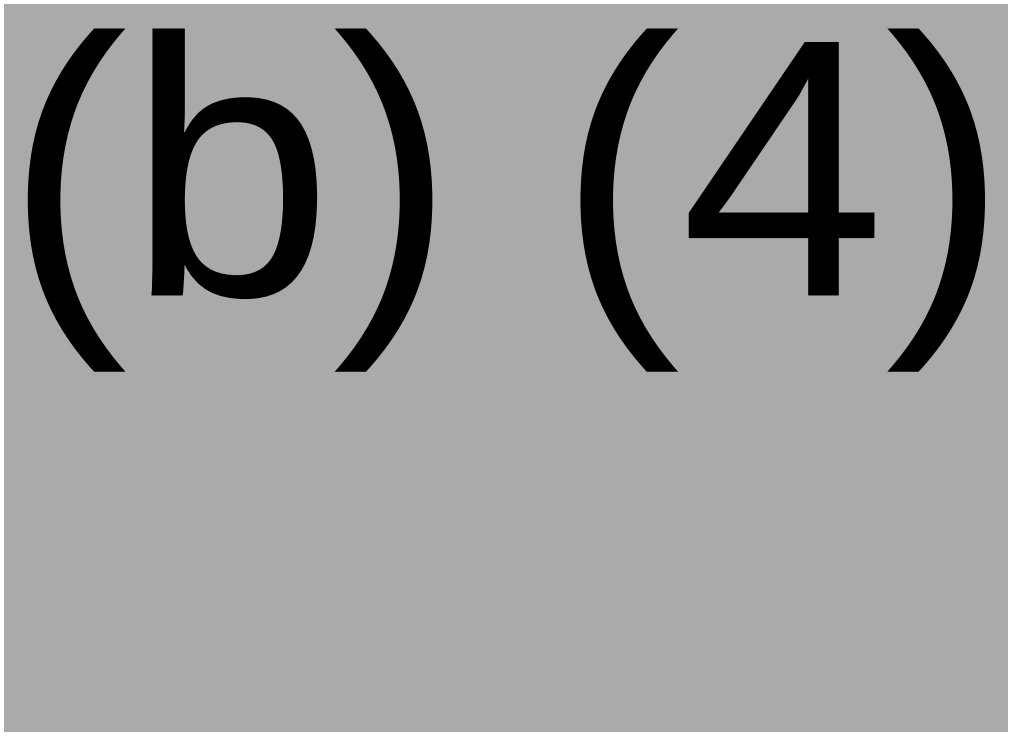
(b) (4) *Qualification Summary*

(b) (4) was initially qualified in 2002 and has ongoing use prior to (b) (4) implementation. Only SIP performance testing was completed due to process history. CIP performance qualification was performed as part of cleaning validation for (b) (4) .

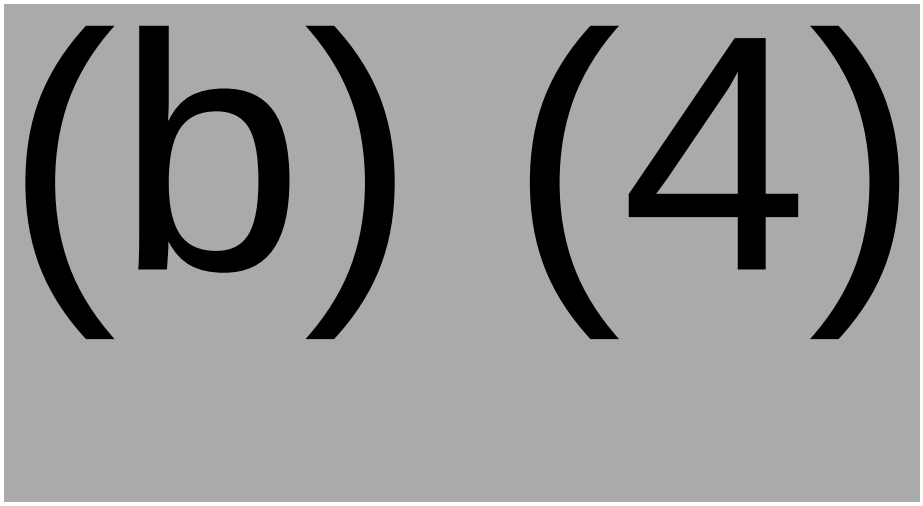
(b) (4)

(b) (4) *Qualification Summary*

Similar to the (b) (4), the (b) (4) had ongoing use prior to implementation of (b) (4). Only SIP qualification testing was required, CIP verification for (b) (4) was performed as part of the cleaning validation.

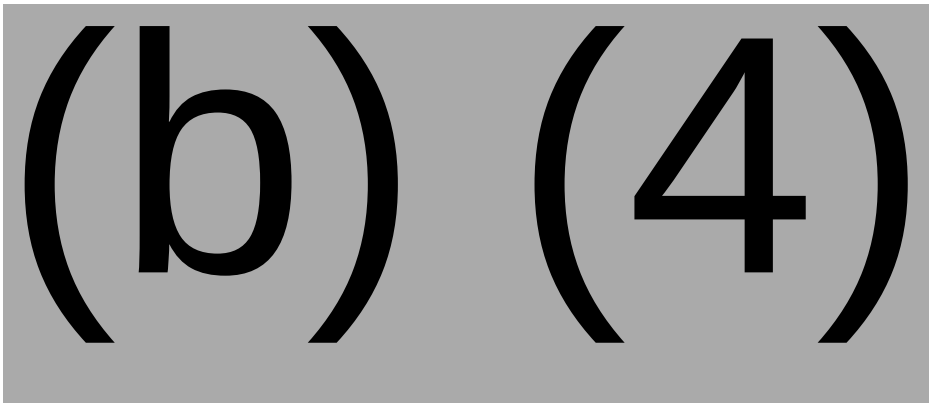


(b) (4)

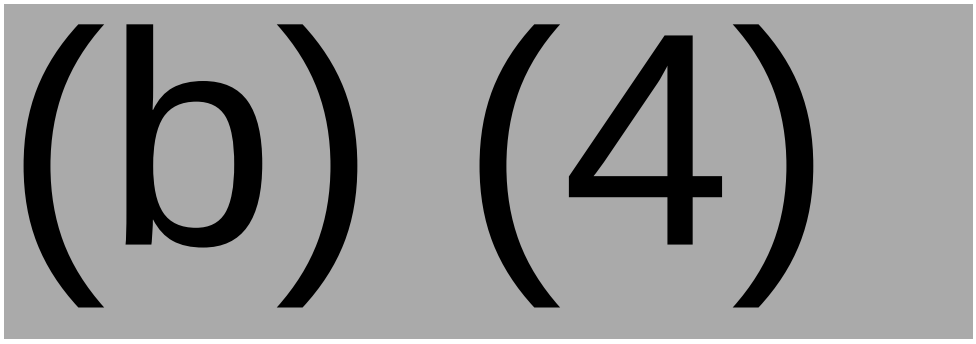


(b) (4)

(b) (4)



(b) (4)



Verification of adequate qualification of process equipment was performed during PLI.

EIR Summary on Process Equipment Qualification: Process Equipment is qualified per established validation protocols and summary report was verified during inspection. Refer to EIR section 9.1 for details.

The following equipment qualification final reports were reviewed and verified during PLI:

(b) (4)

No objectionable findings noted in reviewing equipment qualification reports during PLI.

6. Cleaning Validation

(b) (4) provided the cleaning validation plan VAL-900035-01; however, results of cleaning validation were not provided in the submission. Cleaning verification is required following cleaning execution until cleaning validation is completed according to established SOP GMP-0417, "Equipment Cleaning Program".

a. Equipment Cleaning

(b) (4) stated in their cleaning validation plan (VAL-900035-01) the following requirements for process equipment cleaning:

(b) (4)

Process equipment is cleaned (CIP/COP) and sanitized (chem. SIP/SIP). Clean-hold times for process materials and hold times for (b) (4) are established via validation studies.

The performance of cleaning method is monitored via (b) (4) and testing of (b) (4) samples. (b) (4) analysis are performed on (b) (4) samples and (b) (4) samples are tested for (b) (4). Each sample has associated alert and action limit for designated equipment. Cleaning agents used at (b) (4) include (b) (4). (b) (4) is the initial cleaning agent used in CIP, COP, equipment (b) (4) and manual cleaning. (b) (4) used after (b) (4) and equipment (b) (4) cleaning. (b) (4) is used as a terminal cleaning agent in CIP, COP, equipment (b) (4) and manual cleaning. (b) (4) is used to prepare all cleaning agent solutions and perform equipment rinsing.

Cleaning processes are validated according to approved plans and testing protocols and acceptance criteria includes performance parameter requirements for cleaning agent, product and microbial residues and critical operational parameter requirements.

Verification of adequate cleaning efficacy study performed and validation performed on major process and product contact equipment and acceptable summary data was performed during PLI.

EIR Summary on Equipment Cleaning: Equipment Cleaning Programs were evaluated during inspection. A number of equipment cleaning qualification reports were reviewed and found no objectionable issues.

The following cleaning validation reports were reviewed during the PLI:

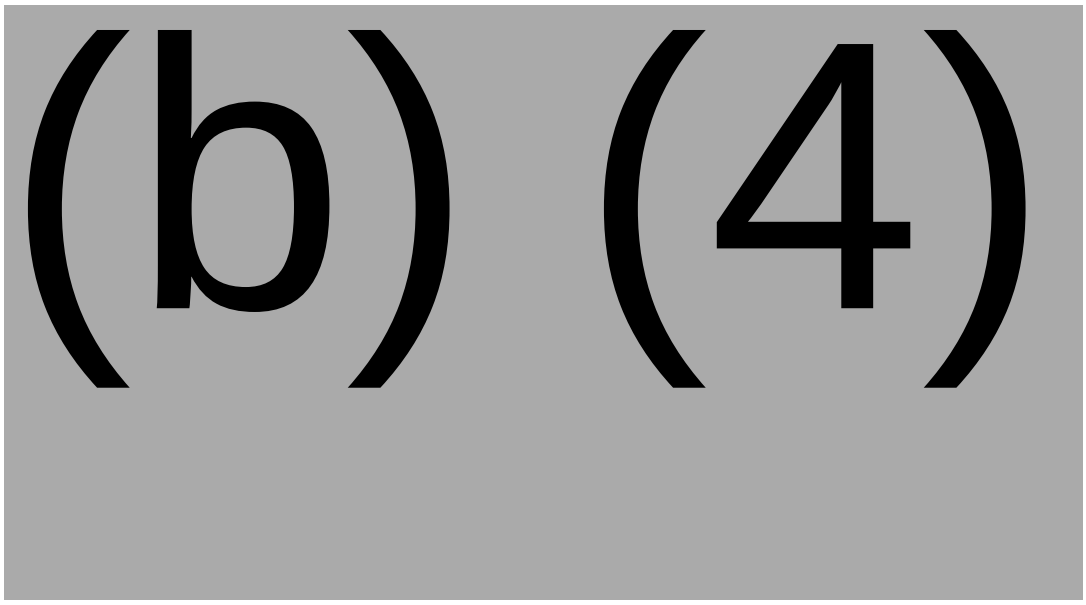
- *Cleaning Validation for* (b) (4) *(VAL-30256-02)*

- *Cleaning Validation for* (b) (4) *(VAL-30250-02)*
- *Cleaning Validation for* (b) (4) *(VAL-30274-02)*
- (b) (4) *Cleaning Cycle Validation (VAL-30239-02)*

The purification process monitoring stations, **also commonly referred to as the** (b) (4) are used to monitor and record data from (b) (4) and (b) (4) steps in the purification and cell culture suites.

The validation included the following equipment: (b) (4)

(b) (4) used the following cleaning testing requirements and acceptance criteria for most of their cleaning validation study and they are listed as following:



Most major equipment for (b) (4) *are shared and* (b) (4) *are used for* (b) (4) *. A List of all product contact equipment (including* (b) (4) *), their cleaning method, use and cleaning validation study status was provided during inspection and included in EIR section 9.2 page 35.*

b. Cleaning of Re-usable (b) (4)

Cleaning Validation Plan (VAL-90035-01) also included requirements for both (b) (4) . A blank run mimicking all aspects of the (b) (4) processes except with no protein loaded is performed and samples are tested for product carry over, (b) (4) . Cleaning validation and acceptance criteria was performed during the validation studies for the (b) (4) usage and review in section c. below.

c. (b) (4) ***Validation Studies***

(b) (4) performed (b) (4) validation studies to confirm the effective lifetime for the reuse of (b) (4) validation studies are being performed at-scale and (b) (4) validation studies are being performed at both small-scale and at scale.

The lifetime study for the (b) (4) to extend to a minimum of (b) (4) product runs was executed per Protocol (VAL-30226-01) and results were summarized in Report (VAL-30226-02).

The lifetime study for the (b) (4) to extend to a minimum of (b) (4) product runs was executed per Protocol (VAL-30227-01) and results were summarized in Report (VAL-30227-02).

(b) (4)

Testing and acceptance criteria performed during the at scale study are listed in table below:

(b) (4)

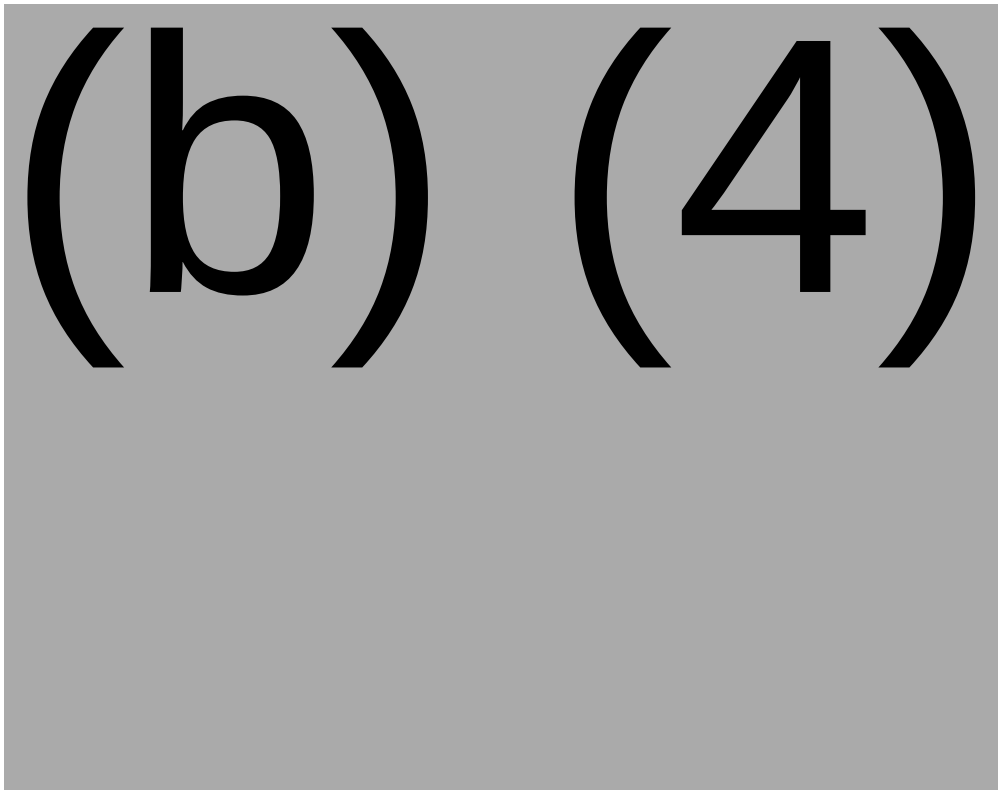
At the time of PLI, the VAL-30226-02 for cleaning of (b) (4) was on going, there was no cleaning validation data provided in the submission to support the cleaning efficacy of the (b) (4). The following CR item was issued to the firm (also see page 2):

Regarding drug substance equipment cleaning validation, please provide the following:

- Data to support the cleaning efficacy of the (b) (4) .

(b) (4)

Testing and acceptance criteria performed during the at scale study are listed in table below:



At the time of PLI, the VAL-30227-02 for cleaning of (b) (4) was on going, there was no cleaning validation data provided in the submission to support the cleaning efficacy of the (b) (4) . The following CR item was issued to the firm (also see page 2):

Regarding drug substance equipment cleaning validation, please provide the following:

- *Data to support the cleaning efficacy of the (b) (4) .*

(b) (4) *Validation Studies*

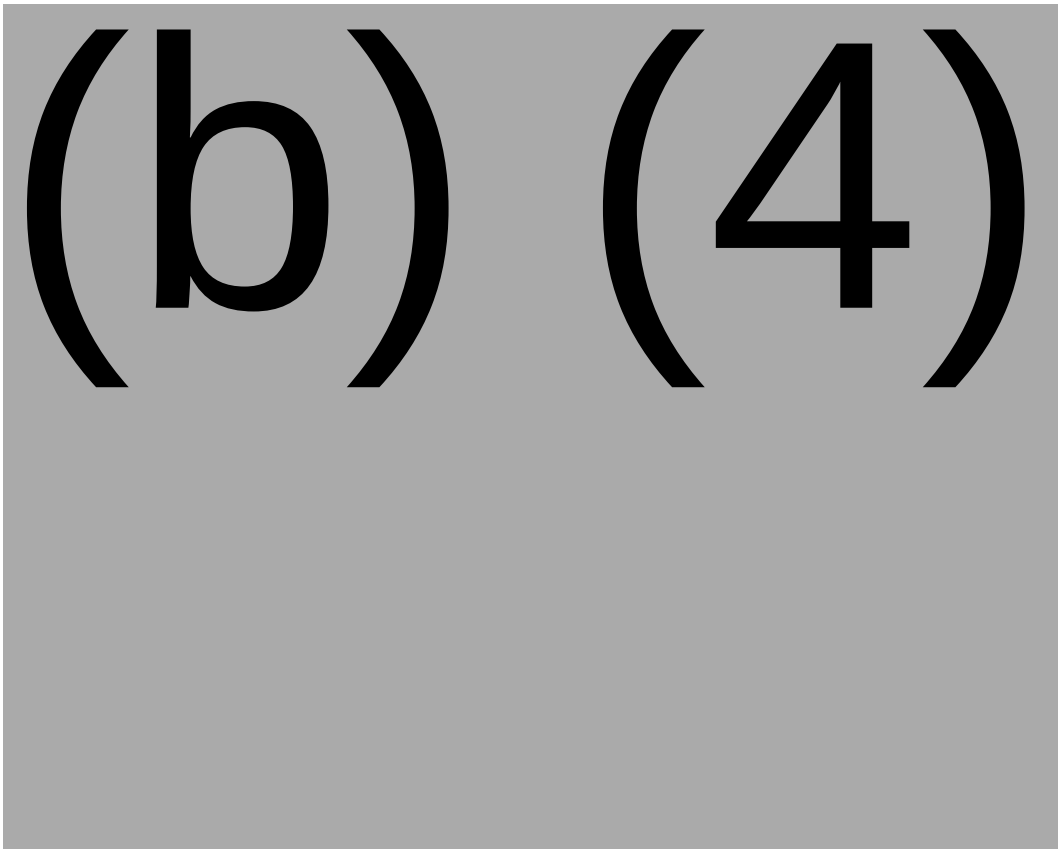
Small scale studies were performed to establish an initial recommended (b) (4) . For each small scale, a total of (b) (4) runs were performed with blank runs every (b) (4) product runs and each run cycle consisted (b) (4)

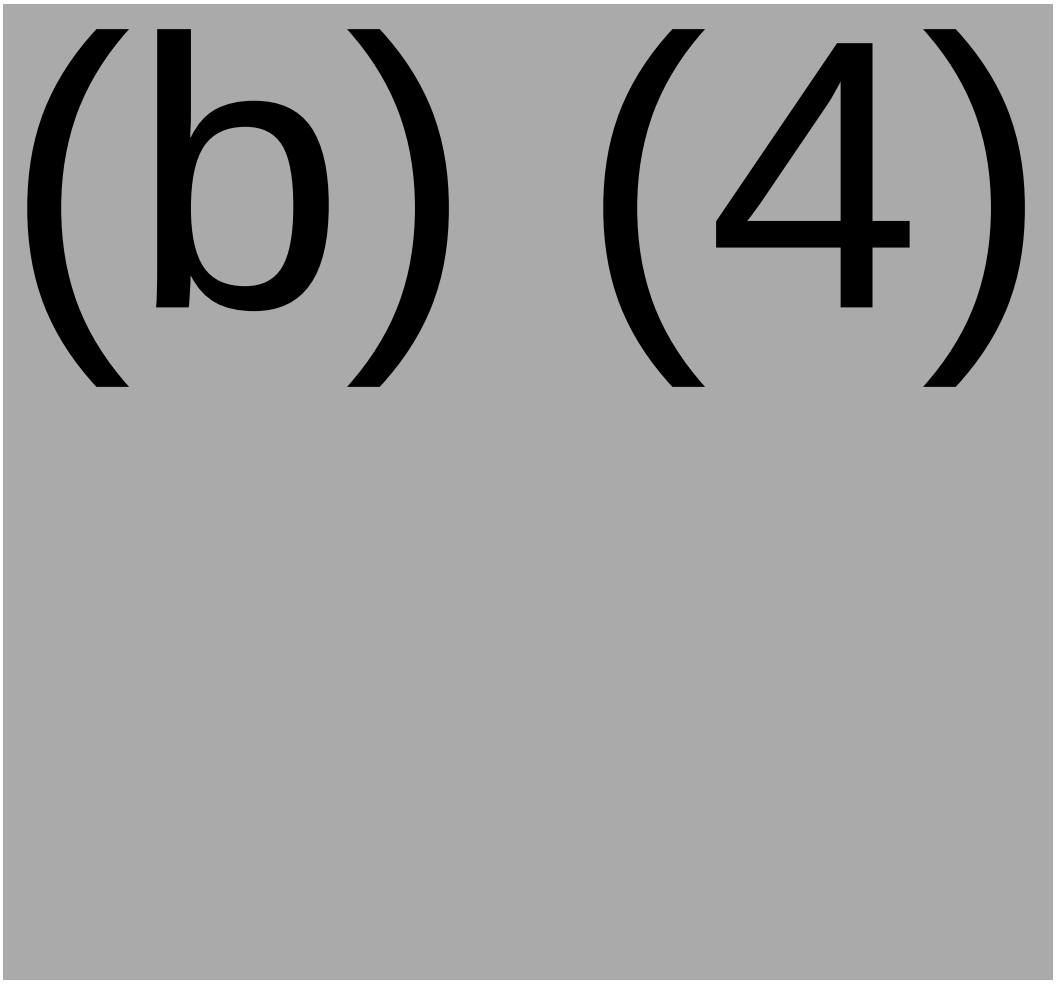
The following small scale (b) (4) studies were performed at (b) (4):

- (b) (4) – (b) (4)-CP-031 (Protocol) and (b) (4)-CR-031 (report)
- (b) (4) – (b) (4)-CP-032 (Protocol) and (b) (4)-CR-032 (report)
- (b) (4) - (b) (4)-CP-033 (Protocol) and (b) (4)-CR-033 (report)
- (b) (4) - (b) (4)-CP-034 (Protocol) and (b) (4)-CR-034 (report)

At scale studies were performed to demonstrate (b) (4) performance and that the (b) (4) performs within the established operating parameters, over multiple uses, meeting designated manufacturing process and product quality performance indicators. For each at scale, a total of (b) (4) product runs were targeted with blank runs every (b) (4) product runs.

The following table lists testing and acceptance criteria for the at scale (b) (4) study:





The following at scale studies were initiated at (b) (4):

- (b) (4) – VAL-30228-01 (Protocol) and VAL-30228-02 (report)
- (b) (4) – VAL-30229-01 (Protocol) and VAL-30229-02 (report)
- (b) (4) - VAL-30230-01 (Protocol) and VAL-30230-02 (report)
- (b) (4) – VAL-30231-01 (Protocol) and VAL-30231-02 (report)

Results of cleaning validation were not provided in submission. Verification and evaluation of cleaning validation adequacy for (b) (4) was performed during PLI.

EIR Summary on cleaning of (b) (4): the (b) (4) study was not complete and not adequate (see 483 item 1).

At the time of PLI, VAL-30228-02, VAL-30229-02, VAL-30230-02 and VAL-30231-02 for the (b) (4) cleaning and monitoring were on going. There was no validation data provided in

the submission to support cleaning and storage of all (b) (4) . The following CR item was issued to the firm (also see page 2):

> Please provide 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.

7. (b) (4) Validation

(b) (4) validation was not provided in the original submission.

Verification of adequate validation for (b) (4) sterilization process was performed during PLI.

EIR Summary on (b) (4) sterilization process validation: (b) (4) used in (b) (4) manufacturing facility was adequately qualified. No objectionable findings noted. Refer to EIR section 9.3 for details.

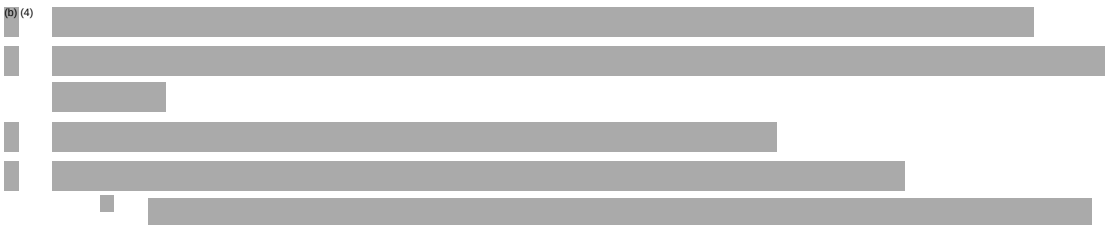
8. Process Validation ((b) (4))

(b) (4) performed (b) (4) consecutive process validation runs for the andexanet alfa DS manufacturing process on (b) (4) combined according to their Process Validation Plan (VAL-90029-01.2) and data was summarized in validation report VAL-30245-01. A summary table of the PPQ lots produced is listed below:

Portola DS Lot Number	(b) (4) Upstream Lot Number	(b) (4) Downstream Lot Number	Manufacturing Line	Date of Manufacture
(b) (4)				

Lot (b) (4) was aborted due to a power failure to the (b) (4) but data was collected up to the (b) (4) step.

Key Operating Parameters (KOPs) with Normal Operating Range (NOR), Critical Process Parameters (CPPs), In-Process Specifications (IPSs) and Limits were set for the following manufacturing steps during the process validation:



(b) (4) reported that all PPQ lots met release specifications with the exception of one protein concentration result for lot (b) (4) being outside of the specification of (b) (4). The result was (b) (4). Investigation for this deviation (DEV-1135) lead to a revision of the manufacturing target protein concentration range (in-process) changed to (b) (4) to account for inherent assay variability. Product and validation impact were excluded and the lot was further processed/filled with the drug product meeting protein concentration release criteria of (b) (4).

Deviations related to validation protocol execution, PPQ parameters and release criteria were evaluated and confirmed to not have process or validation impact. A summary table of the deviations is listed below:

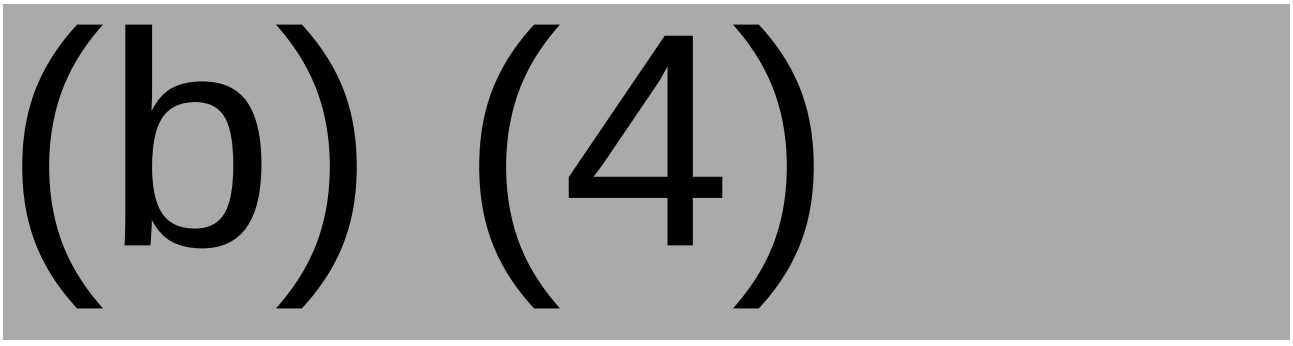
Deviation Type	Deviation #	Description	Impact
Validation Deviation	VAL-30212-01; DEV-001, VAL-30213-01; DEV-001, VAL-30214-01; DEV-001, VAL-30315-01; DEV-001	Protocol generation error due to change of # of PPQ runs on (b) (4).	No impact on product and process
	VAL-30218-01; DEV-001	Protocol execution sampling error occurred during PPQ run (b) (4) when (b) (4) samples were not collected as required.	No impact to product and process because samples were for intermediate product mixing validation and additional sampling was performed from the following manufacturing batch.
Deviations impacting protocol acceptance criteria	DEV-1041 (PPQ lot (b) (4))	(b) (4)	Minimal impact to product quality is expected based on additional testing results

		(b) (4)	and acceptable DS release test results.
	DEV-1567 (PPQ lot (b) (4))	(b) (4) , for (b) (4) had an in-process limit (IPL) for (b) (4)	There was no product impact as the DS Release Specification for (b) (4) . A new (b) (4) will be implemented on (b) (4) via change request CR8639.
	DEV-1062 (PPQ lot (b) (4))	Invalid (b) (4) test at End of Production ((b) (4)), EOP Samples due to (b) (4) not established or maintained at time of testing.	Validation impact was excluded based on passing (b) (4) results for all other upstream and downstream samples.
	DEV-1135 (PPQ lot (b) (4))	Covered in the Process Validation review on page 19	

DMPQ Review Comments: Process parameters were assessed to established normal performance range. (b) (4) in-process control limits appear adequate to support final sterility requirement. No (b) (4) or sterility deviations were reported. Test results in the summary report appear to correlate with the Process Validation Plan. No objectionable findings noted.

9. Hold Time Studies

There are no process intermediates identified for andexanet alfa DS. The manufacturing process is a continuous set of linked unit operations with no points at which material is removed from the processing equipment and independently stored for further processing. Hold time studies were performed according to Hold Time Study Protocol (VAL-30234-01) using PPQ lot samples at (b) (4) step through the remainder of the manufacturing process using small scale equipment with the two exceptions: (b) (4) and (b) (4) steps were combined to represent at least (b) (4) hold time and the (b) (4) step was performed as a (b) (4) step hold time in the study. The hold time steps and conditions included in the study are listed in the table below:



(b) (4)

The following IR (also listed on page 2) was sent to request summary report of the final data generated from the study protocol:

Please provide summary data or report for the hold time study performed per Process Hold Time Study Protocol VAL-30234-01.

DMPQ Review of IR response: the firm responded that the initial small scale Hold Time Study under protocol VAL-30234-01 was halted and closed out due to results not meeting protocol requirements. A second process intermediate hold validation study was developed and described in protocol VAL-30291 using full scale process evaluation and will be conducted to demonstrate the suitability of the MBR-specified process intermediate hold times from (b) (4) *through* (b) (4) *. The firm justified that since the original purpose of the study was to access the cumulative impact of process hold on the finished product, according to PDA TR No. 42, under normal manufacturing conditions, a summation of the maximum unit operation hold times is an unlikely event, and therefore does not require validation.*

10. Product (b) (4) **Validation Study**

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

11. Filter Validation Studies

(b) (4)

(b) (4)

(b) (4)

(b) (4)

12. (b) (4) Clearance Validation Studies

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

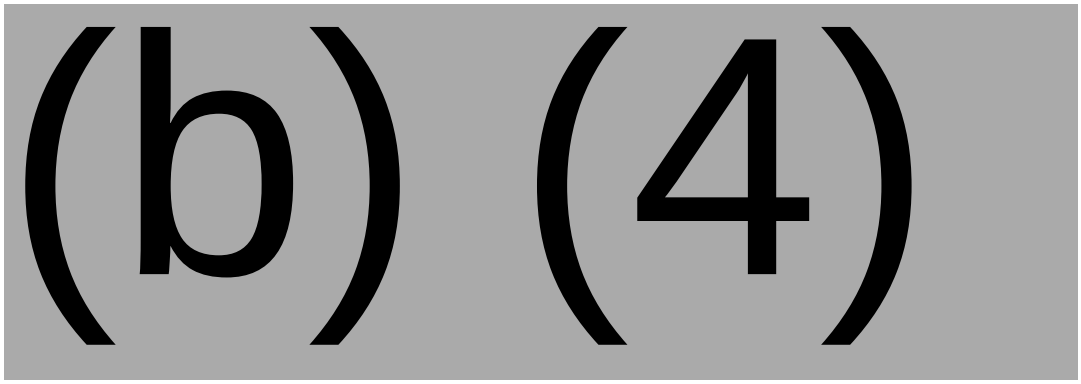
13.Drug Substance Container Closure

(b) (4)

(b) (4)

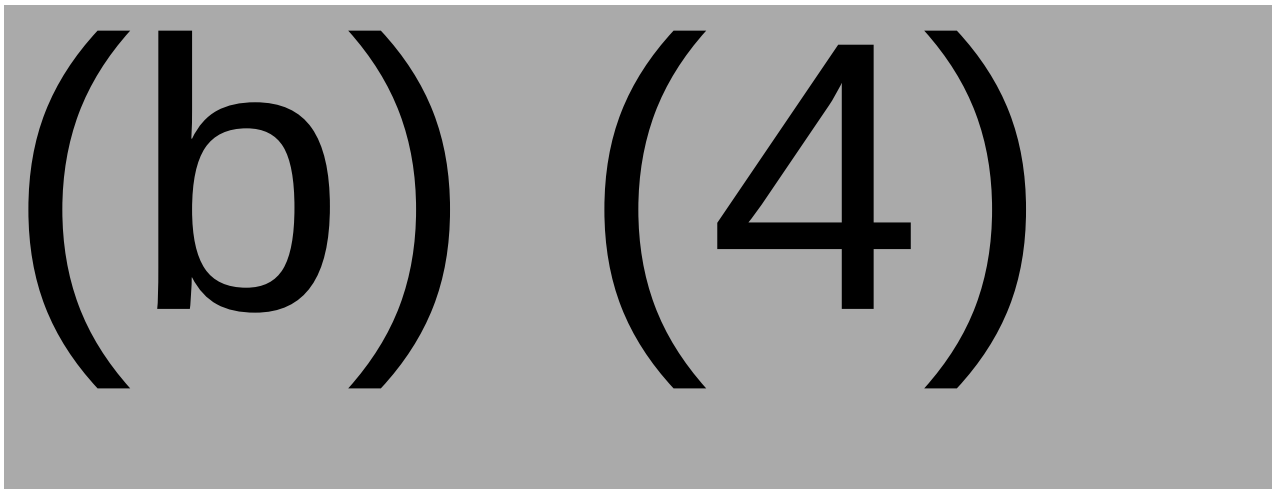
(b) (4)

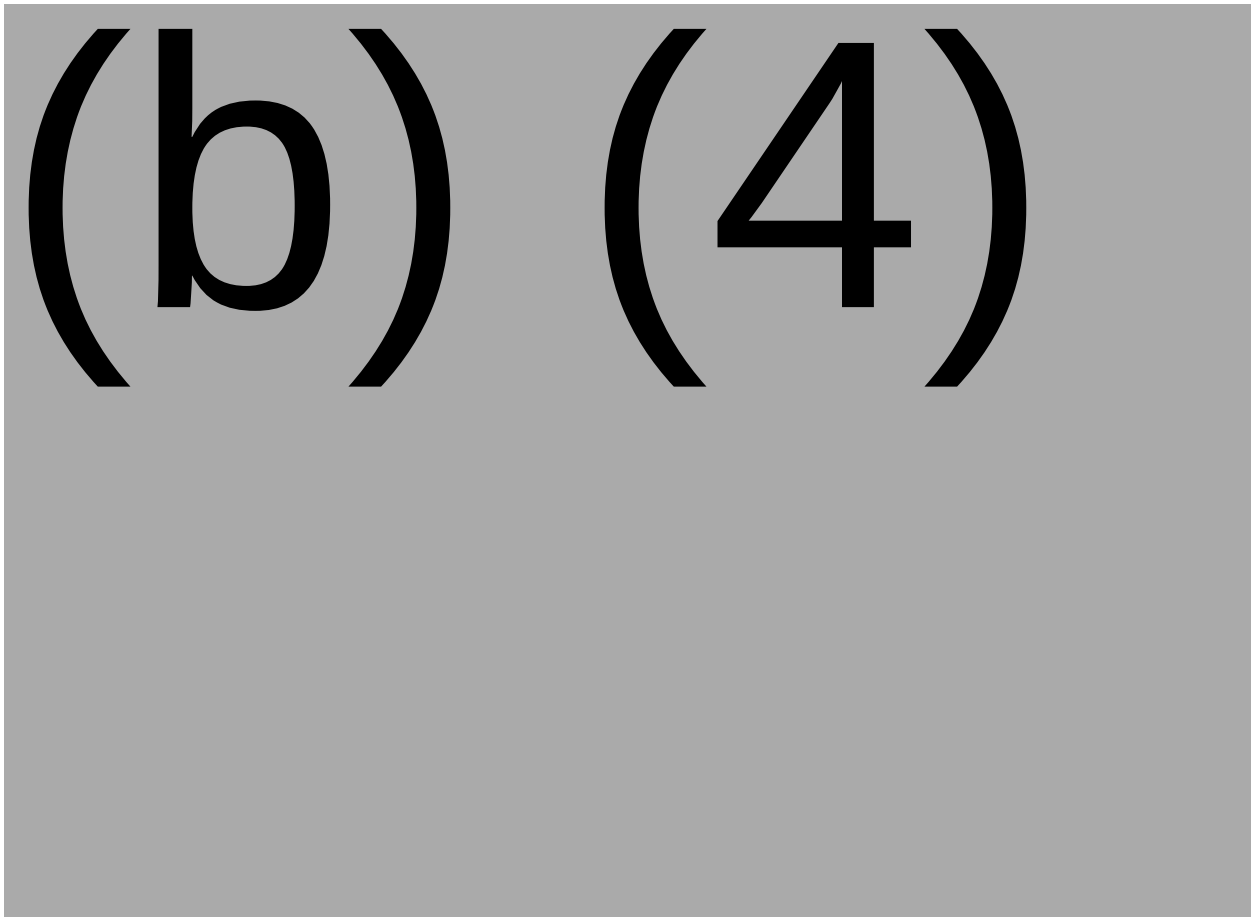
The DS container closure specifications are listed in table below:



The DS is stored at (b) (4) for up to (b) (4) with no product quality change according to available stability data.

14.Drug Substance Testing and Release Specifications





The above specifications are based on data from development, clinical and process validation lots and the firm commits to reassess the data and criteria after manufacture of (b) (4) DS commercial lots.

DMPQ Review Comments: The release specifications appear to correlate with the Process Validation criteria. Justification for specification for (b) (4) appear to be acceptable. Assessment of all other criteria is deferred to DBSQC and/or Product Office.

15. Stability

(b) (4)

For Post Approval Stability, (b) (4) committed to place a minimum of (b) (4) lot of each (b) (4) on stability on an (b) (4) basis for (b) (4) with testing at (b) (4) month intervals for Storage at (b) (4).

(b) (4) testing were not included in the stability testing program but were tested as DS release requirement. The specifications of the stability tests are the same as release acceptance criteria except for the protein concentration by (b) (4) (see release testing criteria table above), the minor difference is justified by the stability data.

16. Shipping Validation

(b) (4) shipping validation runs were conducted for the andexanet alfa DS in the final (b) (4) sterile containers with fill weight of (b) (4). The bottles are capped at a torque setting between (b) (4) and then stored at (b) (4) for minimum (b) (4) prior to shipping to the contract filler. The following IR is requested for the summary data from the executed protocol VAL-80003-01:

Please provide summary data or report for the andexanet alfa drug substance shipping validation protocol VAL-80003-01.

DMPQ Review Comments: The response is acceptable however the validation study is for a max of (b) (4) DS containers max packing in one shipping container. The shipping validation summary report (VAL-80003-02, approved on 02Feb2016) contains shipping validation data for (b) (4) shipping runs for a total of (b) (4) DS containers shipped between 2(b) (4) and (b) (4) under prescribed condition for packing configuration, duration and temperature. Two deviations reported and resolved with no product impactDeviation 001 was initiated as a result of (b) (4) not being calibrated at (b) (4) and did not include post-use calibration.The (b) (4) were used in all (b) (4) validation runs. According to approved protocol, the (b) (4) must be calibrated pre and post use. In this case, the (b) (4) were (b) (4) and not designed for users to perform post use calibration. Product and validation study was excluded based on that the (b) (4) are calibrated by the manufacturer before release for use and acceptable shipping temperature during transit. Deviation 002 was initiated due to a brief temperature excursion ((b) (4)) in all (b) (4) validation runs. The warmest temperature recorded was (b) (4) and all occurrences were at the beginning of a shipment right after the shipment was packaged with a maximum of (b) (4) for temperature to drop below (b) (4) which is the acceptance criteria. Per operation instructions, users are required to warm up the monitors to verify on the screen that the monitors activated successfully prior to packing them in the shipment which is likely the cause during shipment preparation. All temperatures returned with specified range within (b) (4) and mean temperature for all (b) (4) monitors were below (b) (4) throughout the duration of the shipment, no impact is anticipated.

The fill/finish facility for the andexanet alfa drug substance is (b) (4), located in (b) (4).