



Food and Drug Administration
Center for Biologics Evaluation and Research
10903 New Hampshire Ave
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To: Administrative File: STN 125586/0

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Thomas Maruna, RPM, CBER/OBRR/IO

CC: Review Committee Members

From: Christine Harman, Chemist, CMC/Facility Reviewer, CBER/OCBQ/DMPQ/BI

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

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

Applicant: Portola Pharmaceuticals

Product: Coagulation Factor Xa (Recombinant), Inactivated (lyophilized)
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 (Final) Review: Review of original BLA for Andexanet alfa (also including a Comparability Protocol) covering the DMPQ related aspects of the drug product manufacturing and the Comparability Protocol (for drug substance and drug product manufacturing changes) provided in the BLA submission.

Due Date: August 17, 2016

RECOMMENDATION

Based on the information provided in the original BLA and corresponding amendments, the firm should be issued a complete response letter that should include the CR items listed below.

1. A Comparability Protocol (CP) for post-approval changes for drug substance and drug product manufacturing was included in this BLA. After several IRs (August 6, 2016 and May 31, 2016) were sent regarding the CP, the latest version, submitted on June 21, 2016, also included the manufacturing history for the (b) (4) process. We find that the CP cannot be approved as currently designed. These deficiencies that need to be addressed include the following issues for the (b) (4) drug product:

Drug Substance Protocol:

- [illegible]

Drug Product Protocol

- In your response to IR item 5 provided in Amendment 61, page 4, paragraph 3, the following was noted “up to (b) (4) are used of the total (b) (4) on lyophilizer (b) (4) and of the total (b) (4) on lyophilizers (b) (4)”. Given the difference in the number of (b) (4) between the lyophilizers, these lyophilizers do not appear to be equivalent as initially claimed. In addition, to date only (b) (4) runs have been performed on lyophilizer (b) (4) and only (b) (4) runs have been

performed on lyophilizers (b) (4) . Based on this information, we do not agree with the validation strategy proposed in the revised CP regarding the number and type of lots run to date to show comparable results between lyophilizer (b) (4) . Please comment.

Given that (b) (4) does not appear to be in a state of control as evidenced by the manufacturing history provided for (b) (4) , we strongly advise that the CP be withdrawn from the BLA and that the post-approval changes to the (b) (4) drug product manufacturing be submitted as a Prior Approval Supplement after BLA approval.

2. The Proven Acceptable Ranges and Normal Operating Ranges for (b) (4) and (b) (4) indicated for the lyophilization cycle parameters used for the drug product 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 July 1, 2016); however, there was no justification for how the lab scale studies support the lyophilization parameter ranges at commercial scale. Please provide a detailed plan to support these ranges at commercial scale.
3. In regards to CCIT for stability samples performed by (b) (4) , please provide the following:
 - Specific details of the “point of failure” control that is used
 - Please clarify if (b) (4) analysis is performed for product filled vials on stability
 - Provide details, SOPs etc. of the (b) (4) process and how operators are qualified to perform (b) (4) .
 - Results of the (b) (4) stability study (in presence of the product), which was noted in your response to IR item 5 in Amendment 50 (received July 1, 2016), to be conducted at (b) (4) and stability determined by (b) (4) on Days (b) (4) .
4. 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) , including description of course 04-01-C001, which was indicated to be used for qualification of operators noted in your response to IR item 5 in Amendment 50, received July 1, 2016.

Please note that an additional CR item will be included in the CR letter, which is documented in the review of the drug substance manufacturing and involves providing cleaning validation of (b) (4) and validation that supports (b) (4) cleaning, storage and re-use. Please refer to the review memo of the drug substance manufacturing prepared by DMPQ reviewer Joan Johnson for details of this CR item.

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 was also included in the BLA for post-approval manufacturing changes to the Drug Substance and Drug Product manufacturing process. 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 under purview of other offices/divisions as outlined in SOPP 8401.4 is deferred to the appropriate office/division. The sections of the BLA reviewed by DMPQ and are summarized in this review include the following.

*Please note that details of Sections 2.3.S Drug Substance, 3.2.S Drug Substance and 3.2.A.1 (b) (4), relating to the drug substance manufacturing and facilities, was reviewed by DMPQ reviewer, Joan Johnson, and is covered in a separate review memo.

Module 1: Regional

1.1 Forms

- Form FDA 356h

1.2 Cover Letters

1.12 Other Correspondence

- 1.12.14 Environmental Analysis

Module 2: Common Technical Document Summaries

2.2 Introduction

2.3 Quality Summary

- *2.3.S Drug Substance [Substance-Manufacturer]
- 2.3.P Drug Product [Product-Dosage Form-Manufacturer]
- 2.3.A Appendices

Module 3: Quality

*3.2.S Drug Substance

- 3.2.S.1 General Information
- 3.2.S.2. Manufacture
 - 3.2.S.2.1 Manufacturer(s)
 - 3.2.S.2.2 Description of Manufacturing process and Process Controls
 - 3.2.S.2.4 Controls of Critical Steps and Intermediates
 - 3.2.S.2.5 Process Validation
 - 3.2.S.2.6 Manufacturing Process Development
- 3.2.S.6 Container Closure

3.2.P Drug Product [Product-Dosage Form-Manufacturer]

- 3.2.P
 - 3.2.P.1 General Information
 - 3.2.P.2 Pharmaceutical Development
 - 3.2.P.3 Manufacture
 - 3.2.P.3.1 Manufacturer (s)
 - 3.2.P.3.3 Description of Manufacturing process and process controls
 - 3.2.P.3.4 Control of Critical Steps and Intermediates
 - 3.2.P.3.5 Process Validation
 - 3.2.P.7 Container Closure

3.2.A. Appendices

- 3.2.A.1 (b) (4)
 - Facilities and Equipment
 - Facilities Floor plans
- *3.2.A.1 (b) (4)
 - Facilities and Equipment

- Facilities Floor plans
- 3.2.R. Regional Information
 - Comparability Protocols
 - (b) (4) Container Closure Executive Summary

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I. Description of product and proposed indication

Andexanet is a recombinant modified form of fXa that is packaged as a 100mg dose of lyophilized cake or powder for reconstitution to administer by injection. Andexanet alfa is indicated for patients treated with a direct or indirect fXa inhibitor when reversal of anticoagulation is needed in situations that are life threatening or uncontrolled bleeding (b) (4) .

II. Composition of the Drug Product

The composition of the Andexanet alfa was indicated as follows:

Ingredient	Quality Standard	Function	Amount per Vial
andexanet alfa Drug Substance	In house	Active	(b) (4)
Tromethamine (Tris)	(b) (4)	Buffer	(b) (4)
L-Arginine Hydrochloride		Stabilizer	
Sucrose		Stabilizer	
Mannitol		Bulking agent	
Polysorbate 80		Stabilizer	
(b) (4)		(b) (4)	
Water for Injection		Solvent	Removed during lyophilization
(b) (4)		(b) (4)	NA

NA: not applicable; QS Quantum Sufficit (Latin; as much as suffices)

III. Overall Manufacturing and Facilities

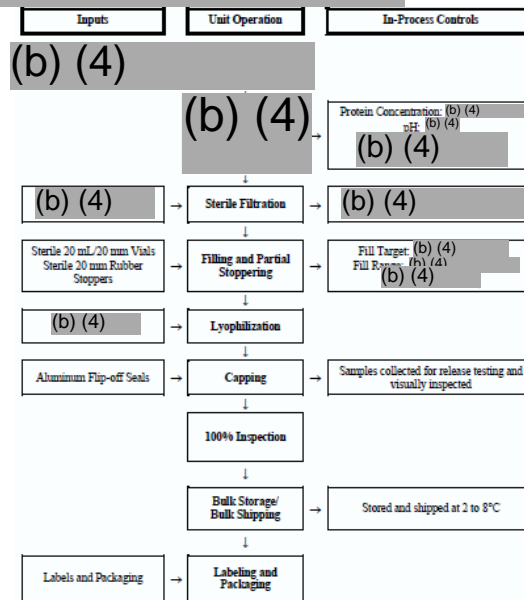
Andexanet Alfa Drug Substance Process Overview- The following process steps are performed at (b) (4)

(b) (4)

(b) (4)

Andexanet Alfa Drug Product Process Overview- The following process steps are performed at

(b) (4)



IV. Drug Substance Manufacture

Details of the overall process, process validation, and activities related to the drug substance manufacturing were provided in the BLA submission located in sections 2.3.S Drug Substance, 3.2.S Drug Substance and 3.2.A.1 (b) (4). The areas related to the drug substance manufacturing provided in the BLA were reviewed by Joan Johnson and are covered in a separate review memo. Please refer to her memo in the EDR for details of the review.

V. Drug Product Manufacture Manufacturing Process

Manufacturing steps of Andexanet alfa drug product (DP) that are performed at DP Manufacturer (b) (4) include the following: (b) (4), sterile filtration, Aseptic Filling and Partial Stoppering, lyophilization, capping, and inspection. The details of these manufacturing steps were described as follows:

- (b) (4)

Reviewer Comments: There was no information in regards to if the (b) (4) are re-used, thus an information request was sent to the firm to clarify if (b) (4) are re-used or are single use. Please see firm's response to IR#7 (item 1) in section "Information Requests" of this memo.

- (b) (4)

- **Sterile Filtration:** (b) (4) andexanet alfa (b) (4) is filtered through (b) (4) filters in series into a (b) (4) intermediate (b) (4) bag (b) (4) located in a Grade (b) (4) area of the fill suite. A (b) (4). The filters are integrity testing (b) (4) their use. Both (b) (4) testing is performed with WFI. Passing (b) (4) testing results must be obtained from at least (b) (4) filter before filling begins.

- **Aseptic Filling and Partial Stoppering:** The sterile filtered andexanet alfa product is filled by weight into washed and depyrogenated 20 mL/20 mm (b) (4) glass vials in a Grade (b) (4) environment under aseptic conditions using the (b) (4) Fill Machine (b) (4) with a fill range of (b) (4). Fill volume limits are converted to weight limits for filling. The filled vials are partially stoppered with sterilized rubber, single-vent lyophilization stoppers. Weight checks are automated and performed on (b) (4) of the vials on-line during filling operations. Adjustment to the pumps is made during filling when necessary to ensure that fill weights remain within the range specified. Vials outside the fill weight range are rejected. The target fill volume is (b) (4) mL which corresponds to a fill weight of (b) (4) g. Vials with fill weights within the range are (b) (4). When all filled vials have been (b) (4). The aseptic filling process is qualified using media fills. Process Time Limits for sterile filtration and aseptic filling were noted as follows:

Process	Description	Limit
Filter/Product Contact Time	Maximum validated product/filter contact time	(b) (4)
Aseptic Filling Time	Time from the start of filling ((b) (4)) to the last container filled	(b) (4)

¹Sterile filtration process has been validated for (b) (4).

²The filling line has been media fill validated for the duration of (b) (4).

Reviewer Comments: There is no description of the aseptic conditions or how the filling line is maintained in Grade (b) (4) environment (i.e. (b) (4)). The firm was issued an IR

asking to provide details for Grade (b) (4) room set up to maintain aseptic conditions. Please refer to section “Information Requests” IR#2 (item 24) for details of firm’s response.

- **Lyophilization:** The lyophilization cycle parameters and NORs are provided in the following tables. At the end of the cycle, the lyophilized vials are (b) (4) with sterile (b) (4) and the vials are fully stoppered (b) (4). The vials are (b) (4) lyophilizer until unloaded into a Grade (b) (4) environment.

Lyophilization Cycle for Andexanet Alfa Drug Product

Step	Set Point	Rate/Duration	Vacuum
(b) (4)	(b) (4)	(b) (4)	(b) (4)

Lyophilization Parameters Summary

Step	Target	NOR
(b) (4)	(b) (4)	(b) (4)

- **Capping:** The fully stoppered vials are unloaded from the lyophilizer by a conveyor to the Capping area sealed with an aluminum flip off seal under Grade (b) (4) supplied air using the (b) (4) Capping Machine ((b) (4)). Each vial is coded with a batch number on the aluminum crimp. Capped vials are placed into trays using the (b) (4) Tray Loader ((b) (4)), palletized and stored at 2-8°C prior to inspection.

- **Inspection:** Unlabeled vials are 100% visually inspected for visual appearance, presence of foreign matter, and intact vials, stoppers and seals. Samples are collected for release testing and are visually inspected.

Reviewer Comments: The firm did not provide any details in regards to supplemental testing for particulates, thus was issued an information requests. Please refer to IR #7, item 3 in "Information Requests: section of memo for details of the firm's response.

Control of Critical Steps and In-Process Testing and Control

Critical Process parameters and in-process testing and controls were indicated for the following process steps:

(b) (4)

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(b) (4)

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Process Validation

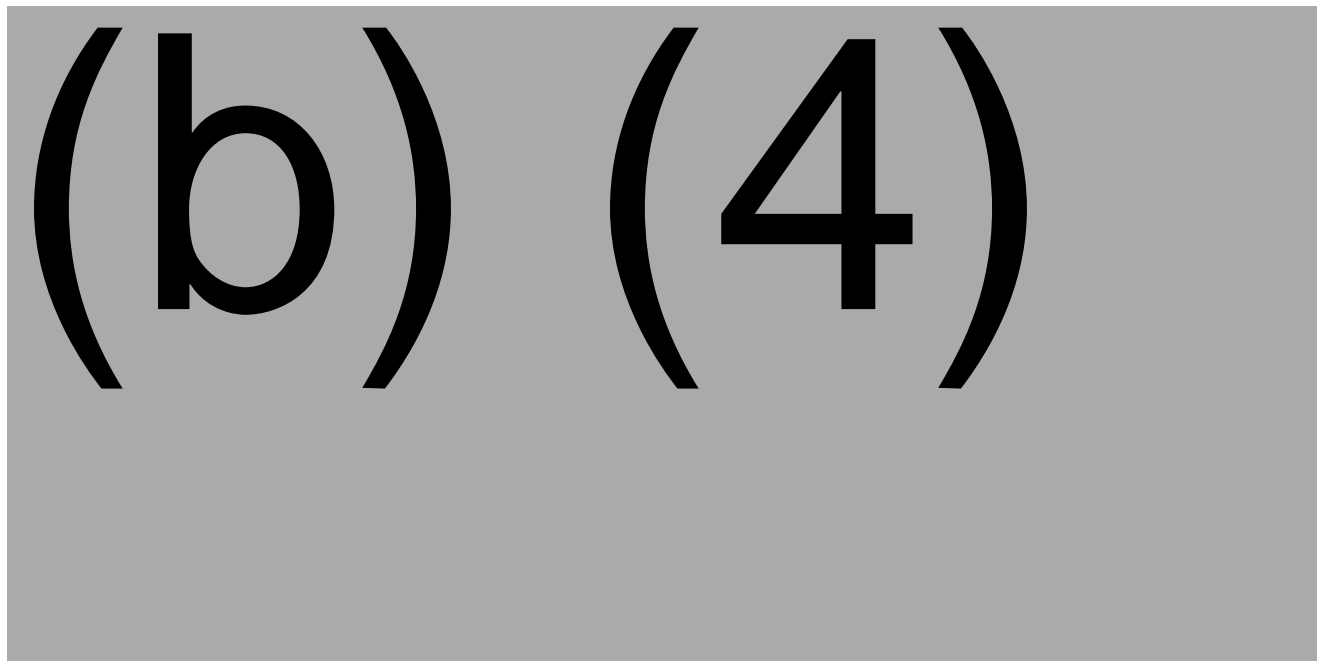
The Process Performance Qualification (PPQ) Protocol 414-21-04-001-P1 "Process Performance Qualification Protocol for Andexanet, PRT064445 Lyophilized Drug Product, 20 mL/20 mm Vial, (b) (4) Fill, 100 mg/Vial Lyo, Fill Line (b) (4)" (effective date 09/11/2015) defines the validation protocol used to demonstrate the consistency and reproducibility of the DP manufacturing process ((b) (4)) performed at (b) (4) r using equipment, (b) (4) Fill Machine ((b) (4)) and Lyophilizer (b) (4). The PPQ executed under the protocol 414-21-001-P1 defines the following acceptance criteria to be considered successful:

- Completion of (b) (4) consecutive PPQ runs
- All in-process controls and release tests must meet the acceptance criteria
- Critical Process Parameters must be operated within the defined operating range

The PPQ protocol 414-21-04-0001-P1 includes the details of the process steps that are covered in the protocol, critical process parameters that are monitored and the associated process ranges, in addition to, quality attributes testing and in-process control testing with associated acceptance criteria. As per the PPQ protocol, (b) (4) consecutive commercial scale validation lots are required. At the time of the BLA submission, the manufacturing and release testing of the first PPQ lot was completed; however, the manufacture and release testing of the remaining (b) (4) PPQ lots was ongoing and was planned to be submitted during the BLA review.

To demonstrate consistency of the process in supporting the BLA, data from (b) (4) consecutive DP lots that include (b) (4) clinical lots manufactured at commercial scale (Lots (b) (4) and (b) (4)), in addition to the (b) (4) completed PPQ lot ((b) (4)) was provided in Report VA-013. Additionally, during the review, data from (b) (4) PPQ runs, PPQ (b) (4) (lot (b) (4)) and PPQ (b) (4) (lot (b) (4)) (not previously included in submission), was provided as report 414-21-04-001-SR2, “Process Performance Qualification Summary Report for Andexanet alfa, PRT064445 Lyophilized Drug Product, 20mL/ 20 mm Vial, (b) (4) mL Fill, 100 mg/Vial Lyo Fill Line (b) (4)” submitted during the review as amendment 23, which was received April 18, 2016.

The following table provides an accounting of the various lots that have been completed and are ongoing to support this BLA submission:



Review of Report VA-013

Report VA-013, “Andexanet alfa Drug Product Consistency Lots Manufacturing Summary Report”, included in the BLA submission, provides the results of a process qualification executed under the Process Qualification Protocol (414-21-04-001SR1). The results provided in this report are from the manufacturing of (b) (4) clinical lots (b) (4) at commercial scale (executed according to PPQ 414-21-04-001SR1), in addition results from the (b) (4) PPQ Lot (b) (4) (executed according to PPQ 414-21-04-001-P1). The Process Qualification protocol 414-21-04-001SR1 is similar to the PPQ Protocol 414-21-04-0001-P1, in regards to commercial scale, process parameters, acceptance criteria, etc., with exceptions noted in regards to testing of concentration (changes are noted as asterisks in tables of results reported below).

Report VA-013 includes a detailed description of the following process steps: (b) (4), sterile filtration, aseptic filling, lyophilization, capping and inspection, in addition to the results generated. A schematic of the process steps covered in this PQ protocol is shown in Figure 1 (in APPENDIX). The results are summarized as follows:

- (b) (4)
(b) (4)
(b) (4)
- **Sterile Filtration:** The (b) (4) solution is filtered with two (b) (4) filters into a sterile (b) (4). Results of the sterile filtration process parameters including (b) (4), Total Validated Volume, Product Contact Temperature, (b) (4) Test, and process time limits (filter/product contact time) and aseptic filling parameters (including Fill volume, filling parameters and filling format) was provided in the follows tables:

(b) (4)

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

- The results provided indicated that all acceptance criteria for all (b) (4) consistency lots in regards to sterile filtration were met and no deviations were indicated.

In section 3.2.P.2.5 Microbiological attributes it was noted that the (b) (4) is determined before sterile filtration with an acceptance limit of (b) (4). Additionally, the DP is tested for sterility and bacterial endotoxins. Endotoxin (b) (4) is specification based on (b) (4) limits for parenteral drug product administered by infusion.

Sterile Filter Validation: During the DP manufacturing process, (b) (4)

(b) (4)

(b) (4)

(b) (4)

- **Aseptic Filling:** The filling process parameters and results from (b) (4) lots consistency lots were reported as follows:

Filling Parameters for Consistency Lots

Process Step	Description	Parameter	(b) (4)	(b) (4)	(b) (4)
Process Parameters					
Filling	Fill Volume	(b) (4)			
	Filling Parameters				
	Filling Format				

*Target was (b) (4), range from (b) (4)

Results in regards to aseptic filling met acceptance criteria and no deviations were noted.

- **Lyophilization Validation:** The lyophilization process parameters and results of the (b) (4) consistency lots were provided as follows.

Process Step	Description	Target	NOR	PAR	Validation Parameter Range	(b) (4)		(b) (4)		(b) (4)	
Process Parameters						Low	High	Low	High	Low	High
(b) (4)											

Reviewer Comments: For each of the process parameters, specifically, the (b) (4) there are several listed ranges that include Normal Operating Range (NOR), Proven Acceptable Range (POR), and a Validation Parameter Range. In addition to this ranges, there is also an indicated target value for each of these process parameters. The target range is within the middle of these NOR, PAR and Validation Parameter range. The ranges provided for each of these process parameters does not seem to be reflected in the actual low and high process parameters used for each of the consistency lots, thus it is not clear how the data provided for the (b) (4) consistency lots supports these ranges indicated. The firm did provide developmental studies for the lyophilization in section 3.2.P.2.3 Manufacturing Process Development (pgs.6-11); however, these studies are not comprehensive in supporting the maximum end of the ranges indicated for the process parameters nor do the studies cover a combination of the process parameters operating at extremes of the indicated operating ranges for the process parameters. The firm was issued several information requests to address the deficiency in the data provided to support the indicated ranges. Please refer to section “Information Requests” IR#2 (item 27), IR# 6 (item 1) and IR#7 (item 4) for details of firm’s response to these IRs.

To evaluate (b) (4) were taken across the lyophilizer (b) (4) including (b) (4) for Lots (b) (4) after completion of the lyophilization cycle. The testing included appearance, moisture content, reconstitution time, solution appearance, protein concentration, pH, direct potency, purity by (b) (4)

(b) (4) and matter (particles). The results of the test attributes appearance, moisture content, reconstitution time, and solution appearance for the Lots (b) (4) were indicated as follows. The other attributes tested (including protein concentration, pH, purity, potency, purity, (b) (4) and particulate matter) which are not included in table below, met the acceptance criteria however, the review and acceptability of these attributes are deferred to product office for final comment.

Lyophilization (b) (4) **Samples,** (b) (4) **Lot** (b) (4)

Test Attribute	Acceptance Criteria/ Specification	(b) (4)	
Lyophilized Product Appearance	White to off-white lyophilized cake		
Moisture Content (b) (4)	(b) (4)		
Reconstitution Time*	(b) (4)		
Solution Appearance	Clear, colorless to slightly yellow solution, essentially free of visible particulates (EFVP).		

CC: Clear, colorless solution, WLC: White Lyophilized cake

* (b) (4)

Lyophilization (b) (4) **Samples,** (b) (4) **Lot** (b) (4)

Test Attribute	Acceptance Criteria/ Specification	(b) (4)	
Lyophilized Product Appearance	White to off-white lyophilized cake		
Moisture Content (b) (4)	(b) (4)		
Reconstitution Time	(b) (4)		

Solution Appearance	Clear, colorless to slightly yellow solution, essentially free of visible particulates (EFVP).	(b) (4)
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CC: Clear, colorless solution, WLC: White Lyophilized cake

According to the results and acceptance criteria reported above, all the acceptance criteria were met and no deviations were indicated in regards to lyophilization.

***Reviewer Comments:** The reconstitution time acceptance criteria is indicated as (b) (4), which seems to be too wide of range and it is not clear what the basis is for this acceptance criteria. For Lot (b) (4) the reconstitution times for sampling at the various (b) (4) on the (b) (4) were between ranged between (b) (4). Also, there seems to be a significant difference in the reconstitution times between Lot (b) (4) and Lot (b) (4) with the reconstitution time for all sample locations for Lot (b) (4) being (b) (4), additionally, in a footnote to the results of mapping samples for Lot (b) (4), indicated that a (b) (4). The firm should provide more details of this method and indicate if different reconstitution methods were used for Lots (b) (4) and (b) (4). An IR was sent to firm to May 12, 2016 to address this significant difference obtained for the reconstitution time and the wide range for the acceptance criteria for the reconstitution time. Please refer to Section "Information Requests" IR#3 (item 1) at end of memo for details of the information provided to address the IR item.*

- **Capping:** The following capping parameters and results of the (b) (4) consistency lots were reported as follows:

(b) (4)

No deviations were noted.

- **Process Time Limits:** The process time limits, acceptance criteria and results of product testing were reported as follows:

(b) (4)

(b) (4)

(b) (4)

(b) (4)

The (b) (4) results were within the acceptance criteria indicated. Review of other testing performed on the process time challenge samples including but not limited to (b) (4) and concentration etc. is deferred to product office for comment on acceptability of results.

Reviewer Comments: For all (b) (4) consistency lots, the process limit times met the indicated acceptance criteria; however, for some of the process steps, the validation lots did not cover the complete range of the process limit (i.e. Process step F, the process limit is noted as (b) (4), whereas (b) (4) lots were between (b) (4). Process step D, regarding the sterile filtration time indicating a process limit of (b) (4); however, for the (b) (4) consistency lot, the actual process time for this process step ranged from (b) (4), was addressed previously in IR#2 sent April 6, 2016. The firm was issued an addition IR to indicate the basis for the process time limit of (b) (4) for the process step F. Please refer to section “Information Request” IR#2 (item 26) and IR#3 (item 5) for details of firm’s responses to these IR items.

Review of Report 414-21-04-001-SR2

Report 414-21-04-001-SR1, “Process Performance Qualification Summary Report for Andexanet Alfa Lyophilized Drug Product 20mL/ 20 mm Vial, (b) (4) mL Fill, 100 mg/Vial Lyo, Fill Line (b) (4)”, submitted as Amendment 23, and includes the complete results from the manufacturing of (b) (4) PPQ lots. The results of PPQ (b) (4) were initially provided in report VA-013 at time of BLA submission. This report 414-21-04-001-SR2 provides updated information that includes data from PPQ (b) (4) and PPQ (b) (4) runs, in addition to PPQ (b) (4).

The results are summarized as follows:

Andexanet alfa formulation was completed in (b) (4) Building (b) (4), Room (b) (4) (Grade (b) (4)). The drug substance is shipped (b) (4) to (b) (4) in (b) (4) containers. The manufacturing lots of bulk drug substance used are summarized in table below:

(b) (4)

- **Sterile Filtration**

Process parameters and time limits for batches (b) (4) were reported as follows for the following process steps:

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

Reviewer Comments: Firm was issued two information requests in regards to the filter product contact time process limit of (b) (4). Please refer to IR#2 (item 26) and IR#6 (item 6) in section “Information Requests” for details of firm’s response.

Filling Parameters and Time limits for batches (b) (4) were reported as follows for the following process steps and process limits:

- Fill Volume (target 1(b) (4), range (b) (4))- reported for all (b) (4) batches as conforms
- Filling Parameters (parameters as per CCOQ)- reported for all (b) (4) batches as conforms
- Filling format ((b) (4))- reported for all (b) (4) batches as (b) (4)
- Process time limit ((b) (4)): includes time from end of (b) (4) to the last (b) (4) of filled vials load onto the lyophilizer (b) (4) maintained at 2-8°C)- reported for batches (b) (4) as (b) (4)

- **Lyophilization**

Critical Process Parameters noted in the report included the following:

(b) (4)

- **Capping**

Capping Parameters and time limits were reported as follows:

(b) (4)

- **Inspection**

Lyophilized vials were (b) (4) visually inspected via manual inspection methods with a process limit of (b) (4) Total Rejects as per SOP 21-01-030, Procedure for Creating Fill Complex Master Batch Records. No inspection rejects were reported during manual inspection of the three batches. The inspection summary was provided as follows:

(b) (4)

An Acceptable Quality Limit (AQL) test of each batch was conducted and met the criteria ((b) (4)) defined in SOP-13-03-010, Monitoring of Manual Inspection, In-Process Inspection, Label Application and Packaging. No rejects were reported during the AQL inspections.

Reviewer Comments: There was no indication that supplementary testing was performed in regards to particulates. According to ((b) (4)), for where the nature of the contents permits only limited capability for particulate detection, the ((b) (4)) inspection of a lot shall be supplemented with the inspection of constituted contents, thus the firm was issued an IR recommending that supplemental testing for particulates, requiring reconstitution (a destructive test) for inspection of visible particles, be performed. For details of firm's response, please refer to section "Information Requests" of memo, IR#7 (item 3).

- **Process Hold time limits**

Process Hold time limits were reported as follows:

((b) (4))

(b) (4)

- **Deviations (Non-conformance)**

The reporting of non-conformances during validation was noted as follows:

No nonconformance reports were generated during the manufacture of PPQ Batch (b) (4) (b) (4), PPQ^{(b) (4)}).

(b) (4)

Reviewer Comments: The non-conformances reported during production of batches (b) (4) is minor given that the product was been unloaded from lyophilizer at the (b) (4) was not maintained, thus the firm's assessment that there is no impact on the process validation is reasonable. In regards to the nonconformance reported for Batch (b) (4), the firm was issued an IR, to provide more details in regards to why the (b) (4) method used was deemed inappropriate, in addition, the firm should provide details of the where in the process is the In-process (b) (4) hold sample represent. Please refer to IR#7 item 6 in the "Information Requests" section of memo for details of the firm's response.

Media Fill Performance Qualification

In section 3.2.P.3.5.2.3, a summary of a media fill Performance Qualification performed in October 2012 on the same filling line, lyophilizer and capping line used for the andexanet alfa DP manufacturing process was provided. Additionally, the results of the two most recent media fills performed December 22-21, 2014 and July 8-9, 2015 according to procedures defined below was also included in this section. The details of the procedures and results are summarized as follows:

- Equipment included (b) (4) filling machine (b) (4) (located in Building (b) (4), Fill Room (b) (4)), (b) (4) freeze dryer, (b) (4) and capping machine (b) (4) with a restricted access barrier system installed.
- (b) (4) media fill runs for PQ were performed using a bracketing approach with a (b) (4) glass vial and a 20 mL/20 mm glass vial, in which the 20 mL/20 mm glass vial is the same vial used for filling andexanet alfa DP
- Each media fill was performed in segments with each segment at minimum of (b) (4) vials filled (batch size for Andexanet is (b) (4) vials):

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

- Fill volume was noted to be sufficient for media to contact all surfaces in addition to promote growth
- Line speed was varied throughout filling process (b) (4) to (b) (4), in addition to incorporation of planned interventions that
- Results were provided as follows:

(b) (4)

(b) (4)

(b) (4)

One deviation was noted and was described briefly as a footnote (*) in the above table as the following: a fill volume deviation for liquid fill portion with a target fill weight of (b) (4) was indicated. The deviation was indicated to not impact the media fill given that the volume was sufficient to contact all internal surfaces and had sufficient headspace to support growth. The acceptance criterion of no more than one positive contaminant was met. The conclusions of the results were stated as follows:

The media fill runs successfully validated the aseptic filling process using (b) (4) filling for the andexanet alfa DP container closure and batch size using the andexanet alfa DP process filling line, lyophilizer and capping machine for (b) (4).

(b) (4)

(b) (4)

(b) (4)

(b) (4)

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types for the formulation and filling equipment was described in section 3.2.P.3.5.2.4 of the BLA and is summarized as follows:

Formulation Equipment-The worst-case durable load includes the most difficult equipment to sterilize, which is based upon past validations for different load configurations yielding consistent cold spots. The PQ consists of a minimum of (b) (4) loaded (b) (4) studies for both the maximum and minimum worst-case load configuration in each (b) (4). Schematics of the maximum and minimum worst-case load configurations including the locations of the placement of (b) (4) were provided for each of the (b) (4).

- Maximum Worst Case Durable Load- (b) (4) PQ runs were performed in each (b) (4) to confirm acceptable (b) (4) and sufficient (b) (4) to achieve a (b) (4) reduction in (b) (4). (b) (4) and (b) (4) were used to evaluate the (b) (4). Each (b) (4) were placed adjacent to (b) (4), with exception for (b) (4) in (b) (4). Locations of the placement of specific (b) (4) were indicated on the schematics of the maximum load configurations provided for (b) (4). The sterilization cycle included (b) (4) cycle with (b) (4) at a set point of (b) (4).

Results of PQ: Table 3.2.P.3.5-24 (in Section 3.2.P.3.5 of BLA) provides an overall summary of the data average (b) (4) data, highest and lowest (b) (4) attained during exposure and the (b) (4) results from all (b) (4) PQ runs performed in each (b) (4) (refer to Table 2 in APPENDIX for complete results).

The highest and lowest average temperature of the (b) (4) were reported for all PQ runs as (b) (4) (ranging from (b) (4)). All (b) (4) exhibited (b) (4). One deviation was indicated in the (b) (4) run in (b) (4), there was (b) (4) after (b) (4). An investigation was initiated for the failing (b) (4). (b) (4) was subsequently repaired and the PQ was completed with Runs (b) (4).

Results of Run (b) (4) performed in (b) (4) was not included in Table 3.2.P.3.5-24, in which only data from Runs (b) (4) were included. The (b) (4) results for these runs indicated (b) (4). No other deviations were indicated.

(b) (4) confirmation of the maximum worst case durable load is performed on (b) (4) and results of the most recent confirmation runs performed in March 2015 (b) (4) were provided for (b) (4). Schematics were also provided indicating the location of the (b) (4) and (b) (4) that were used in the confirmation run.

Results of (b) (4) Confirmation: Table 3.2.P.3.5-25 (refer to Table 3 in APPENDIX for details) includes a summary of the confirmation run performed for each (b) (4). The highest and lowest average temperature values during exposure was reported for all runs as (b) (4) (ranging from (b) (4)). The (b) (4) results for each run was indicated (b) (4). No deviations were noted; however, one (b) (4) did not provide data and was discarded. No other details were provided.

- **Minimum Worst Case Durable Load-** (b) (4) PQ runs with the minimum worst case durable load were performed, March 2005, for (b) (4) to confirm an acceptable (b) (4) and sufficient (b) (4) to achieve a (b) (4). The minimum load configuration consisted of one item that included (b) (4). (b) (4) included (b) (4).

Results: Table 3.2.P.3.5-26 (in section 3.2.P.3.5 of the BLA) provides an overall summary of the data including the average (b) (4) data, highest and lowest (b) (4) attained during exposure and the (b) (4) results from the (b) (4) PQ runs performed in each (b) (4) (Refer to Table 4 in APPENDIX for details). The highest and lowest temperature during exposure for all runs was reported as (b) (4) (ranging from (b) (4)). The (b) (4) for all runs was reported as (b) (4). During Run (b) (4) in (b) (4), one issue was reported involving the (b) (4). This run was invalidated, thus data provided in Table 3.2.P.3.5-26, includes data from Run (b) (4) for (b) (4). No deviations were indicated.

Reviewer Comments: *The minimum worst-case durable load only consisted of one item: a (b) (4); however, there no details as to the number of (b) (4) that were used during the PQ runs. Also, the schematics for the load confirmation for the minimum load were not provided, thus it is not clear where the thermocouples and BIs were placed. Additionally, these PQ runs were performed in March 2005 similar to the time frame in which the maximum worst-case durable load PQ runs were performed; however, the firm did not provide the results of the (b) (4) confirmation runs performed for the (b) (4), which was provided for the maximum worst-case durable load configuration. Although the firm did provide details of the PQ for the (b) (4), this BLA submission did not include the actual report summaries for the OQ and PQ of process equipment including the (b) (4), thus some of the details are missing. The firm was issued an IR April 6, 2016, asking to provide the summaries of the OQ and PQ reports for the (b) (4) (as well as other process equipment), thus the details in regards to the minimum worst-case durable load configuration for the (b) (4) should be included in this request information. However, the OQ/PQ information requested April 6, 2016 did not include these details of the minimum durable load. An IR was issued June 15, 2016, specifically asking to indicate the number and location of the (b) (4), in addition, to indicate why a re-qualification of the minimum load was not performed. Please refer to IR#6 (item 3) for details of the information provided by the firm.*

Filling Equipment- The filling equipment load type (b) (4) is applicable to the andexanet alfa DP manufacturing process and was validated in (b) (4). The (b) (4) maximum worst case durable load confirmation covers load type (b) (4). The (b) (4) load type includes items such as a (b) (4).

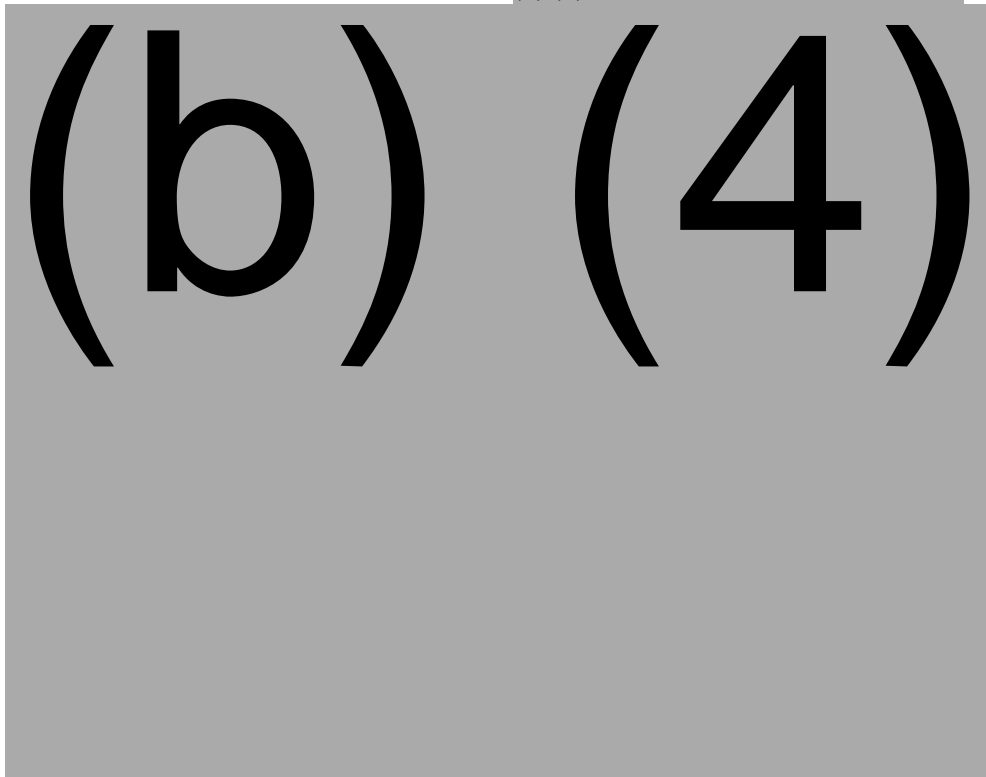
. The schematics of the (b) (4) load configuration were provided and indicate the location of the (b) (4). The sterilization cycle included a (b) (4).

Results: Results from confirmation runs of load type (b) (4) in each (b) (4) performed in December 2012 was provided in Table 3.2.P.3.5-27 in Section 3.2.P.3.5 of the BLA (refer to Table 5 in APPENDIX for details). The highest average temperature and

lowest average temperature during exposure for all runs were reported (b) (4) (ranging between (b) (4)). The (b) (4) from all runs were indicated as (b) (4). No deviations were noted.

Component preparation and sterilization: The results of the PQ for equipment used in component sterilization are summarized as follows:

- Stopper Sterilization Validation- Stoppers are sterilized using (b) (4). The PQ for ready-to-sterilize (RTS) stoppers are based upon size, supplier, quantity of stoppers per bag, and quantity/arrangement of the stopper bags. (b) (4) PQ runs consisting of (b) (4) studies for both the maximum and minimum load configurations for the worst-case stopper identified in each stopper size. Routine confirmations are performed on an (b) (4) basis for the worst-case stoppers that are received RTS, utilizing the maximum load configuration. The (b) (4) confirmation must meet pre-defined acceptance criteria. The following table details the validated status of stopper sterilization using (b) (4).



The andexanet alfa DP 20 mm stoppers are received ready-for-sterilization in a (b) (4) stoppers/bag configuration. Load type (b) (4) was validated for the Andexanet alfa stopper configuration, consisting of placement (b) (4) bags/load. A schematic of stopper sterilization load type 136 was provided and indicates the placements of (b) (4).

(b) (4) used to evaluate the (b) (4). Each (b) (4) was placed adjacent to at least (b) (4). A sterilization cycle includes (b) (4). The (b) (4) were (b) (4). A sterilization cycle consists of (b) (4); production cycle runs included a set point of (b) (4).

Results: Results from confirmation runs performed were provided as follows: 20 mm. All (b) (4) were indicated as (b) (4). No deviations were noted.

(b) (4)

- Vial preparation and Sterilization/Depyrogenation Validation- The 20 mL vials used for Andexanet alfa are washed in the (b) (4) vial washer (b) (4) and depyrogenated in the (b) (4). The units are arranged in-line to automatically deliver the depyrogenated vials to the infeed turntable of (b) (4). The validations for the vial washer and the (b) (4) were referenced as follows:

(b) (4)

The PQ of the Vial Washing machine and (b) (4) were summarized as follows:

Vial Washing machine PQ- The PQ was performed for the (b) (4) Vial Washer (b) (4) using the minimum and maximum container sizes (smallest opening and container volume/largest opening and container volume). The established bracket for PQ includes the (b) (4) and the 20 mL/20 mm vials. Routine confirmations are performed (b) (4) for the smallest and largest container sizes. For PQ, Andexanet alfa DP vials (20 mL/20 mm, part # (b) (4)) are spiked with (b) (4) before washing and evaluated for (b) (4) after washing, in addition to, monitoring particulate

matter content to meet an acceptance criteria of (b) (4) and (b) (4) particles after washing.

The vials are washed at (b) (4) of the main drive product speed (approximately (b) (4)) and reduced WFI (washing) pressure of approximately (b) (4) . The vial washer parameters were noted in Table 3.2.P.3.5-32 in section 3.2.P.3.5 Process Validation/Evaluation in the BLA. These parameters included but not limited to number of (b) (4)

The results of the past and current PQ were indicated as follows:

(b) (4)

The most recent PQ was performed in March 2015 with the results reported as meeting the acceptance criteria for (b) (4) and presence of particulates.

Reviewer Comments: Several comments in regards to the information provided for the PQ of the

(b) (4) are noted as follows:

1. The results of the PQ and the confirmation run were only summarized in the BLA. The actual summaries of the report were not included in the BLA and were requested in an information request sent out April 6, 2016. The firm provided information in Amendment 22 received April 18, 2016. Please refer to IR#2 (item 21 & 22) for details of the information provided.
2. The narrative provided did not indicate the initial (b) (4) vials that were used in the depyrogenation PQ. Additionally, the firm only provided an overall average of the log reduction for each PQ and did not provide the results (the (b) (4) recovered and log reduction) for individual vials after depyrogenation. The firm was issued an information request June 15, 2016 asking to provide these details. Please refer to IR#6 (item 4) for details of the information that was provided.
3. The firm indicated that the (b) (4) 20 mL vial pack was used as worst case with respect to mass, but no other details for why this vial size is considered worst case. The vials used for Andexanet alfa is the 20mL (b) (4) vial size. Thus, an information request was sent to the firm to clarify the rationale for the use of the (b) (4) vial is size based on mass as being the worst case for the depyrogenation PQ. Please refer to IR#6 (item 4) for details of the information provided.

OQ/PQ for Lyophilizer (b) (4)

The summary reports for the OQ and PQ for the lyophilizer was not provided in the BLA; however, a summary of the PQ that was performed for lyophilizer (b) (4) was provided in the narrative of section 3.2.P.3.5.4.1 “PQ of (b) (4) Test” and section 3.2.P.3.5.4.2 “PQ of Lyophilizer (b) (4) Uniformity” of the BLA. A summary report of the OQ for the lyophilizer (b) (4) was requested in an information request issued to the firm April 6, 2016. The firm provided this report in their response that was received April 18, 2016; please refer to IR#2 (item 21 & 22) in section “Information Requests” of this memo for details of the firm’s response and review of reports provided.

The Performance Qualification of Lyophilizer (b) (4) described in sections 3.2.P.3.5.4.1 3.2.P.3.5.4.2 the BLA, included summary of (b) (4) uniformity testing performed for lyophilizer (b) (4). For the (b) (4) testing, (b) (4) PQ runs were performed to demonstrate that lyophilizer 11 can be sealed to achieve a (b) (4) of (b) (4) over a (b) (4) time frame. The PQ leak test results were reported as follows:

(b) (4)

According to the result reported, lyophilizer (b) (4) met the acceptance criterion of (b) (4).

(b) (4) PQ runs were also performed to validate the (b) (4) uniformity. The temperature segments tested (b) (4) except for the (b) (4). After completion of the (b) (4). During the runs, a minimum of (b) (4) were placed in an (b) (4) on each (b) (4) (schematics of

(b) (4) was provided). (b) (4) were calibrated before and after PQ at temperature set points below, at and above the target temperature range.

Results: The average temperature of the (b) (4) was within the acceptance criteria of (b) (4) for each (b) (4) segment after the temperature stabilization. The acceptance criteria of (b) (4) from the programmed set point, was met. Additionally, the specification that all thermocouples were within the (b) (4) of each other was met and (b) (4) test inspection, performed with each run, showed no sign of (b) (4).

(b) (4)

Container Closure for DP

Description: The container closure used for the andexanet alfa DP consists of sterile, depyrogenated 20 mL clear (b) (4) type (b) (4) glass vial with a 20 mm finish, a gray 20 mm (b) (4) and (b) (4) chlorobutyl rubber stopper, and a 20 mm aluminum flip-off seal with a blue polypropylene flip-off cap used as the final seal for the vial and stopper. The following table provides specific details of the container closure and manufacturer/supplier information. The specifications and schematics of the components listed in table below were also provided.

Component	Manufacturer	DMF
-----------	--------------	-----

(b) (4) Type (b) (4) Glass Vial, 20 mL, 20 mm finish	(b) (4)	(b) (4)
(b) (4) Gray 20 mm Lyophilization Stoppers with (b) (4) on product contact surface, polymerized silicone-treated surface (b) (4) on non-product contact surfaces Stoppers washed by (b) (4) (supplied ready to sterilize)	(b) (4)	(b) (4) (b) (4)
20 mm Aluminum Flip-Off Seal with a Blue Polypropylene Flip-off Cap	(b) (4)	NA

The secondary packaging for the labeled DP consists of a paperboard carton which packages four vials in one carton.

Container Closure Integrity Testing (CCIT): CCIT was performed to evaluate the container/closure interface of vial and stopper system used in manufacture of andexanet alfa. The test methodology include a (b) (4) test (VL1407006) using (b) (4) containers from the VL1404005 CCOQ batch to qualify the andexanet alfa DP container closure components. In addition to the description provided in the BLA narrative (section 3.2.P.2.5.1), the container closure validation summary M073-1 was also provided. Details and results of the testing were provided in Section 3.2.P.2.5 and are summarized as follows:

Samples used in CCIT

The container closure components tested included 20 mm (b) (4) grey lyophilization stoppers with (b) (4) on the plug and flange and (b) (4) on the top of the stopper, a 20 mL (b) (4) glass vial and flip-off seal which were subjected to normal manufacturing process preparation and sealed using the same equipment as used in the DP manufacturing process. Residual seal force measurements were documented for information only before and after study. The capping parameters used during the CCOQ VL1404005 for the CCIT testing (VL1407006) included the following:

(b) (4)

Method/Procedure Description

(b) (4)

(b) (4)

In addition to the results provided for the (b) (4) method described in the narrative, the report M-073-1 was provided in section 3.2.R.2 of the BLA. The report, "Container Closure Validation Final Report" prepared by (b) (4) provided a summary of the validation of the container closure test method evaluating the adequacy of the closure in maintaining a sterile barrier. The study involved (b) (4)

. Different types of containers were evaluated which (b) (4). Results reported for the glass vial containers indicated that the (b) (4)

Container Closure Integrity Stability

Additionally included in section 3.2.P.2.5.1, the firm indicated that as part of the stability program, the container closure integrity of andexanet alfa DP is tested (b) (4) by (b) (4) as part of sterility testing. The following details were indicated in regards to this testing:

(b) (4)

(b) (4)

Reviewer Comments: In regards to the information provided for the CCIT the follow issues were identified and three information requests were issued to the firm to clarify the issues:

Information Request sent April 6, 2016 addresses the following items (Please refer to IR#2 in “Information Request” section for details):

- The firm indicated for the initial CCIT, one of the positive controls included the stopper being (b) (4) to simulate a container closure defect. The sensitivity of this method is not adequate for critical leak defects of (b) (4).
- Method validation (which should describe the precision, accuracy, linearity of the positive controls) was not located in the BLA submission
- (b) (4) positive controls are used, (b) (4) control at a concentration of (b) (4). No rationale was provided as to why this concentration was used as a positive control for (b) (4), is this based on the method validation?
- The container closure validation final report M073-1 was provided in the Regional Information Section of the BLA and details a report of positive controls for container closure using (b) (4). The report was prepared by (b) (4). It is not clear if this report is a correct report to support the firm’s CCIT indicated in narrative of the BLA for the following reasons:
 - The report outlines (b) (4) and positive controls in relation to (b) (4) procedures. There is no mention of the positive controls used in the (b) (4) test described in the BLA: no description of the use of (b) (4) was provide in the report summary
 - Report does not serve as a validation of the sensitivity of the positive controls The firm needs to indicate what this report is for and provide a validation of the positive controls used for the (b) (4) method that was described in the BLA.

Information Request sent June 15, 2016 addresses the following items (Please refer to IR#6 in “Information Request” section for details):

- The firm indicated that CCIT will be performed on stability, the firm did not indicate if (b) (4) stability studies were performed to support (b) (4) method performed on samples containing product

Information Request sent July 11, 2016 addresses the following items (Please refer to IR#7 (item2) in “Information Request” section of this memo for details of firm’s response):

- No details of the (b) (4) process, in addition to how the (b) (4) of (b) (4) is validated and firm was asked why (b) (4) analysis is not performed on product filled vials.

Shipping Validation

Bulk Storage/Bulk Shipping, and labeling and packaging are summarized as follows:

- Bulk Storage/Bulk Shipping: (b) (4)

In regards to the shipping validation for the drug product the following was noted:

The shipping validation will be performed according to a pre-approved protocol to demonstrate the packaging configuration protects against the physical impact that may occur during shipping. Shipping systems for maintaining the appropriate temperature ranges for the product will be qualified for product transport.

Reviewer Comments: From what the firm provided, it appears that shipping validation has not been completed. Additionally, very few details were provided on what the shipping validation would entail and what acceptance criterion will be used only noting that the temperature of the vials are monitored during shipment of the unlabeled vials to the labeling and packaging facility, which would be (b) (4) located in (b) (4). The firm references a pre-approved protocol; however, this protocol was not provided in the submission. The firm was issued an information request (IR#3 (item 4)) on June 8, 2016 to address this deficiency. Please refer to IR#4 for details of information provided.

VI. Facilities and Equipment

Drug Substance

General descriptions of the overall facility, equipment, utilities, and cleaning and sterilization processes were provided in the BLA submission. The review of sections of the BLA relating to the facilities and equipment of the drug substance was performed by Joan Johnson and are covered in separate review memo. Please refer to her memo in the EDR for details of the review.

Drug Product Manufacturer- (b) (4)

General Description of Facilities-The facility includes the parenteral manufacturing plant with support laboratories, utility spaces, warehouse space and administrative offices. Additionally, there is a Finishing plant that houses inspection, labeling and packaging and (b) (4) square foot warehouses located within (b) (4) miles of main complex. The main facility complex consists of Buildings (b) (4). The manufacturing of andexanet alfa DP is performed in Building (b) (4) and includes the following steps:

1. (b) (4)
2. Sterile filtration
3. Sterile Filling
4. Lyophilization

An overview of Building (b) (4) was provided as follows: Building (b) (4) is a multi-product facility and includes separate areas for component preparation, formulation, vial filling and lyophilization of DP. The ceiling, floors and walls for the classified areas are constructed of (b) (4) and select floors are covered with (b) (4) and all interior corners are rounded to ease cleaning and sanitization. (b) (4) curtains are suspended from the ceiling in order to provide physical separation between the Class (b) (4) and Class (b) (4) areas and (b) (4) sheets are mounted around specific areas of the filling line. The floor drains are sized for each piece of equipment and include air-breaks to prevent back siphoning. All product contact piping is recessed within the walls and is composed of (b) (4). The electrical supply in the waste room is explosion proof.

Containment/Cross Contamination

Room Classification- All areas within the (b) (4) manufacturing facility are classified according to the production processes performed within that area and permissible level of airborne contamination. There are three classifications within the production environments that

include Class (b) (4), Class (b) (4), Class (b) (4). The following table indicates the production processes and corresponding room classifications in which processes are performed:

Production Process	Room Class
Filling Machine, Lyophilization Loading/Unloading (b) (4)	(b) (4)
Filling and Lyophilization Rooms	
Formulation Room	
Preparation Room (equipment and components)	
Product Delivery Room	
Capping Room	
Auxiliary Areas Adjacent to Production Area	

NC: Not Classified; (b) (4)

The air pressure differentials, relative humidity and temperature are monitored and recorded. Separate air-handling systems are used for each filling suite. Additionally, freezer, coolers and incubators are monitored daily and a generator for emergency power is used for critical systems.

Materials, Components and Equipment Flow- Schematics of the Material and Component flow in Building (b) (4), including the first and second floor (Figure 3.2.A.1-8 (first floor) and Figure 3.2.A.1-9 (second floor)), in addition to, a detailed narrative with specifics on the movement of Drug Substance (DS), clean equipment, vials, and stoppers was provided. The DS is

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

On the (b) (4), stoppers, equipment requiring sterilization and product contact equipment are transported into specific areas through Corridor (b) (4), Component Ingress (b) (4), Preparation Room (b) (4), and Stopper Preparation Room (b) (4) and are then loaded in the (b) (4) for sterilization. After sterilization the stoppers and other equipment are unloaded from Transfer Corridor (b) (4) and moved to Filling Room. The vials are transferred through Corridor (b) (4) to Vial (b) (4) to Vial Preparation (b) (4) for washing. The clean vials are loaded into the (b) (4) and exit to Filling Room (b) (4).

Drug Product (DP) is filled in Filling Room (b) (4), loaded into the lyophilizer in Lyophilization Loading/Unloading Corridor (b) (4), capped/sealed in Capping Room (b) (4) and loaded on trays in Tray Loading Room (b) (4). The lyophilized vials are transported through Corridor (b) (4) and (b) (4) to Airlocks (b) (4). The DP leaves Building (b) (4) and is transported to Warehouse (b) (4) for intermediate storage at 2-8°C or is transported directly to Finishing Operations in Building (b) (4) via (b) (4) transport truck, for visual inspection and packaging.

Personnel flow- Schematics of the Personnel flows for the first and second floors of Building (b) (4) (Section 3.2.A.1 Facilities, (b) (4) , Figure 3.2.A.1-4 (First Floor) and Figure 3.2.A.1-5(Second floor)), in addition to a brief description in the narrative was provided. Only authorized personnel has access to manufacturing areas with specific guidelines for the flow, clothing of visitors and production staff. According to the schematics, personnel move in a uni-directional flow into personnel gowning areas, with a separate exit for de-gowning from critical manufacturing areas (i.e. aseptic processing areas). Gowning procedures are defined for the manufacturing areas and used garments are collected in bins within the locker rooms and removed from for washing and/or disposal at regular intervals. Fill room operators don the following sterile items in order listed: gloves, shoe covers, hood, facemask, gown, goggles and gloves. The filling room operator's hands are sprayed with (b) (4) after donning each item. Gowning requirements for entrance into the Class (b) (4) areas include coveralls and plant uniforms of a (b) (4) , hair net, eye protections, gloves, shoe covers, and beard cover (as applicable). Requirements for entrance into the Finishing areas include company approved uniforms or scrubs, hair net, eye protection, gloves and beard cover (if applicable).

Waste flow- A specific description of the waste flows was not provided in the narrative; however, the following was indicated in regards to contamination from waste:

- Waste receptacles are emptied and sanitized regularly
- Floors are sanitized regularly

Containment Design/Prevention of Cross Contamination- The following was indicated to prevent cross-contamination with other products manufactured in the facility:

- Use of dedicated equipment- All product contact equipment and components used in the manufacture of andexanet alfa DP is product dedicated or single-use only.
- Change over procedures implemented according to SOPs and established validated cleaning procedures that include where applicable, sterilization of equipment between each production run. Equipment is labeled according to cleaning status, and production area is cleared and sanitized according to cleaning/sanitization schedules defined in written procedures.
- Products and intermediates are clearly labeled and identified with batch number and material name. In addition, release status is indicated (i.e. quarantined, etc.) and stored separately based on release status.
- Containment features in relation to contamination from other Products included the following:
 - Only one product filled at time per filling suite
 - Filling suites regularly sanitized per SOP
 - One product formulated at a time per formulation room
 - Exterior of raw materials containers wiped down with approved agent prior to transfer into Class (b) (4)
 - Only sterile product introduced into the Class (b) (4) and Class (b) (4) areas
 - Biologic products utilize single-use or dedicated product-contact equipment
 - Product contact equipment is cleaned in accordance to product specific cleaning validation process
- Containment features in relation to contamination from equipment included the following:

- Identification and segregation of clean versus dirty equipment, in addition to sanitized versus sterilized
- Equipment and materials wiped down with (b) (4) or an approved sanitizing agent prior to placement in Class (b) (4) airlock
- Only approved containers or product contact surfaces used: Type (b) (4), borosilicate glass or food-grade plastics
- Equipment properly maintained through preventative maintenance program
- Validated cycles used for washing and sterilizing product contact equipment.
- Containment features in relation to contamination from people included the following:
 - Increasingly restricted access to controlled manufacturing areas and aseptic filling areas (key card access to Class (b) (4) and Class (b) (4) areas)
 - Gowning and apparel are dedicated for cleanroom use only
 - Restricted Access Barrier System installed in Class (b) (4) filling area. Use of gauntlet gloves whenever possible for aseptic interventions
 - Employee change of clothing/gowning
- A Comparability protocol was prepared by (b) (4) (included in (b) (4) Type V DMF No. (b) (4)) to support a reduced reporting category for the introduction of new products manufactured in shared manufacturing area. Reduced reporting includes reporting on an annual basis rather than CBE-30 Supplement. Products not eligible for reduced reporting will be reported to agency by a CBE-30. Reference as made to DMF No. (b) (4) for review of the Comparability Protocol prepared by Baxter.

Facility Cleaning

The frequency of sanitization increases as the classification level increases. The area of the room with the lowest potential bioburden is sanitized first and the area of the room with the highest potential bioburden is sanitized last. Class (b) (4) and Class aseptic formulation and filling areas are fully sanitized after each production run or validation exercise or a minimum of (b) (4). Other Class (b) (4) and Class (b) (4) areas are fully sanitized (b) (4) during routine production or a minimum of (b) (4) with Class (b) (4) cooling zones sanitized (b) (4). Production items from unclassified warehouse area are sanitized prior to entry into the Class (b) (4) production area and outer packaging is wiped with non-particulating wipes and a sanitizing agent. Routine environmental monitoring of the classified areas confirms the sanitization methods. Manufacturing equipment in the production area is cleaned before and after use. Shared non-production equipment that is unable to be sterilized is sanitized by wiping with non-particulating wipes and an approved sanitizing agent prior to transfer to the Class (b) (4) and Class (b) (4) areas.

Equipment and Equipment Cleaning and Sterilization

Critical process equipment included equipment used for washing, depyrogenation and sterilization of components, in addition to equipment used in formulation, filling, capping, lyophilization, tray loading and in-process checks of andexanet alfa DP. A listing of the critical equipment used in the manufacture of andexanet alfa lyophilized DP was provided as follows:

(b) (4)

(b) (4)

(b) (4) has an ongoing qualification program that assures that the equipment is maintained in a validated state. The firm indicated that all major equipment used were qualified and/or validated prior to use. Process Performance Qualification Protocol for andexanet (414-21-04-001-P1) was provided and describes the overall methodology for the manufacturing of Andexanet Alfa ((b) (4) _____, filtration, filling lyo loading, lyophilization, capping and inspection) and provides references to the reports for the OQ/PQ for facility, equipment, utilities and Systems used in the manufacturing process as indicated in the following table.

(b) (4)

(b) (4)

The review of the OQ/PQ of major equipment used in the DP manufacturing process was previously covered in the Process Validation section of this review memo.

All product contacting components including process tubing, filling needles and the (b) (4) glass carboy are (b) (4), thus cleaning validation was not required for formulation and filling components with the exception for the Lyophilizer (b) (4). A description of the PQ for Clean-in Place (CIP) system and Steam in place (SIP) for the (b) (4) Lyophilizer ((b) (4)) was provided in sections 3.2.P.3.5.5 (Cleaning Validation) and 3.2.P.3.5.4.3 (PQ of Steam in Place SIP) of the BLA. The PQ for CIP was completed from October 2007 to December 2007 with an (b) (4) confirmation performed from 26 July to 03 July 2015. The CIP PQ was described as follows:

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

Results were indicated as follows:

(b) (4)

No deviations were noted.

Specific Systems- Descriptions and procedures for the operation and maintenance of the water purification systems (purified water and WFI), HVAC systems, clean steam (for processing and cleaning/sanitization) and process air were provided and are summarized as follows.

HVAC- The system components of the HVAC system include: (b) (4)

██████████. The AHUs are combination devices for air supply and can be adjusted to convey fresh air only or also include a certain percentage of recirculated air. The fresh air is (b) (4) ██████████ in the unit. The treated fresh air is fed downstream recirculation air units. The air distribution is done by (b) (4) ██████████ controllers. From the room, the exhaust air is fed to the central exhaust air unit. Air extraction is governed by (b) (4) ██████████ flow controllers. The following details were indicated for the Production HVAC system:

Age Group	Gender	Percentage of Respondents
18-29	Female	94%
	Male	88%
30-49	Female	88%
	Male	82%
50-59	Female	82%
	Male	76%
60+	Female	68%
	Male	62%

Reviewer Comments: The information provided was high level and did not include details specific to the aseptic filling area. The schematics for Building (b) (4) Classified Environments (Figure 3.2.A.1-2) did include a listing of the AHUs that service the various areas of the production floor (also including the air differentials); however, the firm did not indicate the number of air changes/hour in the critical areas (Class (b) (4)). Additionally, there were no details of the IQ/OQ, nor a summary of the qualification of the HVAC system. An information request was issued asking to provide a validation summary and include information about the number of air changes in critical manufacturing areas. Please see April 6, 2016 information request (IR#2, item 25) and firm response in “Information Request” section of memo for details.

Water System/Clean Steam- The WFI produced at (b) (4) in Building (b) (4) is used for but not limited to the (b) (4) (b) (4). The WFI system is a closed, re-circulating system with the main distribution loop maintained at a temperature of (b) (4) and with individual (b) (4)

(b) (4)

Microbiological Monitoring of Water Systems: The following water systems were noted to be routinely monitored as follows:

(b) (4)

(b) (4)

(b) (4)

(b) (4)

- Clean and Pure Steam- Clean steam generators in each system are sampled and tested at least (b) (4) for endotoxin and (b) (4)

The following was indicated if the alert and action levels are exceeded:

- If alert level bioburden or (b) (4) is exceeded, the port is sampled and tested for (b) (4) and an investigation is initiated.
- If the action level for bioburden or (b) (4) is exceeded, the port is sampled and tested for (b) (4) additional business days and an investigation is initiated.
- If the alert level for endotoxin is exceeded, the original sample is retested in (b) (4). If all (b) (4) of (b) (4) retest of the original sample are less than the alert level, no further action is required, and the result will be reported as (b) (4). If any of the (b) (4) of the (b) (4) retest of the original sample is greater than the alert level, an investigation is initiated, and the port will be sampled and tested for (b) (4).
- If action level for endotoxin is exceeded, an investigation report is initiated and the original sample is retested in (b) (4). The original duplicate result and the (b) (4) retest results are averaged and the average result is reported. The port is sampled and tested for (b) (4) additional working days.

Other Utilities- Other utilities described for the facilities used in Building (b) (4) include (b) (4)

(b) (4)

Environmental Monitoring Program- A PQ was performed during the initial validation of the Class (b) (4), Class (b) (4) and Class (b) (4) environments. The results of the PQ were used in determining sampling sites, which were incorporated into the routine environmental monitoring program. An Environmental Monitoring Performance Qualification (EMPQ) will be performed in the case of each of the following events: facility construction, facility/room renovation, identification of an environmental monitoring negative trend, assignment of a Change Control Action item or on an as-needed basis as determined by (b) (4) Quality Management.

(b) (4) monitors classified production areas for particulates, airborne microorganisms, and microorganisms on surfaces and personnel in accordance to SOPs. Airborne microorganisms are monitored quantitatively ((b) (4)) or qualitative ((b) (4)). Quantitative air monitoring is performed using (b) (4). (b) (4)

The frequency and location of quantitative monitoring during aseptic operations and when no aseptic operations are in process is indicated in following tables:

Quantitative Monitoring During Aseptic Operations

(b) (4)

Quantitative Monitoring When No Aseptic Operations Are in Progress

(b) (4)

(b) (4)

Qualitative air monitoring is performed using (b) (4) . At the beginning of each production activity (within the Fill Room) (b) (4)

There is continuous monitoring performed for the following areas when in use: class (b) (4) fill room areas, class (b) (4) fill room areas and Class (b) (4) and Class (b) (4) areas used for aseptic formulation. When there are no aseptic operations in progress, there is (b) (4) monitoring in Class (b) (4) and Class (b) (4) fill rooms areas.

Airborne particulates (non-viable quantitative air) are monitored using a particle measuring system in classified areas. Monitoring is continuous in the Class (b) (4) areas and is performed at prescribed intervals in the supporting areas. The frequency and location for particulate monitoring during aseptic operations and when no aseptic operations are in progress are provided in the following tables:

Particulate Monitoring During Aseptic Operations

(b) (4)

Particulate Monitoring When No Aseptic Operations In Progress

(b) (4)

Action Limits have been established for each test method (quantitative and qualitative viable air and dynamic and static non-viable particulates) and when applicable, historical data was analyzed to establish alert limits. The action and alert levels for active air, fallout plate and dynamic and static non-viable particulates were provided in the following tables:

Quantitative Viable Air (Active Air) Levels

(b) (4)

Qualitative Monitoring (Fallout) Levels

(b) (4)

Dynamic Non-Viable Particulate Levels

(b) (4)

Static Non-Viable Particulate Levels

(b) (4)

Surface monitoring of microorganisms on inanimate surfaces and personnel are also performed. Surface monitoring is performed using (b) (4) qualified to evaluate bioburden on surfaces in classified areas. Personnel in Class (b) (4) areas will be monitored during (b) (4) that a qualified person enters a Grade (b) (4) /Class (b) (4) area. The following test sites are monitored: (1)

left hand, (2) right hand, (3) left forearm, (4) right forearm and (5) chest. If an aseptic intervention is performed in the Class (b) (4) area and requires opening the door to the RABS, the operator must perform a (b) (4) following the completion of the aseptic intervention. The following frequency and locations of surface during aseptic processing and when no aseptic processing is in progress were indicated as follows:

(b) (4) **Plate Monitoring During Aseptic Operations**

(b) (4)

(b) (4) **Monitoring When No Aseptic Operations in Progress**

(b) (4)

Action Limits for surface and personnel monitoring were indicated as in the following tables:

(b) (4)

Personnel Monitoring Levels

(b) (4)

(b) (4)

Additionally, on a (b) (4) basis, class (b) (4), Class (b) (4) and Class (b) (4) areas are monitored for the presence of yeast and mold microorganisms. Testing methods for mycological monitoring will include (b) (4) and (b) (4) monitoring using a (b) (4). Anaerobic monitoring of the classified environment is performed during media fills using (b) (4).

For environmental monitoring, when an alert and action level is exceeded, an investigation is performed and based on the investigation, corrective actions to be taken are determined by Quality Assurance and Manufacturing.

Computer Systems- No information was provided in regards to computer systems

Reviewer Comments: The firm was issued an IR (refer to IR#2 in Section "Information Requests" for details) asking to indicate if computer systems are used to control critical manufacturing processes. If computer systems are used, the firm should provide a description of which manufacturing steps the computer system controls, and a summary of the validation, which should include certification that an IQ/OQ was performed, a listing of the parameters monitored and acceptance criteria, and explanation of deviations, excursions and/or failures. Please refer to section "Information Requests" for details of response received by firm.

VII. Comparability Protocol

This BLA, included a comparability protocol (CP) for (post-approval) manufacturing changes to the drug substance and drug product processes described in the original BLA. Initially, two separate CPs, one for drug substance changes and one for drug product changes, were submitted with the BLA, provided in Module 3 (Regional Section) on December 18, 2015. The CPs were initially reviewed and found to be significantly deficient. These deficiencies were communicated to the firm in four separate information requests (refer to section "Information Requests" for reference to the IRs) and telecons held with the firm. The history of the communications (IRs and Telecons) with the firm in regards to the CP is summarized as follows:

- 1) IR#1 (item 1) sent January 25, 2016 in reference to deficiencies in the CP NC-15-0664-P0001 (protocol for changes to Drug Substance) for manufacturing changes that include a scale up and use of (b) (4).
 - a. To address the issues with the CP for the Drug Substance Changes identified DMPQ, the firm provided an addendum protocol to Protocol NC-15-0664-P0001, the addendum to the DS CP was included in Amendment 5.
- 2) IR#2 (DMPQ items 29-30, Product office item 18) sent April 6, 2016, informed firm of deficiencies in the CPs for drug substance and drug product changes, in addition to recommending the CPs for drug substance and drug product be combined.
 - a. Firm provided a "revised" single CP (Amendment 27, received May 2, 2016) that incorporated both the DS and DP manufacturing changes; however, after review of this CP, there were still significant deficiencies. The firm requested a meeting with FDA in regards to a request to change the number of DP lots needed to support the follow up supplement to the CP. A telecon was held with the firm, May 23, 2016, to discuss the number of DP lots needed to support a follow up supplement and during this telecon the firm was informed of substantial deficiencies with "revised" CP provided in Amendment 27, received May 2, 2016.

- Below is a comprehensive review of the original and revised versions of the CP provided during the BLA review.

Protocol NC-15-0664-P0001(01 December 2015), “Andexanet Alfa (PRT064445) Drug Substance Comparability of (b) (4) to (b) (4) Lots” describes the approach for demonstrating comparability of the (b) (4) scale (b) (4) DS representative commercial lots, (b) (4) to the DS manufactured at the (b) (4) from the (b) (4). The following process changes were described in the CP (schematics diagrams were provided in the CP to reflect changes noted below):

(b) (4)

Label	Bar Length (approximate)
(b) (4)	100%
(b) (4)	20%
(b) (4)	95%
(b) (4)	45%
(b) (4)	100%
(b) (4)	85%
(b) (4)	98%
(b) (4)	55%
(b) (4)	100%
(b) (4)	15%

Category	Percentage
I like the people I work with	95%
I like the work itself	95%
I like the location	35%
I like the pay	100%
I like the benefits	100%

Reviewer Comments: Many of the downstream changes indicated were to accommodate the change in scale of the DS generated from (b) (4) as compared to (b) (4)

The CP indicated that three DS lots manufactured from (b) (4) will be compared to (b) (4) PPQ lots from (b) (4) as indicated in the table below:

(b) (4)

The comparison assessment studies included four categories of testing:

- Process Performance Analysis
- Release Testing
- Supplemental Characterization testing
- Side by Side stability testing

For each of the testing categories above, the parameters including critical and key operating process parameters, in process limits, in process specifications and DS release testing) were noted in addition to the acceptance criteria for this testing.

Reviewer Comments: Although the CP provided proposed testing of the process parameters and quality attributes of the DS manufactured from (b) (4) and (b) (4) the CP did not have any information or details in regards to changes in the facility and equipment involved in the manufacturing change to the use the (b) (4) and changes in the downstream process. In an IR sent, January 25, 2016 (IR#1 in "Information Requests"), the firm was asked to provide:

- A detailed description of the changes in the facility (renovations, HVAC, etc.) and the equipment used (b) (4) etc.)
- A listing and description of specific tests that will be performed for the qualification (OQ/PQ) of "new" area and "new" equipment used for the manufacturing change, in addition to a listing of the acceptance criteria that will be used for the qualification testing to be performed.

The review of the proposed testing indicated in the CP to compare DS manufacturing from either, (b) (4) and (b) (4), is deferred to the product office as the testing proposed is more associated with product characterization. The firm did respond to the deficiencies noted by DMPQ in regards to CP NC-15-0664-P0001 and provided an addendum to this protocol which is reviewed below.

Review of Addendum to Protocol NC-15-0664-P0001 provided in Amendment 5 (received February 4, 2016) in response to IR sent to firm on January 25, 2016. The IR issued to firm noted that the CP for the Andexanet Alfa Drug Substance Comparability of (b) (4) to (b) (4) lots did not include information in regards to the equipment qualification testing that would be performed on major equipment. In addition to providing the Addendum to the protocol, the firm also included a validation plan (VAL-90034-01, "Validation Plan for (b) (4) and (b) (4) Facilities, Utilities and Equipment Qualification in Support of (b) (4) Commercial Production". The addendum provided a summary of the OQ/PQ testing for (b) (4) Major Equipment and

Systems in addition to requirements and acceptance criteria. This information is summarized as follows:

Description of facility changes due to the (b) (4) buildout as defined in CR 8382 was indicated as follows:

- The Building (b) (4) Office Area, (b) (4) (Production Facility) and locker rooms were demolished in a phased construction plan to accommodate a new locker room, clean corridor, return corridor, expansion suite, (b) (4) suite and (b) (4) suite.
- Installed Equipment and Utilities dedicated to support (b) (4) included the following:
 - WFI generation and storage distribution system
 - O₂ and CO₂ Storage Distribution System
 - HVAC units to supply (b) (4) areas
- Commission and Qualify Facilities & Equipment

The following systems that support the current (b) (4) (Production Facility (b) (4)) required modification to support (b) (4) :

- WFI0001: Removal of (b) (4) from the WFI distribution system that supplies (b) (4) areas
- CCA0001: Extend the Clean Air Distribution system to supply (b) (4) areas
- FPS0300: Extend Feed Water to supply new WFI still in Building (b) (4)
- BMS0301: Add additional monitoring points to the Building Management System to monitor all new facility and utility equipment
- WNS0001: Add an additional (b) (4)
- AHS0001: Reduce the area served by (b) (4) (remove service to the locker room (b) (4))
- OXY0302: New Oxygen Storage and Distribution System to be added
- CDD0304: New Carbon Dioxide Storage Distribution System to be added.

The following new major equipment was installed in (b) (4) :

Equipment ID	Equipment Description	Validation Number
(b)	(4)	

¹IQ only, operation is controlled by existing equipment Process Monitoring System

As result of changes to the equipment and systems, validation was performed for the new area and on new equipment and systems. A description of OQ/PQ testing that will be performed, in addition to a listing of the corresponding acceptance criteria was provided for the following equipment and systems:

(b) (4) - QC testing including the following:

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

Acceptance Criteria for the (b) (4) was indicated as follows:

(b) (4)

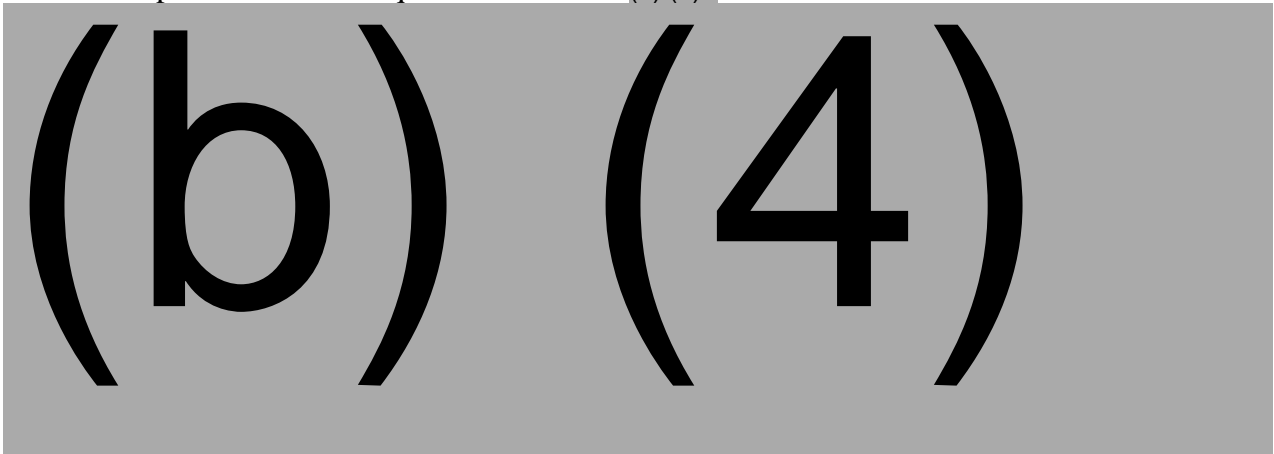
(b) (4)

A large rectangular area of the document is redacted with a solid gray fill. To the left of this area, there are several short, horizontal gray bars of varying lengths, each preceded by a small square bullet point.

CFR 21 Part 11 Testing for the (b) (4) (PMS) includes:

- Logon security
- Access level system log
- System control
- Non-continuous use
- Unique user name and password
- Method run and method modification system log
- Human readable accurate records
- Result file integrity and Method file integrity
- Methods questions signature

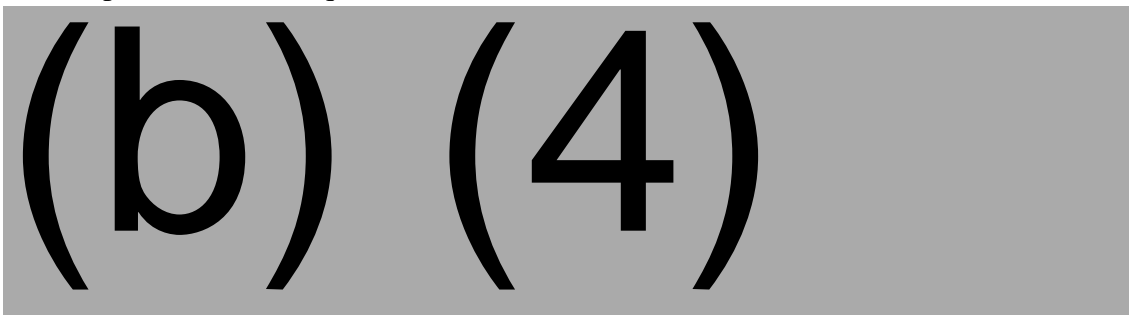
Acceptance Criteria Requirements for the (b) (4) PMS were indicated as follows:

A large rectangular area of the document is redacted with a solid gray fill. In the center of this area, the text "(b) (4)" is written in a large, bold, black font.

(b) (4) Skids- OQ testing included the following:

- Operational and Interlock verification

Acceptance criteria requirements were indicated as follows:

A large rectangular area of the document is redacted with a solid gray fill. In the center of this area, the text "(b) (4)" is written in a large, bold, black font.

HVAC (including (b) (4) suite, (b) (4) suite)- PQ testing consisted of the following:

(b) (4) **Suite-** The HVAC testing is limited to (b) (4) and rooms (b) (4) (b) (4) Suite Entry Airlock), (b) (4) (b) (4) Suite) and (b) (4) (b) (4) Suite Exit Airlock).

- Static non-viable particulate verification and qualification
- Dynamic viable air particulate and viable surface qualification
- Temperature verification
- Cleaning verification
- Differential pressure verification

Acceptance Criteria for testing was indicated as follows:

- Processing rooms shall have temperatures between (b) (4)
- Differential pressure and environmental monitoring requirements as specified in the tables below

(b) (4)

(b) (4) **Suite-** HVAC testing is limited to (b) (4) and rooms (b) (4) (b) (4) Entry Airlock), (b) (4) and (b) (4) (b) (4) Exit Airlock).

- Static non-viable particulate verification and qualification
- Dynamic viable air particulate and viable surface qualification
- Temperature verification
- Cleaning verification
- Differential pressure verification

Acceptance Criteria for testing was indicated as follows:

- Processing rooms shall have temperatures between (b) (4)

- Differential pressure and environmental monitoring requirements as specified in the tables below

(b) (4)

(b) (4) - HVAC testing is limited to (b) (4) and rooms (b) (4) ((b) (4) (b) (4) Entry Airlock), (b) (4) (b) (4) (b) (4) Exit Airlock), (b) (4) (Return Corridor) and (b) (4) (Exit Airlock).

- Static non-viable particulate verification and qualification
- Dynamic viable air particulate and viable surface qualification
- Temperature verification
- Cleaning verification
- Differential pressure verification

Acceptance Criteria for testing was indicated as follows:

- Processing rooms shall have temperatures between (b) (4)
- Differential pressure and environmental monitoring requirements as specified in the tables below

Room Differential Pressure Requirement ((b) (4))

Requirement

(b) (4)

(b) (4) **Suite-** HVAC testing is limited to (b) (4) and rooms (b) (4) (Clean Corridor Entry Airlock), (b) (4) (Clean Corridor), (b) (4) (Clean Corridor), (b) (4) (Clean Corridor), (b) (4) (Clean Corridor), (b) (4) (b) (4) Entry Airlock) and (b) (4) .

- Static non-viable particulate verification
- Dynamic non-viable particulate qualification
- Dynamic viable air particulate and viable surface qualification
- Temperature verification
- Cleaning verification
- Differential pressure verification

Acceptance criteria was indicated as follows:

- Processing rooms shall have temperatures between (b) (4)
- Differential pressure and environmental monitoring requirements as specified as follows:

Room Differential Pressure Requirements (b) (4) Suite)

(b) (4)

WFI system- OQ/PQ testing included the following:

- Power up testing
- Control panel initial settings
- Maintenance verification
- Parameter configurability
- I/O testing
- Dumping operational verification
- Distillation operation verification
- Power failure recovery and shut-down testing
- Password access level set up and verification
- Counters verification
- Post-execution checkout
- Operational verification
- Alarms and interlocks verification
- Water quality verification
- Temperature requirements verification
- Spray device verification
- PQ testing (b) (4) consecutive days)

Acceptance criteria OQ Requirements for WFI system was indicated as follows:

Description of Requirement

(b) (4)

WFI PQ Acceptance Criteria was indicated as follows:

(b) (4)

Oxygen system- OQ/PQ testing indicated as follows:

- System verification
- Manifold operation verification
- Post-fabrication testing verification
- Oxygen distribution monitoring (PQ)

Acceptance criteria for Oxygen System were indicated as follows:

(b) (4)

(b) (4)

Carbon dioxide system- OQ/PQ testing was indicated as follows:

- System verification
- Manifold operation verification
- Post-fabrication testing verification
- Carbon Dioxide Distribution (PQ)

Acceptance criteria requirements for the Carbon Dioxide system was indicated as follows:

(b) (4)

(b) (4)

■ [REDACTED]
■ [REDACTED]

(b) (4)

■ [REDACTED]
■ [REDACTED]
■ [REDACTED]

(b) (4)

The validation plan VAL-90034-01, “(b) (4) and (b) (4) Facilities, Utilities and Equipment Qualification in Support of (b) (4) Commercial Production” was also provided with the addendum and includes additional details to support the addendum and describes the approach and requirements for the qualification of Facilities, Utilities and Equipment, inclusive of computer system validation and Environmental Qualification required for commercial production of (b) (4) in Building (b) (4) on (b) (4) and (b) (4), specifically covering all activities required for qualification impacted as part of the (b) (4) project.

Note: **A pre-license inspection was performed ((b) (4)) in support of the original BLA to cover the Drug Substance Manufacturing process using (b) (4). During this inspection, the inspectors also covered inspection of (b) (4) including the area and documentation associated with (b) (4). The details of the inspection of the (b) (4) are provided in the EIR.

Reviewer Comments: The Addendum to the Drug Substance portion of the CP is acceptable and the results of the proposed testing outlined in the addendum CP and the validation plan VAL-90034-01 for the new equipment and facility areas should be included in the follow –up supplement to the CP. The product office also had issues with the CP for the drug substance changes in regards to the adequacy of the information provided, which was conveyed to the firm, in addition to, IR items from DMPQ. The IR sent to firm from product office in regards to the CPs provided was stated as follows:

“The comparability protocols for the proposed manufacturing changes are deficient. You need to provide clear and specific information on the manufacturing changes that should include, but not limited to, the rationale for the changes; knowledge and understanding of the process the changes are involved in; supporting information; comparability study design and protocol; test methods, justification and validation protocol for the quality attributes to be tested; test methods and acceptance criteria; data analysis strategy including statistic assessment. Please note that deficiencies in the comparability protocol, if not addressed adequately, will negatively affect the outcome of the BLA.”

For details of the IR items sent for DMPQ, please refer to IR#2 items 29 and 30 in section “Information Requests” of the memo for details.

Original CP for Changes in Drug Product Manufacturing

Original version of CP Protocol NC-15-0681-P0001 (issue date: 20 November 2015):

The CP NC-15-0681, “Andexanet alfa (PRT064445) Drug Product (b) (4) versus Drug Product (b) (4) Scale-Up (issued November 20, 2015) describes the approach for demonstrating comparability of the DP (b) (4) used for the (b) (4) batches to the DP (b) (4) scale-up used for (b) (4) process batches. The CP noted the following four process changes in the DP manufacturing of material from (b) (4) from (b) (4) vs (b) (4) from (b) (4) as follows (reference Figure XX in APPENDIX for schematic of process changes):

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

These changes are further detailed in following table:

(b) (4)

To support these changes, the protocol describes the PPQ strategy for addressing the process steps affected by the indicated changes. The process steps for the DP manufacturing affected by the changes include (b) (4), Sterile filtration and Lyophilization. For the PPQ, a total of (b) (4) PPQ lots with a bracketing approach for batch size, having at least (b) (4) run at the minimum and (b) (4) at the maximum batch size to be manufactured.

For (b) (4) the approach was described as follows:

- Worst case combination of the batch size and (b) (4) will be used during the (b) (4) step
- For the minimum batch size, the (b) (4) step will be performed at the (b) (4) limit as this would be the worst case scenario ((b) (4)) for product quality attributes in regards to (b) (4)
- For the maximum batch size, the (b) (4) step will be performed at (b) (4) would be the worst case scenario ((b) (4)) for attributes related to product homogeneity, including pH, protein concentration and (b) (4).
- (b) (4) run, is proposed to run (b) (4) at target speed in comparison to other runs

Reviewer Comments: The proposed strategy for the (b) (4) appears reasonable; however, further review of this approach is deferred to product office.

For Lyophilization the following was described:

- Up to (b) (4) of the lyophilizer(s) will be used for batch sizes manufactured during the PPQ
- The lyophilization cycle will be run at the target process parameters while the ranges will be supported by the process characterization studies

- Samples will be taken at various locations in either a (b) (4) or (b) (4) on each (b) (4) and will be tested for critical quality attributes with the following tests: (b) (4)

- Planned to perform (b) (4) PPQ runs in (b) (4) different lyophilizers (Lyo (b) (4)).

Reviewer Comments: The CP did not provide any details of the IQ/OQ of the lyophilizers or acceptance criteria nor were there details of how the validation of the lyophilization would be performed in regards to the number of (b) (4) used per run/ per lyophilizer. The language used in the CP was very high level and vague in regards to the number of runs / lyophilizer that would be performed, nor were there any justifications of the validation strategy. There were not enough specifics to understand how this validation would be performed in regards to the lyophilization. Additionally, there were no specifics as to the type of information that would be provided to support the follow up supplement after execution of the CP (i.e. results of the OQ/PQ of lyophilizers, lyophilization cycle graphs etc.).

The firm was issued a multi-disciplinary, information request April 6, 2016, prior to the midcycle communication meeting, indicating that the CP was deficient and providing general guidance on what should be included in a CP (see IR#2 items 29-30). Before the midcycle communication meeting held April 8, 2016, Portola sent an email, to CBER March 21, 2016, requesting a teleconference with DMPQ to discuss a modification to the CP for the drug product changes. This modification was in regards to the number of PPQ lots that will be provided to support the CBE-30 follow-up supplement to the CP. In the email the firm indicated that (b) (4) will be shut down for maintenance before all PPQ lots in support of the follow-up CBE-30 could be manufactured and noting that due to this shut down Portola may only be able to get (b) (4) lot manufactured. Thus, Portola was requesting to modify the original CP, which indicated that (b) (4) lots would be provided and was requesting that "FDA accept validation data from (b) (4) DP PPQ lots for the submission of the CBE-30" and that "data for the remaining lot(s) be provided during the review of the CBE-30 or first Annual Report". During this time, we informed Portola that DMPQ could not meet with them to discuss this issue since the CP had not yet been sufficiently reviewed in detail, thus CBER would not be ready to have a productive discussion. After reviewing the CP in sufficient detail, major deficiencies were found, thus Portola was informed that there were major deficiencies in the CP in the IR sent out April 6, 2016, in addition to, conveying these issues at the mid-cycle meeting, recommending the CP be revised. Please reference IR#2 (items 29-30) in "Information Requests" section for details of what was conveyed to the firm. The firm did respond to IR#2 items 29-30 as Amendment 27, received by CBER, May 5, 2016 providing a "revised" CP that combined the DS and DP changes, which is reviewed below.

Revised Combined (b) (4) Drug Product CP (issue date 29 April 2016) provided in Amendment 27:

In response to IR#2 (items 29-30) sent April 6, 2016 (reference "Information Requests" section of memo), the firm provided the revised CP, "Comparability Protocol Andexanet alfa (PRT064445) (b) (4) to (b) (4) and Resulting Drug Product" (encompassing study no. NC-15-0664-P0002 (for (b) (4)) and study no., NC-15-0681-P0002 (for DP)). This CP was provided as amendment 27 received by CBER May 2, 2016. The revised CP included combining of the (b) (4) DP protocols as recommended by CBER in the IR#2 (item 30). The DP portion of the CP was reviewed by DMPQ and is summarized below. Most of the review of the (b) (4) portion of the CP is deferred to the product office, as the protocol pertains to mainly to product office issues relating to the process approach and the firm had

already addressed deficiencies identified by DMPQ relating to the IQ/OQ of equipment and new facilities areas, by providing the Addendum to the (b) (4) protocol NC-15-0664-P0001 previously reviewed above. Thus, the review of (b) (4) portion of the CP will be limited and only focus on DMPQ aspects below. The revised DS (limited review) and DP portion of the protocol is summarized as follows:

(b) (4)

(b) (4)

(b) (4)

(b) (4)

The changes in the (b) (4) manufacturing using the (b) (4) are the same as described in the previous version of the CP, in addition to the operating parameters, in-process limits and acceptance criteria. No additional changes were indicated. In the revised CP, the firm provided more details not previously noted including the following:

- (b) (4)
- Purification suite used for (b) (4) is shared with (b) (4)
- Provided a breakdown of the different process steps providing details of the steps comparing the process (b) (4) and (b) (4), in addition to the in-process parameters and acceptance criteria. This process steps included: (b) (4)

Reviewer Comments: Other than the points noted above, the revisions to the (b) (4) portion of CP only included the combination of the (b) (4) portion with the DP portion and the inclusion of a few additional details. All process parameters, testing to be performed and acceptance criteria were same as previously described. The product office also had major issues with the information provided in the (b) (4) portion of the revised “combined” CP and these issues were conveyed to the firm in a May 23, 2016 telecon, in addition to an information request sent May 31, 2016. The major issues identified by the product office included that (b) (4) did not appear to be in a state of control. This conclusion is based on an inspection of the (b) (4) facility, (b) (4) from (b) (4) in support of the BLA. During the inspection, (b) (4) was out of operation; however, the inspectors were able to review documentation in regards to (b) (4) and included several (b) (4) deviations, specifically numerous issues with (b) (4) were found, resulting in termination of lots (and sublots). Most of the issues with (b) (4) were attributed to deficiency in cleaning of new equipment. Given this knowledge acquired on inspection, the product office asked Portola to revise the CP taking into consideration the totality of data accumulated in the process and development using (b) (4). Portola was advised to revise the CP to include but not limited to the following information:

- Full list of (b) (4) lots initiated in (b) (4), including engineering lots and their disposition
- Description of all related deviations including open deviations
- Description of all CAPAs introduced to address observed manufacturing problems and data to demonstrate these CAPAs were effective
- Description of new validation studies or abbreviated bridging studies performed on (b) (4) equipment including (b) (4) and cleaning validation, (b) (4) studies
- The PPQ should use a bracketing approach in which a minimum number of (b) (4) and all (b) (4) be used to manufacture (b) (4) lots and that a successful PPQ lot be defined as a lot with no failed (b) (4). Additionally, a bracketing approach was recommended in regards to the manufacture of DP lots produced from (b) (4) material, in which at least (b) (4) DP lots per lyophilizer would be needed to support the CP.

This telecon and information request sent to the firm also included additional issues identified by DMPQ in regards to the revision of the DP portion of the revised “combined” CP (refer to review below in regards to the DP portion of the revised “combined” CP and the issues identified). The firm was asked again to revise the CP for both the (b) (4) DP. For details, refer to IR#4 in the “Information Requests” section of this memo.

CP-Drug Product Portion, Using (b) (4) :

The DP Manufacturing History using (b) (4) from (b) (4) was indicated as follows:

DP Lot No.	Vial Configuration (mg/vial)	Mfg. Process	DS Lot	DP DOM	Batch (Designation/Use)
(b) (4)	100	Development	DS development lot	(b) (4)	Development lot
	100	(b) (4)	(b) (4)		Clinical
	100				Clinical
	100				PPQ (Clinical/Commercial)
	100				PPQ (Clinical/Commercial)
	100				PPQ (Clinical/Commercial)

As with the previous CP, the same DP process changes were indicated in the CP and were noted as follows:

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

In this revised CP, the firm provided a Risk Assessment (see Table 6 in APPENDIX) that compares the changes to the process steps including (b) (4) , sterile filtration and lyophilization load and assesses the risk.

According to the Risk Assessment table, the risk of the changes for each of the process steps was indicated as “Low”. The assigned “Low” risk assessment rating for the filter step in regards to the change in the scaling up the (b) (4) area for the increase in batch size is based on the justification that filter validation studies have been conducted evaluating (b) (4) compatibility, (b) (4) and demonstrate acceptability.

The assigned “Low” risk assessment rating for the lyophilization load for the process change in the use of up to (b) (4) as compared to (b) (4) due to increased batch size, is based on the justification that (b) (4) has demonstrated (b) (4) within each lyophilizer are also equivalent. Additionally, (b) (4) are (b) (4) of the capacity of the lyophilizer being well within the validated capabilities of the unit.

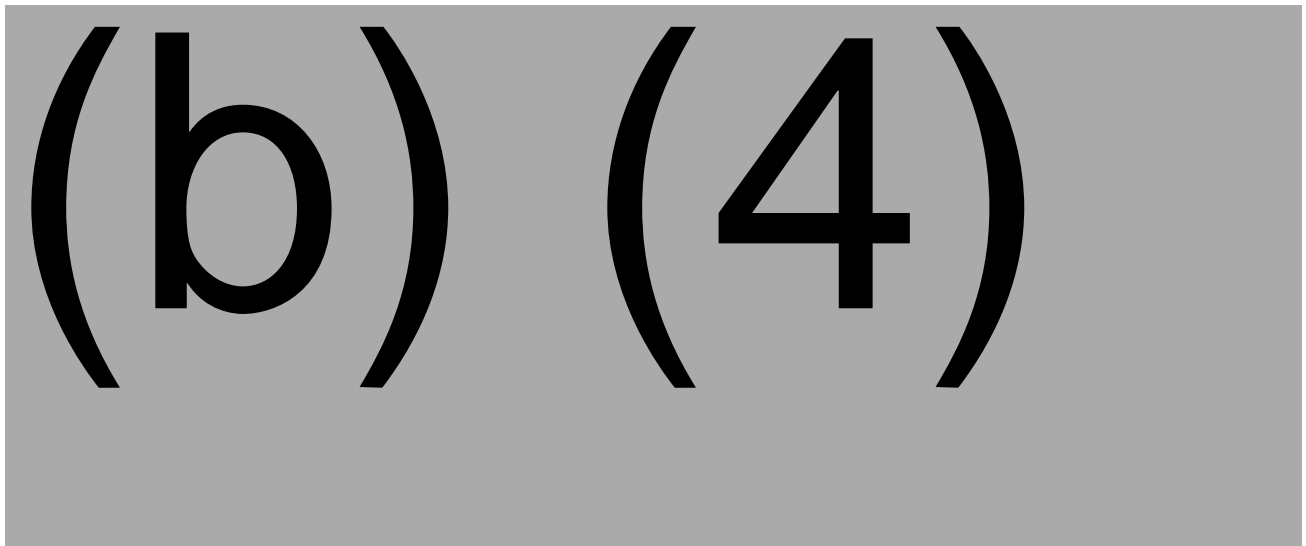
This revised CP proposed the DP comparability assessment studies to include a comparability of (b) (4) GMP DP lots to (b) (4) GMP DP lot. The use of a (b) (4) lot of DP made from (b) (4) was justified as follows:

- The changes between the two processes are minor
- The control strategy is the same
- No CPPs are affected

Additionally, stated in the CP, that the comparability will be limited to the following testing, since the manufacturing changes to (b) (4) are not considered significant.

- In-Process Control testing: to include comparison of results from the in-process control test results for the lots from each process
- Release Testing: to include comparison of results of release testing of lots from each process

In-Process Control testing of (b) (4) and (b) (4) that are to be compared was indicated as follows:



Release testing (and acceptance criteria) include visual appearance (white to off white lyophilized cake), moisture ((b) (4)), reconstitution time ((b) (4)), sterility, and endotoxin ((b) (4)), in addition to testing performed after reconstitution including potency, identity and product quality testing.

The following was indicated to be reported in the follow up supplement to the CP:

- Comparability data obtained and the assessment of the (b) (4) DP lots will be documented in a Comparability Report with reference to the protocol
- Changes to the studies or acceptance criteria described will be listed and justified
- Deviations from the protocol will be documented and discussed in the Comparability Report

Reviewer Comments: The revised CP still has significant deficiencies in regards to the DP portion of the CP, specifically noted as follows:

- The CP does not include a detailed approach as to how the lyophilizers will be validated such as a description of a bracketing strategy detailing the number of runs per lyophilizer and a justification for this strategy. The CP indicates that (b) (4) DP produced from (b) (4) will be performed; and there is no justification provided for why this is sufficient to demonstrate consistency for addition of (b) (4) lyophilizers and additional use of (b) (4).*

- b. The CP does not provide a description of the testing that will be performed to demonstrate the lyophilizers are equivalent. The CP states that the lyophilizers are demonstrated to be equivalent, but there were no details of how the lyophilizers were shown to be equivalent (i.e., specific listing of testing performed and the acceptance criteria as it relates to the lyophilizer operating parameters, specifically, the allowable variance in operating parameters between lyophilizers for determining equivalency).
- c. The CP does not define a product sampling plan for the lyophilization runs (i.e., details of sampling at (b) (4) from each lyophilizer and the number of samples to be taken and tested at each location). Please note that routine release testing is not acceptable to demonstrate consistency of the process for the new lyophilizers.
- d. The CP does not address validation of aseptic processing for the (b) (4) additional lyophilizers.
- e. The CP does not address how the cleaning and sterilization of the (b) (4) additional lyophilizers will be validated.
- f. The CP does not include a detailed description of the data that will be provided to support the follow up supplement. For example, for the validation of additional lyophilizers and (b) (4), we would expect to review the following:
 - o Product testing results of the extended sampling of the lyophilization runs
 - o Lyophilization cycle graphs, monitoring the (b) (4) during the lyophilization runs
 - o Results of IQ/OQ testing and other testing performed demonstrating equivalency of the lyophilizers
 - o Results of media fills performed with the additional lyophilizers
 - o Results of cleaning and sterilization validation of the additional lyophilizers

As previously mentioned, the firm requested a telecon to discuss the number of lots required to support the follow-up CBE-30 for the changes to the (b) (4) DP process. A telecon was held with the firm, May 23, 2016 to discuss the firm's proposals. During the telecon, the firm was informed of the major deficiencies with the CP (provided in Amendment 27) noted above, in addition to the product offices noted deficiencies, specifically for the (b) (4) portion of the CP. Please refer to the telecon minutes from May 23, 2016 in the EDR for details of the discussion. An IR was issued to the firm May 31, 2016 (refer to Section "Information Requests" IR#4 of this memo for details, specifically outlining the deficiencies conveyed to the firm during the telecon. The firm was advised to revise the CP to address the deficiencies and was informed that if the deficiencies were not addressed that the CP would have a negative impact on approval of the BLA. The firm provided a revised version of the CP (for both (b) (4) DP) as Amendment 43, received by CBER June, 21, 2016, which is reviewed below.

Revised CP (Original 29 April 2016; Amended 21 June 2016) received in Amendment 43:

In response to IR#4 (sent May 31, 2016), the firm provided another revised CP, NC-15-0664-P0002-A01 & NC-15-0681-P0002-A01, "Comparability Protocol Andexanet Alfa (PRT064445) (b) (4) to (b) (4) and Resulting Drug Product" covering both changes to the DS and DP. The overall list of CPs covered and/or reference in this revised version were indicated as follows:

Comparability Protocol	Protocol Number
Comparability of Andexanet Drug Product (b) (4) versus (b) (4) Scale-Up	NC-15-0681-P0001
Andexanet Alfa (b) (4) Comparability of (b) (4) to (b) (4) Lots	NC-15-0664-P0001
Andexanet Alfa (b) (4) Comparability of (b) (4) to (b) (4) Lots, Addendum	NC-15-0664-P0001 addendum

Additionally, Process Performance Qualification protocol 414-21-04-002-P1, “Process Performance Qualification Protocol for Andexanet Alfa (PRT064445) 100 mg/vial, (b) (4) Lyophilized Drug Product, 20mL/20 mm vial, (b) (4) Fill, Fill Line (b) (4)” was included in the amendment and provides supporting details to approach described in the section 7.0 Development of Drug Product (b) (4) for (b) (4) of CP. Some of the same information was provided in this revised CP as was previously provided including the history of manufacturing of the DP manufacture with (b) (4) from (b) (4), description of the changes, and the risk assessments. The following review of the revised CP will focus mainly on new information provided in this revised CP, but will include a limited review of the (b) (4) portion of the revised CP as the detailed review of the acceptability of the (b) (4) portion of the CP is deferred to the product office.

CP portion supporting Drug Product Manufacturing Changes

The manufacturing changes covered in drug product portion of CP are the same as previously described including increase in size of (b) (4) of sterile filter, and the use of (b) (4) additional lyophilizers and (b) (4) in number of (b) (4) (from (b) (4)) used in lyophilizer(s). The information in regards to the Drug Product manufacturing changes was described in section 7.0 of the CP.

Drug Product Validation Strategy

The manufacturing history of DP manufactured from (b) (4) from (b) (4) was indicated for the manufacturing history of DP manufactured from (b) (4) from (b) (4).

(b) (4)

The PPQ campaign and the three DP lots of (b) (4) from (b) (4) is indicated as a prospective validation based on (b) (4) consecutive (b) (4) DP lots with a batch size of (b) (4), using Fill Line (b) (4) Fill Machine ((b) (4)) and (b) (4)

(b) (4)

The Process Validation Strategy for (b) (4) DP to be submitted in the CBE-30 (follow-up to CP) was indicated as follows:

(b) (4)

(b) (4) Process Validation Strategy provided in submitted BLA (as D120 update) was noted as follows in support of batch ranges performed in lyophilizer (b) (4)

(b) (4)

Details including in-process controls and acceptance criteria for the following process steps affected by the drug product manufacturing changes covered in the CP are indicated as follows:

(b) (4)

(b) (4)

DP produced from (b) (4) will follow same (b) (4) process with changes to the size of batch (b) (4), which will be (b) (4). Same acceptance criteria for IPC will be applied.

- **Sterile Filtration and Aseptic Filling**

(b) (4)

(b) (4)

Aseptic filling is performed in Grade (b) (4) environment under aseptic conditions. The target fill volume and acceptance criteria range is indicated as follows, which is not changed:

Filling In-Process Controls

(b) (4)

- **Lyophilization**

(b) (4)

[Redacted text block]

(b) (4)

[Redacted text block]

(b) (4)

(b) (4)

Other information provided which was not provided in previous CP include the following:

- Facility areas, critical areas and major equipment used for manufacture of DP from (b) (4) on Fill line (b) (4) are controlled, qualified and/or validated appropriately prior to use. Table 57, “Facilities, Equipment, Utilities and Systems” was provided in the CP and references the IQ/OQ/PQ and confirmation qualifications for critical areas of Building (b) (4), utilities, (b) (4), and all major equipment.
- A description of a media fill performance qualification was completed on Fill Line (b) (4) that included (b) (4) media fill runs using a bracketing approach. Routine media fill challenges are conducted to demonstrate the aseptic filling process is capable of delivering sterile product. Per (b) (4) procedure, utilization of each production Lyophilizer in Building (b) (4) ((b) (4)) is required during the routine media fill challenges (b) (4).

CP portion supporting (b) (4) Manufacturing Changes

Most of the revisions made to the (b) (4) portion of the CP were to address issues and deficiencies identified by the product office; however, some of these revisions are shared between DMPQ and product office and thus were included in this review. Additionally, the (b) (4) portion of the CP included several additional details, relating to DMPQ aspects, which were not included in the previous CP for the (b) (4) manufacturing changes, and therefore were reviewed and noted as follows:

- **Cleaning validations:** The majority of equipment for (b) (4) is disposable, thus no cleaning validation is required. Cleaning validation is currently being performed for any non-disposable equipment for (b) (4) and studies were referenced as follows:

(b) (4)

- (b) (4) **Validations:** (b) (4) will have (b) (4) and hold validations performed for worst-case (b) (4) and media. The validations that are planned were indicated as follows:

(b) (4)

- (b) (4) **Validation:** The (b) (4) Lifetime Validation Reports will be written for the (b) (4) upon completion of the (b) (4). The following reports were indicated as follows:

(b) (4)

- **Manufacturing History on (b) (4) and Reporting of Deviations:** Information in regards to the manufacturing history of (b) (4) was provided in response to product office's request to include the totality of the manufacturing experience in regards to (b) (4), as issues were found during the (b) (4) inspection of the (b) (4) facility. The firm provided the manufacturing history, and details of deviations (categorization etc.) and actions taken to address the deviations noted. Batch history of (b) (4) process was provided as follows:

Manufacturing History of Andexanet Alfa (b) (4) from (b) (4)

(b) (4)

(b) (4)

■ [Redacted]

- Details of manufacturing and deviations of the PPQ Campaigns (campaigns 1 and 2) listed in the above Table, “Manufacturing History of Andexanet Alfa (b) (4) from (b) (4)” were provided in the narrative and are summarized as follows:

(b) (4)

■ [Redacted]

■ [Redacted]

■ [Redacted]

Reviewer Comments: During the PPQ campaigns and verification runs, there were multiple instances reported in regards to issues with (b) (4), either as contamination events in the (b) (4) before (b) (4) or (b) (4) occurring after (b) (4) and in some cases detected in the downstream process. Given the number of incidents of (b) (4) OOS) and that in a majority of the PPQ lots

manufactured on average only (b) (4) of the (b) (4) proceed to the downstream processing, in addition to the other numerous deviations reported, the manufacturing process of (b) (4) clearly does not seem to be in a state of control. This is concerning considering this process change to the (b) (4) manufacturing is being reviewed under a CP provided in this BLA, which would allow a downgrade of the results of this change to a CBE-30. Given the manufacturing history of (b) (4) provided shows in inadequate amount of control of the manufacturing process, a CP and subsequent CBE-30 is not an acceptable regulatory path given the risk of this change in the manufacturing on (b) (4), thus this CP is not acceptable for approval under this BLA. With this basis, I recommend an issuance of a CR letter for this BLA, specifically if this CP is not withdrawn from the BLA.

- **Defined minimum number of (b) (4) to meet criteria- Monte Carlo Assessment**

Analysis: A Monte Carols Simulation Model analysis was performed using (b) (4) process data to assess (b) (4) operation and impact of processing (b) (4) and define the minimum number of (b) (4) needed to meet the criteria for (b) (4) on the downstream process. In the analysis, the probability of success (defined as meeting the acceptance criteria for loading (b) (4) downstream (b) (4)) was predicted based on the number of successful (b) (4) and the average (b) (4) for each of the (b) (4) in the process, including (b) (4) determined by the number of (b) (4) included. The results of the analysis summarized in the following table:

(b) (4)

Based on the model prediction, on average (b) (4) produce sufficient quantities of (b) (4) the downstream (b) (4) within the required (b) (4) limits. Additionally, if (b) (4) are processed, the predicted average (b) (4) falls below the acceptable limit for at least (b) (4)

Reviewer Comments: The CP as proposed is unacceptable and as part of the BLA is basis for recommending a CR letter for the BLA. There are several issues of concern in the firm's approach to the (b) (4) process, in which the firm is proposing the use of (b) (4); however, only requires (b) (4) to meet acceptance criteria for the downstream processing. The following issues are the basis for why this CP unacceptable, thus should be included as CR items (refer to specific wording for CR item 1 in the Recommendation section):

CR Item:

1. The proposed process is designed with the expectation of failure. A minimum number of (b) (4) needed to meet the acceptance criteria for success downstream was determined by a Monte Carlo analysis, which is based on process information from (b) (4). The firm proposes that process uses (b) (4); however, to meet the acceptance criteria of the downstream process, only (b) (4) at the minimum are needed. This process approach appears to indicate an expectation and anticipation of failure, thus additional (b) (4) (more than needed) are incorporated as a process strategy. This is further supported by the manufacturing history of (b) (4) provided in the CP, specifically, out of (b) (4) GMP lots manufactured on (b) (4), only (b) (4) lots had (b) (4) of (b) (4) harvested for downstream process. The other lots included the following:

- a. (b) (4) lot had (b) (4)
- b. (b) (4) lots had (b) (4)
- c. (b) (4) lots were terminated before (b) (4) stage

2. A total of (b) (4) deviations occurred during the manufacturing of (b) (4) GMP lots. Of this, (b) (4) were considered critical. Overall, there were (b) (4) deviations in relation to Overall Cleanliness, (b) (4) deviations in relation to equipment issues, (b) (4) deviations in relation to process knowledge and (b) (4) deviations in relation to operational reliability. There were numerous (and re-occurring) deviations associated with (b) (4) contamination of the (b) (4) before (b) (4) due to issue with (b) (4) cleaning. Additionally, there were numerous (and re-occurring) deviations related to equipment failures including (b) (4) resulting in (b) (4) as a result of issues with the design of (b) (4) system that holds (b) (4) in place.

Given the manufacturing history of (b) (4) and the numerous deviations, the process does not seem to be in state of control, thus the approach to include additionally bioreactors (more than needed) to account for the anticipated failures is not in compliance with cGMPs. Based on the issues noted above, and the risk involved with the process changes, the regulatory path of the CP and follow up supplement is not appropriate. Thus, this CP is not approvable and these major issues with the CP should be clearly conveyed to the firm in the CR letter.

Reporting in Follow-up Supplement

The following was noted in regards the reporting in the follow up supplement after execution of the (b) (4) DP protocols:

- Comparability data obtained and the assessment of the (b) (4) DP lots documented in a Comparability Report with reference to protocol
- Any changes to the studies or acceptance criteria described in the CP will be listed and justified
- Deviations from the protocol will be documented and discussed in the Comparability Report.

Reviewer Comments: Although the revised CP, provided in Amendment 43, addressed most of the deficiencies conveyed to the firm in the May 23, 2016 telecon and the IR sent May 31, 2016, there are still several issues that need clarification and discussion with the firm. These include the following:

- 1) In regards to the PPQ validation plan, the firm was advised to propose a (b) (4) strategy and provide information on all lyophilization runs performed on all (b) (4) lyophilizers to determine if there is sufficient data to support a change in the (b) (4) strategy. The firm did indicate that (b) (4) prospective validation runs of DP from (b) (4) have been performed with (b) (4) run in each of the (b) (4) lyophilizer(s) including (b) (4) and that (b) (4) validation lots of DP from (b) (4) (from data provided to support the BLA) were performed. The overall summary of the lyophilization runs (number of runs and number of (b) (4)) is provided in the following table:

(b) (4)

The firm is not proposing the (b) (4) strategy; however, has indicated that (b) (4) runs using (b) (4) in lyophilizer (b) (4) has been performed (this includes (b) (4) runs performed in support of DP lots from (b) (4) provided in BLA and (b) (4) DP lot from (b) (4) from (b) (4) as noted in the table) and that (b) (4) run using (b) (4) has been performed in each of lyophilizer (b) (4), in addition the firm has indicated that the lyophilizer are shown to be equivalent. This approach may be acceptable as the firm did provide OQ data demonstrating the lyophilizers (b) (4) are equivalent; however, the firm should clarify if (b) (4) are planned to be used in lyophilizer (b) (4), and explain why at least (b) (4) run using (b) (4) in lyophilizer (b) (4) was not included in the validation plan. Additionally, the firm needs to indicate which (b) (4) ((b) (4) in the lyophilizer) in the (b) (4) lyophilizers are being used in the validation.

- 2) In regards to the “Reporting” section of the CP, the firm indicated that comparability data obtained and the assessment of the (b) (4) DP lots will be documented in a Comparability Report with reference to the protocol and that deviations from the protocol will be documented and discussed in the Comparability Report. However, the firm did not provide specifics as to what data would be included in the “Comparability Report”, as conveyed to them in the May 23, 2016 telecon, in addition to the IR sent to them May 31, 2016. Specifically, the firm should provide details of the extending sampling plan ((b) (4) sampling on each (b) (4)). Additionally, the firm did not indicate if the following would be part of the “Comparability Report”. The firm should specifically list in the CP that the following data will be provided in the Comparability Report that will be provided in the follow-up CBE-30.
- Results of extending sampling testing (including number of samples and locations ((b) (4))
 - Results of OQ/PQ for all new equipment and new areas associated with (b) (4) manufacturing changes
 - Results of in-process parameters and product quality attributes (characterization and release testing results) associated with process validation
 - Results of OQ/PQ and other testing performed to demonstrate equivalency of lyophilizers
 - Results of most recent media fills using the lyophilizers
 - Results of most recent cleaning and sterilization validation of the lyophilizers
 - All data relating to lyophilization cycle monitoring

- 3) *In regards to the data to be reported the firm noted the following: “Any changes to the studies or acceptance criteria described in the CP will be listed and justified”. This statement should be clarified and the firm should be informed that there should be no changes to the studies or acceptance criteria and that doing so would lead to an upgrade of the follow up submission. The CP is approved as written which includes procedures and acceptance criteria, thus any changes to how the CP is executed or changes to the acceptance criteria applied will lead to an upgrade from a CBE-30 to a PAS.*

The firm was issued an IR asking to address the issues noted above. Please refer to IR#7 (item 5) in the “Information Request” section of memo for details of the firm’s response.

VIII. Facilities and Inspections

Facilities for Inspection:

(b) (4) [REDACTED]
[REDACTED] [REDACTED] [REDACTED]
[REDACTED]
[REDACTED]

Facilities to waive inspection:

(b) (4) [REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

(b) (4) [REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

Please note all facilities listed above will be included in the compliance check. Please refer to Table 1 in APPENDIX for complete listing of facilities.

IX. Environmental Assessment

In section 1.12.14 of the BLA, the firm requested a categorical exclusion from preparation of an Environmental Assessment in accordance with 21 CFR § 25.25 (d) and based on 21 CFR § 25.31 (c) stating that any action on an NDA, abbreviated application, application for marketing approval of a biologic product, or a supplement to such application, or action on an OTC monograph is categorically excluded and ordinarily does not require the preparation of an EA or an Environmental Impact Statement for substance that occur naturally in the environment when the action does not alter significantly the concentration or distribution of the substance, its metabolites, or degradation product in the environment and that to Portola’s knowledge, no extraordinary circumstances exist.

Reviewer Comments: Based on the information provided, the firm’s request for categorical exclusion from preparation of an Environmental Assessment as per 21 CFR § 25.31(c) is justified.

X. Information Requests

During this primary review, the following information requests were sent to the firm.

IR#1: The following was sent to firm January 25, 2016 and firm's response (see below) received as Amendment 3 (STN 125586/0 eCTD 0003) on February 1, 2016 and Amendment 5 (STN 125586/0 eCTD 005) on February 4, 2016.

1. **The Comparability Protocol provided specifically, NC-15-0664-P0001, “Andexanet Alfa Drug Substance Comparability of (b) (4) to (b) (4) Lots” is missing significant information and details in regards to the changes in the facility and equipment involved in the manufacturing change to use the (b) (4). The comparability protocol should include the following specifics:**

- A detailed description of the changes in the facility (renovations, HVAC, etc.) and the equipment used ((b) (4) etc.).
- A listing and description of specific tests that will be performed for the qualification (OQ/PQ) of the “new” area and the “new” equipment used for the manufacturing change, in addition, a listing of the acceptance criteria that will be used for the qualification testing to be performed.

Firm Response: The firm indicated in this response that the additional information in regards to this item will be submitted 03 February 2016. The official response to this IR item is provided in Amendment 5 (eCTD 0005) received by CBER February 4, 2016. The firm provided an addendum to protocol NC-15-0064-P0001, indicated as “NC-15-0664-P0001 addendum, “Andexanet Alfa (b) (4) Comparability of (b) (4) to (b) (4) Lots, Addendum”. This addendum provided a summary of the OQ/PQ testing for Line C Major Equipment and Systems that include the following:

Description of OQ Testing for:

Category	Value
(B) (4)	10
	10
	50
	10
	100
	30
	10
	20
	30
	40

The review of this information is covered under the Comparability Protocol section of this review memo. Please refer to this section of the memo for details.

Reviewer Comments: The firm has adequately responded to this information request. No further action required in regards to this item.

2. Please indicate the specific labeling activities that are performed at (b) (4) facility. Does this labeling involve primary labeling of the final container or labeling of the secondary packaging?

Firm Response: The firm indicated that the primary labeling of the final container, in addition to the secondary packaging and labeling is conducted at (b) (4)

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

3. Please provide more details for the activities ((b) (4)) QA and Final Batch Disposition) performed at Portola Pharmaceuticals (San Francisco, CA). Do these activities involve handling and storage of ((b) (4)) and/or drug product?

Firm Response: The firm indicated that Portola Quality Assurance provides quality oversight of Portola products manufactured and tested at Contract Manufacturing Organizations through approval of master batch records, change control documents, analytical method validation protocols and reports and specifications. The firm confirmed that there are no manufacturing, quality control, storage or handling activities performed at Portola. Additionally, the firm indicated that final batch disposition is performed by Portola Quality Assurance after review of the executed batch records, investigation reports, and vendor provided Certificate of Analysis and analytical data.

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

IR#2: The following information request was sent to the firm April 6, 2016 as part of a multi-disciplinary IR. The DMPQ items relevant to this review include IR items 19-30 of this information request. The response from firm for items 19-30 was received April 18, 2016 by CBER as amendment 22 (0022). Responses are provided below.

19. Please provide the Container Closure Integrity Test (CCIT) validation report LL1404006 that was referenced in Table 3.2.P.3.5-1 “Protocols and Reports Supporting Andexanet Alfa Drug Product Validation” and that was briefly described in Section 3.2.P.2.5 Microbiological Attributes of the BLA submission. This report should include sensitivity data to support the use of the positive controls in testing. Please note that the positive control, in which the stopper was ((b) (4)), is not adequate to simulate a critical leak defect. To support sensitivity, we recommend that the defect diameter be as small as reasonably possible (i.e. sensitivity data should include a minimum ((b) (4))

_____.

Firm Response: The firm provided Container Closure Integrity Test Validation Report VL1404006 with this amendment as this report was not provided in the original BLA. The firm indicated that Report VL1404006 was performed April 24, 2014 according to ((b) (4)) SOP 04-06-46, *Integrity Challenge for Container Closure/Closure Interfaces Using Vials*, to initially qualify the integrity of the container closure system. At the time the validation was performed, a ((b) (4)) was accepted practice as the point of failure control. On December 3, 2014 the governing SOP 04-06-46 was revised and requires both a point of failure control prepared utilizing a ((b) (4)) container with an inner diameter equal to the defined point of failure size of ((b) (4)) and a positive control ((b) (4)) for each container closure integrity challenge performed. The contents of the challenge containers will be free from ((b) (4)) when visibly compared to the positive and negative controls. In addition, the contents will be analytically tested for ((b) (4)) content by QC per SOP 09-03-007, ((b) (4)) *Detection for Container Closure Integrity*. The ((b) (4)) of the WFI filled challenge containers must be less than or equal to the ((b) (4)) of the ((b) (4)) standard. The point of failure (POF) and limit of detection (LOD) were

determined as outlined in SOP 04-01-046 Determination of Sensitivity and Point of Failure for Container Closure Interfaces, Using the (b) (4) Challenge.

In August 6, 2015, VL1507010 was performed according to SOP 04-06-046 using the same primary component as those tested initially in VL1404006. The POF control was prepared utilizing a vial with a (b) (4) and positive control was (b) (4). The vials were visually inspected for (b) (4) in comparison to the positive and negative control containers. Both VL1404006 and VL1507010 were performed with product filled vials. The firm indicated that all acceptance criteria in the testing protocol SOP-04-06-046 were met.

Reviewer Comments: In the response, the firm indicated that the CCIT was re-performed according to the revised SOP that changed the preparation of the POF control from using a (b) (4) to a (b) (4) container with an inner diameter equal to (b) (4) and referenced report VL1507010 (performed August 6, 2015) that documents this testing. This revised positive control with the (b) (4) is an acceptable positive control for a critical defect. However, the firm did not include this report in the amendment, only providing the report VL1404006, which is the testing performed with the POF control using the (b) (4) in the stopper. The firm was issued an additional information request (reference IR#6, item 5, below for details) asking to provide the report VL1507010 and the SOP 04-01-046. Additionally, the firm was advised that a study of (b) (4) stability in presence of product is needed, if performing CCIT on stability, and to provide a plan for this study if not yet performed. Please refer to IR#6 (item 5) below for details of firm response to this addition IR.

- 20. The report M073-1 “Container Closure Summary Report” was provided in Section 3.2.R Regional Information of the BLA and describes the use of (b) (4) and then subjected to (b) (4). Please indicate the purpose of this report as it does not seem to connect to the CCIT information provided in Section 3.2.P.2.5 (b) (4) Attributes of the BLA submission. Additionally, this report was not referenced nor summarized in Section 3.2.P.2.5 of the BLA submission. Please provide more details for the purpose and scope of this report, in particular, please describe how this report supports the (b) (4) testing described in Section 3.2.P.2.5 of the BLA submission.**

Firm Response: The firm indicated that the (b) (4) method as per (b) (4) was used for CCIT of andexanet alfa. The validation report VL1404006 for was included in this amendment as this was not provided in the original BLA. The M073-1 report provided was included in error and is not connected to the CCIT information provided in section 3.2.P.2.5 (b) (4) Attributes of the BLA.

Reviewer Comments: The firm has adequately addressed this information request no further action is needed.

- 21. Please provide summaries of the OQ reports referenced in Table 3.2.A.1-3 “Equipment OQ/PQ Summary” in Section 3.2.A.1 Facilities and Equipment - (b) (4) of the BLA submission for the following equipment.**

(b) (4)

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Firm Response: The firm provided the following report summaries which were reviewed and are summarized as follows:

(b) (4)

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

(b) (4) deviations were indicated and included one relating to (b) (4) test and (b) (4) deviations relating to performance verification.

The (b) (4) test deviation involved the following:

The (b) (4) code comparison between Freezer Dryer (b) (4) and Freeze Dryer (b) (4) for identifying differentiating modules that require additional function verification, in which one module found in (b) (4) did not exist in (b) (4) program; however it was identified that this module in (b) (4) was not subjected to functional verification testing in LY11

The performance verification deviations included:

- 1) Pre-calibration failed on the (b) (4) used for (b) (4) Test. The test was repeated with successfully pre-calibrated (b) (4) with acceptable results. Deviation indicated as minor.
- 2) (b) (4) tests were not performed as per procedures. These tests were repeated as per the procedure with successful results. Deviation indicated as minor.
- 3) The (b) (4) acceptance criteria of (b) (4) was not achieved. The test requires (b) (4) . At end of the rest, a total of (b) (4) . The reason for this was due to (b) (4)

(b) (4)

. Deviation indicated as major.

* Additional functional verification testing was performed for (b) (4) in a separate QO Addendum protocol VL0806017. The reported for this protocol was provided and is review below:

Reviewer Comments: The deviations in regards to addendum OQ report VL0612006 indicated as minor were adequately addressed and no further action needed. The deviation relating to the (b) (4) capacity, indicated as major, was adequately described and given that only (b) (4) is used in the DP manufacturing process for andexanet, the reduced (b) (4) capacity (based on use of (b) (4)) from (b) (4) is not a significant impact for use in the andexanet alfa manufacturing process.

Report VL0806017 is an addendum report to provide summary of results of testing that was not included in the original protocol. This addendum included the following OQ testing (functional testing) for freeze dryer (b) (4):

(b) (4)

[Redacted text block containing multiple lines of information, likely a table or list of test results, all obscured by (b) (4) redaction.]

Three deviations were noted and included the following:

Deviation 1: The (b) (4) cycle functional verification tests were not included in the (b) (4) Addendum OQ protocol. The test functions were added to the Addendum protocol and testing under deviation 1. The testing was

report VL0805028 covers IQ/OQ for changes involving an upgrade with an addition of (b) (4) to better control the amount of (b) (4). Two deviations were noted and resolved. Report VL1208018 performed in August 2012, covers the IQ/OQ and PQ of the utilization of gauntlets on (b) (4). Testing included (b) (4). All testing met acceptance criteria and no deviations were reported.

Report VL14004005-VL1505011 is summary of the Component Compatibility Operational Qualification (CCOQ) of 20mL/20mm Components using the (b) (4) Filling Machine ((b) (4)) and Capper ((b) (4)) performed April 23 and May 12 (addendum) using component combinations dimensionally and functional equivalent to andexanet alfa project. The containers were filled to target weight of (b) (4) using format (b) (4), a dosing station position equal to (b) (4) and stopper station of (b) (4). The qualified fill machine, (b) (4) change parts were indicated in the report. Stopper preparation and handling were also detailed in the report. Equipment covered in the CCOQ included Filling machine (b) (4) Lyophilizers, and (b) (4) Capper (b) (4). No deviations were indicated.

Reviewer Comments: The CCOQ of the use of the filler with the other major equipment in the filling process ((b) (4)), freezer dryer and capper) was also discussed in the narrative of the BLA. This report is acceptable. No further action needed.

(b) (4) (VL0802056)
VL0802056 provides summary of the OQ performed in August 2006 by (b) (4). All OQ testing was performed and met acceptance criteria. Four deviations were indicated in the report summary and detailed descriptions were provided for the two major deviations relating to alarms and the (b) (4) both of which require software changes. Retesting was performed and deviations were resolved.

(b) (4) ((b) (4): VL0510060, VL0705051; (b) (4) VL0510060, VL0705051; (b) (4): VL0510059, VL0705052)
Summary reports of the three (b) (4) were provided and indicate that an operational qualification was performed and was successful. For (b) (4), (b) (4) minor deviations were reported (date of report 20 Jan 2005); for the (b) (4), (b) (4) minor deviations were noted (date of report 26-OCT-2005); and for (b) (4) minor deviations were reported (date of report 19-JAN-2005). According to reports all deviations were corrected and closed and after approval of all deviations, all results were within acceptance criteria.

Reviewer Comments: The PQ of (b) (4) were described in sufficient detail in the BLA, thus these documents only supplemented what was previously provided. No further action needed.

22. Please provide summaries of the following validations referenced in Table 3.2.P.3.5-1 “Protocols and Reports Supporting Andexanet Alfa Drug Product Validation” (refer to Section 3.2.P.5 Process Validation and/or Evaluation, pg. 5)

a. Formulation Equipment Sterilization Validation

- b. Filling Equipment Sterilization Validation
- c. (b) (4) Performance Qualification
- d. (b) (4) Performance Qualification
- e. Lyophilizer Validation
- f. Media Fill Performance Qualification and Confirmation

Firm Response: The firm did not provide the actual summary reports, but did indicate the specific location in the BLA that covers the information in regards to the validations listed above.

Reviewer Comments: These summaries were provided in the narrative of the BLA and provided sufficient detail for review. The review of this information is described in the “Process Validation” section of this memo.

23. Please indicate if (b) (4) is used in the manufacturing process of Andexanet alfa DP and if so, please indicate if the use is product contact. Additionally, you indicated that (b) (4) is used as a (b) (4), thus is product contact. Please, indicate how (b) (4) (if applicable) are filtered and monitored for purity and microbial content (i.e. details of sterile filtration, filter integrity testing).

Firm Response: The firm indicated that process (b) (4) is used in the manufacturing process of Andexanet alfa DP but does not have product contact. Additionally, the firm confirmed that lyophilized vials are (b) (4) prior to being stoppered. The (b) (4) is filtered using redundant (b) (4) filters. A (b) (4) test is performing using (b) (4) batch. The (b) (4) value is (b) (4). Nitrogen at all sample points is tested (b) (4) identity.

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

24. Please provide a detailed description of the aseptic filling area, and the RABS enclosure. Please indicate if the RABS is an opened or closed RABS and how the RABS is decontaminated before a filling is performed.

(b) (4)

(b) (4)

Reviewer Comments: The firm's response is adequate. No further action is needed.

25. In reference to the HVAC system, please provide a qualification summary and indicate the number of air exchanges/hour in the rooms of the aseptic core.

Firm Response: The firm provided the summary report "Qualification for HVAC Line (b) (4) Fill Room and Lyophilization Corridor". The qualification report covers the HVAC units (b) (4) which service the Grade (b) (4) areas for products manufactured on Fill Line (b) (4) and Building (b) (4) lyophilizer (including the lyo loading and unloading corridor) including rooms (b) (4) at (b) (4). The qualification activities covered in this report include Design Qualification, Installation Qualification and Operational Qualification. The DQ and IQ were performed successfully and no deviations noted. The Operational Qualifications performed were referenced. Testing performed for the operational qualification included (b) (4)

. All tests were successfully completely and met acceptance criteria. Several addendum installation and operational qualification addendums were also briefly described which were performed in adding of new equipment and changes to ductwork.

Room Air Changes Summary provided in the report included the following:

(b) (4)

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

26. In reference to Table 3.2.P.3.-10 Sterile Filtration Parameters for Consistency Lots (Section 3.2.P.5 Process Validation and/or Evaluation, pg.17), the NOR/Target range for Filter/Product Contact Time is indicated as (b) (4) and PAR (Proven Acceptable Range) is indicated as (b) (4); however, for the data for the (b) (4) lots provided ((b) (4)) the filter/product contact process times range from (b) (4). Please note that set process time limits should be close to actual production. Please comment and provide a justification for the filter/product contact limits indicated.

Firm Response: The firm indicated that the PAR of (b) (4) was determined based on the filter comparability study that was performed as part of the filter validation. In this study, the filters were evaluated for product (b) (4) change, flow rate change, weight changes and visual changes following exposure to andexanet alfa (b) (4) for (b) (4). The NOR of (b) (4) was set based on ambient processing time requirements at (b) (4) and is supported via hold time challenge study referencing section 3.2.P.5.1.1 of the BLA. The firm indicated that the filter/product contact process time is not a critical process parameter for andexanet alfa DP manufacturing process.

Reviewer Comments: The firm's response is not adequate. The firm's basis of the PARs is not acceptable in that the filter compatibility is not the only factor to consider when establishing a production time limit, in addition, the firm's indication that the filter/product contact time is not a critical process parameter is not adequate. The total time of filtration should be limited to prevent microorganisms from penetrating the filter, thus should prevent a significant increase in bioburden. The firm performed a microbial retention study with a maximum filter/product contact time of (b) (4). Additionally, the firm's process validation runs are (b) (4), thus the firm was issued an IR to provide a revised time for this process limit to be more aligned with the process capability and the microbial retention study. Please refer to IR#6(item 6) in section "Information Requests" for details of firm's response.

27. Please note that the ranges indicated in Table 3.2.P.3.5-12, "Lyophilization Process Parameters and Hold Temperature for the Consistency Lots" for the (b) (4) with NOR as (b) (4), PAR (b) (4) and Validation parameter range of (b) (4) and for the (b) (4) with NOR, PAR and Validation Parameter Range of (b) (4) are not supported by data. Please comment on the determination of these ranges and how these ranges are supported.

Firm Response: The firm indicated that process characterization studies using a DoE model were conducted to determine the ranges for the (b) (4) with NOR as (b) (4) and PAR (b) (4) and Validation parameter range (b) (4) and for (b) (4) with NOR, PAR and Validation Parameter of (b) (4) as discussed in Section 3.2.P.2.3.2.2 and indicated in Table 3.2.P.3.5-12. Additionally, the firm noted that the (b) (4) and (b) (4) ranges were studies in a DoE evaluation effect of parameter ranges on output parameters and DP quality attributes (at time zero and on stability at (b) (4) for 3 months). The ranges studied described in Table 3.2.P.2.3-12 and outputs parameters and DP quality attributes evaluated are described in Table 3.2.P.2.3-12. The ranges studies had no impact on output parameters such as (b) (4); also the product temperatures throughout the ranges studied were below the (b) (4) of (b) (4). Also, the firm indicated that no significant changes in DP quality attributes were observed.

Reviewer Comments: The firm's response is significantly inadequate. The firm did not provide any new information, only referencing information provided in the original BLA, which had been reviewed previously and found to not provide sufficient information to support the ranges described in Table 3.2.P.3.5-12 (PARs and NORs for

(b) (4) and (b) (4). In re-reviewing these sections of BLA in regards to their reason, the following deficiencies were identified:

- No details were provided in how the process characterization studies using the DoE model were conducted or what these DoE experiments involved such as what actual parameters were used in experimental runs (if performed). The firm only provided ranges in a table and no raw data was provided.
- No data was provided in the referenced sections in regards to the product testing the firm indicated that was performed, only a listing of the testing that was used to evaluate the product.
- In sections referenced in the firm's response, there was description that (b) (4) and (b) (4) did not have a significant effect on time of completion, although theoretically, these two parameters should have an effect. Thus, the firm indicated that a model was determined where the (b) (4) and (b) (4) affected the product temperature. The following model, Figure 3.2.P.2.3-7, "(b) (4) Model" was provided in section 3.2.P.2.3.2.2 of the BLA:

(b) (4)

(b) (4)

Thus to address these deficiencies noted above the firm was issued an additional information request asking to provide all raw data the supports of the PARs and NORs described for the lyophilization validation. For details of firm's response please refer to IR#6(item 1).

28. Please provide details of the procedures for final batch release after primary labeling and packaging has been performed. These details should include

information in regards to the location in which the following activities are performed: sampling for release testing, quality control, storage of lot retains and lots before final distribution. Please detail the roles and responsibilities of each facility involved in the batch release process.

Firm Response: The firm indicated that primary labeling and packaging is performed at (b) (4). The primary label is applied to the drug product vial and then four labeled vials are placed into secondary packaging with insert. (b) (4) reviews the record and confirms the correct labels and packaging materials are used for the operation. Executed batch records are sent to Portola for review. The final batch release after primary labeling and packaging is performed by Portola Quality Assurance. No quality control samples are taken after primary labeling and packaging. Each lot of drug product in stoppered and sealed vials has a unique batch number applied to the seal at the fill/finish manufacturer ((b) (4)). Lot release testing to confirm identity, purity and potency is performed on the drug product. At primary labeling and packaging, the unique fill/finish batch number is confirmed and recorded in the production record to confirm the correct product is being labeled. After primary labeling and packaging, QA retains samples will be taken and stored by (b) (4). The labeled and packaged drug product will be stored at (b) (4) until Portola QA approved release of the finished drug product to the specialty warehouse for distribution.

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

- 29. There are major deficiencies in the two comparability protocols that were provided in the BLA submission to cover changes to the DS and DP manufacturing process. Please note that a comparability protocol is a well-defined, written plan for assessing the effect of specific CMC changes. A comparability protocol should describe the changes that are covered under the protocol and specifies the tests and studies that will be performed, including analytical procedures that will be used and acceptance criteria for each specified test that will be achieved to demonstrate that the specific changes do not adversely affect the product. In addition, specifics of the type and amount of data (i.e. number of batches) generated from execution of the protocol should be clearly indicated. The data provided in the follow-up CBE-30 should include results of all tests and studies specified in the CP, discussions of any deviations that occurred during the tests or studies, a summary of any investigations performed and other pertinent information.**

Firm Response: Response provided addresses items 29-30. See response described below in IR item 30

- 30. As previously noted, two CPs were provided in your BLA submission, one which relates to the manufacturing changes to the Drug Substance (use of (b) (4)) (NC-15-0664-P0001) and the other which relates to DP manufacturing changes using the DS manufactured with (b) (4) (NC-15-0681-P0001). Please indicate if separate CBE-30s will be submitted. We highly recommend that the two CPs be combined into one covering the overall manufacturing changes to DS and DP, thus to**

simplify the submitting of data into a single CBE-30 submission given that the manufacturing changes to DS and DP are interrelated.

Firm Response: Portola provided a response to in Amendment 22 for addressing items 29-30 indicating that Portola requested an extension to provide a single revised CP that would include the following:

- Information on the manufacturing changes associated with the scale increase and the rationale for the changes, including a discussion of Critical Process Parameters for affected steps
- Evaluation of the potential impact of the scale increase on the quality attributes of andexanet alfa
- Justification for the quality attributes to be tested and process steps that will be evaluated
- Test methods for evaluation of the quality attributes and their validation status
- Number of andexanet alfa DS and DP batches to be assessed
- Data analysis strategy including statistical assessment and acceptance criteria that will enable an objective assessment of the comparability of the pre- and post-scale change andexanet alfa.

Portola provided the single revised CP “Comparability Protocol Andexanet alfa (PRT064445) (b) (4) to (b) (4) Drug Substance and Resulting Drug Product” (encompassing study no., NC-15-0664-P0002 (for DS) and study no., NC-15-0681-P0002 (for DP)) as Amendment 27, received by CBER May 2, 2016. This revised CP was extensively reviewed in section “Comparability Protocol” of this memo.

Reviewer Comments: After review of this protocol, major deficiencies were identified by DMPQ and the product office. These deficiencies were conveyed to the firm in a May 23, 2016 telecon, in addition to an IR sent May 31, 2016. For details please refer to IR#4 (below).

IR#3: The following information request was sent to the firm May 12, 2016 and firm’s response received by CBER as Amendment 33 (eCTD 0033) on May 27, 2016

- 1. Please provide the basis for the acceptance criteria of (b) (4) for the reconstitution time of the lyophilized product. In addition, please explain the significant difference in the reconstitution time of the lyophilization (b) (4) samples between Lot (b) (4) with reconstitution times ranging from (b) (4) as compared to Lot (b) (4) with reconstitutions time ranging from (b) (4). Additionally, please provide more details in regards to the (b) (4) used for Lot (b) (4) resulting in (b) (4) reconstitution times as footnoted in Table 3.2.P.3.5-13, pg. 19-20 in Section 3.2.P.3.5 Process Validation and or Evaluation of submission and indicate if different reconstitution methods were used for Lot (b) (4) and Lot (b) (4).**

Firm Response: The firm noted that the reconstitution procedure is conducted by (b) (4) time period follow by (b) (4) of the contents of the vial. Vials are (b) (4) until completion of reconstitution. The firm indicated that the reconstitution method used for the testing of lyophilization (b) (4) samples for Lot (b) (4), the first (b) (4) GMP lot manufactured, was conducted in a (b) (4) and did not follow the (b) (4) procedure

described above. For the (b) (4) PPQ lots (b) (4), the reconstitution method using the (b) (4) was followed. The results of the (b) (4) lots were provided in Day 120 update to the BLA as links in this amendment as was provided in amendment 23. The reconstitution time were indicated as follows:

(b) (4)

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

2. In reference to the lyophilization (b) (4) samples for lot (b) (4) and lot (b) (4), please indicate how many samples were tested from each of the (b) (4) noted in Tables 3.2.P.3.5-13 and 3.2.P.3.5-13.

Firm Response: The firm indicated that (b) (4) and (b) (4) samples were tested for each (b) (4) and that the results were summarized in Table 3.2.P.3.5-13 and Table 3.2.P.3.5-14.

Reviewer Comments: The firm indicated that multiple samples were taken at each (b) (4); however, only (b) (4) result was reported in the table for the testing parameters including moisture content, appearance, reconstitution, thus an additional IR was issued asking firm to provide all results from samples tested. Refer to IR#5 (item 1(d)) for details of the firm's response.

3. Please provide the lyophilization cycle graphs, monitoring the (b) (4) during the lyophilization cycle, for the consistency lots (b) (4) and (b) (4) (if available).

Firm Response: The firm provided the data that included the raw data of the lyophilization cycle for lots (b) (4) and (b) (4) (PDFs of the actual strip chart recordings), in addition provided Lyophilization Cycle Monitoring forms from the executed batch record, with recordings of the (b) (4) recorded at indicated times and identifying the step and phase of process that were recorded during the lyophilization cycle for (b) (4) and (b) (4).

Reviewer Comments: With the data provided, it was difficult to understand what was being monitored in the cycle. The strip chart recordings were difficult to read and did not have labels to identify what was being monitored. Additionally, the lyophilization cycle

monitoring form recorded the (b) (4) and (b) (4) at various time intervals and did not include monitoring of the product temperature, and the data was presented in a table format, thus it was difficult to determine when (b) (4) was completed and when secondary drying began. The firm was issued an additional information request to clarify if product temperature was being monitored and to also appropriately label the stages in the strip charts provided. Please refer to IR#5 (all items) for firm's response.

4. In 3.2.P.3.5 Process Validation and or Evaluation, you indicated that the shipping validation will be performed according to a pre-approved protocol. Please provide the shipping validation protocol and indicate when shipping validation covering the transport of the final product (filled at (b) (4)) to Packaging Coordinators for primary labeling will be completed.

Firm Response: The firm provided protocol VA.016/0 that covers the transport of the final product (filled at (b) (4)) to (b) (4) for primary labeling will be completed by 30 June 2016. The protocol included the following details:

- Packaging configuration consists of a corrugate shipping case, comprised of (b) (4)
(b) (4)
(b) (4)
- Shippers will be closed and sealed with standard shipping tape
- (b) (4) replicates of the shippers will be tested
- For this shipping validation, Placebo to Match Andexanet alfa 100 mg/vial will be utilized, as this represent the commercial container closure system
- Each commercial shipper will be subjected to (b) (4)
(b) (4), an industry recognized standard for validation the impact of the distribution cycle for a package design. Specifically, (b) (4) was selected as most applicable to supply chain for Andexanet alfa/vial (b) (4) vials
- An Assurance Level (AL) I is being used and comprises the following hazard elements:
 - (b) (4)
 - (b) (4)
 - (b) (4)
 - (b) (4)
 - (b) (4)
 - (b) (4)
 - (b) (4)
- Following testing Distribution Cycle testing and post-test (b) (4), Container Closure Integrity testing using a (b) (4) challenge method will be performed on a sample of the product vials to demonstrate that the integrity of the container closure system has been maintained.
- Portola will manually package (b) (4) full shipping cases for the testing described in the protocol
- (b) (4) Testing will be performed at (b) (4) a contract test laboratory in (b) (4)
- CCIT will be managed by (b) (4)

process time limit for (b) (4). No change in the drug product attributes was observed following storage of the drug product vials at (b) (4) for up to (b) (4). The firm indicated that the storage of vials for process step (b) (4) will occur in temperature controlled areas. Fully stoppered vials are stored in a temperature controlled Grade (b) (4) area until sealing occurs. The sealed vials are stored in a temperature controlled area prior to palletization. Additionally, the firm noted that the hold time up to (b) (4) was challenged for PPQ lot (b) (4) with no effect on product quality attributes.

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

IR#4: The following information request was sent to firm May 31, 2016, as a follow up written IR for issues discussed during the May 23, 2016 telecon with the firm (refer to EDR for details in the telecon minutes). The firm response was received June 22, 2016 as Amendment 4 (eCTD 0043).

“We will not comment on the appropriateness of the proposed review category until we have a chance to review the completed Comparability Protocol (CP). As of now, your revised CP “Comparability Protocol Andexanet Alfa (PRT064445) (b) (4) to (b) (4) Drug Substance and Resulting Drug Product” is still deficient, and will not support a downgrade of the submission for (b) (4) from a *Prior Approval Supplement* to a *CBE-30 Supplement*.

We have reviewed your revised CP submitted in Amendment 27 to STN 125586/0 dated 29 April 2016. Your revised CP is to support changes in the manufacturing processes of the Drug Substance (DS) and Drug Product (DP), specifically those related to the use of (b) (4), the use of (b) (4) new lyophilizers, and additional (b) (4) in the lyophilizers. As discussed during our teleconference on 23 May 2016, we have summarized for you the following deficiencies in the form of an information request:

1) Drug Substance:

- a. The CP does not describe nor takes into consideration the totality of data gathered in process and product development. The missing evidence includes two failed (b) (4) Process Performance Qualification (PPQ) campaigns and repeated excursions which had resulted in the termination of (b) (4) out of (b) (4) of initiated DS lots. (b) (4) was out of operation during the Pre-License Inspection (PLI) on (b) (4). FDA inspectors had reviewed the investigations of several (b) (4) deviations and informed Portola and (b) (4) that (b) (4) was not in a state of control as was evidenced from (b) (4) inability to consistently manufacture DS lots in accordance with established process parameters. Please revise the CP to provide the following information listed below:**
 - full list of all DS lots initiated in (b) (4), including engineering lots, and their dispositions
 - description of all deviations, including open deviations
 - description of all Corrective and Preventive Actions (CAPAs) implemented to address the observed manufacturing problems, and the data to demonstrate that these CAPAs are effective.

- b. The CP does not provide sufficient information on the substantive differences in equipment used in (b) (4). For example, during the (b) (4) PLI, (b) (4) provided evidence that (b) (4) deviations were caused by deficiencies in the cleaning procedures of the new equipment in (b) (4). Therefore, the revised CP should include description of new validation studies or abbreviated bridging studies performed on the (b) (4) equipment, including (b) (4) and cleaning validation, (b) (4) studies.
- c. Since the (b) (4) upstream process may include variable numbers of (b) (4), the PPQ study should use a bracketing approach in which the minimally acceptable number of (b) (4) and all (b) (4) are used to manufacture successful DS lots. In addition, please define a successful PPQ lot as a lot with no failed (b) (4). A similar bracketing approach should be used in the manufacture of DP lots produced from (b) (4) DS lots. Please refer to comments on the validation of DP manufacturing process below.
- d. To demonstrate process consistency, please provide data from (b) (4) consecutive DS lots. The (b) (4) consecutive lots may include the (b) (4) PPQ lots.
- e. Please include product activity and antigen levels in the assessment of the performance for most of the unit operations. Please use these parameters to calculate process yield and recovery, and add them as performance attributes for comparison between (b) (4) and (b) (4).
- f. Please update the acceptance criteria in the CP with quantitative values or ranges for the following methods that you were advised to do in our Information Request dated 6 April 2016:
- (b) (4)
 - (b) (4)
 - (b) (4)
 - (b) (4)
 - (b) (4)
- g. Please revise the acceptance criteria in Table 34 on Page 44 so that the term “comparable” is defined prospectively and objectively for each test attribute to clearly establish limits for success. Specifically, in addition to meeting release specifications and process parameters, results generated from (b) (4) should be analyzed against those from (b) (4) for any biases.
- h. Please include in the comparability exercise the analysis of results from all DS lots, including the pre-PPQ campaign lots, manufactured using the proposed commercial procedure in (b) (4), in addition to those from the (b) (4) PPQ DS lots.
- i. Please enroll the DP lots manufactured using the (b) (4) DS lots in stability studies, and compare their stability trends to those of (b) (4).

2) Drug Product:

- g. The CP does not include a detailed approach as to how the lyophilizers will be validated such as a description of a bracketing strategy detailing the number of runs per lyophilizer and a justification for this strategy. The CP indicates that (b) (4) DP produced from DS from (b) (4) will be performed; and there is no justification provided for why this is sufficient to demonstrate consistency for addition of (b) (4) lyophilizers and additional use of (b) (4).
- h. The CP does not provide a description of the testing that will be performed to demonstrate the lyophilizers are equivalent. The CP states that the lyophilizers are demonstrated to be equivalent, but there were no details of how the lyophilizers were shown to be equivalent (i.e., specific listing of testing performed and the acceptance criteria as it relates to the lyophilizer operating parameters, specifically, the allowable variance in operating parameters between lyophilizers for determining equivalency).
- i. The CP does not define a product sampling plan for the lyophilization runs (i.e., details of sampling at pertinent (b) (4) from each lyophilizer and the number of samples to be taken and tested at each location). Please note that routine release testing is not acceptable to demonstrate consistency of the process for the new lyophilizers.
- j. The CP does not address validation of aseptic processing for the (b) (4) additional lyophilizers.
- k. The CP does not address how the cleaning and sterilization of the (b) (4) additional lyophilizers will be validated.
- l. The CP does not include a detailed description of the data that will be provided to support the follow up supplement. For example, for the validation of additional lyophilizers and (b) (4), we would expect to review the following:

 - Product testing results of the extended sampling of the lyophilization runs
 - Lyophilization cycle graphs, monitoring the (b) (4) and product temperature during the lyophilization runs
 - Results of IQ/OQ testing and other testing performed demonstrating equivalency of the lyophilizers
 - Results of media fills performed with the additional lyophilizers
 - Results of cleaning and sterilization validation of the additional lyophilizers

Based on the lack of a detailed plan (protocol), we do not agree with your assessment that (b) (4) DP lot is sufficient to support the follow up supplement. Generally, for addition of multiple lyophilizers, we expect a bracketing strategy such as (b) (4), which is (b) (4) runs in one lyophilizer to demonstrate consistency, and (b) (4) run in each of the other additional lyophilizers (demonstrated as equivalent) for further confirmation the process is consistent. In demonstrating PQ of additional lyophilizers, the use of placebo with product vials located at pertinent locations for testing may be acceptable if the placebo adequately represents and is scientifically justified that all the relevant physical characteristics of the drug product under conditions that the drug product will see during lyophilization.

Please be advised that the CP covering changes to the DS and DP manufacturing processes must be very detailed and outline specifically the data that will be provided to support the subsequent CBE-30 supplement. If the CP is deficient, this can negatively impact the review process and the outcome of your BLA. Additionally, in the event that we approve the CP and allow a downgrade of the submission for (b) (4), if the subsequent CBE-30 supplement does not contain all the supporting information, as specified in the CP or if the results fail to meet the acceptance criteria and conditions specified in the CP, the submission will be upgraded to a Prior Approval Supplement. Please refer to the Draft Guidance “Comparability Protocols for Human Drugs and Biologics: Chemistry, Manufacturing and Controls Information, April 2016 for additional information in regards to the expectations for Comparability Protocols.”

Firm Response: The firm provided a revised CP (Original 29 April 2016; Amended 21 June 2016) NC-15-0664-P0002 & NC-15-0681-P0002, “Comparability Protocol Andexanet Alfa (PRT064445) (b) (4) to (b) (4) Drug Substance and Resulting Drug Product” covering both changes to the DS and DP. This version of the CP included revisions to address the deficiencies that were conveyed to the firm. The revised CP provided by the firm is extensively reviewed in section “Comparability Protocol” of this memo.

Reviewer Comments: After a review of the CP, several issues/discrepancies were identified that need clarification:

- 1) In regards to the PPQ validation plan, the firm was advised to propose a (b) (4) strategy and provide information on all lyophilization runs performed on all (b) (4) lyophilizers to determine if there is sufficient data to support a change in the (b) (4) strategy. The firm did indicate that (b) (4) prospective validation runs of DP from (b) (4) have been performed with (b) (4) run in each of the (b) (4) lyophilizer(s) including (b) (4) and that (b) (4) validation lots of DP from (b) (4) (from data provided to support the BLA) were performed. The overall summary of the lyophilization runs (number of runs and number of (b) (4)) is provided in the following table:

(b) (4)

The firm is not proposing the (b) (4) strategy; however, has indicated that (b) (4) runs using (b) (4) in lyophilizer (b) (4) has been performed (this includes (b) (4) runs performed in support of DP lots from (b) (4) provided in BLA and (b) (4) DP lot from (b) (4) as noted in the table) and that (b) (4) run using (b) (4) has been performed in each of lyophilizer (b) (4), in addition the firm has indicated that the lyophilizer are shown to be equivalent. This approach may be acceptable as the firm did provide OQ data demonstrating the lyophilizers (b) (4) are equivalent; however, the firm should clarify if (b) (4) are planned to be used in lyophilizer (b) (4), and explain why at least (b) (4) run using (b) (4) in lyophilizer (b) (4) was not included in the validation plan. Additionally, the firm needs to indicate which (b) (4) ((b) (4) in the lyophilizer) in the (b) (4) lyophilizers are being used in the validation.

2) In regards to the “Reporting” section of the CP, the firm indicated that comparability data obtained and the assessment of the DS and DP lots will be documented in a Comparability Report with reference to the protocol and that deviations from the protocol will be documented and discussed in the Comparability Report. However, the firm did not provide specifics as to what data would be included in the “Comparability Report”, as conveyed to them in the May 23, 2016 telecon, in addition to the IR sent to them May 31, 2016. Specifically, the firm should provide details of the extending sampling plan ((b) (4)). Additionally, the firm did not indicate if the following would be part of the “Comparability Report”. The firm should specifically list in the CP that the following data will be provided in the Comparability Report that will be provided in the follow-up CBE-30.

- Results of extending sampling testing (including number of samples and ((b) (4)) of sampling ((b) (4)))
- Results of OQ/PQ for all new equipment and new areas associated with drug substance manufacturing changes
- Results of OQ/PQ and other testing performed to demonstrate equivalency of lyophilizers
- Results of most recent media fills using the lyophilizers
- Results of most recent cleaning and sterilization validation of the lyophilizers
- All data relating to lyophilization cycle monitoring
- Results of in-process parameters and product quality attributes (characterization and release testing results) associated with process validation

3) In regards to the data to be reported the firm noted the following: “Any changes to the studies or acceptance criteria described in the CP will be listed and justified”. This statement should be clarified and the firm should be informed that there should be no changes to the studies or acceptance criteria and that doing so would lead to an upgrade of the follow up submission. The CP is approved as written which includes procedures and acceptance criteria, thus any changes to how the CP is executed or changes to the acceptance criteria applied will lead to an upgrade from a CBE-30 to a PAS.

The firm was issued an IR asking to address the issues noted above. Please refer to IR#7 (item 5) below for details of the firm’s response.

IR#5: The following information request was sent to the firm June 8, 2016 and firm’s response was received by CBER June 27, 2016 as Amendment 44 (eCTD 0044).

1. **In regards to the information provided in Amendment 33 (received May 27, 2016), including the lyophilization cycle charts and monitoring information of the ((b) (4)), and lyophilization ((b) (4)) samples, please note and respond to the following:**
 - a. **The lyophilization cycle charts provided did not provide sufficient details as to determine what is being assessed and monitored. Please describe the information provided in the graph (i.e. indicate scales, and labels for product temperature, ((b) (4)), in addition to labeling of the stage of the cycle ((b) (4)).**

Firm Response: The firm indicated that the lyophilizer is operated, controlled and monitored using a (b) (4). At the beginning of the lyophilization cycle, the save cycle format for andexanet alfa is selected and each parameter from (b) (4) is verified against the batch record. In-process cycle monitoring is performed for each cycle by trained Lyophilization Monitoring Technicians per established SOP 05-06-013 Preparation and Operation of the Line 8 Freeze-Dryers". The monitoring begins when the lyophilization cycle advances from (b) (4). The routine monitoring checks are documented on (b) (4) Form 05-06-F003 Lyophilization Cycle Monitoring Form (forms provided for lots (b) (4)) and critical values ((b) (4)) are recorded real-time from the (b) (4) unit graphic screen. As part of the monitoring, the strip chart is verified to ensure it is printing properly. Cycle deviations will produce Alarms, which are documented on the Lyophilization Cycle Monitoring Form and when warranted, escalated to area supervisor. Cycle deviations are evaluated against (b) (4) SOP 21-01-016 Handling Freeze Dryer Cycle Deviations. Upon completion of the lyophilization cycle, the strip chart and cycle monitoring forms are reviewed against the lyophilization cycle parameters for lots (b) (4) by qualified lyophilization technician to ensure batch meets all cycle parameters, which is documented in the batch record.

Lyophilization cycle strip charts were provided with labeling of the scale, critical parameters and stages of lyophilization, in addition, an entire lyophilization layout was provided so that entire cycle can be viewed at once.

Reviewer Comments: The charts provided were easier to read in regards to recognizing the different stages and critical parameters. (b) (4) was not one of the monitored parameters. The cycle was clearly observed and appears to be time based. No other additional information is needed in regards to this IR item.

- b. **Please indicate where the data listed in the "Lyophilization Cycle Monitoring forms" for Lot (b) (4) and Lot (b) (4) originates from (i.e. are these values handwritten from an electronic readout or are these values pulled from the chart recordings that were provided). Additionally, please indicate the timepoints used for monitoring critical lyophilization parameters, for example are the critical parameters monitored every 10 min, every hour etc. and provide a justification for why the time interval for monitoring the parameters was used. It should be noted that in the Lyophilization Cycle Monitoring form, there is no column for (b) (4) values. Please indicate if (b) (4) was monitored during the validation runs.**

Firm Response: The firm indicated that the data listed in the Lyophilization Cycle Monitoring forms are documented in real-time by the Lyophilization technicians reading the (b) (4) unit graphic screen. The critical parameters are routinely monitored with a target of every (b) (4). A retrospective review is performed for the previous (b) (4) at each monitoring and all alarms are reviewed

for that (b) (4). The time interval represents the historical practices at the (b) (4) facility. Additionally, the firm indicated that there are no (b) (4) probes utilized during the GMP production lyophilization cycles. The reason is that the system is (b) (4)

(b) (4). The lyophilizer contains (b) (4). Rather than (b) (4) is controlled and monitored.

Reviewer Comments: For the validation runs, it appears the firm did not monitor the (b) (4), thus relying on the monitoring of the (b) (4). The firm did provide developmental data that did monitor the (b) (4) at the lyophilization set points, thus the lack of monitoring the (b) (4) during the process validation in this instance, is not a significant risk to warrant a CR, thus no further action is needed to address this IR item.

- c. **Please clarify how QA determines that the critical process parameters for** (b) (4).

Firm Response: The firm indicated that the executed batch record documentation is reviewed by Quality Assurance (A) Batch Release personnel for compliance and completeness. As part of the QA review, the strip chart and cycle monitoring forms are reviewed against the Lyophilization parameters for lots (b) (4), which are listed in the batch record. Specifically, QA ensures set points and durations listed in the batch record were met for each phase and that alarms were appropriately addressed.

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

- d. **In regards to the lyophilization (b) (4) samples, you indicated that (b) (4) samples for Lot (b) (4) and (b) (4) samples for Lot (b) (4) were tested from each (b) (4) of the freeze dryer. Please provide the product testing results for these additional samples as Tables 3.2.P.3.5-13 and 3.2.P.3.5-14 only provide one testing result for each sampled (b) (4).**

Firm Response: The firm indicated that in the original BLA submission, lyophilization (b) (4) sample data from the process consistency lot (first clinical GMP lot) (b) (4) in addition to the first PPQ lot (b) (4) that samples were tested as follows:

For (b) (4)

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

(b) (4)

Results of the (b) (4) experiment runs including the product temperature were indicated as follows:

(b) (4)

The (b) (4) ranges as determined by (b) (4) ranged from (b) (4), which is within the (b) (4) of (b) (4). The product (b) (4) ranged from (b) (4); all below the (b) (4) temperature (b) (4) of (b) (4). The firm indicated that based on this experimental data, the entire range of the (b) (4) and the (b) (4) was deemed acceptable and used to establish the PARs and that this data is the basis of the model prediction provided as Figure 3.2.P.2.3-7 in the BLA submission. Additionally, the firm indicated that the quality attributes of the product from the experiment runs were tested including cake appearance, moisture, reconstitution time, solution appearance, pH (b) (4), protein concentration, (b) (4), direct potency and particulate matter. The results were provided as follows:

Moisture, Appearance and Reconstitution Time Results

Run	Drug Product Cake Appearance	Reconstituted Solution Appearance	Reconstitution Time (sec) ^a
(b) (4)	Intact cake	Clear, no color, no particles	(b) (4)
	Intact cake	Clear, no color, no particles	
	Intact cake	Clear, no color, no particles	
	Intact cake	Clear, no color, no particles	
	Intact cake	Clear, no color, no particles	
	Intact cake	Clear, no color, no particles	
	Intact cake	Clear, no color, no particles	

Moisture, pH, (b) (4), Concentration, Direct Potency and Particles Results

Run Number	Moisture (%)	pH	(b) (4)	Concentration (mg/mL)	Direct Potency	(b) (4)	(b) (4)
(b) (4)							

Note: All assays performed in a development laboratory

(b) (4)

Reviewer Comments: The firm performed (b) (4) experimental runs that do cover the maximum and minimum of the PARs for (b) (4) and (b) (4) and provided product testing; however, the runs were not performed on a commercial scale and no justification was provided as to how an increase in scale would affect the parameter ranges. The firm was issued an additional request asking to indicate how the PAR ranges established from runs on a lab scale will be applied to commercial production and asking them to indicate what actions are taken if the lyophilization parameters would deviate from the target set points at the commercial scale. For details of firm response, please refer to IR#7(item 4) below.

- For your developmental lyophilization studies, which provide the basis for (b) (4) parameters, a (b) (4) was used with the justification that the (b) (4) is considered representative of the DP since the amount of protein present is a small fraction of the mass of the DP, thus will not have an effect on thermal behavior. Please provide data that supports this rationale.

Firm Response: The firm indicated that the results from DP vials were used to set the lyophilization drying conditions. The developmental studies (provided in section 3.2.P.2.3.5.1 in BLA) for the lyophilization cycle were performed using all DP, all (b) (4) vials and a combination of DP and (b) (4) filled vials. The same (b) (4) lyophilization cycle was performed on a (b) (4) of the lyophilizer with either all (b) (4) or all DP vials ((b) (4)). Additional runs included combination of (b) (4) and DP vials ((b) (4)). The product temperatures were measured in different (b) (4) in addition to the (b) (4) times. The (b) (4) times were similar and below the (b) (4) time of (b) (4). The product temperatures in the corresponding (b) (4) were similar and below the (b) (4) of (b) (4) in all lyophilization experiments. The (b) (4) parameters were set based on the thermal behavior of the DP vials.

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

3. In reference to section 3.2.P.3.5.2.4.1 of the BLA, specifically in regards to the sterilization validation (PQ) of the worst case minimum durable load consisting of the (b) (4), please indicate the number and locations the (b) (4) used in the PQ. Additionally, the PQ of the worst case minimum durable load provided for (b) (4) was performed in March 2005, please indicate why a re-qualification of the minimum load was not performed.

Firm Response: The firm indicated that (b) (4) . A (b) (4) were placed in the (b) (4), near the (b) (4). The minimum load was not re-qualified because (b) (4) considered the maximum load the more difficult challenge. However, (b) (4) has begun performing confirmations since 22 July 2015 of the worst case minimum load (b) (4). Now the maximum load and minimum load are confirmed (b) (4).

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

4. In reference to the PQ for the (b) (4), please indicate the initial amount of (b) (4) of the (b) (4) vials, and provide the amount of (b) (4) recovered from each vial after (b) (4), and indicate the corresponding log reduction data for each vial for all PQ runs. Additionally, please clarify the rationale for the use of the (b) (4) vial as the worst case vial pack in terms of mass.

Firm Response: The firm indicated provided the following information relating to the (b) (4) amount after the (b) (4) cycle and the log reduction for the (b) (4) vials as follows:

(b) (4)

(b) (4)

In regards to the worst case vial pack used in the PQ, the firm indicated the rationale for worst case (b) (4) vial is that this pack when loaded into the (b) (4) provides the greatest mass of all vials for all projects (b) (4). Using the mass approach as the bracketing scheme, the PQ was performed for this vial and all other vial sizes whose pack in (b) (4) is less mass are deemed qualified. The PQ was performed at the (b) (4). During product manufacture, all vials are processed at (b) (4) than the validation set point and are processed at a (b) (4).

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

5. In reference to the response for IR item # 19 provided in Amendment 22, please provide CCIT validation report VL1507010, which should include all results (raw data) obtained from the study. Additionally, please provide the revised SOP 04-01-046, “Determination of Sensitivity and Point of Failure for Container/Closure Interfaces, Using the (b) (4) Challenge” that describes the point of failure controls (including the (b) (4) container with failure size (b) (4) and the spiked (b) (4)). Please note that if you plan to perform CCIT on stability, you will need data to support (b) (4) stability in the presence of the product. Please provide your plans for these studies if not yet performed.

Firm Response: The firm indicated that CCIT was performed at (b) (4) for sterility assurance studies and at (b) (4) for the DP stability studies. The firm provided the following reports and SOPs requested for review:

- Validation Report VL1507010, “Summary of the 20 mL/20 mm Vial Container Closure Integrity Test for (b) (4)”
- SOP-04-06-046 “Integrity Challenge for Container Closure Interfaces Using Vials”
- Protocol 04-01-046, “Determination of Sensitivity and Point of Failure for Container/Closure Interfaces, Using the (b) (4) Challenge”
- Validation Report VL1604002, “Summary of the 10 mL/20 mm Vial Container Closure Integrity Test Method Qualification (re-performance of the point of failure study, which demonstrated the (b) (4) is the sensitivity of the (b) (4) method).
- (b) (4) Method Validation
- (b) (4) LOD of (b) (4)

The validation reports and SOPs are summarized as follows:

Validation Report VL1604002 (dated April 21, 2016): This report summarized the requalification of the CCIT method, specifically challenging the point of failure used for the (b) (4) container/closure test. The report is generated from execution of Protocol 04-01-046, “Determination of Sensitivity and Point of Failure for Container/Closure Interfaces, Using the (b) (4) Challenge”, which supplements SOP-04-06-046 (issue date 19-AUG-2015, effective date 31-AUG-2016). Protocol 04-01-046 and SOP-04-06-046 describe procedures for determining the sensitivity of the point of failure for container

closure Interfaces, using the (b) (4) challenge. The Protocol 04-01-046 and corresponding validation report VL1604002 involved challenging (b) (4) breach sizes ((b) (4)) created using a (b) (4) (performed by vendor (b) (4)), in (b) (4) locations on the vial ((b) (4)). The components used in the study were noted as follows:

Component	Description	(b) (4) Part #
Vial	10 mL/ 20 mm Tubing (b) (4)	(b) (4)
Stopper	20 mm (b) (4)	(b) (4)
Seal	20 mm (b) (4) Royal Blue	(b) (4)

(b) (4)

(b) (4)

Vials were removed from (b) (4). Vials were then visually examined for evidence of (b) (4) in comparison to a positive and negative control. A second person verified the results. Vials were also analyzed by (b) (4) in comparison to (b) (4) control (Limit of Detection (LOD) for the (b) (4) method is (b) (4)).

Results: Report provided raw data from each of the hole sizes tested ((b) (4)) that included the (b) (4) results for each of the (b) (4) vials tested with each hole size, in addition to (b) (4) result of the standard. The overall results were indicated as follows:

(b) (4)

(b) (4)

[Redacted text block]

Results were reported as follows:

- LOD for instrument #(b) (4) was shown to correspond to an (b) (4) of (b) (4), which is approximate value of (b) (4). For instrument #(b) (4) the LOD (b) (4) was (b) (4) which is approximate value of (b) (4).

Summary Report M121-2 (completion date 17 Feb 2005, report date 22 Feb 2005): This report summarized the validation of the (b) (4) test method used to evaluate the container closure system performed at (b) (4). This report is an addendum validation to determine the effect of the defect size and variance in the pressure on test results. The evaluation was limited to glass crimp top vials. The procedure was described as follows:

(b) (4)

[Redacted text block]

Results: Vials for both vial sizes and for each defect size had consistent visible (b) (4). Vials that were properly sealed showed on visible (b) (4).

In reference to performing CCIT on stability, Portola commits to providing data to support (b) (4) stability in presence of product. Portola will contract (b) (4) to perform a (b) (4) stability study in the presence of the product and will provide data to FDA by 29 July 2016. The study will be conducted at (b) (4) concentrations ((b) (4) (b) (4)) and stability will be determined by (b) (4) on Days (b) (4). Both negative and positive controls will be tested at each timepoint.

Reviewer Comments: In reviewing the information provided in regards to CCIT, the following was identified:

1. The firm indicated in the report that (b) (4) analysis is not performed because the vials were filled with (b) (4) and not (b) (4). The firm was issued an information request asking why (b) (4) analysis is not performed on product vials. Please refer to IR#7 (item 2) for details of firm's response.
2. The CCIT information provided was very disjointed and difficult to connect as report summaries and methods were provided were performed by two different manufacturer/laboratories and the validation reports and methods provided are addendums of re-qualification performed due to changes to the CCIT method around the time of the manufacturing of the process validation lots. The changes to the CCIT method mainly relate to changes in the use of positive controls. The firm indicated that (b) (4), the drug product manufacturer, performs the CCIT for sterility assurance as it relates to production, whereas, (b) (4) is performing the CCIT as part of the DP stability testing plan. The firm provided summary validation reports for the CCIT method performed at both (b) (4) and (b) (4).

At (b) (4), the SOPs were changed to include a Point of Failure (POF) control of from a (b) (4) in stopper of container closure to vial with a (b) (4) hole. This is a more acceptable POF control. The firm provided the re-qualification of the use of this control, but the report provided data from testing performed on 12 month stability samples, thus not clear why (b) (4) was performing this testing on stability samples when the firm indicated that (b) (4) is responsible for this testing. Additionally, summary validation reports prepared by (b) (4) were provided demonstrating the validation of the (b) (4) method and determining the LOD of the (b) (4) used in the (b) (4) method. The summary reports provided were high level and did not include sufficient details in reference to the positive controls use; thus it is not clear if the same POF control (vial with (b) (4) hole) used in the (b) (4) CCIT studies was used in the method validations performed by (b) (4).

These discrepancies in the CCIT information provided may not be grave concern given that the DP is lyophilized and tested for moisture on stability. Thus, if there is a leak or comprise in the container closure, the moisture testing results would indicate an issue with the container closure. However, there are still outstanding details that the firm should clarify. Given that the firm is receiving a CR letter in regards to other issues in the BLA, the firm can address these deficiencies with the following CR letter item:

CR letter Item: In regards to CCIT for stability samples performed by (b) (4), please provide the following:

- Specific details of the point of failure control that is used
- Indicate if only (b) (4) is performed for product filled vials
- Provide details, SOPs etc. of the (b) (4) process and how operators are qualified to perform (b) (4).
- Results of the (b) (4) stability (in the presence of the product) study indicated to be conducted at (b) (4) and stability determined by (b) (4) on Days (b) (4).

6. In reference to your response to IR item #26 provided in Amendment 22, regarding the determination of the PAR and NOR for the filter/product contact process limit of (b) (4) and (b) (4), please note that product/filter comparability is not the only factor to consider when establishing production time limits. The total time for the product filtration should be limited to an established maximum to prevent microorganisms from penetrating the filter. Such a time limit should also prevent a significant increase in upstream (b) (4) load. Given that the microbial filter retention study was performed with a product/filter contact time of (b) (4) and that process time for the sterile filtration of validation lots (b) (4) was performed in (b) (4), the process limit should be adjusted accordingly to be more aligned with your process capability and the bacterial retention study. Please provide a revised time limit for review.

Firm Response: The firm agreed to revise the filtration time NOR to (b) (4). The NOR will be reassessed after manufacturing of (b) (4) DP batches has been completed.

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

IR#7: The following information request was sent to the firm July 11, 2016 and response from the firm was received July 25, 2016 as Amendment 61 (eCTD 0064):

1. Please indicate if the (b) (4) used for the intermediate storage and shipping of the BDS from (b) (4) to (b) (4) are re-used. If bottles are re-used, please indicate how these (b) (4) are cleaned and sterilized (if applicable).

Firm Response: The firm indicated that the (b) (4) used for the intermediate storage and shipping of BDS from (b) (4) to (b) (4) are (b) (4).

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

2. In reference to report VAL1507010, (b) (4) analysis was not performed in this CCIT study due to the samples containing (b) (4) rather than (b) (4), thus samples were (b) (4) by comparison to the positive control and negative controls. Please indicate the specific procedures that are used for the (b) (4) of the presence of (b) (4) performed at (b) (4) (e.g. (b) (4) used, number of operators used to verify a result etc.) and provide details for how the operators were qualified. Additionally, please indicate why (b) (4) analysis is not performed on product filled vials.

Firm Response: The firm provided a brief description of the (b) (4) process which is indicated as follows:

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

(b) (4)
(b) (4)
(b) (4)
(b) (4)
In regards to (b) (4) analysis, the firm indicated that (b) (4) analysis is not performed for (b) (4) filled vials because the procedure requires (b) (4) testing standards for each individual CCI test. This results in (b) (4)

(b) (4). It was determined that the (b) (4) for the purpose of (b) (4) analysis is not value added because the (b) (4) has proven sufficient. Additionally, the firm noted that (b) (4) was observed to be more sensitive than (b) (4) analytical testing of challenge containers as indicated in the point of failure study, VL164002.

Reviewer Comments: The firm did not adequately address this IR item. Specifically, the firm did not provide sufficient details in regards to how operators are qualified. The firm indicated that operators are qualified according to course 04-01-C001, but did not provide details for what is involved in qualifying an operator for (b) (4). Given that the firm indicates that the (b) (4) process is more sensitive than (b) (4) analysis, thus relies on this analysis with product filled vials, the firm should provide more details on the qualification of operators who perform this process. Additionally, the firm should include details for how (b) (4) is performed at (b) (4), as this IR refers to performing visual inspection for CCIT at (b) (4). The following CR item, extended to address CCIT deficiencies in relation to (b) (4), ((b) (4) CR items repeated below), should be included in the CR letter.

CR letter Item

In regards to CCIT method performed at (b) (4), please provide details, SOPs, etc. for the following:

- **Qualification of the operators that perform (b) (4), including description of course 04-01-C001, indicated to be used for qualification of operators**
3. **Concerning the 100% (b) (4) of lyophilized vials; where the nature of the contents permits only limited capability for particulate detection, we recommend that the 100% inspection of a batch be supplemented with the inspection of reconstituted (e.g., dried) contents of a sample of containers from the batch. Please note that the destructive nature of supplemental AQL testing requires the use of a smaller sample size than those traditionally used for non-destructive AQL sample plans. Doubling sampling plans that are described in (b) (4) allow for secondary samples/assessments.**

Firm Response: The firm indicated that Portola has implemented the inspection of reconstituted vials of drug product. This Quality Control test is performed at (b) (4) and conforms to (b) (4). Consistent with (b) (4), a reduced sample size of (b) (4) vials is used to complete this test.

Reviewer Comments: The firm's response is adequate and no further action needed.

4. **In your response to IR item 1 in Amendment 50, you indicated that the (b) (4) experimental runs were used to establish the PARs for (b) (4)**

(b) (4) and (b) (4) were performed in a lab scale (b) (4) freeze dryer, which was demonstrated to be similar to the (b) (4) in regards to the (b) (4) rates, thus these experimental runs were not performed on a commercial scale. Please indicate how these PAR ranges for (b) (4) and (b) (4) will be applied in commercial production. Specifically, if the lyophilization parameters were to deviate from the target set points, but remain within the PAR (or NOR), what actions would be taken?

Firm Response: The firm indicated that the lyophilization process parameters, (b) (4) and (b) (4) will be monitored during the commercial production. No action will be taken if the parameters remain within the current PARs as there were no critical process parameters identified for the DP process. The PARs/NORs will be re-evaluated once manufacturing of (b) (4) DP manufacturing lots is completed.

Reviewer Comments: The firm's response is not adequate; as the firm did not acknowledge that the PARs and NORs are not validated on a commercial scale given that no action will be taken if there are deviations from the target set point. Thus, the firm seems to accept these ranges as validated at commercial scale, whereas the process validation data provided does not support these ranges. This inadequacy will be addressed as a CR item to be included in the CR letter.

CR letter Item: The Proven Acceptable Ranges and Normal Operating Ranges for (b) (4) and (b) (4) indicated for the lyophilization cycle parameters used for the drug product 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 July 1, 2016) that explored these ranges and this data was used to establish the ranges; however, there was no justification for how the lab scale studies support the lyophilization parameter ranges on a commercial scale. Please provide a detailed plan to support these ranges on a commercial scale.

5. In reference to the revised CP provided in Amendment 43, please note and respond to the following:

- a. Please indicate if (b) (4) will be used in lyophilizer (b) (4). If (b) (4) will be used, please indicate why (b) (4) run using (b) (4) was not included as part of the validation strategy given that (b) (4) runs using (b) (4) had been performed in lyophilizer (b) (4) previously.

Firm Response: The firm indicated the plan proposed in the revised CP is consistent with the (b) (4) strategy the FDA advised in the May 31st Information Request and Advice. The firm noted that the "(b) (4)" is represented by the (b) (4) DP runs from (b) (4) provided in the BLA, and (b) (4) are represented by additional (b) (4) DP (b) (4) validation lots. Additionally, the firm indicated that their strategy proposed in the CP includes an additional run (b) (4), giving a (b) (4) strategy, that provides (b) (4) additional lots for process validation from each of the (b) (4) lyophilizers used on fill line (b) (4) (lyo (b) (4)) including one MAX and one MIN condition for number of (b) (4) used. The firm re-iterated that the data was provided in Amendment 43 that demonstrates that the (b) (4)

lyophilizers are equivalent in performance. The firm highlighted that the studies demonstrating equivalency were performed in all (b) (4) lyophilizers at aggressive operating conditions, maximum load with all (b) (4) and at maximum flow rate achievable for all (b) (4) lyophilizers. The study incorporated model (b) (4) formulation processed under aggressive conditions and samples were taken from (b) (4) for the representative (b) (4) in all (b) (4) lyophilizers. The indicated that the data demonstrated that the (b) (4) within each lyophilizer are also equivalent based on evaluation and moisture content. The firm further indicated that the conditions used for andexanet alfa are conservative, resulting in a slower drying process and does not use an entirely full dryer; up to (b) (4) are used of the total (b) (4) on lyophilizer (b) (4) and of the total (b) (4) on lyophilizers (b) (4). The firm concluded that given the known operational capabilities of all (b) (4) lyophilizers, the lyophilization equivalency data, performing a (b) (4) run in all (b) (4) lyophilizers, including (b) (4) is not required while incorporating a bracketing validation approach. Also included in firm's response, was the rationale that limiting the use of a lyophilizer to specific (b) (4) number is not need, since the (b) (4) within the lyophilizer are also equivalent for process parameter performance and product quality as per lyophilization equivalency data.

Reviewer Comments: The firm's response is significantly inadequate in regards three points. Specifically:

- 1) Additionally, the firm's response in regards to the strategy is misrepresented, in that the (b) (4) strategy that was initially advised included (b) (4) runs using (b) (4) in lyophilizer (b) (4) (or other) with (b) (4) additional run using (b) (4) in each of the other (b) (4) lyophilizers (demonstrated to be equivalent). If the firm's plan was to use (b) (4) in all (b) (4) lyophilizers, than the validation strategy should reflect (b) (4) runs using (b) (4) in (b) (4) lyophilizer, with (b) (4) run in each of the other lyophilizers using (b) (4). The data indicated by the firm to represent the "(b) (4)" in their validation strategy refers to data from the BLA includes (b) (4) runs using (b) (4) in lyophilizer (b) (4), thus this validation data does not truly represent the process change indicated in the CP in regards to lyophilization, where (b) (4) in the lyophilizer(s) will be used to accommodate the change in scale of the (b) (4) produced from (b) (4).*
- 2) In the firm's response the following was noted "up to (b) (4) are used of the total (b) (4) on lyophilizer (b) (4) and of the total (b) (4) on lyophilizers (b) (4)". This statement indicates that the lyophilizers are not actually equivalent as initially claimed, given that lyophilizers (b) (4) have (b) (4) the number of (b) (4) as compared to lyophilizer (b) (4). Additionally, given this, more information is also needed in regards to the dimensions of the (b) (4) in comparing the (b) (4) differently sized lyophilizers. Based on this difference, the firm's validation strategy is significantly inadequate.*
- 3) Additionally, in the firm's response, it was re-iterated multiple times claiming that the lyophilizers are equivalent in regards to parameter performance, product quality etc., but all the data referred to was not available for review given that this change is under a CP, in which the equivalency data would normally be submitted in the follow up CBE-30, thus it is difficult to determine if the validation strategy proposed is adequate without reviewing the data and*

assessing if equivalency has been demonstrated. Considering that there is a difference in the size of lyophilizer (b) (4) and lyophilizers (b) (4), it is not clear if the lyophilizers are equivalent as the firm initially claimed.

These issues will be addressed by the following CR item to be included in the CR letter:

CR Letter Item: In your response to IR item 5 (a&b) provided in Amendment 61, specifically on page 4, paragraph 3 of your response, the following was noted “up to (b) (4) are used of the total (b) (4) on lyophilizer (b) (4) and a total of the total of (b) (4) on lyophilizers (b) (4)”. Given the difference in the number of (b) (4) between the lyophilizers, these lyophilizers do not appear to be equivalent as initially claimed. Based on this premise, we do not agree with the validation strategy proposed in the revised CP, thus your validation strategy must be significantly revised. Please comment.

- b. The specific shelf numbers that will be used in the validation were not indicated in the CP. Please note that the specific (b) (4) used in the validation need to be specifically defined in the CP.

Firm Response: The firm responded to both 5 a & b as combined response and is summarized above in 5(a) above. In the response provided, the firm did not indicate the specific (b) (4) in the lyophilizers that will be included in the validation.

Reviewer Comments: The firm indicated in their response, the limiting lyophilizer use to a specific (b) (4) is not needed since the (b) (4) within the lyophilizer are also equivalent for process parameter performance and product quality as per lyophilization equivalency data. This is not an adequate response and is indirectly addressed in the CR item above, which states that the lyophilizers are not equivalent and that the validation strategy must be revised.

- c. In reference to section 11.0 Reporting, in the CP, you indicated that the assessment of the DS and DP lots will be documented in a Comparability Report and this report will be provided in the follow-up CBE-30 supplement; however, there were no details or specifics in regards to the type of data that would be included in this report. Please provide a detailed accounting of what data will be provided in the Comparability Report to support the DS and DP manufacturing changes. Specifically, the type of data should include but is not limited to the following:

- i. Results of extending sampling testing (including number of samples and locations of sampling ((b) (4)))
- ii. Results of OQ/PQ for all new equipment and new areas associated with drug substance manufacturing changes
- iii. Results of OQ/PQ and other testing to demonstrate equivalency of lyophilizers (please note that although some of this data was provided in the revised CP, all data should also be included in the Comparability Report provided in the follow up CBE-30 supplement)
- iv. All data relating to lyophilization cycle monitoring

- v. Results of in-process parameters and product quality attributes (characterization and release testing results) associated with process validation
- vi. Results of the most recent media fills using the lyophilizers (b) (4)
- vii. Results of the most recent cleaning and sterilization validation of the lyophilizers

Please note the above items are not an all-encompassing list of data that should be included. The items noted above mainly refer to data needed to support the Drug Product manufacturing changes, thus, additional data to support the drug substance manufacturing changes will need to be considered.

Firm Response: The firm provided a comprehensive listing of the data that will be provided including:

- (b) (4) PPQ Validation Dataset summarized in following table:

(b) (4)

- OQ/PQ results for all new equipment, summarized in the following table:

(b) (4)

The firm indicated that the (b) (4) new (b) (4), listed in the following table, considered major pieces of equipment will not have qualification data summarized in the updated BLA since only an IQ was performed for them. These (b) (4) are controlled by previously existing fully qualified Process Monitoring Station Skids ((b) (4)) also used for (b) (4) manufacturing.

(b) (4)

- Reports from lyo-equivalency can be provided
- Results of in-process parameters and product quality attributes (characterization and release testing) associated with process validation will be included in the report
- The following data will be provided in the report in regards to the drug substance: Release testing (comparison of results from lot release testing from each process), Supplemental characterization, Process Control Analysis (Critical Process Parameters, In-Process Specifications, In-Process Limits and Key Operating Parameters), and Side-by-Side Stability testing
- Media fill PPQ including (b) (4) media fill runs will be provided

- Clean in place and Sterilization in Place PQs for additional lyophilizers will be provided

(b) (4)

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

- d. In reference to Section 11.0 Reporting of the CP, the following was stated “Any changes to the studies or acceptance criteria described in the CP will be listed and justified”. Please note that this CP is an agreed upon plan, which includes the procedures and acceptance criteria, thus any changes to the CP in relation to procedures or the acceptance criteria applied may result in the follow up supplement being upgraded to a PAS supplement.

Firm Response: The firm did not give a response or comment to this IR item. This item did not request a response, as was only to inform the firm that changes to the CP in regards to the procedures and acceptance criteria will result in an upgrade of the follow up submission to the CP. The firm chose not to respond.

Reviewer Comments: Given that this CP is not approvable as stated in previous sections of this review memo, this IR item is no longer applicable as the all paths for the CP (withdrawn or not) will require an upgrade to a PAS for the manufacturing changes to the drug substance and drug product after BLA approval. This will be clearly stated and included as a CR letter item.

6. Please provide non-conformance report 230315 (Local NCR) /994240 (Corporate PCR) in regards to an (b) (4) OOS result for In-process (b) (4) hold sample during manufacture of batch (b) (4). Additionally, please include more details as to why the (b) (4) method used was deemed inappropriate and where in the process the (b) (4) hold sample is taken for testing.

Firm Response: The firm indicated that the (b) (4) method SOP 08-02-050, “Inhibition/Enhancement (b) (4) Testing Using the (b) (4)”, which was used, is not the most appropriate method to test the (b) (4) sample as it was difficult to (b) (4)

. Thus, a decision was made to use a (b) (4) method, SOP-08-02-035, “(b) (4)”, which has been successfully used for finished product, end of formulation, (b) (4) hold and (b) (4) hold samples with no system suitability issues and this method has been validated. The firm provided the Non-conformance report #9942240 (as requested), and the SOP and validation report for the (b) (4) method, all of which were reviewed and are summarized as follows:

- **Event PR#99240, “(b) (4) OOS for (b) (4) hour hold sample”:**
This report (initiated 11/12/15) summarizes OOS result for (b) (4) testing of the (b) (4) in-process sample (occurrence date 11/9/15). The result was indicated as (b) (4) which did not meet the specification of (b) (4). Details of

the investigation included an interview of the analyst, in which a few unusual circumstances were observed during analysis that included repeated issues with passing system suitability in order to generate results and this issue was also noted during method development of the (b) (4). The analyst described that the sample was somewhat (b) (4) and the (b) (4) was having issues (b) (4)

(b) (4). The investigation also included a method review that further identified the issues with the (b) (4) method and that the multiple suitability failures with the (b) (4) method should have prompted to change to a (b) (4) method that is used for the final finished product. Thus, from the investigation, the (b) (4) method was found to be inappropriate and a change was made to use the (b) (4) method.

- **SOP 08-02-035, “(b) (4) Determination by (b) (4)” and BER15-08-002, “(b) (4) Method Development and Validation Report for (b) (4): PRT064445 10mg/mL”:** This report includes the results of characterization and development study (to determine most acceptable (b) (4) ranges to be used, and demonstrate the ruggedness of the (b) (4) range) in addition to a validation of the (b) (4) method testing (b) (4) GMP batches. Results of the validation were indicated as passing.

In completing the response to this IR item, the firm indicated that the (b) (4) hold sample, is the (b) (4) sample taken in the formulation area and referenced this step (as 3.39) in the executed batch record although batch record was not provided. According to the process steps indicated in the PPQ report for PPQ lots (b) (4), the (b) (4) sample represents the time from end of (b) (4), plus (b) (4) at (b) (4) conditions, thus the sample is taken (b) (4) after (b) (4), which is before sterile filtration.

Reviewer Comments: The firm has adequately addressed this IR as the firm's determination of the root cause indicating the assay was not appropriate based on the nature of the testing system and viscosity of the sample seems reasonable based on the investigation conducted, thus no further action needed.

XI. APPENDIX

Table 1: Facilities and Inspections

Manufacturing/ Testing activities	Inspection/ Waiver Required?	Compliance Check Required for Approval?	RMS-BLA Entry Required?	Comments
(b) (4)				
(b) (4) Manufacturing	Yes	Yes	Yes	Although this firm was recently inspected in (b) (4) (GMP inspection by Team Bio) and classified NAI, the firm has new manufacturing space for the use of (b) (4) included as a CP provided in BLA. <u>Inspection needed</u>
(b) (4) Release Testing	No	Yes	Yes	
Drug Product Release Testing	Yes	Yes	Yes	<u>Inspection needed</u>
(b) (4)				
Manufacturing/ Testing activities	Inspection/ Waiver Required?	Compliance Check Required for Approval?	RMS-BLA Entry Required?	Comments
(b) (4) Release Testing	No	No	Yes	Inspection of drug substance testing sites is not required
(b) (4) release testing	No	No	Yes	Inspection of drug substance testing sites is not required
(b) (4)				

(b) (4)				
Manufacturing/ Testing activities	Inspection/ Waiver Required?	Compliance Check Required for Approval?	RMS-BLA Entry Required?	Comments
Drug Product Manufacturer	Yes	Yes	Yes	Inspection can be <u>waived</u> since this facility has good compliance history. The last two inspections: (b) (4), PAI approval inspection performed by Larry Austin, DET-DO for NDA for (b) (4) classified NAI (b) (4), Routine Surveillance inspection) performed by Robert Barbosa, DET-DO classified as NAI
Drug Product Release Testing (includes Sterility and Endotoxin)	Yes	Yes	Yes	See comments above
(b) (4)				
Manufacturing/ Testing activities	Inspection/ Waiver Required ?	Compliance Check Required for Approval?	RMS-BLA Entry Required?	Comments
Drug Product Release testing (Includes testing of particulate matter)	Yes	Yes	Yes	Inspection can be <u>waived</u> since this facility has good compliance history. The last two inspections: (b) (4), Level I QSIT medical device inspection in accordance with C.P. 7382.845 by Daniel Lahar, classified NAI (b) (4), GLP inspection as per C.P. 7348-808 by Marc Jackson, DET-DO, classified NAI
Drug Product	Yes	Yes	Yes	Inspection can be

Stability Testing (includes CCIT)				<u>waived</u> . As noted previous, last two inspection NAI
(b) (4) Release Testing for Sterility	No	No	Yes	
(b) (4)				
Manufacturing/ Testing activities	Inspection/ Waiver Required?	Compliance Check Required for Approval?	RMS-BLA Entry Required?	Comments
Labeling (includes primary labeling) and secondary packaging	Yes	No	Yes	Waiver
Portola Pharmaceuticals, Inc. 270 East Grand Avenue South San Francisco, CA 94080 FEI: 3006788147				
Manufacturing/ Testing activities	Inspection/ Waiver Required?	Compliance Check Required for Approval?	RMS-BLA Entry Required?	Comments
Drug substance QA Final Batch Disposition	No?	No	Yes	Not sure if this activity needs to be documented in the RMS-BLA
Final Drug Product Release	No?	No	Yes	Need more details as to what this final drug product release involves. Portola is a virtual company and thus this activity may solely be an administrative function and not actual testing, thus would not require an inspection.
(b) (4)				
Manufacturing/ Testing	Inspection/ Waiver	Compliance Check	RMS-BLA Entry	Comments

activities	Required?	Required for Approval?	Required?	
(b) (4) release testing	No	No	Yes	The activity performed by this facility is not required to have an inspection. Not sure if this activity needs to be documented in the RMS-BLA
(b) (4)				
Manufacturing/ Testing activities	Inspection/ Waiver Required?	Compliance Check Required for Approval?	RMS-BLA Entry Required?	Comments
(b) (4) release testing:	No	No	Yes	The activity performed by this facility is not required to have an inspection.
(b) (4)				
Manufacturing/ Testing activities	Inspection/ Waiver Required?	Compliance Check Required for Approval?	RMS-BLA Entry Required?	Comments
(b) (4) production	No	No	Yes	The activity performed by this facility is not required to have an inspection.
(b) (4) storage	No	No	Yes	Same as above
(b) (4) release testing	No	No	Yes	Same as above

Figure 1: Andexanet Alfa DP, manufacturing process flow chart for (b) (4) scale up (originally as Figure 3.1 in CP NC-15-0681-P0001)

