From: Maruna, Thomas
Sent: Tuesday, May 31, 2016 2:25 PM
To: 'Janice Castillo'
Cc: Ovanesov, Mikhail V.; Harman, Christine
Subject: 31-May-2016 Information Request and Advice - BLA 125586.0 - Response Required by 21-June-2016

Importance: High

Portola Pharmaceuticals Inc.
Attention: Ms. Janice Castillo
May 31, 2016
Sent by email

FDA Information Request and Advise to Portola regarding their 11 May 2016 request to
discuss the revised Comparability Protocol "Andexanet Alfa (PRT064445) (b) (4) (b) (4) to (b) (4) Resulting Drug Product

Dear Ms. Castillo:

We are reviewing your December 17, 2015 biologics license application (BLA) for the
following:

STN	Name of Biological Products
125586/0	Coagulation Factor Xa (Recombinant), Inactivated

We have determined that the following information is necessary to continue our review:

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) 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:

- o full list of all DS lots initiated in (b) (4), including engineering lots, and their dispositions
- o description of all deviations, including open deviations
- o 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:

- potency of the product to be described in absolute values, instead of percentages, referencing some publicly available standards;
- identity by a (b) (4) method;
- (b) (4) and (b) (4) content; and
- identity and quantity of excipients - sucrose, mannitol and Polysorbate 80.

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:

a. 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).

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 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.

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:

- 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

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

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.

The review of this submission is on-going and issues may be added, expanded upon, or modified
as we continue to review this submission.

You are required to submit your responses as an amendment to this file by close-of-business,
Friday, June 21, 2016.

The action due date for these files is August 17, 2016.

If you have any questions, please contact me.

Respectfully,

Thomas J. Maruna, MSc, MLS(ASCP), CPH
Lieutenant, U.S. Public Health Service
Senior Regulatory Management Officer
FDA/CBER/OBRR/IO
thomas.maruna@fda.hhs.gov
Office: (240) 402-8454