

From: Do, Yu
To: ["jcastillo@portola.com"](mailto:jcastillo@portola.com)
Cc: [Maruna, Thomas](#)
Subject: Information Request: Response Due by Tuesday, July 12, 2016 - Original BLA, BL 125586/0, Coagulation Factor Xa (Recombinant), Inactivated
Date: Friday, July 08, 2016 10:01:00 PM
Importance: High

Portola Pharmaceuticals, Inc.
Attention: Ms. Janice Castillo
July 8, 2016

Dear Ms. Castillo:

We are reviewing your December 18, 2015, biologics license application (BLA) 125586/0 for Coagulation Factor Xa (Recombinant), Inactivated. We determined that the following information is necessary to continue our review:

1. In your response to Observation Item 1b in Form FDA 483, you stated that the out-of-specification (OOS) results for the (b) (4) of andexanet alfa in batch (b) (4) were caused by acceptance criterion that did not fully represent assay and process variability. You also stated that the (b) (4) are expected to be fully functional, and that your proposal to widen the specification is based on process capability and assay precision. However, your response did not address the cause(s) for the increase in the levels of these (b) (4) observed (i) at several unit operations, (ii) after the introduction of (b) (4) and (iii) over time in stability studies. Therefore, please provide additional explanations on the following items:
 - a. Please explain how the available clinical data support the increase in the acceptance criterion of the (b) (4) from (b) (4). Please compare the ranges of (b) (4) levels in the (b) (4) batches used in the completed Phase 1-3 clinical trials to those in the (b) (4) batches used in the ongoing clinical trials.
 - b. With reference to your Final Investigation Report for deviation DEV-1632, please describe your investigation on the sources and levels of (b) (4) responsible for the formation of the (b) (4) throughout the manufacturing process and during storage of the (b) (4) and lyophilized Final Drug Product (FDP). In addition, please describe your investigation on the identity of the (b) (4) responsible for the (b) (4) of the protein, and the corrective and preventive actions implemented to remove the (b) (4).
 - c. Please provide a summary of risk assessment of the (b) (4), which should include, but not be limited to, the impact of the (b) (4) on the purity, quality, potency, and stability as they are related to the safety and effectiveness of the product. In addition, please list the levels of (b) (4) at release in all your manufactured (b) (4) FDP lots and those enrolled in the ongoing stability studies at all available time points, including any OOS stability results (above 17).

- d. Please summarize the data you have collected to date to evaluate the impact of the (b) (4) on (i) the reversal of anti-FXa activity of andexanet alfa, (ii) its interactions with TFPI, and (iii) its circulatory half-life. Please explain the data you have collected on the purified (b) (4) presented in Figure 3.2.S.3.1-13 of the BLA.
- e. Please justify the specification limit of (b) (4) based on the data from the available (b) (4) FDP batches. Please note that the levels of (b) (4) in all (b) (4) batches, except batch (b) (4), were within the (b) (4) specification limit at release, and that method variability was ruled out as a source of OOS result for batch (b) (4). Your investigations suggest that the increase in the (b) (4) in batch (b) (4) was caused by the (b) (4) used in the (b) (4) step, which means that batch (b) (4) is outside the proposed commercial process capability. Also, please note that method precision should be established and controlled by analytical tools such as repeat testing and system suitability controls.
- f. Regarding your lot release process, please specify the date on which the proposed commercial (b) (4) FDP release specifications (for all release assays) and associated stability specifications were introduced. If you are using release specifications which differ from those described in the BLA, please explain the difference.

The review of this submission is ongoing and issues may be added, expanded upon, or modified as we continue to review this submission. Please submit your response as an amendment to this file by close of business on July 12, 2016, referencing the date of this request. If you anticipate you will not be able to respond by this date, please contact the Agency immediately so a new response date can be identified.

If we determine that your response to this information request constitutes a major amendment, we will notify you in writing.

The action due date for this file is August 17, 2016.

Please acknowledge receipt of this request and contact Lieutenant Thomas Maruna at (240) 402-8454 or Thomas.Maruna@fda.hhs.gov if you have any questions.

Sincerely,

Yu Do, M.S.
Regulatory Project Manager
FDA/OMPT/CBER/OBRR/RPMS
(240) 402-8343
yu.do@fda.hhs.gov

"THIS MESSAGE IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on

the content of this communication is not authorized. If you have received this document in error, please immediately notify the sender by e-mail or phone."