

From: Thompson, Edward
Sent: Wednesday, June 22, 2016 2:14 PM
To: 'Janice Castillo'
Cc: Maruna, Thomas
Subject: Information Request - BLA 125586.0

Portola Pharmaceuticals Inc.
Attention: Ms. Janice Castillo
June 22, 2016
Sent by email

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:

21 June 2016 CMC Information Request Regarding Release Specifications:

1. With reference to your 20 April 2016 responses to our Information Request dated 06 April 2016,
 - a. Your proposal to develop specifications and validate new (b) (4) method after October 2016 is not acceptable because this will preclude the FDA from reviewing the information before the goal date. We recommend you to continue to develop your current (b) (4) method which is already partially validated. Please introduce release specifications for identity by (b) (4) using your current (b) (4) method; and submit the specifications and justifications to the BLA by 01 August 2016. Please also commit to completing the validation studies of this method by 31 October 2016; and re-evaluate the release specifications after you have obtained data from (b) (4) batches of (b) (4) drug product; or (b) (4) post licensure, whichever comes first.
 - b. We disagree with your statement that “(b) (4) content is also not thought to affect the PK/PD of andexanet”. Please use the available data obtained with the assays of your choice to introduce release specifications for the (b) (4) and (b) (4) content by 01 August 2016. Please also commit to completing the validation studies of these methods by 31 October 2016 and re-evaluate the release specifications after you have obtained data from (b) (4) batches of (b) (4) drug product; or (b) (4) post licensure, whichever comes first.

c. We disagree with your proposal to monitor the concentrations of excipients with the in-process control and surrogate assays. Andexanet alfa is administered at high doses, which poses concerns of potential toxicity in patients who are sensitive to sucrose and mannitol. Please introduce specifications for sucrose and mannitol by 01 August 2016. Please also commit to completing the validation studies of these methods by 31 October 2016; and re-evaluate the release specifications after you have obtained data from 20 batches of drug product; or one year post licensure, whichever comes first.

d. We acknowledge your commitment to “develop and validate a potency unit based on the reference units of fXa activity” and “will perform feasibility studies by modifications of the assays currently used for direct and indirect fXa inhibitors”. However, it is imperative to introduce a product-specific unit prior to product licensure because as we have noted in the Information Request dated 06 April 2016, the use of percentage unit is not suitable for the evaluation of the stability of the product because the stability of the reference standard is not established. Therefore, we disagree with your proposal to delay characterization of the reference standards. By 01 August 2016, please assign a direct potency and an indirect potency of your primary product-specific standard. It can be arbitrarily assigned as 1 direct unit/mL and 1 indirect unit/mL, respectively; and this unitage can then be used to set your release specifications accordingly. In addition, please apply this unitage to evaluate the potencies of all of your reference standards - primary, secondary or working - in direct and indirect units in side-by-side studies by 31 October 2016.

2. With reference to your justification for specification for endotoxins in the Drug Product ((b) (4)) which is derived from a maximum dose of (b) (4) for a (b) (4) individual, please note that this specification limit is very close to the compendial infusion limit for endotoxins. Since you are considering the use of higher doses in the future, please revise this specification based on the manufacturing capability.

3. Please include endotoxin values in the Certificate of Analysis for Drug Product batches (b) (4) (#(b) (4)) and (b) (4) (#(b) (4)).

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

Please submit your responses as an amendment to this file by close-of-business, July 1, 2016.

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

If you have any questions, please contact Thomas Maruna at (240) 402-8454.

Sincerely,

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