

From: Maruna, Thomas
Sent: Wednesday, February 17, 2016 1:38 PM
To: 'Janice Castillo'
Cc: Ovanesov, Mikhail V.
Subject: Information Request - BLA 125586.0 - Please Respond by March 3, 2016

Importance: High

Portola Pharmaceuticals Inc.
Attention: Ms. Janice Castillo
February 17, 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 determined that the following information is necessary to continue our review:

1. With reference to **Module 3: Quality**, please provide the following:

- a. An explanation of the batch numbering system, including information regarding any (b) (4) or intermediates and batch size or scale (**Section 3.2.S.2.2**);
- b. The container closure system(s) used for storage of the drug substance (DS) (details in **Section 3.2.S.6.**); and storage and shipping conditions for the DS (**Section 3.2.S.2.2**);
- c. In-process control testing for (b) (4) (**Section 3.2.S.4.2**);
- d. Stability protocol and data, including those for (b) (4) burden, to support the stability and shipping conditions of the DS (**Section 3.2.S.7.3**);
- e. Description and status update on the validation studies to support the in-process hold-times in the manufacture of the Drug Product (DP) (**Section 3.2.P.3.5**);
- f. Standard Operating Procedures (SOPs) in **Sections 3.2.S.4** and **3.2.P.5** for all the analytical methods used for the release of the DS and DP, respectively;
- g. Update on the *Adventitious Agents Safety Evaluation* report (**Section 3.2.A.2**) with information on measures to assure sterility, which should include, but not be limited to, the description of sterility testing and measures to prevent and control potential contamination;
- h. Analysis and risk assessment of the extractables and leachables in **Sections 3.2.S.3.2** and **3.2.P.5.5 Impurities** for materials used in the manufacture of the (b) (4) DP, respectively;
- i. Document AD-2015-001-007 Version 3 referenced in **Section 3.2.S.4.5**. Please also correct any links to this document.

2. With reference to Clinical Study Protocols, e.g., protocol 15-507 dated 09 June 2015, in which you stated that “*blood specimens will continue to be evaluated for antibodies against andexanet and against fX and fXa. Samples that are positive for antibodies will be further assayed for the ability to neutralize the activity of andexanet, fX or fXa*”, please
 - a. Develop and validate assays to measure the activity of the antibodies that inhibit the activities of endogenous human Factors X and Xa. For example, the anti-Factor X inhibitor assay should be based on the (b) (4) assay for Factor X activity, and the results should be presented in (b) (4) of anti-Factor X activity;
 - b. Assess how the presence of the anti-Factor Xa inhibitory antibodies may interfere with the assays used to evaluate the pharmacodynamics, pharmacokinetics, and immunogenicity in the clinical studies;
 - c. Test the retained clinical samples for anti-Factor X and anti-Factor Xa inhibitory antibodies;
 - d. Provide a timeline for the completion of the activities described in items 2.a., 2.b. and 2.c.
3. With reference to **Section 5.3.1.4.**, please provide the following:
 - a. A table summarizing all the analytical methods used in the assessment of pharmacokinetics, pharmacodynamics and immunogenicity in the clinical studies. For each of the methods and its respective method revisions, please include the following information: the principle and intended use of the method, the protocol number and title of the clinical studies in which the method was used, and the date of introduction of the method;
 - b. Information to support the comparability of different versions of a method that was changed between or during the clinical studies. The methods should include, but not be limited to, the thrombin generation assay.

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 March 3, 2016 referencing the date of this request.

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

If you have any questions, please contact me.

Very Respectfully,

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