DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

Our STN: BL 125586/0

BLA FILING NOTIFICATION

Portola Pharmaceuticals Inc.
Attention: Ms. Janice Castillo
270 East Grand Avenue
South San Francisco, CA 94080

Dear Ms. Castillo:

This letter is in regard to your biologics license application (BLA) submitted under section 351 of the Public Health Service Act.

We have completed an initial review of your application dated December 17, 2015, for Coagulation Factor Xa (Recombinant), Inactivated to determine its acceptability for filing. Under 21 CFR 601.2(a), we have filed your application today. The review classification for this application is Priority. Therefore, the review goal date is August 17, 2016. This acknowledgment of filing does not mean that we have issued a license nor does it represent any evaluation of the adequacy of the data submitted.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which include the timeframes for FDA internal milestone meetings. We plan to hold our internal mid-cycle review meeting on March 24, 2016. Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process.

We will contact you regarding your proposed labeling no later than July 18, 2016. If post marketing study commitments (506B) are required, we will contact you no later than July 18, 2016.

We are currently planning to hold a Blood Products Advisory Committee meeting to discuss this application.

While conducting our filing review, we identified the following potential review issues:

1. Based on our preliminary review, the ongoing phase 3-4 ANNEXA-4 trial does not appear to be "adequate and well-controlled" within the meaning of our Subpart E - Accelerated Approval regulations and guidance for the design and conduct of the postmarketing confirmatory trial in subjects with acute major bleeding. Failure to resolve

outstanding design and control issues may adversely impact the regulatory decision taken on this application. Please refer to the Guidance for Industry Expedited Programs for Serious Conditions – Drugs and Biologics, Section VII. D. 2 at: www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm358301.pdf

2. There does not appear to be sufficient evidence to support an indication of reversal of anticoagulation for patients treated with the indirect FXa inhibitors.

    a. Only a very small number of healthy volunteer subjects in a single phase 2 trial have been evaluated for reversal of a single indirect FXa inhibitor, enoxaparin, using the dosage regimen that is recommended in the draft package insert.

    b. In addition, based on the dual mechanisms of action of enoxaparin the proposed surrogate endpoint of FXa inhibitory activity is unlikely to reasonably predict clinical benefit for reversal of enoxaparin related bleeding.

    Further review for the BLA for this indication will require the submission of additional evidence.

3. You are seeking an indication for use for reversal of anticoagulation in patients requiring reversal for (b) (4). To support this indication, please provide adequate and well-controlled safety and efficacy data from subjects requiring reversal of anticoagulation for (b) (4).

4. Please provide the case report form for every subject, including those subjects who prematurely discontinued Coagulation Factor Xa (Recombinant), Inactivated, as agreed to during the October 8, 2015 Pre-BLA meeting between FDA and Portola.

5. Please provide a discussion and analysis of submitted interim safety and efficacy data from the 17 subjects with acute major bleeding from the ongoing phase 3-4 ANNEXA-4 study. When submitting additional data from this study with your 3 month safety update, please also provide a discussion and analysis of cumulative interim safety and efficacy data.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our complete review. Issues may be added, deleted, expanded upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application. Following a review of the application, we shall advise you in writing of any action we have taken and request additional information if needed.

If you have any questions, please contact the Regulatory Project Manager, LT Thomas J. Maruna, USPHS, MSc, MLS (ASCP), CPH at (240) 402-8454 or thomas.maruna@fda.hhs.gov.

Sincerely,

Basil Golding, MD
Director
Division of Hematology Research and Review
Office of Blood Research and Review
Center for Biologics Evaluation and Research