

From: Maruna, Thomas
Sent: Monday, March 14, 2016 9:44 AM
To: 'Janice Castillo'
Subject: Information Request - BLA 125586.0 - Please Respond by the Dates Outlined Below

Importance: High

Portola Pharmaceuticals Inc.
Attention: Ms. Janice Castillo
March 14, 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:

CLINICAL – Please Respond by March 15, 2016

1. Please provide subject narratives and case report forms (CRFs) for each subject that experienced an infusion-related reaction. The narrative should include a summary of the subject's characteristics (age, sex, race, co-morbidities), the clinical presentation (associated adverse events, changes in vitals, timing of the reaction in relation to the infusion of the study product), any interventions administered, and an assessment of causality and status of resolution of the event.
2. For studies 14-503 and 14-504, please provide, in tabular format, a summary of ECG measurement (HR, PR duration, QRS duration, QT duration, QTcF, and RR duration) and changes from Baseline for all subjects with new post-baseline abnormal PR or QT values. Please also provide all ECG tracings for each subject.

In-Support Testing – Please Respond by March 28, 2016

3. CBER finds the endotoxin qualification report, VAL-60003-04, TME-0003: Determination Using the (b) (4) Method, unacceptable for Drug Product (DP) since the qualification was performed in (b) (4) but release testing is performed at (b) (4). Method qualification should be performed in the same facility where the testing is performed. CBER request an endotoxin qualification report showing the DP is suitable for the intended method performed at (b) (4)

4. CBER finds recovery of (b) (4) in the presence of fXa (b) (4) using (b) (4) at (b) (4) as submitted in bioburden qualification report, VAL-60002-05, TME-0002: Membrane Filtration Test for Bioburden in Product Samples, unacceptable. According to (b) (4) the recovery of (b) (4) ((b) (4) in the presence of product must not differ by a factor greater than (b) (4) from the value of its respective positive control. The recovery of (b) (4) was found to be (b) (4) as the positive control (b) (4) was (b) (4) and the product inoculated with the (b) (4) was (b) (4). This was reported as a deviation in the qualification report and upon investigation found acceptable because document QC-0247, Bioburden Qualification, does not have an upper limit on percent recovery. However, CBER finds this unacceptable and requests the requalification of (b) (4) in the presence of fXa (b) (4) using (b) (4) at 30-(b) (4) for CBER's continued review.
5. Please provide endotoxin qualification protocol, VAL-60003-03, TME-0003: Determination Using the (b) (4) Method.
6. Please provide bioburden qualification protocol, VAL-60002-04, TME-0002: Membrane Filtration Test for Bioburden in Product Samples.

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 the dates noted above 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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