

From: Maruna, Thomas
Sent: Thursday, May 12, 2016 6:05 PM
To: 'Janice Castillo'
Cc: Ovanosov, Mikhail V.; Levi, Mark; simleen.kaur@fda.hhs.gov; Harman, Christine
Subject: 12-May-2016 Information Request - BLA 125586.0 - Response Required
by 18-May-2016

Importance: High

Portola Pharmaceuticals Inc.
Attention: Ms. Janice Castillo
May 12, 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 Inactivated	Coagulation Factor Xa (Recombinant), Inactivated

We have determined that the following information is necessary to continue our review:

CMC - Facility

1. Please provide the basis for the acceptance criteria of ? (b) (4) for the reconstitution time of the lyophilized product. In addition, please explain the significant difference in the reconstitution time of the lyophilization mapping samples between Lot (b) (4) with reconstitution times ranging from (b) (4) as compared to Lot (b) (4) with reconstitutions time ranging from 2-3 min. Please provide more details in regards to the developmental reconstitution method used for the Lot (b) (4) lyophilization mapping samples and indicate if the same reconstitution method was used for testing of the Lot (b) (4) lyophilization mapping samples.

2. In reference to the lyophilization mapping samples for lot (b) (4) and lot (b) (4) please indicate how many samples were tested from each of the locations (including front (b) (4)) noted in Tables 3.2.P.3.5-13 and

3.2.P.3.5-14.

3. Please provide the lyophilization cycle graphs, monitoring the (b) (4) (b) (4) during the lyophilization cycle, for the consistency lots (b) (4) (if available).

4. In 3.2.P.3.5 Process Validation and or Evaluation, you indicated that the shipping validation will be performed according to a pre-approved protocol. Please provide the shipping validation protocol and indicate when shipping validation covering the transport of the final product (filled at (b) (4) to Packaging Coordinators for primary labeling will be completed.

5. In regards to the process time limits for the manufacturing operations defined in table 3.2.P.3.5-16, "Process Times for Consistency Lots", please indicate the support for the process limit of (b) (4) at room temperature for process step (b) (4) as the (b) (4) consistency lots provided does not cover this (b) (4) limit.

CMC- Analytical Methods and Validation

6. In your validation of the Purity by (b) (4) (b) (4) (3.2.S.4.2.7) your robustness study is insufficient. Please evaluate robustness of your assay method by varying critical operating parameters of your procedure and submit for review.

7. In your validation of the Protein Concentration by (b) (4) (3.2.S.4.2.6) your robustness study is insufficient. Please evaluate robustness of your assay method by varying critical operating parameters of your procedure and submit for review.

8. In your validation of Moisture by (b) (4) (3.2.P.5.2.3) you did not determine the accuracy of the method. Please evaluate the accuracy of the method and submit for review.

CMC - In-Support Testing

9. (b) (4) provide (b) (4) results for (b) (4) (lot number: 140075) used in the (b) (4) test qualification study as reported in document: VAL-60003-04, TME-

0003 (Determination Using the (b) (4) Method) by (b) (4) (b) (4) .

10. Please provide complete procedure used for sterility test qualification study performed by (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.

You are required to submit your responses as an amendment to this file no-later-than May 26, 2016.

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

If you have any questions, please contact me.

Respectfully,

Thomas J. Maruna, MSc, MLS(ASCP), CPH
Lieutenant, U.S. Public Health Service
Senior Regulatory Management Officer
FDA/CBER/OBRR/IO
thomas.maruna@fda.hhs.gov
Office: (240) 402-8454