

From: Maruna, Thomas
Sent: Monday, July 11, 2016 1:57 PM
To: 'Janice Castillo'
Cc: Ovanesov, Mikhail V.; Harman, Christine
Subject: 11-Jul-2016 Information Request - BLA 125586.0 - Response required by dates identified below

Importance: High

Portola Pharmaceuticals Inc.
Attention: Ms. Janice Castillo
July 11, 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 require the following information to be submitted to continue our review:

CMC Facility (Response due no-later-than July 22, 2016)

1. Please indicate if the (b) (4) used for the intermediate storage and shipping of the BDS from (b) (4) to (b) (4) are re-used. If (b) (4) are re-used, please indicate how these (b) (4) are cleaned and sterilized (if applicable).
2. In reference to report VAL1507010, (b) (4) analysis was not performed in this CCIT study due to the samples containing (b) (4) rather than (b) (4), thus samples were (b) (4) by comparison to the positive control and negative controls. Please indicate the specific procedures that are used for the (b) (4) of the presence of (b) (4) performed at (b) (4) (e.g. (b) (4) used, number of operators used to verify a result etc.) and provide details for how the operators were qualified. Additionally, please indicate why (b) (4) analysis is not performed on product filled vials.
3. Concerning the 100% (b) (4) of lyophilized vials; where the nature of the contents permits only limited capability for particulate detection, we recommend that the 100% inspection of a batch be supplemented with the inspection of reconstituted (e.g., dried) contents of a sample of containers from the batch. Please note that the destructive nature of supplemental AQL testing requires the use of a smaller sample size than those

traditionally used for non-destructive AQL sample plans. Doubling sampling plans that are described in ANSI/ASQ Z1.4 allow for secondary samples/assessments.

4. In your response to IR item 1 in Amendment 50, you indicated that the (b) (4) experimental runs were used to establish the PARs for (b) (4) and (b) (4) were performed in a lab-scale (b) (4) freeze dryer, which was demonstrated to be similar to the (b) (4) in regards to the (b) (4) rates, thus these experimental runs were not performed on a commercial scale. Please indicate how these PAR ranges for (b) (4) and (b) (4) will be applied in commercial production. Specifically, if the lyophilization parameters were to deviate from the target set points, but remain within the PAR (or NOR), what actions would be taken?
5. In reference to the revised CP provided in Amendment 43, please note and respond to the following:
 - a. Please indicate if (b) (4) will be used in lyophilizer (b) (4). If (b) (4) will be used, please indicate why one run using (b) (4) was not included as part of the validation strategy given that (b) (4) runs using (b) (4) had been performed in lyophilizer (b) (4) previously.
 - b. The specific (b) (4) numbers that will be used in the validation were not indicated in the CP. Please note that the specific (b) (4) used in the validation need to be specifically defined in the CP.
 - c. In reference to section 11.0 Reporting, in the CP, you indicated that the assessment of the (b) (4) DP lots will be documented in a Comparability Report and this report will be provided in the follow-up CBE-30 supplement; however, there were no details or specifics in regards to the type of data that would be included in this report. Please provide a detailed accounting of what data will be provided in the Comparability Report to support the (b) (4) DP manufacturing changes. Specifically, the type of data should include but is not limited to the following:
 - i. Results of extending sampling testing (including number of samples and locations of sampling (b) (4))
 - ii. Results of OQ/PQ for all new equipment and new areas associated with (b) (4) manufacturing changes
 - iii. Results of OQ/PQ and other testing to demonstrate equivalency of lyophilizers (please note that although some of this data was provided in the revised CP, all data should also be included in the Comparability Report provided in the follow up CBE-30 supplement)
 - iv. All data relating to lyophilization cycle monitoring
 - v. Results of in-process parameters and product quality attributes (characterization and release testing results) associated with process validation
 - vi. Results of the most recent media fills using the lyophilizers (b) (4)

- vii. Results of the most recent cleaning and sterilization validation of the lyophilizers

Please note the above items are not an all-encompassing list of data that should be included. The items noted above mainly refer to data needed to support the Drug Product manufacturing changes, thus, additional data to support the (b) (4) manufacturing changes will need to be considered.

6. In reference to Section 11.0 Reporting of the CP, the following was stated “Any changes to the studies or acceptance criteria described in the CP will be listed and justified”. Please note that this CP is an agreed upon plan, which includes the procedures and acceptance criteria, thus any changes to the CP in relation to procedures or the acceptance criteria applied may result in the follow up supplement being upgraded to a PAS supplement.

Standards and Quality Control (Response due no-later-than July 12, 2016)

7. We have reviewed the following assays for the (b) (4) drug product submitted under STN 125586/0, and the additional information you provided in 125586/0.53.

Direct and Indirect Potency Assays

You have stated in Amendment 53 that the Direct and Indirect Potency Assays were not implemented at the time the two lots of the drug product, M7173A and M7177A, were tested and hence you are not able to provide the requested potency data. However, we noticed in your stability data that you present Direct and Indirect potency data for lot M7177A (see Table 3.2.P.8.3-5). Please provide your most recent data for your Direct and Indirect Potency measurements for lot M7177A, which you obtained as part of the stability test, as well as the manufacturing and/or projected expiration date for the lot. Also, please determine the potency of lot M7173A using the Direct and Indirect potency assays and provide us your most recent results. If you are unable to provide this information, please send us two additional lots of drug product for which you have test results, for example, lots (b) (4), as well as the manufacturing and/or expiration dates, along with your Direct and Indirect potency results for the two lots you send. If you choose to send us samples, rather than submitting the potency results of lot M7173A, please also provide sufficient quantities of (b) (4) to enable us to carry out this test at least twice for each lot.

You may send the samples to:

Grainne Tobin
Center for Biological Evaluation and Research
Division of Biological Standards and Quality Control
10903 New Hampshire Avenue
WO75, G-717

Silver Spring, MD 20993-0002

If you cannot provide a complete response by July 12, 2016, please provide a timeline for a complete response and a clear plan for resolution of this issue in a timely manner.

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 by **July 12 and 22, 2016**.

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

If you have any questions, please contact me.

Very Respectfully,

Thomas J. Maruna, MSc, MLS(ASCP), CPH

Lieutenant, U.S. Public Health Service

Senior Regulatory Management Officer

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