

From: Maruna, Thomas
Sent: Tuesday, June 07, 2016 12:30 PM
To: 'Janice Castillo'
Cc: Ovanesov, Mikhail V.; Ertel, Donald (Donald.Ertel@fda.hhs.gov);
(b) (4)
Subject: 07-Jun-2016 Inspection-related Information Request ((b) (4)) -
BLA 125586.0 - Response Required by 30-June-2016

Importance: High

Portola Pharmaceuticals Inc.
Attention: Ms. Janice Castillo
June 7, 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

Advice and Information Request regarding (b) (4) responses to the observations in the form 483 issued during Pre License Inspection (b) (4):

1. On behalf of the agency, please submit the following comments to (b) (4).
 - a. With reference to your response to Observation item # 1:

We disagree with your conclusion that the process validation for (b) (4) is complete because at least one process parameter, (b) (4), was not investigated during the completed process qualification studies. We also disagree with your proposal to widen the specification limits for the (b) (4) before the completion of your investigations into the effect of elevated (b) (4) on (b) (4) performance, and the effect of the (b) (4) on TFPI inhibition. In addition, we disagree with your conclusion that the process performance qualification series for (b) (4) is complete because (b) (4) was not in a state of control during the (b) (4) inspection. We acknowledge your commitment:

- To update the Process Validation documents POL-1510 *Policy for Process Design – Stage 1 of Process Validation* and POL-1512 *Policy for*

Continued Process Verification (CPV) – Stage 3 of Process Validation with new information about all currently understood process parameters;

- To complete the investigations on the effect of (b) (4) on the performance of the (b) (4) steps in the Characterization Protocol (b) (4)-CP-054;
- To complete the trend investigation into the levels of (b) (4) that exceeded the in-process limit (IPL);
- To re-assess the in-process limit for (b) (4) levels in the (b) (4);
- To complete the investigation on the increased levels of the (b) (4) observed during the small-scale validation study on hold times (VAL-30234-01);
- To update the master batch record (MBR) to include instructions for more accurate temperature measurements and implement control on buffer temperatures at the point of use.

Please submit the following documents in an amendment to the BLA by 30 June 2016:

1. The final reports and supporting documentation for the above listed studies which you have committed to perform,
2. The *Final Report* for the *At-scale* (b) (4) Study (VAL-30230-02.1, approved 11 May 2016), and
3. All related Deviation Reports, either closed or open (including DEV-1484, DEV-1498, DEV-1573, and DEV-1632).

In addition, please prepare an amendment to the (b) (4) process validation report with an explanation of the new control strategy for process parameters.

b. With reference to your response to Observation item # 4:

Your response is not acceptable because your proposal does not address the root cause of your failure to follow your standard operating procedure for deviation management. Your delay in opening an official deviation record is due to your practice of consulting your client before official documentation of the deviation. Please ensure the timely initiation and accurate maintenance of manufacturing records by opening deviation records promptly prior to your communication with anyone outside of (b) (4).

2. The Agency recommends a teleconference (with the inspection team) to discuss any questions or concerns about this Information Request and our expectations for a revised response to your 483 observations. We can make ourselves available tomorrow 08 June 2016 or Thursday 09 June 2016. If you would like a teleconference, please communicate a proposed time on either day so that we can confirm our availability.

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 close-of-business, Friday, **June 30, 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

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