

**From:** Maruna, Thomas  
**Sent:** Wednesday, June 15, 2016 11:32 AM  
**To:** 'Janice Castillo'  
**Cc:** Harman, Christine; Ovanesov, Mikhail V.  
**Subject:** 15-Jun-2016 Information Request - BLA 125586.0 - Response Required by 30-June-2016

**Importance:** High

Portola Pharmaceuticals Inc.  
Attention: Ms. Janice Castillo  
June 15, 2016  
Sent by email

Dear Ms. Castillo:

We are reviewing your December 17, 2015 biologics license application (BLA) for the following:

<b>STN</b>	<b>Name of Biological Products</b>
125586/0	Coagulation Factor Xa (Recombinant), Inactivated

We have reviewed the following quality assays for the (b) (4) drug product and their validation reports submitted under STN 125586/0, and the additional information you provided in 125586/0.36, and have the following Information Request:

1. Please provide all raw data that supports the PARs for the (b) (4) and the (b) (4) noted in Table 3.2.P.2.3-13, "Lyophilization Characterization Parameters and Ranges" in section 3.2.P.2.3 of the BLA. Please note theoretical data (as shown in Figure 3.2.P.2.3.7, "(b) (4) Product Temperature Model") is not an acceptable method for setting ranges associated with (b) (4) and (b) (4). When controlling set-points for (b) (4) and (b) (4) are specified as ranges, a minimum of (b) (4) runs are needed to encompass the high and low possible combinations. If there is no raw data to support these parameter ranges, then the ranges must be adjusted accordingly.
2. For your developmental lyophilization studies, which provide the basis for (b) (4) drying parameters, a placebo was used with the justification that the placebo is considered representative of the DP since the amount of protein present is a small fraction of the mass of the DP, thus will not have an effect on thermal behavior. Please provide data that supports this rationale.
3. In reference to section 3.2.P.3.5.2.4.1 of the BLA, specifically in regards to the sterilization validation (PQ) of the worst case minimum durable load consisting of the (b) (4) and (b) (4) connected, please indicate the number and locations the

temperature sensors and BIs used in the PQ. Additionally, the PQ of the worst case minimum durable load provided for (b) (4) was performed in March 2005, please indicate why a re-qualification of the minimum load was not performed.

4. In reference to the PQ for the (b) (4), please indicate the initial amount of endotoxin (b) (4) “endotoxin” (b) (4), and provide the amount of endotoxin recovered from each (b) (4), and indicate the corresponding log reduction data for each (b) (4) for all PQ runs. Additionally, please clarify the rationale for the use of the (b) (4) vial as the worst case (b) (4) pack in terms of mass.
5. In reference to the response for IR item # 19 provided in Amendment 22, please provide CCIT validation report VL1507010, which should include all results (raw data) obtained from the study. Additionally, please provide the revised SOP 04-01-046, “*Determination of Sensitivity and Point of Failure for Container/Closure Interfaces, Using the (b) (4) Challenge*” that describes the point of failure controls (including the (b) (4) container with failure size (b) (4) and the spiked (b) (4)). Please note that if you plan to perform CCIT on stability, you will need data to support (b) (4) stability in the presence of the product. Please provide your plans for these studies if not yet performed.
6. In reference to your response to IR item #26 provided in Amendment 22, regarding the determination of the PAR and NOR for the filter/product contact process limit of (b) (4) and (b) (4), please note that product/filter comparability is not the only factor to consider when establishing production time limits. The total time for the product filtration should be limited to an established maximum to prevent microorganisms from penetrating the filter. Such a time limit should also prevent a significant increase in upstream bioburden and endotoxin load. Given that the (b) (4) retention study was performed with a product/filter contact time of (b) (4) and that process time for the sterile filtration of validation lots (b) (4) was performed in (b) (4), the process limit should be adjusted accordingly to be more aligned with your process capability and the bacterial retention study. Please provide a revised time limit for review.

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 June 30, 2016.**

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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