From: Maruna, Thomas
Sent: Wednesday, April 06, 2016 10:52 AM
To: 'Janice Castillo'
Subject: Extensive Information Request - BLA 125586.0 - Multiple Response Dates

Portola Pharmaceuticals Inc.
Attention: Ms. Janice Castillo
April 6, 2016
Sent by email

Dear Ms. Castillo:

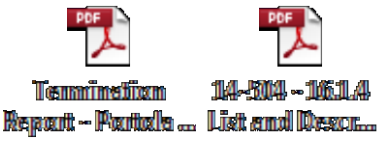
We are reviewing your December 17, 2015 biologics license application (BLA) for the following:

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

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

BIMO – Please respond by April 20, 2016

Note attached documents



1. During the inspection of Dr. Anson Lam at West Coast Clinical Trials (WCCT) in Cypress, CA, the FDA investigator reviewed the **Termination Report dated September 15, 2015** that accounts for the 358 volunteers who were screened, prematurely terminated, and completed the study. Out of those volunteers, the study site also reported to you the following accounting of study subjects who were prematurely terminated: 34 subjects withdrawn because cohort filled; 27 screen failed on D-1; 10 withdrew consent; and 2 lost to follow-up. Please provide your response to the following requests:

   Please define the meaning of the following terms as used in the report
   a. Enrolled
   b. Prematurely terminated
   c. Screen failed on D-1
   d. Lost to follow-up

   Regarding "27 screen failed on D-1; 10 withdrew consent"

a. Were they considered "enrolled" into the study and given the 4-digit identification number (refer to Protocol 14-504 Section 5.1.1)?
b. Provide reasons why 10 subjects withdrew consent. Were any subjects who withdrew consent randomized?

Regarding the two subjects who were lost to follow-up

e. What are their subject identifiers?
f. Are they the same subjects listed in the DS tabulation dataset as not completing the study ((b) (6))? If not, please submit their case report forms.
g. Please submit copies of all communication logs or documentation related to efforts to contact the two subjects who are counted as "lost to follow-up" in the Termination Report dated September 15, 2015.

2. Please provide the case report forms for subjects (b) (6) .

3. In the **Disposition (DS) tabulation dataset**, also mentioned in questions #1 and #2 above, we notice two early terminations of subjects from the study. In your **Study Report** for Andexanet for Protocol 14-504, Section 10.1 Disposition of Subjects (page 60) states,

> "In Part 2, 39 subjects received rivaroxaban and were randomized; 26 were randomized to andexanet and 13 subjects were randomized to placebo. Two subjects, both in the andexanet treatment group, did not complete the study: Subject (b) (6) withdrew from the study, underwent study procedures through Discharge Day 8 and an Early Termination Visit on Day 33, and Subject (b) (6) was lost to follow-up and did not undergo any study procedures after Study Day 15 (Listing 16.2.8.2.4b)."

However, the **Clinical Overview** report page 59 states,

> "In Study 14-504, subjects were administered rivaroxaban; 27 subjects were enrolled into Part 1 (andexanet 800 mg bolus only) and 26 subjects enrolled into Part 2 (800 mg bolus plus 8 mg/minute 120 minute infusion). There were no early terminations or dropouts."

Please explain this discrepancy. Also, please define the meaning of early terminations or dropouts used in the clinical overview report quoted above. Lastly, please confirm whether or not the data collected from the two early termination subjects were used in the efficacy analyses.

4. Please provide your response to the following requests regarding the **ECG tabulation dataset**:

a. Was the Interpretation/Finding of the ECG from the computer print outs from the ECG machines, then the clinical investigator verified/reviewed the reading or did the clinical investigator perform "manual" readings?
b. Please explain the multiple readings of ECG per visit, scheduled and unscheduled. Refer to Subjects (b) (6) as some examples. It appears that the unscheduled ECGs were performed for the same date and time as scheduled.
c. There are many instances of abnormal ECG readings that were interpreted as "not clinically significant." Specifically, approximately 113 abnormal ECGs were collected during the scheduled visits and approximately 70 were from unscheduled visits of about 15 study subjects. Please explain what triggered the performance of so many unscheduled ECGs. Please provide the explanation of the analysis of these ECGs and identify who read and interpreted the ECGs.

5. More than one study conducted by Dr. Lam is referenced in your BLA STN 125586. The "**16.1.4 List and Description of Investigators**" report in the application indicates that WCCT was given site identification number (ID) #002. However, the tabulation datasets show that the datasets collected for Protocol 14-504 are from a clinical study site #1. Please explain which is the correct ID number for the site. Please confirm the site location and dates for all datasets and analysis in the application "Protocol 14-504" folder.

CLINICAL – Please respond by April 13, 2016

6. Regarding the confirmatory study (14-505) please:

    a. Clarify if review notes or standard scoring sheets from the Endpoint Adjudication Committee are available for review. FDA considers these as source documents. If available, please submit these data as an amendment to the biologics licensing application. FDA needs this information to verify the ratings reported in the submission.
    b. Provide the formal results of all imaging (e.g., baseline and follow-up CT, MRI or echocardiograms) for all bleeding and/or adverse events for which imaging was required. For unscheduled test, please also specify the reason for the additional testing.

CMC (Product) – Please respond by April 20, 2016

7. You used (b) (4) to characterize the thermodynamics and stoichiometry of the interaction between andexanet alfa and (b) (4) Please expand the study to include rivoroxaban, edoxaban and apixaban. Specifically, please repeat the (b) (4) experiments presented in BLA section 3.2.S.3.1.19 *Elucidation of Structure and Other Characteristics* and IND section 3.2.S.3.1.11, using all four inhibitors (b) (4),

rivaroxaban, edoxaban and apixaban and representative (b) (4) batches from (b) (4) batches) and (b) (4) batches). Please submit the final study report as an amendment to the BLA by 17 June 2016.

8. In the specifications of the (b) (4) Drug Product (DP), you have not provided a parameter(s) to monitor (b) (4) of the protein. Your data for characterization of andexanet alfa (section 3.2.S.3.1) indicate that the protein has at least (b) (4) sites for (b) (4) , which are (b) (4) respectively (Table 3.2.S.3.1-7). Therefore, the theoretical (b) (4) of the protein to (b) (4) However, in Table 3.2.S.3.1-8, you reported a ratio of (b) (4) , indicating that (b) (4) of the (b) (4) , and/or (b) (4) of the protein is incomplete. In addition, the information provided in Figure 3.2.S.3.1.1-3 is not consistent with your analytical data because it does not show (b) (4) , but does show (b) (4) other sites and only (b) (4) on the molecule. Therefore, please correct Figure 3.2.S.3.1.1-3 to show all (b) (4) sites with the respective (b) (4) positions and provide a clear assessment of the (b) (4) of the (b) (4) (b) (4) on the protein in the eCTD file.

9. The proposed release specifications of (b) (4) DP for identity, (b) (4) and excipients are deficient. Andexanet alfa is a mutated coagulation factor product manufactured at large scale, formulated at high concentration and administered at high doses. To provide assurance of consistent product quality and to compensate for the limited manufacturing experience, please develop new (b) (4) DP release assays and propose release specifications to control the following parameters:

    a. identity by protein structure, e.g., the (b) (4) method described under *Justification of Specification* section 3.2.S.4.5.2.6;
    b. (b) (4) ; and
    c. identity and quantity of excipients - sucrose, mannitol and Polysorbate 80

10. In the specifications of the (b) (4) DP (e.g., section 3.2.P.5.1), the Direct and Indirect Potencies are expressed in percentage units relative to a reference standard. However, the use of percentage unit is not suitable for the evaluation of the stability of the product because the stability of the reference standard is not established. To establish a reliable reference standard throughout the life-cycle of the product, please develop a potency unit that is traceable to international reference preparations distributed by the (b) (4) (b) (4) (b) (4) (b) (4) . In this case, the potency unit could be defined as follows: " (b) (4) (b) (4) ." Please update the specifications of the (b) (4) DP accordingly.

11. In the *Justification of Specifications* of the (b) (4) DP (sections 3.2.S.4.5 and 3.2.P.5.6, respectively), you have not provided an assessment of the critical quality attributes of the

product and their relative importance (such as arbitrary scores) for the product's safety and efficacy. Considering our comments above (1-3), please provide these data and update the eCTD file accordingly.

12. In the specifications of the DP (section 3.2.P.5.1), please clarify which compound corresponds to the parameter "Concentration by (b) (4) Please revise this parameter to "Protein Concentration by (b) (4)

13. In the specifications for the (b) (4) DP under "Test/Test Method" for compendial methods, please refer to the specific chapters of the compendia (e.g., (b) (4) for (b) (4) , *etc*.).

14. Your March 3, 2016 response to our February 17, 2016 request to develop assays for anti-drug antibodies that may bind or neutralize endogenous Coagulation Factors X and Xa is not acceptable. Please note that the development of neutralizing antibodies against Factors X and Xa is an unwanted immune response to a therapeutic protein product as defined in the FDA 2014 *Guidance for Industry Immunogenicity Assessment for Therapeutic Protein Products.* To ensure protection of clinical study participants from exposure to a product with a non-redundant endogenous counterpart, you are required to have a means of testing for neutralizing antibodies against endogenous Factors X and Xa.

    FDA had requested Portola to develop these assays during the pre-IND meeting on 16 June 2009 (CRMTS # 7089, Ref. PS000698), and Portola had included a commitment to develop these assays in the original IND submitted on 15 March 2012. You reiterated this commitment in your Clinical Study Protocol 15-507 dated 09 June 2015. To comply with FDA requirements and your prior commitments, you must develop and validate assays for antibodies that inhibit the activities of endogenous human Factors X and Xa. For example, the anti-Factor X inhibitory antibody assay should be based on the (b) (4) (b) (4) assay for Factor X activity, and the results should be presented in (b) (4) (b) (4) of anti-Factor X activity. By April 12, 2016, please provide a timeline for the analytical studies you will conduct to comply with this request. In addition, please include this timeline in *Clinical Study Protocol 15-507* and inform the clinical investigators accordingly.

15. Your March 3, 2016 response to our February 17, 2016 request to assess the interference of anti-Factor Xa inhibitory antibody on the pharmacodynamics, pharmacokinetics, and immunogenicity assays is not acceptable. For example, you need to validate the assays for dRVVT, thrombin generation, PT, aPTT and ACT for antibody interference. This information is required to support the claim of lack of immunogenic response with neutralizing activity for Factors X and Xa, which you made in the *Prescribing Information, Risk Management Plan* (1.16.1 Risk Management), *Clinical Study Protocols* and your March 3, 2016 response to our information request. *FDA Draft Guidance for Industry: Assay Development for Immunogenicity Testing of Therapeutic Proteins* also instructs you to study the interference of anti-Factor Xa inhibitory antibodies with all binding immunogenicity assays. By April 5, 2016, please provide a timeline for the analytical studies you will conduct to comply with this request.

16. In your March 3, 2016 amendment, *Table A1-2: Antibody Assays*, you stated that assays for anti-andexanet, anti-Factor X and anti-Factor Xa antibody were first used on January 1, 2013. However, the data on these antibodies were reported as early as September 19, 2012, in an information package for the End-of-Phase 1 meeting. Please explain this inconsistency and provide detailed information on any immunogenicity assays used prior to January 1, 2013.

17. Regarding the two thrombin generation assays described in your March 3, 2016 amendment (the original Portola's method and the currently used commercially available CAT method) used in Phase 1, Phase 2 and Phase 3/4 clinical trials, your justification for assay comparability presented in the March 3, 2016 response is not acceptable. The sensitivity of the thrombin generation assay to the action of pro- and anti-coagulant molecules is known to depend on tissue factor concentration, plasma dilution and procoagulant lipid vesicle concentration. Therefore, please provide a side-by-side comparison of the (b) (4) thrombin generation assays to demonstrate the comparability of responses to the activities of the study drugs (including but not be limited to andexanet alfa, (b) (4) rivoroxaban, edoxaban and apixaban and their combinations) and antibodies (including inhibitory antibodies to Factor X and andexanet alfa). In addition, the original Portola assay utilized a substantially higher level of tissue factor reagent ((b) (4) (b) (4) in the commercial CAT reagent), suggesting that the Portola assay is less sensitive to tissue factor-dependent anti-TFPI action of andexanet alfa. Since the sensitivity to TFPI inhibition has been previously demonstrated by the CAT method, please use CAT to repeat studies of anti-TFPI action of andexanet as described in NC-12-0451-R0001 *PRT064445 activity and interaction with fXa*(b) (4).

18. The comparability protocols for the proposed manufacturing changes are deficient. You need to provide clear and specific information on the manufacturing changes that should include, but not be limited to, the rationale for the changes; knowledge and understanding of the process the changes are involved in; supporting information; comparability study design and protocol; test methods, justification and validation protocol for the quality attributes to be tested; test methods and acceptance criteria; and data analysis strategy including statistic assessment. Please note that deficiencies in the comparability protocol, if not addressed adequately, will negatively affect the outcome of the BLA.

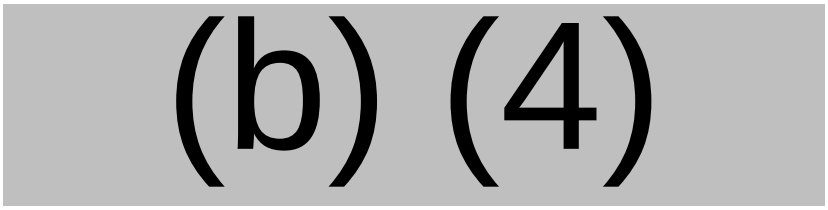
CMC (Facility) – Please respond by April 15, 2016

19. Please provide the Container Closure Integrity Test (CCIT) validation report VL1404006 that was referenced in Table 3.2.P.3.5-1 "Protocols and Reports Supporting Andexanet Alfa Drug Product Validation" and that was briefly described in Section 3.2.P.2.5 Microbiological Attributes of the BLA submission. This report should include sensitivity data to support the use of the positive controls in the testing. Please note that the positive control, in which the stopper was (b) (4), is not adequate to simulate a critical leak defect. To support sensitivity, we recommend that the defect diameter be as small as reasonably possible (i.e. sensitivity data should include a

minimum (b) (4) .

20. The report M073-1 "Container Closure Summary Report" was provided in Section 3.2.R Regional Information of the BLA and describes the use of various containers punctured with different needle gauges and then subjected to microbial ingress. Please indicate the purpose of this report as it does not seem to connect to the CCIT information provided in Section 3.2.P.2.5 Microbiological Attributes of the BLA submission. Additionally, this report was not referenced nor summarized in Section 3.2.P.2.5 of the BLA submission. Please provide more details for the purpose and scope of this report, in particular, please describe how this report supports the dye ingress testing described in Section 3.2.P.2.5 of the BLA submission.

21. Please provide summaries of the OQ reports referenced in Table 3.2.A.1-3 "Equipment OQ/PQ Summary" in Section 3.2.A.1 Facilities and Equipment -Baxter of the BLA submission for the following equipment.



22. Please provide summaries of the following validations referenced in Table 3.2.P.3.5-1 "Protocols and Reports Supporting Andexanet Alfa Drug Product Validation" (refer to Section 3.2.P.5 Process Validaiton and/or Evalution, pg. 5)

    a. Formulation Equipment Sterilization Validation
    b. Filling Equipment Sterilization Validation
    c. (b) (4) Performance Qualification
    d. (b) (4) Performance Qualification
    e. Lyophilizer Validation
    f. Media Fill Performance Qualification and Confirmation

23. Please indicate if (b) (4) is used in the manufacturing process of Andexanet alfa DP and if so, please indicate if the use is product contact. Additionally, you indicated that (b) (4) is used as a (b) (4), thus is product contact. Please, indicate how (b) (4) (if applicable) are filtered and monitored for purity and microbial content (i.e. details of sterile filtration, filter integrity testing).

24. Please provide a detailed description of the aseptic filling area, and the (b) (4) enclosure. Please indicate if the (b) (4) is an opened or closed (b) (4) and how the (b) (4) is decontaminated before a filling is performed.

25. In reference to the HVAC system, please provide a qualification summary and indicate the number of air exchanges/hour in the rooms of the aseptic core.

26. In reference to Table 3.2.P.3.-10 Sterile Filtration Parameters for Consistency Lots (Section 3.2.P.5 Process Validation and/or Evaluation, pg.17), the NOR/Target range for Filter/Product Contact Time is indicated as (b) (4) and PAR (Proven Acceptable Range) is indicated as (b) (4); however, for the data for the (b) (4) lots provided (b) (4)) the filter/product contact process times range from (b) (4) (b) (4). Please note that set process time limits should be close to actual production. Please comment and provide a justification for the filter/product contact limits indicated.

27. Please note that the ranges indicated in Table 3.2.P.3.5-12, "Lyophilization Process Parameters and Hold Temperature for the Consistency Lots" for the (b) (4) with NOR as (b) (4), PAR (b) (4) and Validation parameter range of 8-12 and for the (b) (4) with NOR, PAR and Validation Parameter Range of (b) (4) are not supported by data. Please comment on the determination of these ranges and how these ranges are supported.

28. Please provide details of the procedures for final batch release after primary labeling and packaging has been performed. These details should include information in regards to the location in which the following activities are performed: sampling for release testing, quality control, storage of lot retains and lots before final distribution. Please detail the roles and responsibilities of each facility involved in the batch release process.

29. There are major deficiencies in the two comparability protocols that were provided in the BLA submission to cover changes to the (b) (4) DP manufacturing process. Please note that a comparability protocol is a well-defined, written plan for assessing the effect of specific CMC changes. A comparability protocol should describe the changes that are covered under the protocol and specifies the tests and studies that will be performed, including analytical procedures that will be used and acceptance criteria for each specified test that will be achieved to demonstrate that the specific changes do not adversely affect the product. In addition, specifics of the type and amount of data (i.e number of batches) generated from execution of the protocol should be clearly indicated. The data provided in the follow-up CBE-30 should include results of all tests and studies specified in the CP, discussions of any deviations that occurred during the tests or studies, a summary of any investigations performed and other pertinent information.

30. As previously noted, two CPs were provided in your BLA submission, one which relates to the manufacturing changes to the (b) (4)) (NC-15-0664-P0001) and the other which relates to DP manufacturing changes using the (b) (4) manufactured with (b) (4) (NC-15-0681-P0001). Please indicate if separate CBE-30s will be submitted. We highly recommend that the two CPs be combined into one covering the overall manufacturing changes to (b) (4) DP, thus to simplify the submitting of data into a single CBE-30 submission given that the manufacturing changes to (b) (4) DP are interrelated.

DBSQC (Samples and Reagents) – Please Respond by April 20, 2016

31. Please provide 10 ml of formulated Andexanet alfa drug product (STN: 125586) obtained from the manufacturing line before the lyophilization step for evaluation in our laboratory in support of your BLA submission. You may send us non-cGMP drug product (but not drug substance) in lieu of the drug product formulated under cGMP, as long as the product is scientifically representative of the drug product final formulation.

    Please ship the sample to the address listed below:
    Mark Levi
    Center for Biological Evaluation and Research
    Division of Biological Standards and Quality Control
    10903 New Hampshire Avenue
    WO75, G-662
    Silver Spring, MD 20993-0002

DBSQC (In-Support testing) - Please respond by April 13, 2016

32. Please provide the positive product control concentration used for spiking the test samples and their percent recovery results obtained during the endotoxin test qualifications as reported in documents: VAL-60003-04, TME-0003 (Determination Using the (b) (4) Method) by (b) (4) and (b) (4) 15-08-002 ((b) (4) Method Development and Validation Report for Client414-103: PRT064445 10mg/mL) by (b) (4) .

33. Please provide an estimated completion date for requalification of (b) (4) in the presence of fXa (b) (4) using (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.

Please submit your responses as an amendment to this file by the dates noted above referencing the date of this request. If you are unable to comply with the requested dates, please propose a reasonable alternative date to respond.

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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