DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

August 17, 2016

Our STN: BL 125586/0 **BLA COMPLETE RESPONSE**

Portola Pharmaceuticals, Inc.
Attention: Ms. Janice Castillo
270 East Grand Avenue
South San Francisco, CA 94080

Dear Ms. Castillo:

This letter is in regard to your biologics license application (BLA) for Coagulation Factor Xa (Recombinant), Inactivated, manufactured at your contract manufacturing locations (b) (4) and (b) (4), and submitted under section 351 of the Public Health Service Act (42 U.S.C. 262).

We have completed our review of all submissions made relating to this BLA with the exception of the labeling amendment dated 8 July 2016, amendments with promotional materials dated 11 July, 12 July, 18 July, 04 and 12 August 2016, the clinical and preclinical amendment dated 19 July, and the clinical protocol amendments dated 4 August and 5 August 2016. The scope of this letter does not encompass dosing regimens of longer than 2 hours.

Based on the current status of review, we have concluded that we cannot grant final approval because of the deficiencies outlined in this document. In your complete response to this letter you may reference applicable sections of the amendments that have not yet been reviewed and we will address those sections accordingly.

CMC:

We acknowledge that ANDEXAA is a breakthrough therapy developed for an indication that addresses an urgent unmet medical need. As such, FDA is committed to working with Portola to advance your manufacturing program. We have submitted multiple requests for information (IRs), and we have received your responses. We have determined that these responses to our IRs are incomplete. The information needed for approval is outlined below in detail:

1. The data you provided in your responses to the Form FDA 483 issued on (b) (4) do not adequately address the deficiencies in the validation of the ANDEXXA manufacturing process that were identified during the Pre-License Inspection (PLI) of the (b) (4) facility. The ANDEXXA process is not validated to assure reasonable control of sources of variability that could affect production output and to assure that the process is capable of consistently delivering a product of well-defined quality. Current good manufacturing practice (CGMP) requires that manufacturing

processes be designed and controlled to assure that in-process materials and the finished product consistently and reliably meet pre-determined quality requirements. Please address the following deficiencies:

a) Complete the validation studies for the clearance of all impurities and submit the final study reports to demonstrate identification and control of these impurities. This is needed to assure process consistency and establish a process control strategy which will ensure the quality of the commercially manufactured product.

   You provided incomplete information regarding (b) (4) impurities. In the final report for the deviation investigation *DEV-1632* submitted on 30 June 2016, you stated that "(b) (4) *would be more likely to promote* (b) (4) *including the* (b) (4) *that may lead to* (b) (4) *product percentage*." In the 17 July 2016 amendment to the BLA, you explained that several investigations on (b) (4) impurities are ongoing and acknowledged that "*As of yet, we have not identified the source of the* (b) (4) *in the upstream process.*" Please note that impurity clearance studies are considered critical to the process qualification stage of process validation (reference is made to the 2011 *FDA Guidance on Process Validation*) and therefore prior to submission to FDA these studies should be reviewed and approved by your quality assurance unit to document the use of sound scientific methodology and principles with adequate data to support the conclusions.

b) Demonstrate that the trends in the purity and stability attributes of the (b) (4) Final Drug Product (FDP) do not adversely affect the quality, safety, purity, or potency of the product as they relate to its safety and effectiveness. These trends were observed after the introduction of the proposed commercial Process 3.

   Demonstrated lack of analytical comparability between the materials manufactured using the previous (b) (4) and the proposed commercial (b) (4) is of concern because Phase 3 clinical studies were exclusively supported by (b) (4) materials. Please also address the following evidence of the reduced capacity of (b) (4) in clearing (b) (4) impurities:

   i. Analysis of consecutive BDS batches in Figure 5b of the Investigation Final Report for *DEV-1632* (submitted in your 30 June 2016 amendment) demonstrates that both the levels of the (b) (4) and batch-to-batch variability in the (b) (4) were increased when (b) (4) was replaced with (b) (4).

   ii. Results of the accelerated stability studies indicated an increase in (b) (4) degradation in (b) (4) batches as evidenced by the adverse trends observed in (b) (4) and (b) (4). Results from both methods demonstrated a (b) (4)

of the (b) (4) and a (b) (4) in the main product (b) (4) when comparing materials from (b) (4) to those from (b) (4).

iii. Adverse trends in real-time stability for the (b) (4) were observed for (b) (4) batch (b) (4) and the FDP batch (b) (4) (which was manufactured using this (b) (4) batch).

iv. Data on (b) (4) modifications provided on 29 July 2016 indicated that (b) (4) batches were (b) (4) content and (b) (4) when compared to (b) (4) batches.

c) Submit the final reports of process validation studies to demonstrate the effectiveness of the control strategy for the newly established critical process parameter - (b) (4) - in assuring the consistency of (b) (4) performance and (b) (4) quality. Provide a timeline for the completion of the associated process validation activities.

d) During the PLI, we observed that (b) (4) were associated with a (b) (4) in yield at the (b) (4) step and loss of control over the content of the (b) (4) in the (b) (4). We acknowledge your 30 June 2016 commitment to implement and validate new equipment to control (b) (4) at the point of use no earlier than 15 November 2016, which is after the PDUFA V Action Date, and also does not include a "no later than" date. Please clarify your intent and timeline.

e) Complete the validation of hold times for process intermediates during the manufacture of the (b) (4) and demonstrate the control over the (b) (4) and other quality attributes of the (b) (4). As you reported on 11 July 2016, the validation study performed per process hold time study protocol *VAL-30234-01* failed due to an (b) (4) in the (b) (4) at the (b) (4) step. You had not identified the root cause for this deviation, and have initiated a new study per validation protocol *VAL-30291-01* which will be completed by 31 October 2016, which is also after the PDUFA V Action Date.

f) Ensure that the FDP process performance qualification (PPQ) studies, and all manufacturing activities, are conducted in compliance with CGMP requirements. We note that these requirements were not followed when out of specification (OOS) (b) (4) batch (b) (4) and Out of Limit (OOL) (b) (4) batch (b) (4) were mixed with conforming (b) (4) batches to manufacture three PPQ FDP batches that met specifications as described below:

i. According to the aforementioned deviation investigation *DEV-1632*, (b) (4) batch (b) (4) ((b) (4) number (b) (4)) was not released because the release testing for the (b) (4) was OOS ((b) (4)). Nevertheless, the final validation report for the ANDEXXA FDP process states that on 09 November 2015 Portola authorized the use of this batch for the production of PPQ FDP batch (b) (4). As documented in the

same report, batch (b) (4) was (b) (4) with portions of (b) (4) batches (b) (4), which were well within specification for the (b) (4). As a result of this (b) (4), the content of the (b) (4) was (b) (4) to 1(b) (4) in FDP batch (b) (4), which was within the release specification and this batch met the pre-determined acceptance criteria for the lyophilized vial finished product testing and was reported in *3.2.P.5.4 Batch Analyses*. Blending OOS and/or OOL batches with batches that are within specification is not considered to be acceptable CGMP.

ii. The amount of protein for (b) (4) process parameter "(b) (4)" exceeded the allowable range (which is reported in the BLA as (b) (4)). A total of (b) (4) of (b) (4) Batch (b) (4) was used in the manufacture of all (b) (4) FDP PPQ batches, which corresponds to (b) (4) of andexanet alfa in this (b) (4). PPQ batches (b) (4) met the release acceptance criteria and were used in primary stability studies. PPQ batch (b) (4) was also released for use in humans.

Please explain how these occurrences will be prevented in the future and report on the current disposition of these PPQ batches, which cannot be used to support the process validation.

2. The proposed release specifications for the (b) (4) FDP are incomplete and not representative of the experience with the proposed commercial process. We acknowledge your proposal to use (b) (4) release data to derive (b) (4) release specifications but do not find it acceptable because:

- The comparability of the (b) (4) and (b) (4) materials has yet to be established;

- Empirical (b) (4) data are limited and insufficient to support the critical analytical methods used to monitor the identity, purity and potency of the (b) (4) (these methods were replaced after the introduction of (b) (4), when only (b) (4) batches were manufactured and with the simultaneous introduction of the proposed (b) (4) specifications);

- Data obtained with the previous versions of methods for identity, purity, and potency was not trended quantitatively and therefore the comparability between the different versions of these methods, and different versions of processes, is not established.

To provide assurance of consistent product quality, please address the following deficiencies with release methods and specifications:

a) Base all (b) (4) specifications on available (b) (4) manufacturing data, and FDP specifications on data from batch analyses of the FDP, not the (b) (4). The proposed specifications are deficient because they were developed prior to the

execution of the (b) (4) PPQ campaign, when data from only (b) (4) out of (b) (4) currently manufactured (b) (4) batches were available. To develop meaningful specifications, use data from all (b) (4) FDP batches that were manufactured in compliance with the proposed control strategy and CGMP. Exclude the data for all batches that are not manufactured by the proposed commercial process, such as all (b) (4) batches and batch (b) (4), which was manufactured at (b) (4).

b) In reference to our Information Request (IR) dated 07 April 2016 and your 20 April, 08 July and 29 July 2016 responses, which are incomplete:

i. Validate the (b) (4) assay as an identity test for andexanet alfa based on protein structure, and validate the methods for determining the (b) (4) and (b) (4) content.

ii. Validate the analytical methods and establish release specifications for the excipients mannitol, sucrose, and Polysorbate 80. Please also qualify all compendial analytical methods used for the release of raw materials intended for FDP formulation.

iii. Develop and validate potency units for ANDEXXA to replace the current unit of "*percent of a reference standard.*" The existing percentage approach is not suitable for the evaluation of the stability of the product because the stability of the reference standard is not established. To address these deficiencies, the new potency units should be traceable to the international reference preparations distributed by the (b) (4). Refer to the (b) (4) for examples. To illustrate a specific example of a possible method, the units can be defined as follows: "(b) (4)"

c) Develop quantitative acceptance criteria for the (b) (4) resolved by (b) (4). ANDEXXA is a heterogeneous mutated protein product comprised of more than (b) (4) and additional variants with different (b) (4) modifications and (b) (4) content. Additional purity specifications are needed to demonstrate control over all (b) (4) forms that may arise during the purification process.

These quantitative parameters may be used to investigate the comparability of the (b) (4) and (b) (4) materials, as well as the (b) (4) and lyophilized (FDP) formulations of (b) (4) materials. Please also explain why the product is treated with (b) (4) before (b) (4). The treatment (b) (4) , and in turn gives results that are not representative of the actual composition of the product.

d) Your justification for proposed specifications for Visual Appearance for (b) (4) reconstituted FDP ("*Clear, colorless to slightly yellow solution, essentially free of visible particulates*") is not acceptable. The presence of visible particles may indicate issues with protein solubility and stability. Revise the acceptance criteria to require "*Clear, colorless to slightly yellow solution, **free** of visible particles*".

e) In reference to our IR dated 01 June 2016 and your 15 June and 19 July 2016 responses which are incomplete, develop a potency assay and associated release specifications to measure the inhibition of Tissue Factor Pathway Inhibitor (TFPI) activity by ANDEXXA FDP. Please base your assay for TFPI inhibition activity on the thrombin generation test (TGT) used as a biomarker in Phase 3 clinical studies.

f) In reference to our IR dated 22 June 2016 and your 08 July 2016 response which is incomplete, develop and validate a new method for the evaluation of endotoxins in FDP with a limit of detection comparable to that of the method used for (b) (4) release. Your specification for endotoxins in the FDP ((b) (4)) is very close to the compendial infusion limit for endotoxins and can be reduced as demonstrated by the capability of your manufacturing process.

g) We acknowledge your commitment to replace a commercially available assay for the measurement of Chinese Hamster Ovary (CHO) (b) (4) impurities with an ANDEXXA process-specific method. A new release method is required because (b) (4) impurities are suspected to originate from CHO cells. A process-specific (b) (4) preparation should be prepared from a representative cell culture campaign using a relevant null cell line (the production cell line minus the product-coding sequence). Please refer to the ICH Guideline Q6B *Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products*. This (b) (4) preparation should then be used to generate the antibodies used in the assay for (b) (4) impurities. Adequate coverage of the (b) (4) P antibodies for CHO-derived impurities should be established.

h) In reference to our IR dated 07 June 2016 and your 30 June and 13 July 2016 responses which are incomplete, develop new specifications for the (b) (4) to utilize the demonstrated sensitivity of this parameter to changes in critical process parameters and the purity of ANDEXXA. Support the specifications with a report on risk assessment of the (b) (4) and (b) (4) -producing impurities. This should include, but not be limited to, their impact on the purity,

quality, potency, and stability of the product as they are related to its safety and effectiveness. In addition, please:

i. Provide complete reports for the investigations into the root causes behind the observed changes in product quality attributes after the introduction of (b) (4), which were evidenced by the increase in the levels of (b) (4) observed (i) at several unit operations (such as (b) (4)), (ii) in hold time studies, (iii) after the introduction of (b) (4), and (iv) over time in stability studies (under both accelerated and real-time conditions). These investigations should include, but not be limited to, evaluation of the effect of (b) (4), inconsistent impurity clearance and extended hold times on process performance.

ii. Use (b) (4) methods for the measurement of the (b) (4) to compare the (b) (4) and (b) (4) batches, and to monitor the changes in the (b) (4) in stability studies for the (b) (4) FDP.

iii. Explain how the available clinical data support the (b) (4) specifications. In your response, use (b) (4) methods to detect the ranges of levels for each (b) (4) in all batches used in the completed clinical trials and address the possible effect of the (b) (4) on the ANDEXXA circulatory half-life. With reference to your proposal to increase the acceptance criterion of the (b) (4) by the existing (b) (4) method from (b) (4) to (b) (4), please note that the clinical batches contained less than half of the (b) (4) as defined by the increased upper specification limit, which does not support such an increase.

iv. Use (b) (4) methods to compare the specific potencies of the (b) (4) with the other product-related molecular forms of ANDEXXA. In addition to validated potency methods, we suggest using a biomarker assay, e.g., TF-activated TGT.

i) Because the Phase 3 studies were conducted using materials manufactured by (b) (4), please justify the proposed commercial release specifications for all release methods with the analytical studies of clinical batches. In these studies, the clinical batches and representative (b) (4) batches should be compared side by side using fully validated release methods and the pharmacodynamics methods used in the clinical trials to demonstrate the ANDEXXA effect, including the clinical assay TF-activated TGT and TFPI activity assays.

j) Please note that your justifications for specifications should explain how the finalized specifications and validated release methods will demonstrate the consistent performance of your manufacturing process to produce drug product with the appropriate identity, quality, safety, purity, and potency attributes.

3. In reference to our IR about ANDEXXA potency standards dated 12 February 2016 and your 22 February, 20 April, 18 May, 06 June, 21 June, 27 June, 06 July, 08 July, 13 July and 29 July 2016 responses which are incomplete, please note that a Primary Reference Standard (PRS) is required to control and preserve the existing and new unitages of the potency of ANDEXXA. A secondary standard is needed for routine control of the manufacturing process and QC of product quality. The PRS is critical in maintaining a consistent potency unit and allows "like vs like" comparisons when changes are made in assay reagents or methodologies, and manufacturing process. To demonstrate control over potency unitage, please:

    a) Provide your reference standard qualification protocol for review.

    b) Qualify and establish (b) (4) lot of andexanet alfa as the PRS and ensure that your Working Reference Standards are qualified against this PRS over the product life-cycle. You should perform an adequate number of replicate analyses to qualify the reference standards so that the potency can be assigned with sufficient statistical power.

    c) Qualify the reference standards independently for both the direct and the indirect potency assays.

    d) Provide detailed information on the method and reagents used in the assignment of potency to the PRS and secondary standards, studies to monitor the stability of the reference standards, and protocol for the replacement or replenishment of these reference standards.

    e) List all reference standards used thus far for the release testing of (b) (4) FDP batches and in stability studies. In addition, apply new potency unitage to evaluate the potencies of all of your reference standards – primary, secondary or working – in direct and indirect units in side-by-side comparative studies.

    f) Provide the reasons for the replacement of previous standards and the actions taken to ensure the linkage of products made as the manufacturing process was changed; as well as the preservation of the potency unit in stability studies.

       For example, reference standard Lot # (b) (4) was qualified on 10 November 2015 but was no longer available for use on 15 July 2016. Please provide the investigation report for its OOS pH result (pH (b) (4) was outside of the specification criterion of (b) (4)) which occurred on 16 March 2016 and explain the impact of this deviation on reference standard continuity.

4. The proposed shelf-lives of the commercial product are not supported with sufficient (b) (4) manufacturing experience. Your proposal to use (b) (4) stability data to support the stability of the (b) (4) product is not acceptable because of the following reasons:

- The comparability of the (b) (4) and (b) (4) materials has yet to be established.

- Empirical stability data on the batches for both processes are limited and insufficient because the critical analytical methods used to monitor the identity, purity and potency of ANDEXXA were introduced shortly after (b) (4) introduction. In addition, only the old methods continue to be used in many of the initiated stability studies.

- Stability data obtained with the previous versions of these methods were not trended quantitatively and therefore the linkage between the data from the old and new methods is not well established.

To demonstrate product stability over time:

a) Retest all available (b) (4) and (b) (4) batches using the new, validated release methods to demonstrate that the old batches meet all the stability specifications and possess comparable stability profiles.

b) Investigate all adverse stability trends of all available data, which should include, but not be limited to, every (b) (4) and (b) (4) as resolved by your new and old methods. For example, please explain the steady (b) (4) in the (b) (4) by the (b) (4) which was observed in (b) (4) FDP batch (b) (4) in real-time and accelerated stability studies. Please explain how this (b) (4) is related to the (b) (4) detected by the new (b) (4) methods.

c) Describe all OOS results in completed and ongoing stability studies, including accelerated stability and stability of reference materials. For example, an OOS result for potency of (b) (4) of storage at (b) (4) occurred on 30 July 2015. The deviation investigation was closed on 14 October 2015 but this OOS was not reported in the BLA.

d) Complete the in-use stability studies during which product compatibility with intravenous administration devices was also investigated. Please include assessment of parameters for microbiology, purity by (b) (4), and direct and indirect potency over the proposed 24-hour period.

5. Please address the following deficiencies in in-process control parameters:

a) Include (b) (4) testing as a *critical* process parameter for the (b) (4) step. We acknowledge that you are performing (b) (4) and (b) (4) testing as non-critical process parameters, however, the proposed surrogate critical control parameters, such as (b) (4), by themselves are not sufficient to ensure the effectiveness of this (b) (4) step.

b) Explain the validation and criticality status for the process parameter (b) (4). (b) (4) related parameters, (b) (4) targets, are listed in Table 35: (b) (4) *and* (b) (4) *Andexanet* (b) (4) *Manufacturing Process Changes* of the 21 June 2016 amendment to *Comparability Protocol Andexanet Alfa (PRT064445)* (b) (4) *to* (b) (4) *Resulting Drug Product*. These parameters are not described in the BLA.

c) List the validated (b) (4) FDP fill volume ranges for the commercial (b) (4), the expected scaled-up (b) (4) (known as (b) (4)) and the Gen2 process at Lonza. In your response, please provide a table with the following information:

i. BDS batch fill volume range (formulated at (b) (4))

ii. FDP batch fill volume range (formulated at 10 mg/mL)

iii. Total BDS yield ((b) (4))

iv. Number of BDS batches needed to produce 1 FDP batch

v. Number of vials per FDP batch

6. In reference to our IR dated 01 June 2016 and your 15 June 2016 response, which is incomplete, develop the (b) (4) assay for the characterization of the interactions between the (b) (4) and TFPI and perform the following studies:

a) Use representative (b) (4) batches from (b) (4) ((b) (4) batches) and (b) (4) ((b) (4) batches) to study interactions between (b) (4) and TFPI. We are aware that the reported K_d values for Factor Xa and TFPI are near the limit of resolution of the (b) (4) assay and that the (b) (4) might be too steep to resolve the K_d accurately due to the high c-value. However, the same experiments can provide an accurate assessment of n and ΔH - the former is an indicator of drug activity, and the latter of batch-to-batch variability and micro-heterogeneity within individual batches.

b) Use (b) (4) to investigate the interactions of the (b) (4) of andexanet alfa with TFPI.

c) Investigate the sensitivity of the (b) (4) method to evaluate the (b) (4) of ANDEXXA and consider including the (b) (4) assay in the (b) (4) release specifications. Establish acceptance criteria for its interactions with direct FXa inhibitors for these thermodynamics and stoichiometry parameters - K_d, ΔH, TΔS, ΔG and n.

7. (b) (4) of your FDP (b) (4) samples, including (b) (4) batches of lyophilized drug product, (b) (4) lot of pre-lyophillized solution and the "reference standard", which we analyzed by (b) (4) using a (b) (4) all show (b) (4), in addition to (b) (4) for (b) (4), when (b) (4) is replaced by (b) (4) in the (b) (4). Please identify the proteins in these (b) (4).

8. In reference to the latest version of the Comparability Protocol (CP) for post-approval changes for (b) (4) FDP manufacture submitted on 21 June 2016, which also included the manufacturing history for the (b) (4) process, we find that the CP cannot be approved as currently designed. The following deficiencies need to be addressed:

    a) Drug Substance Protocol:

        i. (b) (4)

            1) (b) (4)

            2) (b) (4)

                - (b) (4)
                - (b) (4)
                - (b) (4)

- (b) (4)

Given the manufacturing history of (b) (4) and the numerous deviations resulting in (b) (4) failures and lot terminations, the (b) (4) process does not appear to be in a state of control. In addition, including additional (b) (4) (more than needed) to account for anticipated failures is not acceptable CGMP.

ii. Deviation investigation DEV-2188- (b) (4), Lot (b) (4), reviewed on inspection of (b) (4), documents an OOS for (b) (4) in the (b) (4), and (b) (4) failures in multiple downstream steps and (b) (4). Because the root cause was determined to be a (b) (4) cleaning failure, please provide the completed investigation and any corrective actions associated with deviation DEV-2188-A86U03 since at the time of the inspection (18-22 April 2016), the investigation was still in progress.

iii. Please investigate the impact of (b) (4) manufacturing trends on operating parameters by studying the differences in trends and bias in process parameters for (b) (4) and (b) (4) batches. In this analysis, study the yields for every unit operation of (b) (4) process as well as the overall yield as (b) (4).

iv. Please study the comparability of (b) (4) and (b) (4) batches using representative pharmacodynamics assays used in the clinical trials, including the TGT.

b) Drug Product Protocol:

i. In your response to IR item 5 provided in Amendment 61, page 4, paragraph 3, the following was noted "*up to* (b) (4) *are used of the total* (b) (4) *on lyophilizer* (b) (4) *and of the total* (b) (4) *on lyophilizers* (b) (4)." Given the difference in the number of (b) (4) between the lyophilizers, these lyophilizers do not appear to be equivalent as initially claimed. In addition, to date only (b) (4) runs have been performed on lyophilizer (b) (4) and only (b) (4) runs have been performed on lyophilizers (b) (4). Based on this information, we do not agree with the validation strategy proposed in the revised CP regarding the number and type of lots run to date to show comparable results between lyophilizer (b) (4) vs (b) (4). Please comment.

Given that (b) (4) does not appear to be in a state of control as evidenced by the manufacturing history provided for (b) (4), we strongly advise that the CP be withdrawn from the BLA and that the post-approval changes to (b) (4) FDP be submitted as a Prior Approval Supplement after BLA approval.

9. The Proven Acceptable Ranges and Normal Operating Ranges for (b) (4) and (b) (4) indicated for the lyophilization cycle parameters used for the FDP manufacturing are not supported by the process validation provided in the BLA. Results of (b) (4) lab-scale experiments were provided in amendment 50 (received 1 July 1 2016); however, there was no justification for how the lab-scale studies support the lyophilization parameter ranges at commercial scale. Please provide a detailed plan to support these ranges at commercial scale.

10. In regards to the Container Closure Integrity Testing (CCIT) for stability samples performed by (b) (4), which was incomplete, please provide the following:

    a) Specific details of the "point of failure" control that was used.

    b) Clarify if (b) (4) analysis was performed for product filled vials on stability.

    c) Provide details, SOPs etc. of the (b) (4) process and how operators are qualified to perform visual inspection.

    d) Results of the (b) (4) study (in the presence of the product), which was noted in your response to IR item 5 in Amendment 50 (received 01 July 2016), to be conducted at (b) (4) and stability determined by (b) (4) on Days (b) (4).

11. In regards to CCIT method performed at (b) (4), please provide details, SOPs, etc. in reference to the qualification of the operators that perform (b) (4). Include a description of course 04-01-C001, which was used for the qualification of operators noted in your response to IR item 5 in Amendment 50, received July 1, 2016.

12. Regarding (b) (4) equipment cleaning validation, please provide the following:

    a) Validation data to support the effectiveness of the cleaning of the (b) (4).

    b) Validation data to support the cleaning and storage of all (b) (4). In addition, please indicate the frequency in monitoring the (b) (4) during storage.

13. In reference to our IR on immunogenicity methods dated 17 February 2016 and your 03 March, 20 April, 08 July and 29 July 2016 responses, which are incomplete, we request that you develop and validate assays to measure the activity of the antibodies that bind (b) (4) or inhibit the activities of endogenous human Factors X and Xa. In your response, please address the following requests:

    a) Develop and validate the assay using clinically relevant methods (e.g., (b) (4)), and report the results in (b) (4) .

    b) 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 2014 *FDA Guidance for Industry Immunogenicity Assessment for Therapeutic Protein Products.* To ensure protection of confirmatory 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 previously requested that you develop these assays during the pre-IND meeting on 16 June 2009 (CRMTS #7089, Ref. PS000698), and you included a commitment to develop these assays in the original IND submitted on 15 March 2012 and in your Clinical Study Protocol 15-507 dated 09 June 2015.

    c) Develop an assay to assess the development of (b) (4) antibodies in subjects who have participated in the clinical studies. (b) (4) impurities are suspected to originate from CHO cells, which may be present in the FDP as evidenced from the formation of (b) (4) in stability studies.

    d) Use validated immunogenicity methods to:

        i. Assess how the presence of anti-Factor X/FXa inhibitory antibodies may interfere with the assays used to evaluate the pharmacodynamics, pharmacokinetics, and immunogenicity in the clinical studies.

        ii. Test retained clinical samples for anti-Factor X and anti-Factor Xa inhibitory antibodies and (b) (4) antibodies.

14. In reference to our IR on pharmacodynamics methods dated 17 February 2016 and your 03 March, 20 April, 08 July and 29 July 2016 responses, which are incomplete, please provide the reports of bioanalytical studies which you have committed to perform to establish the comparability, or lack thereof, between the three versions of the TGT assay. The three versions are (i) the in-house TF-activated (b) (4) (TF(b) (4)) method used in the Phases 1 and 2 clinical trials, (ii) the commercially available TF-activated CAT (TF-CAT), and (iii) the in-house contact-activated modification of the CAT method. The latter two assays were used in the phase 3 and 3b/4 trials. These studies should include side-by-side testing of samples spiked with ANDEXXA and FXa inhibitors and retrospective analyses of data from the clinical trials.

Please also address the following examples of incorrect presentation and interpretation of TGT data in the BLA:

a) On page 9 of the 27 July 2016 meeting materials, you claimed similarity between the correlation graphs of anti-FXa activity and TGT in the Phase 2 and Phase 3 clinical trials. However, you compared the mean TGT Phase 2 data from all (placebo and ANDEXXA-treated) subjects to the mean ETP Phase 3 data from the placebo arm only. Please revise these graphs to present data from the placebo and ANDEXXA arms separately.

b) Your 03 March 2016 response states that the TG(b) (4) and CAT methods are similar. However, there appears to be a stronger effect of ANDEXXA on TF-activated TGT elevation (e.g., during the first 3 hours post-bolus) in the Phase 3 studies, as compared to the effect report in the Phase 2 study.

   For example, analysis of the clinical study data presented in Table A1-5 provided in your 03 March 2016 amendment demonstrates that in the apixaban studies, TF-RFU was elevated above the pre-apixaban baseline by 29% (Study 12-502, Module 1) and TF-CAT was elevated by 66% (Study 14-503 Part 1) and 40% (Study 14-503 Part 2). In the rivaroxaban studies, TF(b) (4) was elevated by 15% (Study 12-502, Module 2) and TF-CAT was elevated by 30% (Study 14-504 Part 1) and 39% (Study 14-504 Part 2). In contrast to the differences in TGT elevation, TF(b) (4) and TF-CAT were inhibited to a similar degree by apixaban (50% inhibition in both methods) and rivaroxaban (80% in TF-RFU and 71% in TF-CAT). Please explain these findings and perform the anti-FXa activity versus TGT comparison separately for each of the FXa inhibitors.

c) The preclinical report for study NC-15-0659-R0001 states that "andexanet alone had minimal effect in the absence of rivaroxaban." However, the raw data you submitted on 17 July 2016 to support this report show a 50% increase and 40% shortening in the commonly used TGT parameters, thrombin peak height and time to thrombin peak, respectively. These findings suggest that the effect of ANDEXXA is not represented by the presented parameter of the TGT method, ETP.

15. In the 19 July 2016 re-analysis of the data from a subset of subjects in the Phase 3 clinical trial, you explained that the elevation of TGT over the pre-inhibitor treatment baseline was mediated by the inhibition of plasma TFPI activity, as evidenced by a reduced elevation in a contact-activated TGT assay. The finding that inhibition of TFPI was contributing to the procoagulant activity observed in the clinical studies implies a need to address this phenomenon in product labeling to assure that physicians will understand the effect of administration of ANDEXXA and the potential for enhanced thrombogenicity. To address this issue:

a) Please propose language for the Package Insert that will inform physicians of this incompletely characterized phenomenon and the potential risk of enhanced and prolonged thrombogenicity that it may cause.

b) Please perform additional analyses to delineate the magnitudes and durations of the respective contributions of anti-FXa reversal and TFPI inhibition on TGT elevation as a basis for relabeling of the product. The following approach is suggested to ensure that the relationship between the duration and magnitude of TGT elevation, and the reversal of anti-FXa activity is properly investigated:

    i. Re-evaluate the conclusions regarding the contribution of anti-FXa activity reversal to the TGT elevation. Because the TF-activated TGT method you used was not specific to the effect of anti-FXa activity reversal, we conclude that a contact coagulation pathway-activated TGT (which you referred to as (b) (4) TGT) should be used instead of, or in addition to, the TF-activated TGT whenever you present the TGT results as evidence of the potentially hemostatic outcome of anti-FXa activity reversal by ANDEXXA;

    ii. Re-analyze your TF-activated TGT assay data using the parameters suitable for evaluation of TFPI effect. For example, your data suggest that ETP is significantly less sensitive than the *thrombin peak height* to the procoagulant effect of TFPI inhibition by ANDEXXA. The use of a single parameter, e.g., *ETP*, could therefore be misleading;

    iii. Compare the contributions of the anti-FXa reversal and TFPI inhibition actions of ANDEXXA to TGT elevation as you have already started doing in amendment dated 19 July 2016 by comparing the time courses of TF-activated TGT and contact-activated TGT methods;

    iv. To demonstrate that the anti-FXa activity reversal, and not TFPI inhibition, was responsible for the successful normalization of the TGT, please apply the same statistical criteria you previously used in the Phase 3 study;

    v. To facilitate the review of these data by the FDA, please re-plot all the graphs that show the time-courses of anti-FXa and TGT elevation using:

        1. The same time scales of no less than 24 hours after an ANDEXXA bolus. Your presentation of anti-FXa activity over 12 hours and TGT over 22 hours created a misleading

appearance of good correlation between the duration of anti-FXa reversal (which is short) and that of elevation of TF-activated TGT (which is sustained);

2. Error bars calculated as the standard deviation of the mean for all data points, which should include the pre-treatment (the so-called normal TGT range presented as a horizontal gray area on the TGT graphs) for the ANDEXXA and placebo arms of the study. Your proposal to compare two standard deviations of the pre-treatment levels of TGT with a standard error of the mean for the ANDEXXA arm creates an incorrect impression that the elevation of TGT after ANDEXXA administration remains within the "normal TGT range" while in fact a substantial elevation over the pre-treatment baseline was observed in the Phase 3 studies.

vi. Please also reference the communication from FDA on 1 June 2016, which you have not yet addressed.

CLINICAL:

16. Confirmatory Study:

You are seeking Accelerated Approval of ANDEXXA for patients treated with direct or indirect FXa inhibitors when reversal is needed due to life threatening or uncontrolled bleeding. Under the Accelerated Approval Pathway, agreement is needed on the design of the confirmatory trial prior to approval of your biologic license application. We have not reached an agreement with you on the design of the confirmatory trial, ANNEXA-4 (Study 14-505). Complete review of the amendment to the ANNEXA-4 protocol submitted on August 4, 2016, and the revised Usual Care Cohort Study Protocol submitted on August 5, 2016 is pending. We look forward to ongoing discussions to finalize the study design. Listed below are some of the issues that require additional discussion. Other issues may be identified as we review the submitted protocols listed above.

a) We have determined that the preliminary results from some of the first 35 subjects in the ANNEXA-4 study are difficult to interpret for both efficacy and safety because not all subjects with gastrointestinal (GI) bleeding met eligibility criteria for having an acute major or life-threatening bleed, some non-visible bleeding events (e.g., hematemesis and melena) seem to have resolved prior to treatment with your product, and questions about the adjudication process made it difficult for FDA to confirm successful hemostatic efficacy. In addition, the efficacy data from the healthy volunteer study demonstrates that the reversal of anti-Factor Xa (FXa) activity is transient for subjects treated for apixaban and rivaroxaban. The transient nature of the reversal raises uncertainties with regard to efficacy in

patients with intracranial hemorrhage (ICH) where sustained reversal is associated with hemostatic benefits.

We therefore recommend that you restrict future enrollment of the ANNEXA-4 study to patients with ICH and enroll a comparable number of ICH patients in the Usual Care Cohort Study in order to evaluate the effect of sustained anti-FXa activity reversal in preventing hematoma expansion in subjects who experience ICH related to apixaban and rivaroxaban. Please reference the communication from FDA on 18 July 2016 under IND 15089 for further details.

b) We have not reached an agreement regarding the primary efficacy endpoint that determines the success of the ANNEXA-4 study. We acknowledge your commitment to initiate a prospective control cohort study (Usual Care Cohort Study) and plan to develop success criteria based on the data from this cohort control population. However, our ability to assess whether the revised design of ANNEXA-4 is interpretable depends on the details of the Usual Care Cohort Study, and the statistical analysis plan, which have not yet been fully reviewed and agreed upon between Portola and FDA.

17. Not Enough Evidence to Fully Support the Indication Sought:

The indication submitted for review for ANDEXXA was for "patients treated with a direct or indirect FXa inhibitor when reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding." The following problems were identified in the review of your application:

a) Edoxaban
The data for edoxaban are insufficient. The limited depth of reversal of the anti-FXa activity raises concerns that the proposed dose may be insufficient to result in substantial reduction in anti-FXa activity. The interpretability of efficacy is further limited by the number of healthy volunteers exposed to the dose proposed and the absence of threshold levels known to be predictive for hemostasis. We recommend that you conduct additional studies to identify a dosing regimen that will result in a sustained reduction in anti-FXa activity that is comparable to the depth of reversal achieved with apixaban and rivaroxaban. The safety and efficacy of this proposed dosing regimen should ultimately be evaluated in the confirmatory study.

b) Enoxaparin
The data for enoxaparin are insufficient for the following reasons: The mechanism of action of enoxaparin is based on dual pathways that affect Factors Xa and IIa in the coagulation cascade. The availability of protamine for reversal of enoxaparin-related bleeding further complicates the assertion that this is an unmet medical need, warranting additional justification. In order to support the use of anti-FXa activity as a surrogate for achieving adequate hemostasis in patients with acute major enoxaparin- related bleeding, we would need to understand the activity of ANDEXXA on Factor IIa. Please submit data to

establish that anti-FXa activity is reasonably likely to predict clinical benefit in view of its dual mechanism of anticoagulant activity. If you are unable to establish that anti-FXa activity is reasonably likely to predict the clinical benefit of ANDEXXA for enoxaparin-related bleeding we advise that you evaluate the hemostatic efficacy of your product in the target population pre-licensure.

In addition, the proposed dose (bolus + infusion) has not been evaluated in the only study (Study 12-502) that you have provided to support enoxaparin reversal. Study 12-502 included bolus dose only data without evaluating the infusion regimen. The data are not sufficient to establish the safety and efficacy of the proposed dose. We recommend that you evaluate the safety and efficacy of the bolus + infusion dose in phase 3 studies of ANDEXXA.

ADDITIONAL COMMENTS:

STATISTICAL:

18. In your response dated 5 July 2016 (125586/0/52, response to statistics IR), for question 1c, you confirmed that the mITT set for the placebo group, part 1, included 14 subjects for Study 14-504. However, in response to question 1d, you acknowledged that only 13 subjects from the placebo group were included in the primary analysis based on mITT set. Please update this analysis (Study Report 14-504 [Part 1] Table 11) by including all 14 subjects, using the pre-specified missing data imputation method.

PDUFA V APPLICANT INTERVIEW:

FDA has contracted with Eastern Research Group, Inc. (ERG) to conduct an independent interim and final assessment of the Program for Enhanced Review Transparency and Communication for NME NDAs and Original BLAs under PDUFA V ('the Program'). The PDUFA V Commitment Letter states that these assessments will include interviews with applicants following FDA action on applications reviewed in the Program. For this purpose, first-cycle actions include approvals, complete responses, and withdrawals after filing. The purpose of the interview is to better understand applicant experiences with the Program and its ability to improve transparency and communication during FDA review.

ERG will contact you to schedule a PDUFA V applicant interview and provide specifics about the interview process. Your responses during the interview will be confidential with respect to the FDA review team. ERG has signed a non-disclosure agreement and will not disclose any identifying information to anyone outside their project team. They will report only anonymized results and findings in the interim and final assessments. Members of the FDA review team will be interviewed by ERG separately. While your participation in the interview is voluntary, your feedback will be helpful to these assessments.

Within one year after the date of this letter, you are required to resubmit or withdraw the application (21 CFR 601.3(b)). If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 601.3(c). You may also request an extension of time in which to resubmit the application. A resubmission must fully

address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

You may request a meeting or teleconference with us to discuss the steps necessary for approval.

For PDUFA products, please submit your meeting request as described in our guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants,* dated May 2009. This document is available on the internet at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf, and CBER's *SOPP 8101.1: Scheduling and Conduct of Regulatory Review Meetings with Sponsors and Applicants*. This document is available on the internet at http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ProceduresSOPPs/ucm079448.htm. Both documents may be requested from the Office of Communication, Outreach, and Development, at (240) 402-8020.

If you have any questions regarding the above, please contact the Regulatory Project Manager, Thomas J. Maruna, MSc, MLS(ASCP), CPH at (240) 402-8454 or thomas.maruna@fda.hhs.gov.

Sincerely,

Jay Epstein, MD
Director
Office of Blood Research and Review
Center for Biologics Evaluation and Research