

Meeting Response

Our Reference: BLA 125586/O
CRMTS 10471

TODAY'S DATE: October 12, 2016 **PAGES:** 21

TO: Ms. Janice Castillo
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SUBJECT: Summary of FDA Internal Meeting

PRODUCT: Coagulation Factor Xa (Recombinant), Inactivated

PROPOSED INDICATION: For patients treated with a direct or indirect FXa inhibitor when reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding

CBER Attendees:

Najat Bouchkouj, MD (OBRR/DHCR)
Yolanda Branch, PhD (OBRR/DHCR)
Wilson Bryan, MD (OCTGT/DCEPT)
Mr. John Eltermann (OCBQ/DMPQ)
Jay S. Epstein, MD (OBRR)
Mahmood Farshid, PhD (OBRR/DHRR)
Bindu George, MD (OBRR/DHCR)
Basil Golding, MD (OBRR/DHRR)
Christine Harman, PhD (OCBQ/DMPQ)
Timothy Lee, PhD (OBRR/DHRR)

Mark Levi, PhD (OBRR/IO)
Iftekhar Mahmood, PhD (OBRR/DHCR)
Thomas J. Maruna, MS (OBRR/IO)
Mikhail Ovanesov, PhD (OBRR/DHRR)
Anne M. Pilaro, PhD (OBRR/DHCR)
Ms. Carolyn Renshaw (OCBQ/DMPQ)
Patrick Riggins, PhD (OCBQ/DRPM)
Stephanie Simek, PhD (OCBQ)
Ramani Sista, PhD (OCBQ/DRPM)
Nicole Verdun, MD (OBRR)

Although we continue to reserve October 17, 2016, 2:30 p.m. – 4:30 p.m., EDT, for a face-to-face meeting with you regarding this product, if you find that our attached responses and advice are sufficiently clear and complete to obviate the need for further discussion, please inform us in writing as soon as possible so that we may clear the meeting time. These responses would then become the official FDA responses to your questions. Alternatively, if you have questions regarding specific responses or advice, please inform us so that the appropriate members of the

review committee can provide clarification during the reserved meeting time. Note that if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our pre-meeting (preliminary) responses, we may not be prepared to discuss and/or to reach agreement on such changes at the meeting.

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for October 17, 2016, 2:30 p.m. – 4:30 p.m., EDT, between Portola Pharmaceuticals, Inc. and the Center for Biologics Research and Review. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face-to-face to teleconference). Contact the Regulatory Project Manager (RPM) if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

Please include a reference to CRMTS 10471 in your future submissions related to the subject product.

Questions from the Applicant:

Applicant Question 1a:

Portola acknowledges the request for supplementary validation studies to establish impurity clearance and confirms that this study will be performed and the data included in the resubmission. Portola does not believe the current data set supports that there is a (b) (4) impurity in the (b) (4) that is generating the (b) (4). Clearance of potential (b) (4) impurities will be demonstrated by evaluation of the levels of the (b) (4) by (b) (4) (as (b) (4) methods) and (b) (4) by the Process-specific assay in the (b) (4) and in in-process (b) (4) of the downstream process for (b) (4) representative (b) (4) batches. The study will be designed to demonstrate no increase in (b) (4) levels across the purification process when the samples are (b) (4) through a combination of (b) (4). In addition, as described in the following response strategies, validation data from the (b) (4) control (Comments 1c & 1d) and hold time stability (Comment 1e.) studies will provide further evidence that (b) (4) impurities are cleared through the downstream process. Furthermore, a root cause analysis will be provided for previous findings on “failed” hold time studies (Comment 1e.). Finally, to support a lack of (b) (4) activity in the (b) (4) levels will be trended on stability with robust and (b) (4) methods (Comment 1d). All validation protocols and reports will be reviewed and approved by the Portola Quality Assurance unit.

Does FDA concur that documenting the removal of (b) (4) and control of the (b) (4) will be sufficient to complete the Validation studies to demonstrate clearance & control of impurities?

FDA Response to Question 1a:

No, the scope of your proposed studies is not sufficient to demonstrate control over the manufacturing process. In addition to the proposed evaluation of the levels of the (b) (4) [REDACTED], please characterize the identity and biochemical properties of the impurities, including those with (b) (4) [REDACTED], and demonstrate clearance of the impurities on the basis of their observed characteristics. For example, you had described some of the ongoing impurity identity studies in the July 17, 2016, amendment to the BLA. We agree that it would be helpful to demonstrate no increase in (b) (4) [REDACTED] levels across the purification process when the samples are (b) (4) [REDACTED] through a combination of (b) (4) [REDACTED].

Applicant Question 1b:

Portola acknowledges the request to demonstrate that the apparent trends in the purity and stability attributes of the (b) (4) [REDACTED] and Final Drug Product (FDP) for (b) (4) [REDACTED] do not adversely affect the quality, safety, purity, or potency of the product as they relate to its safety and effectiveness.

Portola confirms that it will provide in the resubmission an analysis and discussion of any purity and stability data, generated by testing with the new and revised assays, which demonstrates trends that may adversely affect the quality, safety, purity, or potency of the product. In addition to a thorough assessment of the current (b) (4) [REDACTED] data, and data from an (b) (4) [REDACTED] method ((b) (4) [REDACTED]) for quantitating (b) (4) [REDACTED] levels will be included in the assessment. Trending of data from side-by-side batch analysis release data, and purity and potency evaluation including samples that are enriched in the (b) (4) [REDACTED] product-related substance will also be assessed.

Does FDA agree with this approach?

FDA Response to Question 1b:

Yes, we agree with your approach and acknowledge your commitment to provide analysis and discussion of all purity and stability data, generated by testing with the new and revised assays, which demonstrate trends that may adversely affect the quality, safety, purity, or potency of the product. We also agree that it would be helpful to trend data from side-by-side batch analyses and purity and potency evaluations, and inclusion of samples that are enriched in the (b) (4) [REDACTED] product-related substances.

Applicant Question 1b(i):

Portola acknowledges the request to address the apparent increase in both the levels of the (b) (4) [REDACTED] and batch-to-batch variability in the (b) (4) [REDACTED] when (b) (4) [REDACTED] was replaced with (b) (4) [REDACTED].

It should be noted that data in Figure 5b of the Investigation Report for DEV-1632 was not generated in a side by side manner and only includes (b) (4) [REDACTED] batches. Therefore, Portola proposes to provide in the resubmission a more comprehensive data set (all available (b) (4) [REDACTED] lots manufactured to date) generated in a side-by-side manner by the validated (b) (4) [REDACTED] methods. This will provide more informative evidence of the capacity of (b) (4) [REDACTED] to

produce levels of the (b) (4) consistent with those seen in (b) (4). The side-by-side data will be statistically analyzed for trends in (b) (4) levels and the comparability of (b) (4).

Does FDA agree with this approach to addressing the (b) (4) levels between (b) (4) as well as the batch-to-batch variability within a Process?

FDA Response to Question 1b(i):

Yes, we agree with your plan to conduct a comparative study by performing side-by-side testing of all available (b) (4) lots using the validated (b) (4) methods. However, in your report, please also explain how the variability of the analytical methods was responsible for the apparent increase in both the levels of the (b) (4) and batch-to-batch variability in the (b) (4) when (b) (4) was replaced with (b) (4).

Applicant Question 1b(ii):

Portola commits to statistically evaluate (b) (4) data from all accelerated stability studies for an increase in rate of (b) (4) formation in (b) (4) batches. It should be noted that the (b) (4) is a characterization method that does not accurately discriminate between the (b) (4). In addition, Portola will provide data supporting that (b) (4) variants, which are generated under (b) (4). Furthermore, reassessment of the (b) (4) data from the (b) (4) Comparability study, in conjunction with preliminary stability data from the new (b) (4) assay, indicate that there are no adverse trends in (b) (4) levels beyond assay variability. Given limitations of the (b) (4) and the (b) (4) assays, Portola will provide (b) (4) data as the definitive evidence of (b) (4) level control and comparability in the submission.

Does FDA agree with using the totality ((b) (4)) of the data to examine the apparent adverse stability trends seen for (b) (4)?

FDA Response to Question 1b(ii):

Yes, we agree with your plan to statistically evaluate (b) (4) data from all accelerated stability studies, and supplement it with (b) (4) data to demonstrate control of the (b) (4). With reference to your hypothesis that an apparent increase in the (b) (4) was caused by the interference of the (b) (4) variants in the detection of the (b) (4) by (b) (4), please assess the effects of (b) (4) on the purity and potency of andexanet alfa.

Applicant Question 1b(iii):

Portola acknowledges that the 6 month data submitted in the BLA for batch (b) (4) suggested an apparent adverse stability trend. However, the 9 and 12 month stability points have now been completed and the additional data show that there is no adverse

stability trend beyond expected analytical variability of the (b) (4) method. These data will be provided in the resubmission.

Does FDA agree with this approach?

FDA Response to Question 1b(iii):

Yes. In addition, please evaluate the root cause for the adverse stability trends observed in the early stages of the real-time stability studies.

Applicant Question 1c:

Portola acknowledges the request 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.

Portola commits to conduct a prospective supplementary validation study to specifically demonstrate the effectiveness of the control strategy for (b) (4), which is a critical process parameter for the (b) (4) step, for (b) (4) representative batches of (b) (4). Consistency of (b) (4) performance will be demonstrated by successfully meeting the IPL acceptance criteria for the (b) (4) step. (b) (4) quality will be confirmed by complete release testing, including all of the new or revised assays. Portola intends to conduct the validation studies for the control of (b) (4) (b) (4) prior to implementation of the (b) (4). Once the (b) (4) is installed and an IQ/OQ is performed, a PQ will be performed to demonstrate (b) (4) control under the validated manufacturing conditions. Portola will include the (b) (4) -control validation report as well as the PQ report for the (b) (4) in the resubmission. In addition, Portola commits to including in the resubmission an addendum to the existing PPQ report that demonstrates the effectiveness of the control strategy for critical process parameters and key operating parameters established since submission of the BLA.

Does the Agency agree with the staged approach, first validating the (b) (4) control parameters for the (b) (4) step, followed by the implementation and qualification of the (b) (4) to control (b) (4) within validated ranges?

FDA Response to Question 1c:

We are unable to agree with the described proposal because you did not provide a rationale for conducting the validation studies for the control of (b) (4) before implementation of the (b) (4). Our understanding is that if the (b) (4) is being added to the process to provide control of the (b) (4) of the (b) (4) during the (b) (4) step, then the (b) (4) should be installed and qualified before the process validation of the (b) (4) step.

Applicant Question 1d:

Portola did not provide a question for 1d.

Applicant Question 1e:

Portola did not provide a question for 1e.

Applicant Question 1f(i):

Does the Agency agree that the description of the decisions and timing behind using (b) (4) lot (b) (4) for the FDP PPQ support the inclusion of this batch in the PPQ series? Does the Agency agree with Portola's approach on determining the disposition of this batch?

FDA Response to Question 1f(i):

No, we do not agree with the inclusion of the out-of-specification (OOS) (b) (4) batch (b) (4) in the FDP PPQ series and Portola's approach on determining the disposition of this batch.

Please provide, for our review, all supporting documentation regarding the use of the OOS (b) (4) batch in FDP production, and the decisions that led to the disposition of the affected (b) (4) FDP batches. In your response, please provide a list of all the deviation investigations regarding the use of the OOS batch, which were opened at (b) (4), (b) (4) and Portola, and related CAPAs, and explain why this information was not provided in Portola's BLA and (b) (4) FDP PPQ report. Specifically, please describe the measures that were put in place to prevent the recurrence of these deviations. Please support your conclusions with references to the relevant Quality Agreements and Quality Assurance SOPs at Portola, (b) (4), as well as at (b) (4).

Applicant Question 1f(i & ii):

Does the Agency agree that the totality of the FDP data, as outlined in Table 4, support the consistency and validation of the FDP process?

FDA Response to Question 1f(i & ii):

No. Please refer to FDA Response to Question 1f(i).

Applicant Question 2a:

Portola did not provide a question for 2a.

Applicant Question 2b(i):

Portola acknowledges the request to validate a (b) (4) assay as an identity test for andexanet alfa, and to validate the methods for determining the (b) (4) and (b) (4) content.

As described in the 20 April, 08 July, and 29 July 2016 responses, Portola will provide in the resubmission validation reports for the (b) (4) assay, the (b) (4) method for determining the (b) (4), and the (b) (4) content assay, and justifications for proposed specifications

Does FDA agree with this approach?

FDA Response to Question 2b(i):

Yes.

Applicant Question 2b(ii), Parts 1 & 2:

As described in the IR response of 08 July 2016 (SN0055), Portola will provide in the resubmission analytical methods for the mannitol, sucrose, and Polysorbate 80 FDP assays. All available released lots of (b) (4) andexanet alfa FDP will be tested by the validated assays to establish commercial specifications. Portola will provide validation reports and justifications for the proposed specifications.

Portola will provide summaries of the compendial method verifications performed for the analytical methods used for release of raw materials intended for the FDP formulation.

Does FDA agree with this approach?

FDA Response to Question 2b(ii), Parts 1 & 2:

Yes.

Applicant Question 2b(iii):

Portola acknowledges the request to develop and validate potency units for andexanet alfa to replace the current unit of “percent of a reference standard.”

Portola commits to validate potency units to andexanet alfa reference standard for direct and indirect assays by January 2017. (Please refer to response in 3d.)

Does FDA agree with this approach?

FDA Response to Question 2b(iii):

Yes. However, in addition to validating the potency units of the reference standards, please also establish a correlation between the existing and new potency units such that the results of the previous stability studies and batch analyses expressed in the old potency units could be made relevant to the specification limits expressed in the new potency units.

Applicant Question 2c:

Does FDA agree that the totality of andexanet alfa variants can be controlled with this matrix approach?

FDA Response to Question 2c:

Yes, your proposal to demonstrate control over all product-related variants by using a matrix approach appears reasonable. However, in your response, please provide trending graphs for all the (b) (4), including those for which quantitative acceptance criteria will not be developed.

Applicant Question 2d:

Portola acknowledges the request to eliminate the “report visible particles” from the (b) (4) specification. It is acknowledged that visible particulates could be indicative of protein solubility and stability issues. Therefore, Portola agrees to revise the specification for Visual Appearance for (b) (4) to “Clear, colorless to slightly yellow solution, essentially free of visible particulates.” This specification for (b) (4) provides control for, and is consistent with, drug product requirements in (b) (4)

(b) (4) in that the inspection process shall be designed and qualified to ensure that every lot of parenteral preparations is essentially free from visible particulates.

In regards to the request to revise the FDP specification at lot release, Portola believes the **FDP specification provided to FDA, “essentially free...” complies with (b) (4)** requirements as well as ICH Q6B, Particulate matter: Parenteral products should have appropriate acceptance criteria for particulate matter. This will normally include acceptance criteria for visible particulates and /or clarity of solution, as well as for sub-visible particulates as appropriate. Lastly, Portola feels the FDP specification as provided is consistent with industry standards and global regulatory expectations.

Does FDA agree with this approach?

FDA Response to Question 2d:

Yes, we agree with the proposed specification for the release of (b) (4) reconstituted FDP **expressed as “Clear, colorless to slightly yellow solution, essentially free of visible particulates.”**

Applicant Question 2e:

As stated in our IR response of 15 June 2016 (SN0039), Portola is developing a (b) (4) assay and release specifications to measure the inhibition of TFPI activity by AndexXa FDP. Portola proposes to modify the (b) (4)

. The units of the assay will be defined using the new units to be incorporated into the (b) (4), to be traceable to the international reference preparations distributed by the (b) (4).

In addition, Portola will use the CAT Thrombin Generation assay used in clinical studies to characterize the TFPI interaction by (b) (4) parameters as part of the characterization and validation of the new TFPI (b) (4) assay.

Does the agency agree with this proposal for development and validation of a release assay to measure the inhibition of TFPI activity by AndexXa FDP?

FDA Response to Question 2e:

No. Your current (b) (4) assay is not suitable for the evaluation of the inhibition of TFPI activity by andexanet alfa because this assay does not measure the interaction of TFPI with its biological target, Tissue Factor/Coagulation Factor VIIa complex, nor does it measure the reversal of the inhibition of Factor X activation by this complex.

Applicant Question 2f:

Portola did not provide a question for 2f.

Applicant Question 2g:

As discussed with FDA at the October 2014 Type C meeting as well as at the pre-BLA CMC meeting in July 2015, Portola has initiated development of a process-specific (b) (4) method. We have generated a process-specific (b) (4) preparation using (b) (4)

(b) (4). A bridging study will be performed to compare (b) (4) results from the new process specific assay to that of the (b) (4) commercially available (b) (4) assay currently used for release testing. This data will be provided in the BLA resubmission. Portola will develop specifications for the new (b) (4) assay which will be justified statistically by manufacturing lot history and clinical experience.

Does FDA agree with the proposed bridging approach?

FDA Response to Question 2g:

Yes. In addition, please use samples of representative process intermediates to demonstrate that the new process-specific (b) (4) assay is at least as sensitive as the currently used commercially available (b) (4) assay (b) (4).

Applicant Question 2h & 2h(i):

Portola acknowledges the request to develop new specifications for the (b) (4) and provide complete reports for the investigations into the root causes behind the observed changes in product quality attributes after the introduction of (b) (4). See sections 1b, 1c, 1d, 1e. for Portola's commitments in regards to these requests.

As discussed in the Introduction Section, Portola will provide a risk-assessment of the (b) (4) and the (b) (4) impurities and their impact on the purity, quality, potency, and stability of the product.

Does FDA agree with this approach?

FDA Response to Question 2h & 2h(i):

Yes.

Applicant Question 2h(ii):

Portola will use the current quantitative (b) (4) method and the new (b) (4) method, once validated, for the measurement of the (b) (4) to compare the (b) (4) batches, and to monitor the (b) (4) in stability studies for the (b) (4) FDP. This approach is more fully described in the response to Question 2c. Specifically, all available (b) (4) FDP batches will be tested side-by-side and the data analyzed by the appropriate statistical methods. (b) (4) is currently used for stability studies, and the (b) (4) method, once validated, will be added to the stability protocol as an addendum and used as the (b) (4)

method for monitoring the (b) (4) in stability studies for the (b) (4) FDP going forward.

Does FDA agree with the use of (b) (4) to as the (b) (4) method?

FDA Response to Question 2h(ii):

We agree that the use of improved and (b) (4) methods is essential in demonstrating control over the (b) (4) at release and in stability studies. However, without reviewing the assay qualification data, we are unable to comment on the suitability of the (b) (4) assay for this purpose.

Applicant Question 2h(iii):

Portola acknowledges the request to explain how the available clinical data support the (b) (4) specifications, and to 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. Portola will analyze the available (b) (4) batches, side-by-side, by the (b) (4) method and the validated (b) (4) (proposed (b) (4) method) method in order to establish the ranges of levels for the (b) (4) in all released batches, including those used in the completed clinical trials. This will provide a more statistically significant sampling than used previously. As described in the Portola IR response of 13 July 2016 (SN0059), Portola anticipates the precision of the (b) (4) based (b) (4) method to be superior to that of the (b) (4) method, allowing for a revised specification for (b) (4). Furthermore, the analysis of all available batches of (b) (4), compared to the limited batches that were used to derive the (b) (4) specification is anticipated to more accurately reflect the capabilities of the manufacturing process and align the specification with the (b) (4) levels observed in the clinical batches. This side-by-side (b) (4) data will be used to justify how the available clinical data supports the (b) (4) specification, and discussed in the Justification of Specifications.

Does FDA agree with this approach to developing new specifications for the (b) (4) and explaining how the available clinical data supports the (b) (4) specifications?

FDA Response to Question 2h(iii):

Yes.

Applicant Question 2h(iv):

Portola acknowledges the request to use (b) (4) methods to compare the specific potencies of the (b) (4) with the other product-related molecular forms of AndexXa, and the suggestion to use a biomarker assay, e.g., (b) (4), in addition to validated potency method.

Portola is developing biochemical methods to generate a test sample that is a (b) (4) of AndexXa (b) (4) for the (b) (4), but that will still be a (b) (4) of all the (b) (4). This test sample will be used to evaluate the (b) (4) in (b) (4) studies (see question 6b below) and other functional assays. This (b) (4) will be compared in the (b) (4) assay to the lot of AndexXa (b) (4) from which it was

derived, as well as all the direct, indirect, and the new TFPI (b) (4) assays. In addition, the (b) (4) sample will also be analyzed in the (b) (4) assay to compare against the (b) (4) starting material, using (b) (4) parameters. Portola will also analyze data from prior studies where (b) (4) was used in the (b) (4) method to (b) (4) and identify (b) (4) present in each (b) (4). The (b) (4) data will be further analyzed to (b) (4) the (b) (4) which contain various (b) (4), and the potency of these (b) (4) will be compared to that of (b) (4).

Does FDA agree with this approach?

FDA Response to Question 2h(iv):

Yes. In addition, please demonstrate parallelism between the dose-response curve of the (b) (4) material and that of the ordinary (b) (4) batch in the proposed potency assays and (b) (4) TG assay. Furthermore, because the (b) (4) of andexanet alfa may be produced by (b) (4) by Factor Xa and because high amounts of human Factor Xa are used as a reagent in your potency assay, please evaluate the effect of this Factor Xa on the generation of (b) (4) in the potency assay.

Applicant Question 2i:

Portola did not provide a question for 2i.

Applicant Question 2j:

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

Portola will provide a complete justification of the specifications, using appropriate statistical methodology for defining both release and end of shelf life specifications, taking manufacturing process consistency and data obtained from lots used in clinical studies into consideration. The justification will include how the additional release methods will further demonstrate consistent performance of our manufacturing process.

Does FDA agree with this approach?

FDA Response to Question 2j:

Yes. In your response, please also provide the raw data and the results of your statistical analyses.

Applicant Question 3a:

Portola's current reference standard Lot (b) (4) was qualified against an approved specification document. Portola will calibrate this standard with the (b) (4) reagents (refer to question 2b (iii)). Portola will use this reference standard until a new PRS is manufactured and qualified for use. (Refer to question 3b.)

Does the agency agree that PTLA can continue to use the existing RS, standardized against the WHO Standards, while developing the PRS in parallel.

FDA Response to Question 3a:

No. Please develop a primary reference standard (PRS) and a qualification protocol for the preparation of subsequent RS, which will ensure consistency of the characteristics of all RS, including its potency unit, throughout the life-cycle of the product. With reference to the proposed use of the existing RS Lot (b) (4), please describe the measures you have in place that can ensure the continuity and comparability of the quality and characteristics of previous, current, and future RS, such as evaluation of stability and process development investigations.

Applicant Question 3b:

Portola did not provide a question for 3b.

Applicant Question 3c:

Portola did not provide a question for 3c.

Applicant Question 3d:

Portola will assign potency to the PRS. The 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 will be provided in the resubmission.

Primary and Working reference standards will be calibrated against (b) (4) reagents.

(b) (4) in the Direct Potency Assay and (b) (4) in the Indirect Potency Assay. The IC50s of (b) (4) determinations will be averaged to determine a mean IC50 for each assay. For Direct Potency the IC50 value will represent (b) (4) AndexXa Direct Potency Units and will be described as the (b) (4)

(b) (4). For Indirect Potency, the IC50 value will represent (b) (4) AndexXa Indirect Potency Units and will be described as the (b) (4)

Portola will provide the requested protocol for the replenishment of these reference standards in the resubmissions.

Does the agency agree with this approach?

FDA Response to Question 3d:

Yes. Please note that (b) (4) is finalizing the development of a new standard for human Factor Xa activity. We recommend using this new standard in place of, or in addition to, the (b) (4).

Applicant Question 3e:

Portola did not provide a question for 3e.

Applicant Question 3f:

Portola did not provide a question for 3f.

Applicant Question 4a:

Portola will retest all available (b) (4) batches using the new validated release methods to demonstrate that the old batches meet shelf-life specifications, and proposed comparable stability profiles. Portola plans to evaluate the comparability of (b) (4) and if demonstrated will evaluate the (b) (4) stability data to propose a shelf-life for (b) (4) product.

Does FDA agree that, if comparability is demonstrated, the retest data will be sufficient to establish a proposed shelf-life for commercial (b) (4) drug product?

FDA Response to Question 4a:

Yes, we agree that, if comparability between (b) (4) batches is demonstrated, (b) (4) data can be used to support a proposed shelf-life for the commercial (b) (4) drug product.

Applicant Question 4b:

Portola did not provide a question for 4b.

Applicant Question 4c:

Portola did not provide a question for 4c.

Applicant Question 4d:

Portola did not provide a question for 4d.

Applicant Question 5a:

Portola acknowledges the request to include (b) (4) as a critical process parameter for the (b) (4) step. Portola will revise the status of the (b) (4) of the (b) (4) to a Critical Process Parameter.

Does FDA agree with this approach to revision of the (b) (4) parameter designation?

FDA Response to Question 5a:

Yes.

Applicant Question 5b:

Portola did not provide a question for 5b.

Applicant Question 5c(i to v):

Portola proposes that if comparability between first generation (GEN1) (b) (4) manufactured at (b) (4) and second generation (GEN2) product, manufactured at Lonza (Porriño, Spain) is demonstrated with analytical and PK/PD and safety data, approval of GEN2 can be achieved by a Prior-approval Supplement (PAS).

Does the Agency agree?

FDA Response to Question 5c(i to v):

This question is outside the scope of the CR Letter and will be discussed in a separate meeting for the GEN 2 process. Moreover, it is premature to discuss the regulatory pathway for the GEN2 process before we resolve all the deficiencies in the current process. In general, FDA and Portola would need to agree on the extent of the comparative studies and the criteria for establishing comparability between the (b) (4) manufactured at (b) (4) and the GEN2 preparations manufactured at Lonza in Spain. The GEN2 process introduces several manufacturing changes that are considered significant; for example, the (b) (4) step may change the (b) (4)

that are found in the current (b) (4) andexanet alfa product. These changes may affect the quality, purity or potency of the product.

Applicant Question 6a:

Portola will evaluate the suitability of the (b) (4) method for assessing interactions of TFPI and andexanet alfa (b) (4). As we mentioned in the IR response dated 15 June 2016, Portola has not performed (b) (4) experiments to examine protein:protein interactions with andexanet alfa. All previous (b) (4) studies with andexanet alfa have measured the interaction with small-molecule inhibitors. Since the method may not be readily suitable for measuring the high-affinity interactions between andexanet alfa and TFPI, method development may be required. If the assay performance is suitable for the requested parameters (n and ΔH), Portola will proceed with characterization studies to compare (b) (4) (b) (4) batches) and (b) (4) (b) (4) batches) using this (b) (4) method.

Does FDA agree with this approach?

FDA Response to Question 6a:

Yes.

Applicant Question 6b:

Portola did not provide a question for 6b.

Applicant Question 6c:

Portola acknowledges the request to investigate the sensitivity of the (b) (4) method to evaluate the (b) (4) of AndexXa and to consider including the (b) (4) assay in the (b) (4) release specifications.

*Portola agrees to investigate the sensitivity of the (b) (4) method to evaluate the (b) (4) of AndexXa and to consider including the (b) (4) assay in the (b) (4) release **specification focusing on the (b) (4) parameters of ΔH and n .** However, Portola has not been able to identify a contract lab that has this instrumentation available to run under GMP conditions, therefore we will not be able to incorporate (b) (4) into testing as a release assay. All (b) (4) studies to date have been run at Portola as characterization assays in a non-GMP environment. In addition, the currently proposed potency assays for release*

(including the new TFPI (b) (4) assay described in question 2 e above) are considered sufficient to address all mechanisms of action of andexanet.

Does FDA agree with the proposed plan to address the questions raised in 6 a, b, and c?

What samples are to be tested to address the question raised in 6c above?

FDA Response to Question 6c:

Yes, we agree with the proposed plan to address the questions raised in Questions 6a, 6 b, and 6c. With reference to Question 6c, we recommend using (b) (4) samples to investigate the sensitivity of the (b) (4) method to evaluate the (b) (4) of ANDEXXA.

Applicant Question 7:

Portola acknowledges the request to identify the (b) (4) in the (b) (4) identified by FDA using a (b) (4)

Portola has observed similar (b) (4) when using (b) (4) and has identified the (b) (4) to comprise primarily of the intact (b) (4), which are controlled by the (b) (4) method. Portola developed and validated the (b) (4) method with (b) (4) in the (b) (4) as a method intended to monitor and control the levels of (b) (4) species. See response to question 2(c) for a more complete discussion of the (b) (4) method.

Does FDA agree this adequately explains the (b) (4) observation made by FDA using the alternate (b) (4)?

FDA Response to Question 7:

Yes. However, please also demonstrate that the intact and (b) (4) forms are properly controlled by the remaining release assays.

Applicant Question 8:

Portola did not provide a question for #8.

Applicant Question 9:

Does the provided justification clarify how the lab-scale studies support the lyophilization parameter ranges at commercial scale?

FDA Response to Question 9:

We acknowledge that extensive studies have been performed by (b) (4) including comparability and scalability studies that were used to set and support the design space. However, we have not had the opportunity to review these studies, thus we cannot adequately assess the justification provided. Based on this, we recommend the following be provided in the BLA resubmission:

- a. All comparative and scalability studies performed that were used to determine the design space and to explore parameters in the lab-scale lyophilizer and that are

indicated to support the comparability of the small and commercial scale lyophilizers for setting the parameter ranges for the commercial scale lyophilizer.

- b. Indicate how the NORs and PARs are acceptable considering the comparison of the dryer load and capacity of the lab scale lyophilizer vs. the commercial scale lyophilizer .
- c. A plan to perform and submit results of at least two commercial runs at the high and low ends of the PARs to verify the PARs at the commercial scale.

Applicant Question 10:

Portola asks that FDA confirms a “point of failure” control is a positive control for a container/closure defect.

FDA Response to Question 10:

Please provide **detailed information of the “control” that is used to demonstrate the** sensitivity of the test in detecting a critical defect in the container closure. The point of failure sample should be positive in the testing. Please note, as indicated in past communications, to support sensitivity of the container closure integrity testing, we recommend that the defect diameter be as small as reasonably possible.

Applicant Question 11:

Portola acknowledges the request for details, SOPs, a description of course 04-01-C001 etc. in reference to the qualification of the operators that perform (b) (4) for the CCIT method performed at (b) (4). Portola will provide in the resubmission of the BLA the description of course 04-01-C001, that was used for the qualification of operators as noted in our response to IR item 5 in Amendment 50, and a copy of Course 04-01-C001.

Does FDA agree with this approach?

FDA Response to Question 11:

Yes, we agree with the approach to providing the course description of qualifying operators for (b) (4) for CCIT. Additionally, please also provide in the BLA resubmission, relevant SOPs used for performing (b) (4) for CCIT and indicate the acceptance criteria used.

Applicant Question 12a & 12b:

Portola did not provide a question for 12a & 12b.

Applicant Question 13a:

Portola did not provide a question for 13a.

Applicant Question 13b:

Portola is developing an (b) (4) assay and will use it to test for (b) (4). This assay was not developed previously, as we have routinely screened for antibodies against native fX or fXa in all

our clinical studies to date, and have yet to identify a sample that was positive for antibodies against fX or fXa.

Does FDA agree with this approach?

FDA Response to Question 13b:

Yes. Please also cross-validate the existing (b) (4) assay for (b) (4) with (1) the proposed (b) (4) test for (b) (4), and (2) the (b) (4) assay for (b) (4) in human plasma in the phase 1 clinical studies.

Applicant Question 13c:

In order to use the limited plasma samples retained from the completed clinical studies, Portola proposes to split the retained samples for (b) (4) and anti-FX/Xa neutralizing antibody tests. For the (b) (4) assay, Portola proposes to use the retained plasma samples in the Phase 2 study (Study 12-502) with the highest andexanet doses with apixaban (module 1, cohort 6) and rivaroxaban (module 2, cohort 5). Does the agency agree with this proposed testing approach?

FDA Response to Question 13c:

No, your sample testing plan is not sufficiently detailed and justified. Please provide an immunogenicity testing plan to include, but not be limited to the following:

- 1) The evaluation of retained samples positive for anti-andexanet alfa antibodies;
- 2) The availability of the samples at time-points at sufficient time intervals following andexanet alfa dosing at which antibody development would be expected to occur, e.g., 14, 21, or 28 days post-dose;
- 3) The availability of samples from sufficient numbers of subjects or patients at these later time-points for the antibody results to be meaningful;
- 4) The additional data from the ongoing confirmatory study (ANNEXA-4);
- 5) The clarification on how the samples will be split.

Applicant Question 13d(i):

Portola is assessing possible interference by antibodies to fX or fXa, using a surrogate anti-human fX/fXa neutralizing antibody, in the following PD assays: anti-fXa and thrombin generation, as well as the clotting assays (b) (4). We are also assessing the possible interference of antibodies in the assay used to determine andexanet PK.

Does the Agency agree with this testing approach?

FDA Response to Question 13d(i):

Yes.

Applicant Question 13d(ii):

Please refer to our response to Question 13c) for the (b) (4) assay. Portola proposes to test the retained plasma samples from the Phase 2 study (Study 12-502) with the highest andexanet doses with apixaban (module 1, cohort 6) and rivaroxaban (module 2, cohort 5).

For anti-fX/fXa neutralizing antibody tests, Portola proposes to test the following retained clinical samples from the Phase 3 studies: Although there may be limited availability of the retained samples from Part 2 of Phase 3 studies that have already been used for non-TF initiated thrombin generation, we propose to test any remaining samples from Part 2 of the Phase 3 studies (Study 14-503 and 14-504) with apixaban and rivaroxaban for potential presence of anti-fX/fXa neutralizing antibody activities, as these cohorts represent the highest andexanet doses tested in the Phase 3 studies.

Overall timeline for generating data to address these responses is dependent upon how long it takes to develop and validate the new assay being requested, and on how many samples FDA wants tested in the assays.

Do the responses provided to question 13 d, parts i and ii, satisfy the requested requirements?

Does the agency agree with the proposed testing schema of retained clinical samples?

FDA Response to Question 13d(ii):

No, please refer to FDA Response to Question 13c.

Applicant Question 14a:

Portola did not provide a question for 14a.

Applicant Question 14b:

We have addressed this question in our previous IR response, dated 19 July 2016 (Response to Question 2), and agree with your assessment. We will include this explanation again in the BLA resubmission. In addition, Portola will provide anti-fXa activity versus TGT comparison separately for each of the fXa inhibitors (apixaban, rivaroxaban, edoxaban) as part of the resubmission.

Please confirm that the above anti-fXa vs TGT comparisons are for each fXa inhibitor (apixaban, rivaroxaban, edoxaban) in the Phase 2 and Phase 3 clinical studies, similar to Table A1-5 referenced-above, to compare the relative changes from pre-andexanet time point to 2 min post-andexanet bolus, for anti-fXa and TGT, respectively.

FDA Response to Question 14b:

We are unable to confirm the receipt of your response to Question 14b. Please provide a reference to the document from your July 19, 2016, submission in which the explanation of the differences in TGT assay results in phase 1 and 2 versus phase 3 studies can be found.

With reference to the requested anti-FXa vs. TGT comparison, in addition to the Day 1 Pre-dose, pre-andexanet alfa, and 2 min post-andexanet bolus time-points described in Table A1-5, please provide the correlation between the anti-FXa and TGT data obtained during the first 3 hours after andexanet alfa bolus and plot these correlations as graphs referenced in the CR letter question 14a.

Applicant Question 14c:

Portola did not provide a question for 14c.

Applicant Question 15a:

Portola did not provide a question for 15a.

Applicant Question 15b(i & ii):

Portola did not provide a question for 15b(i & ii).

Applicant Question 15b(iii):

Portola has previously provided a subset of the requested data set in our submission for the 19 July 2016 meeting. We will supply the complete data set using all available samples from Part 2 of the 14-503 and 14-504 studies as part of the BLA resubmission. Portola will also provide a side-by-side comparison for the time course between TF- and Actin FS-initiated thrombin generation.

Does the FDA agree with this approach?

FDA Response to Question 15b(iii):

Yes. In addition to the time courses, please also provide your interpretation of the contributions of the anti-FXa reversal and TFPI inhibition actions of ANDEXXA to TGT elevation, and full method qualification reports for all TGT methods used in these studies.

Applicant Question 15b(iv):

Portola did not provide a question for 15b(iv).

Applicant Question 15b(v) 1 & 2:

Portola did not provide a question for 15b(v) 1 & 2.

Applicant Question 15b(vi) in reference to Question 1.b.iv:

In our 19 July 2016 (SN0060) response, Portola provided additional TFPI activity data from the Phase 1 study. As previously committed, we will provide all the TFPI data from Phase 1 and 2, including total and free TFPI antigen levels, as well as the correlation between TFPI activity and the “free” TFPI levels determined using the (b) (4) assay from the Phase 1 study. In addition, we will include graphs of the “free” and total TFPI from all Phase 2 studies to show the time course of TFPI levels.

Would this approach to the data requested satisfy the above request for the resubmission?

FDA Response to Question 15b(vi) in reference to Question 1.b.iv:

No, your proposed response does not directly address the magnitude of the inhibition of TFPI activity and the timing of the resumption of TFPI activity to either the pre-andexanet treatment baseline or the normal range. We agree that the re-analysis of the levels of TFPI activity and TFPI antigen in retained samples may be helpful. However, you also need to demonstrate that the available data-points are sufficient to describe the effect of the andexanet dose (bolus and bolus plus infusion) on the timing of the changes in TFPI activity in anticoagulated and non-anticoagulated subjects. In addition, you need to demonstrate the equivalency of the TFPI activity assay used in the Phase 1 studies and the TFPI antigen assay(s) used in the Phase 2 and 3 studies.

Applicant Question 15b(vi) in reference to Question 1.c.xii:

Portola is performing the requested studies using (b) (4) cells, repeating the prior work described in the Study # NC-15-0662-R0001, with all four inhibitors, in the presence and absence of plasma proteins. These additional data and updated report will be available by December 2016 and included in the BLA resubmission.

Portola has carefully considered the extent of the work being required by the Agency and the time needed to complete the work. The company has also taken into consideration the unmet medical need that is addressed by AndexXa, a Breakthrough product, i.e., there is no approved reversal agent for the fXa inhibitors, and the safety profile of the product thus far, including the bleeding patient data from the ongoing ANNEXA-4 study. We believe that the majority of the deficiencies in the control strategy for the AndexXa manufacturing process that were identified by the Agency could be addressed in a March 2016 resubmission of the BLA for (b) (4). The remaining items, beyond March, which would be in progress at the time of resubmission, would be completed as Post-Approval Commitments (refer to table, page 13). Furthermore, we believe this proposal meets the spirit and intent of PDUFA V and the Guidelines for Expedited Programs.

Does the Agency agree that the proposed data package as outlined in the response strategies is sufficient to support a March 2017 resubmission?

FDA Response to Question 15b(vi) in reference to Question 1.c.xii:

With reference to Questions 1.c.xi and 1.c.xii from the June 1, 2016, request for information, please note that you were to justify statements regarding the properties of andexanet alfa with experimental data that were not presented, e.g., that rivaroxaban blocks the interaction of TFPI and andexanet alfa. If you do not have evidence to confirm the validity of the referenced statements, you may choose to withdraw them from the BLA.

Additional FDA Questions/Comments:

1. With reference to the table of on page 13 of your September 22, 2016, briefing document in which you described the timing of deliverables, we cannot agree to your proposal to submit some of the items as postmarketing commitments because these items are essential in bridging the study results from different phases of product development, specifically:

- a. The development of a PRS (Primary Reference Standard) and link back to all RS and clinical lots (May 2017);
- b. The development of bioassays for (b) (4) (June 2017) and TFPI activity and TFPI antigen (March 2017).

END