



Our Reference: BLA 125586/o

Date: November 25, 2016

Portola Pharmaceuticals Inc.

**ATTENTION: Ms. Janice Castillo**

270 East Grand Avenue  
South San Francisco, CA 94080

Dear Ms. Castillo:

Attached is a copy of the memorandum summarizing your October 27, 2016 Type-A Biologics License Application (BLA) meeting with CBER. This memorandum constitutes the official record of the meeting. If your understanding of the meeting outcomes differs from those expressed in this summary, it is your responsibility to communicate with CBER as soon as possible.

Please include a reference to BLA 125586 in your future submissions related to the subject product.

If you have any questions, please contact me at [thomas.maruna@fda.hhs.gov](mailto:thomas.maruna@fda.hhs.gov).

Sincerely,

Thomas J. Maruna, MSc, MLS(ASCP), CPH  
Lieutenant Commander, USPHS  
Senior Regulatory Management Officer  
Division of Regulatory Project Management  
Office of Tissues and Advanced Therapies  
Center for Biologics Evaluation and Research

## Meeting Summary

**Meeting ID #:** CRMTS 10481  
**Application:** BLA 125586/o  
**Product name:** Coagulation Factor Xa (Recombinant), Inactivated  
**Proposed indication:** For patients treated with a direct or indirect Factor Xa inhibitor when reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding  
**Applicant:** Portola Pharmaceuticals Inc.  
**Meeting type:** Type A  
**Meeting category:** BLA  
**Meeting date & time:** October 27, 2016, 2:00 pm – 4:00 pm, ET  
**Meeting format:** Face-to-face  
**Meeting Recorder:** Mark Levi, PhD

### Preliminary Responses sent

#### FDA Participants:

John Eltermann, Director, CBER/OCBQ/DMPQ  
Mahmood Farshid, PhD, Deputy Director, CBER/OTAT/DPPT  
Basil Golding, MD, Director, CBER/OTAT/DPPT  
Christine Harman, PhD, Chemist, CBER/OCBQ/DMPQ/BI  
Tim Lee, PhD, Acting Chief, CBER/OTAT/DPPT/HB  
Mark Levi, PhD, Regulatory Manager, CBER/OTAT/DRPM/BII  
Thomas J. Maruna, MSc, Senior Regulatory Manager, CBER/OTAT/DRPM/BII  
Mikhail Ovanesov, PhD, Research Biologist, CBER/OTAT/DPPT/HB  
Patrick Riggins, PhD, Chief, CBER/OTAT/DRPM/BII  
Stephanie Simek, PhD, Deputy Director, CBER/OTAT  
Deborah Trout, Team Lead, CBER/OCBQ/DMPQ/BI

#### Applicant Attendees:

Michele Bronson, PhD, Vice President, Program Management  
Janice Castillo, Senior Vice President, Regulatory Affairs  
Pamely Conley, PhD, Vice President, Biology  
John Curnutte, MD, PhD, Executive Vice President, Research and Development  
William Lis, Chief Executive Officer  
Andrew Ramelmeier, PhD, Senior Vice President, Technical Operations Biologics

(b) (4)

**Background and Objectives:**

Portola submitted a meeting request on October 4, 2016, to discuss a regulatory pathway to provide the second generation (GEN 2) ANDEXXA product manufactured by Lonza to patients as soon as possible, and to discuss the regulatory feasibility of (b) (4) at (b) (4). The pre-meeting materials were submitted on October 4, 2016.

FDA provided its proposed responses to Portola's questions on October 12, 2016. After reviewing the proposed responses, Portola notified FDA on October 20, 2016, of its decision to limit the meeting to discuss only FDA Additional Questions/Comments # 1 and 2.

**General discussion:**

Portola stated that the ANDEXXA program is in jeopardy, and that the FDA's help is critical to getting the program back on track. Portola committed to working in partnership with the Agency and providing whatever data/information is necessary to approve ANDEXXA, and to provide the assurance that their commitments will be executed in a quality manner.

Portola explained that their lifecycle management plan included initial launch material from (b) (4), followed immediately by a material manufactured from a scaled-up process of (b) (4) denoted as (b) (4) to be submitted in a Changes-Being-Effectuated in 30 days (CBE-30) supplement to the approved BLA to ensure increased commercial supply. However, Portola always believed that the manufacturing capacity of (b) (4) will not be sufficient to fulfill the market demand for ANDEXXA beyond 1 year after product launch. To address market demands in the USA and abroad, Portola has been working on expanding the manufacturing capacity with a GEN 2 product manufactured at the 10,000 L scale by Lonza Biopharma, initially at their Porriño, Spain facility and then possibly at a (b) (4). Compared to the (b) (4) process, the GEN 2 process was designed to provide for (b) (4)

Portola stated that it firmly believes that the GEN 2 process is the only viable option to ensure the continual supply of ANDEXXA in the long term. Therefore, Portola requested this meeting to obtain advice from the FDA on the appropriate pathway to bringing the GEN 2 product to market, preferably (b) (4) process is approved, and under the existing BLA STN 125586. An IND amendment to introduce this material into the clinic is now planned for mid-November, and a Prior Approval Supplement (PAS) to BLA STN 125586 is envisioned for mid-2017.

FDA reiterated its commitment to work with Portola on ANDEXXA development. However, FDA will not be able to comment on Portola's business plans in deciding where and how the product is to be manufactured. Furthermore, the BLA is not yet approved, and Portola should first and foremost take responsibility for demonstrating that ANDEXXA is safe and effective, and that the manufacturing process is properly validated, in a state of control and in compliance with cGMP regulations. As for the introduction of the GEN 2 process, all planned manufacturing modifications will need to

be supported with sufficient evidence to demonstrate that the manufacturing process is validated, controlled and robust, and the modified product meets all standards for safety and efficacy. FDA also stated that it will not discuss the GEN 2 clinical development program during this meeting because Portola has not requested participation of FDA's clinical and pre-clinical reviewers.

**FDA General Comment to the Applicant:**

The answers we are providing below are based on our regulatory and scientific assessment of the available information submitted to us throughout the developmental stages of your product; and should not be construed as our preference to any of your business plans in deciding where and how the product is to be manufactured.

**Additional Discussion:**

Portola acknowledged FDA's position and stated that Portola is not expecting definitive answers but is interested in any strategic advice the Agency would be able to provide.

**Questions from the Applicant:**

**Chemistry Manufacturing and Controls**

***Applicant Question 1:***

*The overarching question for the Agency is how do we get GEN 2 product to market as soon as possible? This should take into account the following possibilities and their impact on the approval pathway for GEN 2:*

- a. (b) (4) continues to support (b) (4) efforts, i.e., continued production of (b) (4) material, release and stability testing and assay development.
- b. (b) (4) halts all production of (b) (4) material, release and stability testing and assay development.

**FDA Response to Question 1:**

With the issuance of the CR Letter on 17 August 2016, we had delineated the deficiencies you need to address in order to support the approval of the BLA for your GEN 1 product. We had also extended our help to you to facilitate your preparation of the complete response to the CR Letter, which would appear to be the most direct way to bring your product to market.

With regard to the development of the GEN 2 product, please first refer to the summary dated 19 July 2013 for your meeting under CRMTS # 8972, in which we provided you with recommendations on how this product should be developed, and shared with you our concerns on your proposed changes to the GEN 1 manufacturing process as described in the IND/BLA. Since you have not addressed these concerns or responded to our recommendation in your meeting request/package, we are unable to answer your question regarding the GEN 2 product.

**Summary of Discussion:**

FDA requested clarification on Portola's plan to include the (b) (4) process in their response to the CR letter. FDA explained that its feedback during the previous meeting under CRMTS 10471 was applicable only to the deficiencies of the (b) (4) process. If Portola decides to forgo the (b) (4) process, another discussion on the BLA will be needed. FDA noted that the Agency defers to Portola to make its own business decisions, such as inclusion of the (b) (4) process in the response to the CR Letter and securing reliable contract manufacturing partners.

Portola confirmed that the (b) (4) process is still the basis for the ongoing application process and product characterization studies as discussed with the FDA in the meeting under CRMTS 10471. Portola's complete response to the CR Letter will be based on the (b) (4) process, and the GEN 2 material will be introduced after BLA approval. However, Portola believed that from a commercial point of view, the (b) (4) process will have to be (b) (4) with the GEN 2 process, which is more cost-effective.

FDA noted that it is not able to comment on Portola's plans to (b) (4) process with the GEN 2 process because, until today, Portola has not discussed with the Agency the plans. FDA reminded Portola that Portola had presented its GEN 2 process to the Agency only once, at the 19 July 2013 meeting under CRMTS 8972, and at that time, the Agency had determined that the differences between the (b) (4) and GEN 2 processes are so significant that material made using the GEN 2 process should be designated as a (b) (4). FDA stated that Portola's Briefing Document for CRMTS 10481 contains only a brief description of the GEN 2 process. But, in the Agency's preliminary assessment, the GEN 2 product is not comparable to the GEN 1 product; therefore the GEN 2 product would most likely need to be evaluated in clinical trials separately from those conducted to support the development of the GEN 1 process. It is possible that a new (b) (4) the GEN 2 process and this can be furthered discussed. FDA also noted that Portola has not yet provided a response to FDA's concerns regarding the GEN 2 product/process that were conveyed to Portola in CRMTS 8972 in 2013.

**Applicant Question 2:**

*Would any of the following represent an acceptable regulatory pathway?*

- a. *Approval of (b) (4) and a PAS for approval of GEN 2*
  - i. *Would the FDA approve (b) (4) as the initial commercial supply until GEN 2 PAS is approved?*
  - ii. *Would FDA consider reducing the CRL requirements for the GEN 1, (b) (4) approval, so that efforts and resources could be dedicated to these items as they apply to GEN 2 which has a greater capacity to supply the market long term?*
  - iii. *Would FDA consider the inclusion of both the (b) (4) process and the GEN 2 process as part of the resubmission for initial approval?*
- b. *(b) (4) is not approvable and GEN 2 is submitted for initial approval*

- i. *Would Portola be able to submit GEN 2 in response to the CRL (with the appropriate bridging data to GEN 1), without any impact on the review timeline?*

**FDA Response to Question 2:**

No. Specifically,

a.i. The approval of the (b) (4) process will depend on the quality and content of your complete response to the CR letter, i.e., how thoroughly you fulfill your commitments and how adequately you address our comments as described in our 12 October 2016 Preliminary Response for CRMTS 10471. Please refer to our response to Question 1 on the development of the GEN 2 product.

a.ii. No, a complete response to the CR Letter is required for us to continue our review of your BLA.

a.iii. Please refer to our response to Question 1 on the development of the GEN 2 product.

b.i. Once again, the approval, and the review timeline, of the (b) (4) process depends on the quality and content of your complete response to the CR Letter, i.e., how thoroughly you fulfill your commitments and how adequately you address our comments as described in our 12 October 2016 Preliminary Response for CRMTS 10471. Again, please refer to our response to Question 1 on the development of the GEN 2 product.

We are not able to comment on the impact of GEN 2 process on the review timeline. Moreover, as stated in our 19 July 2013 summary, *“The introduction of the proposed manufacturing changes constitutes a (b) (4)”,* GEN 2 is not suitable to be included in the complete response to the CR Letter under STN 125586/o. In addition, our advice provided in our 12 October 2016 Preliminary Response was applicable to (b) (4) only. If you decide to (b) (4) GEN 2 process further discussion with OTAT will be needed. Prior to any discussion you will need to address comments stated below in “Additional FDA questions/comments”.

**Summary of Discussion:**

FDA stated that discussion of the regulatory pathway for the GEN 2 product as part of STN 125586 is premature. A meeting with FDA will be needed to discuss the GEN 2 product with reviewers from all relevant disciplines present, i.e., clinical, product and pharmacology/toxicology. Portola should also provide a response to the 19 July 2013 FDA comments for the meeting under CRMTS 8972.

Portola responded that they took note of FDA’s concerns discussed under CRMTS 8972, and used FDA’s feedback in designing the GEN 2 process. Portola stated that some of the previously planned manufacturing changes were either not introduced or scaled back in an attempt to make the GEN 2 process more similar to the GEN 1 process. FDA

responded that they are not able to comment on this GEN 2 development strategy because Portola did not discuss its plans with the FDA, and that the differences between the GEN 1 and GEN 2 processes are still significant.

FDA reiterated that further discussion with OTAT will be needed for the development of the GEN 2 process.

***Applicant Question 3:***

*Does FDA consider (b) (4) approvable in the future for manufacturing andexanet?*

**FDA Response to Question 3:**

We are not able to assess the approvability of the (b) (4) process because you have not provided us with a sufficiently detailed developmental plan for the (b) (4) process, including your plan to address the deficiencies described in the CR Letter. Please be informed that a re-inspection of the (b) (4) facility will be needed to support the introduction of the (b) (4) process.

**Summary of Discussion:**

Portola stated that they estimated that many studies are needed to address the problems with the (b) (4) process, and pursuing further development of (b) (4) would delay the development of the (b) (4) and GEN 2 processes. Therefore, Portola proposed that (b) (4) will not be included in the response to CR Letter. FDA noted that they are not able to comment on the studies needed to address the problems with (b) (4) because Portola did not provide any information on the current status of (b) (4) .

Portola shared their current assessment that no material from (b) (4) can be used in clinical trials because FDA has indicated in the CR Letter that (b) (4) was not cGMP compliant. FDA agreed that only cGMP-compliant material should be used in clinical trials, but noted that the Agency has not made their final determination regarding the cGMP status of (b) (4) .

FDA reiterated their concerns regarding the design of the process which allows for failure of up to (b) (4) out of (b) (4) in the manufacture of a “successful” batch. Portola noted that the (b) (4) process was designed to consider a known observation that (b) (4) are less reliable compared to the (b) (4) . FDA responded that Portola did not discuss their (b) (4) development strategy with the FDA prior to BLA submission. This is unlike previous productive discussions regarding the problems with (b) (4) , e.g., increased (b) (4) during BDS PPQ campaign, which were resolved ahead of BLA submission. FDA noted that no information about the (b) (4) problems was presented for review, and the description of (b) (4) in the original Comparability Protocol was inaccurate. FDA explained that (b) (4) was determined not suitable for the CBE-30 supplement approval pathway because of the scope of problems uncovered during inspection, which were confirmed by numerous process failures as presented in the revised Comparability Protocol. FDA remains concerned that Portola has no control over the (b) (4) process as seen from the different root causes identified during the investigations of the numerous failures in (b) (4) manufacture. Portola reiterated their

conclusion that (b) (4) is problematic and it will not be included in the complete response to the CR Letter.

**Additional FDA Questions/Comments:**

1. To facilitate further discussion of the GEN 2 process, please provide the following information:
  - a. An update on the developmental activities on the GEN 2 process that you have performed since the previous discussion on the GEN 2 process in July 2013 under IND 15089, CRMTS #8972;

**Summary of Discussion:**

Portola agreed to provide this information in future IND amendments.

- b. Response to our 19 July 2013 comments regarding the impact of the GEN 2 major manufacturing changes on the quality, safety and efficacy of the product;

**Summary of Discussion:**

Portola stated that the results of analytical comparability studies are presented in the slide deck submitted to the FDA 1 day prior the meeting. The data presented are a preview of a full comparability data package Portola will send to the FDA in November that will include the items requested by the FDA in their communication of 20 October 2016. Portola believes that these comparability studies are aligned with the appropriate FDA guidance documents in that they are based on suitable analytical techniques, knowledge of the molecule, and the relationship between quality attributes and safety and efficacy.

FDA stated that their reviewers did not have time to review the final version of the submitted slides. In FDA's preliminary assessment, the basic deficiencies with ANDEXXA's GEN 1 and GEN 2 processes remained as follows:

1. Comparability between (b) (4) has not been established.
2. Characterization of anti-TFPI activity in the (b) (4) is deficient.
3. Absence of a well-established reference standard to connect the (b) (4) from various developmental phases.
4. Effect of andexanet alfa on TFPI activity is not established in either animal or human studies.

FDA stated that from the slides, it is obvious that (1) the studies have not yet been completed or have deficiencies so the November amendment to the IND will be deficient on this basis; and (2) there are differences between the GEN 1 and GEN 2 materials.

FDA pointed out the following specific concerns with the presented slides but noted that these concerns are only preliminary and more issues may be added after the data are submitted for formal review:



- Slide #5: (b) (4) should be (b) (4) to see what other product-related substances are there.
- Slide #6: Although the GEN 2 material may be more (b) (4) in terms of (b) (4) impurity content, the proportions of these impurities are different. Also, Portola should provide the data for (b) (4).
- Slide #7: Again, difference in proportion of (b) (4) is seen.
- Slide #8: Using “(b) (4)” is misleading. If we use “(b) (4)”, (b) (4) material is not comparable to GEN 2 and (b) (4) materials. FDA recommended that actual data should be presented for review along with “(b) (4)”.
- Slides 9 & 10: Again, using “(b) (4)” is misleading. If we use “(b) (4)”, (b) (4) material is not comparable to GEN 2 material. FDA suggested that an animal PK study to show that the difference does not affect PK would be helpful. Portola noted that they would prefer to run a PK in humans because conducting animal PK studies will delay their clinical development program.
- Slides 11 & 12: The proportions of (b) (4) are different.
- Slide 13: The data are not acceptable because a single reference standard should be used to measure potency of all materials.
- Slide #14: Regarding slide 14:
  - Portola is at its own risk to submit the amendment to the IND, which may result in its being put on clinical hold.
  - The Agency has already pointed out some deficiencies and that additional data are needed. So, it would be more productive to address these deficiencies adequately rather than to trying to meet the November time-line.
  - There are deficiencies in Portola’s analytical methods that need to be fixed before their results can be relied upon to support their conclusion, e.g., reference standards, potency units, etc.
  - Anti-TFPI activity is an important parameter and should be examined in detail.
- Slide #16: Looking at the binding to anti-FXa inhibitors is not sufficient because the interaction of the rest of andexanet contributes to the formation of the TFPI/TF/FVIIa complex.

With its preliminary assessment, FDA concluded that the material manufactured using the GEN 2 process amounts to a (b) (4), and therefore analytical

comparability studies alone would not be sufficient to support the introduction of the GEN 2 material into the ongoing Phase 3/4 studies.

**Post-meeting note:**

Please note that the analytical methods used in the studies have to be demonstrated to be sensitive enough to detect changes should they arise. This will require some additional verification studies, e.g., using denatured samples and spiking them in DS preparations to show that the method can quantitatively detect defects in the molecule.

- a. The licensure status and compliance history of the Lonza Biopharma facility in Porriño, Spain;

**Summary of Discussion:**

Portola stated that the Lonza Biopharma facility in Porriño, Spain has good compliance history. The most recent FDA inspection of Lonza in Porrino, Spain was a PAI in (b) (4) .

- b. Your effort to (b) (4) using traditional (b) (4) ; and

**Summary of Discussion:**

Portola stated that they tried and failed to introduce the (b) (4) process to the Lonza Biopharma facility in Porriño, Spain, possibly due to differences in the equipment at (b) (4) and Lonza. FDA noted that this information may be helpful and should be submitted in the GEN 2 data package.

- c. Your effort to address issues related to the (b) (4) on which the (b) (4) process is based.

**Summary of Discussion:**

Portola stated that they are not pursuing (b) (4) development at this time.

5. Your assessment of market demand is based on the all-inclusive indications for ANDEXXA to which we have not agreed. Please perform another assessment based on the more limited indications agreed upon by the Agency.

**Summary of Discussion:**

This question was not discussed during this meeting.

6. With reference to your planned PK/PD comparability study in humans and submission of the analytical data on the GEN 2 (b) (4) as an amendment to the IND, please note that the FDA has not agreed that comparability is a feasible approach to introduce the GEN 2 (b) (4) . Therefore, you are at your own risk to submit analytical data on the GEN 2 material to request its use in the current clinical trials. The IND will likely be placed on clinical hold if we conclude that the data do not support the comparability of the GEN 1 and GEN 2 materials.

**Summary of Discussion:**

Portola requested FDA's clarification on the rationale behind designating the GEN 2 material as (b) (4). Portola acknowledged some differences but stated that analytical testing to date demonstrates that the GEN 2 (b) (4) is comparable to the GEN 1 (b) (4) in both composition and activity. For example, no new isoforms were found.

FDA explained that GEN 2 introduces many major manufacturing changes that may have significant impact on the identity, strength, quality, purity or potency of the product as they may relate to its safety and efficacy. There are still much we do not know about the molecule and its manufacturing process as evidenced by the extensive list of deficiencies identified in the CR Letter. The relationship between quality attributes and safety and efficacy is still being evaluated in the ongoing clinical trials. For example, differences of andexanet alfa effects in the clinical studies for different inhibitors suggest that the (b) (4) may work differently *in vivo*. With the GEN 2 process, the FDA has specific concerns about product safety (immunogenicity and thrombogenicity) and efficacy (anti-TFPI activity versus anti-FXa activity reversal effects). That is why analytical characterization by itself is not sufficient to support the use of the GEN 2 material in the clinics.

Portola reiterated that they do not wish to conduct animal studies on the GEN 2 material because it will cause a significant delay to ANDEXXA commercialization.

**Additional Discussion:**

Portola stated that an IND amendment would be submitted in the next month (November) to support the human PK/PD study with pharmacology/toxicology information. FDA noted that if the purpose of this CMC amendment to the IND is to support the use of the GEN 2 material in clinical trials, Portola should discuss their clinical program with the clinical and pharmacology/toxicology reviewers. FDA recommended that Portola submits a meeting request to discuss the GEN 2 developmental program. The briefing package for this meeting should contain clinical, preclinical and product information as is expected for a formal pre-IND meeting. Regarding the scope of CMC information in the briefing document, FDA recommended that the submission should be sufficiently detailed, but does not need to contain amount of data required to support a full BLA. It may also be helpful to the FDA for Portola to update their progress in addressing the issues with the (b) (4) process, and summarize it in the GEN 2 meeting briefing document.

With regard to lyophilization, FDA noted that the scale-up process requires re-validation and facility inspection. Portola stated that they had a plan for such. In regards to past discussion of issues with the lyophilization validation provided in the BLA, Portola asked FDA, if tightening the limits of the NOR and PAR would address the FDA concerns with the small scale data not demonstrating sufficient robustness to support the process at commercial scale. The FDA agreed that the ranges could be tightened and that the tightened ranges should be supported by the parameters used for the validation runs performed at commercial scale that was provided in the BLA. If an NOR range is exceeded a deviation should be initiated. The investigation associated with the deviation would evaluate product impact, and additional testing or monitoring required.

Developmental studies could be leveraged to support release of the lot, provided the investigation's conclusions support this outcome.

**Addendum to the meeting minutes:**

The following advice was provided to Portola on November 11, 2016 in regards to the scope of manufacturing information needed for the Briefing Document to discuss the GEN 2 developmental program:

Please refer to item #1 under *Additional FDA Questions/Comments* in our 20 October 2016 response to your questions on GEN 2 for the meeting under CRMTS 10481. In addition to providing an update on the developmental activities on the GEN 2 process that you have performed since the previous discussion on the GEN 2 process in July 2013 under IND 15089, CRMTS 8972, please also include:

1. Portola's rationales to introduce the specific changes to the manufacturing processes, e.g., (b) (4) .
2. Summary data to support that these changes have resulted in the kind of improvements that Portola is aiming for. The results can be from lab-scale, pilot-scale or commercial scale studies. The studies should assess the effect of these changes on the performance of the manufacturing process and quality of the product. It would also be informative for Portola to report to FDA both failures and successes during the developmental process of the various unit operations.
3. A response to our 19 July 2013 comments regarding the impact of the GEN 2 major manufacturing changes on the quality, safety and efficacy of the product.

**Decisions made and/or agreements reached:**

There will need to be a meeting with the FDA to discuss the GEN 2 process with reviewers from all relevant disciplines present, clinical, pharmacology/toxicology and CMC. The FDA does not recommend submitting CMC data on the GEN 2 process as an amendment to the IND because a clinical hold may be warranted.

**Issues requiring further discussion:**

Portola should either propose animal studies to support the introduction of the (b) (4) process or provide rationales for not including new pharmacology/toxicology studies to support the GEN 2 introduction.

FDA will assess the analytical comparability report when it is provided to support the use of GEN 2 DP in human PK/PD studies. Portola will compare the GEN 2 material to both of the GEN 1 materials, from (b) (4) .

**Action items:**

Portola will submit a meeting request followed by a briefing document with summary data to support the development of the GEN 2 process, which will include results from comparability studies for the GEN 1 and GEN 2 materials, as well as the clinical study protocol to support the use of the GEN 2 material in clinical studies. The meeting request will include questions on all relevant disciplines and participation of CMC, pharmacology/toxicology, and clinical reviewers.

**Attachments/Handouts:**

Slide Deck, submitted by Portola October 26, 2016

**Clinical Comments with respect to Portola's October 20, 2016 email:**

1. *The BLA resubmission can exclude enoxaparin and edoxaban. These two fXa inhibitors (b) (4) .*

**FDA response:**

We have no objection if you want to resubmit the BLA with a proposed indication that is limited to reversal of the anticoagulant effect of rivaroxaban and apixaban. Excluding edoxaban and enoxaparin from the proposed indication would likely facilitate marketing approval of your product. If your product receives marketing approval, (b) (4)

However, regardless of the specific indication statement, your BLA resubmission must include updated safety data on all subjects who have been exposed to your product, including subjects who received your product for some indication other than the proposed indication. For example, even though your revised indication statement might be limited to rivaroxaban and apixaban, your safety database must include data on subjects who were exposed to your product to reverse any anticoagulant.

2. *Agreement on the ANNEXA-4 and Usual Care Cohort (UCC) Studies will be sufficient for approval. Regarding the UCC Study, this means a show of good faith efforts by Portola to start the study.*

**FDA Response:**

Based on our review of your original BLA submission, it appears that agreement on the design of the ANNEXA-4 and Usual Care Cohort (UCC) Studies would be sufficient for marketing approval of your product. However, our review of your BLA resubmission, particularly the safety database, may identify additional issues that would need to be addressed prior to marketing approval.

Initial enrollment of subjects into the UCC Study is important as evidence of your commitment to completing a confirmatory study.

**END**