



Meeting Response

Our Reference: BLA 125586/0
CRMTS 10481

TODAY'S DATE: October 20, 2016 **PAGES:** 5

TO: Ms. Janice Castillo
Portola Pharmaceuticals Inc.
Email address: jcastillo@portola.com

FROM: Thomas J. Maruna, MSc, MLS(ASCP), CPH
Lieutenant Commander, U.S. Public Health Service
Senior Regulatory Management Officer
Office of Tissues and Advanced Therapies
Email address: thomas.maruna@fda.hhs.gov

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:

Mr. John Eltermann (OCBQ/DMPQ)
Mahmood Farshid, PhD (OTAT/DPPT)
Basil Golding, MD (OTAT/DPPT)
Christine Harman (OCBQ/DMPQ)
Larissa Lapteva, MD (OTAT/DCEPT)
Timothy Lee, PhD (OTAT/DPPT)
Mark Levi, PhD (OTAT/DRPM)

Thomas J. Maruna, MSc (OTAT/DRPM)
Mikhail Ovanesov, PhD (OTAT/DPPT)
Ms. Carolyn Renshaw (OCBQ/DMPQ)
Patrick Riggins, PhD (OTAT/DRPM)
Stephanie Simek, PhD (OTAT)
Ramani Sista, PharmD (OTAT/DRPM)
Ms. Deborah Trout (OCBQ/DMPQ)

Although we continue to reserve October 27, 2016, 2 pm – 4 pm, ET, 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 27, 2016, 2 pm – 4 pm, ET, 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 BLA 125586/0 in your future submissions related to the subject product.

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.

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.

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 (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 Line A/B 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”.

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.

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;
 - 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;
 - c. The licensure status and compliance history of the Lonza Biopharma facility in Porriño, Spain;
 - d. Your effort to (b) (4) using traditional (b) (4); and
 - e. Your effort to address issues related to the (b) (4) on which the (b) (4) process is based.

2. 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.
3. With reference to your planned PK/PD comparability study in humans and submission of the analytical data on 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.

END