

RECORD OF TELEPHONE CONVERSATION

Submission Information

Application Type	BLA
STN	125586/0
Review Office	OBRR
Applicant	Portola Pharmaceuticals / Lic. # 2017
Product	Coagulation Factor Xa (Recombinant), Inactivated
Trans-BLA Group:	No

Telecon Details

Telecon Date/Time	09 June 2016, 2:00 PM
Author	MARUNA, THOMAS J.
Outside Phone Number	877-668-4490
FDA Originated?	YES
Communication Categories	OT - Other
Related STNs	None
Related PMCs	None
Telecon Summary	Discussion on Portola's approach to respond to inspectional 483 observations noted at (b) (4) and timeline for response
FDA Participants	Thomas J. Maruna, MSc, MLS(ASCP) (OBRR/IO) Mikhail Ovanesov, PhD (OBRR/DHRR/LH) Joan Johnson (OCBQ/DMPQ) Donald Ertel, MT(ASCP) (OCBQ/DMPQ)

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Applicant Participants	<u>Portola</u> Andrew Ramelmeier, Senior Vice President, Technical Operations, Biologics Janice Castillo, Senior Vice President, Regulatory Affairs and Quality Assurance Michele Bronson, Vice President, Program Management Evan Susser, Senior Director, Quality Assurance Brian Schrup, Senior Director, Quality Systems Evangelia Raptis-Zarou, Associate Director, Regulatory Affairs (b) (4) (b) (4) (b) (4)
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Telecon Body:

Portola stated that they want to gain FDA's concurrence with Portola's approach to addressing FDA's feedback. Portola wanted to ensure that their revised responses will be acceptable to the FDA.

FDA noted that FDA is unable to comment on the acceptability of the proposed responses. FDA would need to review the data to determine the acceptability of the responses. During the teleconference, FDA clarified that FDA can provide concurrence on the timeline of data submission, and the scope of the documents that Portola (b) (4) plan to submit. Portola agreed with this approach.

Portola went on to present a slide deck submitted via email on June 9, 2016 (attached).

Discussion

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With reference to the following quote from FDA's Advice and Information Request regarding (b) (4) responses to the observations in the *Form FDA 483* issued during the Pre-License Inspection on (b) (4): "*We disagree with your conclusion that the process validation for (b) (4) is complete because at least one process parameter, (b) (4), was not investigated during the completed process qualification studies*", Portola proposed that (b) (4) will submit an amended (b) (4) validation report to fully address the (b) (4) issue when the study is completed.

FDA reminded Portola (b) (4) to remain cognizant of the action due date (17 August 2016) with respect to the timing of their response.

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Slide 4

With respect to FDA's comment on the specification limits, "*We also disagree with your proposal to widen the specification limits for the (b) (4) before the completion of your investigations into the effect of (b) (4) on (b) (4) performance, and the effect of the (b) (4) on TFPI inhibition*", (b) (4) proposed to submit the report for (b) (4)-CP-054 upon its completion. Concerning the effect of the (b) (4) on TFPI inhibition, Portola plans to discuss it with the FDA as part of their response to a separate FDA's requests for information on TFPI. Portola is drafting a response to the information request concerning the TFPI issue and plans to discuss this with the FDA at the June 22, 2016 meeting with the Center Director.

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Concerning the FDA comments on (b) (4) PPQ report, "*we disagree with your conclusion that the process performance qualification series for (b) (4) is complete because (b) (4) was not in a state of control during the (b) (4) inspection*," (b) (4) proposed that the future CBE-30 supplement will contain both the (b) (4) PPQ report and the completed deviation investigation reports as well as all supporting documents to address observations identified during the inspection. To facilitate the FDA review of the (b) (4) validation studies, (b) (4) suggested providing these reports by the end of June 2016.

FDA responded that although Portola (b) (4) can submit these data, FDA will not commit to reviewing them within the BLA review cycle because process validation for (b) (4) is not part of the BLA review. (b) (4) was inspected as part of the review of the *Comparability Protocol* for (b) (4) and (b) (4). During the inspection closeout meeting on April 22, the FDA inspectors shared their observation that (b) (4) was not in a state of control during the inspection, but they did not include this observation in the *FDA Form 483* and therefore (b) (4) was not expected to respond.

FDA recommended submitting the completed (b) (4) process validation reports and all related data in the proposed CBE-30 supplement. Further, FDA noted that this information is not required to close the inspection. With reference to the cited FDA comments that the (b) (4) PPQ series is incomplete, FDA explained that they were responding to the statements provided by (b) (4) in their responses to *Form FDA 483*. To facilitate the review process, (b) (4) was advised to remove their statements regarding the state of (b) (4) validation from their responses to *Form FDA 483*.

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(b) (4) proposed to submit the following documents in an amendment to the BLA by June 30, 2016:

- The final reports and supporting documentation for the studies which (b) (4) have described in their responses to *Form FDA 483*,

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- The Final Report for the At-scale (b) (4) Study (VAL-30230-02.1, approved May 11, 2016), and
- All related Deviation Reports, either closed or open (including DEV-1484, DEV-1498, DEV-1573, and DEV-1632).

In addition, at the advice of FDA received in response to their June 7, 2016 email, (b) (4) will prepare an amendment to the (b) (4) process validation report with an explanation of the new control strategy for process parameters.

FDA agreed to the scope of the documents to be submitted to the BLA.

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(b) (4) proposed the following dates to submit the respective documents:

June 30, 2016: (b) (4)-CP-054, Amendment to (b) (4) PPQ report

After June 30, 2016: (b) (4) PPQ report will be submitted as part of CBE-30 supplement

FDA agreed to (b) (4) proposed dates.

Slide 8 – Observation 4

With reference to the FDA comments on Observation 4 in *Form FDA 483*, “*Your response is not acceptable because your proposal does not address the root cause of your failure to follow your standard operating procedure for deviation management. Your delay in opening an official deviation record is due to your practice of consulting your client before official documentation of the deviation. Please ensure the timely initiation and accurate maintenance of manufacturing records by opening deviation records promptly prior to your communication with anyone outside of (b) (4)*”

(b) (4) stated that they recognize their responsibility for cGMP compliance.

Slide 9 – Observation 4

(b) (4) proposed the following approach in addressing Observation 4:

- (b) (4) acknowledges that the manufacturer is the sole accountable party for cGMP compliance for the manufacture and testing of andexanet at its facilities
- (b) (4) is revising deviation management SOP (GMP-0263) to decouple deviation initiation from informing client prior to deviation record being opened
- In addition to monitoring adherence to this expectation, (b) (4) will commence training on the revised deviation management SOP by June 30, 2016

FDA agreed with (b) (4) proposed approach on addressing this observation.

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Additional Discussion

FDA requested a revised response to *Form FDA 483*, including a cover letter referencing this June 9, 2016 teleconference with the FDA inspection team as part of their June 30, 2016 amendment. Portola/(b) (4) agreed to do so.

Attachments

1. Portola's slide deck dated June 9, 2016, titled *FDA Feedback on 483 Responses*