

From: Hooban, Christopher
Sent: Thursday, June 30, 2016 3:27 PM
To: jcastillo@portola.com
Cc: Valencia, Iliana
Subject: RE: BLA 125586 - ANDEXXA Questions regarding FDA RFIs

Ms. Janice Castillo:

Thank you for acknowledging that our requests are reasonable and we in turn appreciate that you are working on the assays needed to add to the release specifications. Although the determination of criticality of quality attributes is part of the review process, we do in general consider all parameters included in release specifications to be critical.

Please note that the referenced information requests were reiterations of our earlier communications with you so most of the issues are not new. In addition, these requests are in line with FDA review practices that additional issues would be added, expanded upon or modified as we continue to review your submission. It is not possible for us to cover all topics of review in pre-submission meetings because we do not have all the information to determine what are deficient and what additional information is needed to remedy them.

To facilitate our discussion on your proposal, we ask that you address each of our information request items thoroughly and submit your rationales for new proposals on the development and introduction for the specific methods and specifications in an amendment to the BLA. We are now extending your response date to 8 July 2016 so that you can have time to better prepare your responses. If there is need for further discussion, we can then schedule a teleconference after we have reviewed your responses.

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From: Valencia, Iliana
Sent: Wednesday, June 29, 2016 7:21 PM
To: Janice Castillo
Cc: Ovanesov, Mikhail V.; Lee, Timothy
Subject: RE: BLA 125586 - ANDEXXA Questions regarding FDA RFIs

Dear Ms. Castillo,

We appreciate you are seeking clarification. Your request for clarification comes within a day to the date of the expected response (by July 1st). This places a tremendous burden on the FDA timelines and staff. We may not be able to comply with a request for a teleconference tomorrow, June 30th. The review committee will need time to review your comments and questions before we can hold a teleconference to discuss.

Tomorrow I will let you know if the team can address any or all of your comments; or if we will need additional time to review. This, however, does not preclude you from the responsibility to respond as requested.

Sincerely,

Iliana
240.402.8444
Iliana.valencia@fda.hhs.gov

From: Janice Castillo [mailto:jcastillo@Portola.com]
Sent: Wednesday, June 29, 2016 6:47 PM
To: Valencia, Iliana
Cc: Ovanesov, Mikhail V.; Lee, Timothy
Subject: BLA 125586 - ANDEXXA Questions regarding FDA RFIs

Dear Iliana,

FDA has required a July 1st response to their RFIs dated 22 June and 28 June regarding the addition of release specifications and validation of specific assays. Portola requests a teleconference with the appropriate CMC reviewers tomorrow, 30 June, to discuss our concerns regarding these RFIs and our

proposed responses for mitigation. Our concerns and proposed responses are briefly noted below:

* FDA's requests are reasonable and we will add the specific release specifications to the CoA when the assays are validated. We are currently working on some of the assays and will begin efforts on the new ones requested by the FDA. We note that none of the assays requested are tests for Critical Quality Attributes.

* Good Manufacturing Practices require that specifications reflect the variability of the assay and the process capability, within limits defined by our clinical experience and other information relevant to product quality. Specifications for commercial products are therefore required to be set using validated methods. Portola's GMP Quality System aligns with this requirement and would not allow for the establishment of specifications and release of commercial product using non-validated assays.

* We are very concerned by the timing of FDA's requests and their potential for impact on product launch. Portola presented proposed specifications in both the October and November 2014 Type C CMC meetings, as well as at our October 2015 pre- BLA meeting. Other than

(b) (4), the FDA has not discussed or proposed testing and specification requirements for (b) (4), or the excipients (sucrose, mannitol and Polysorbate80).

* If the Agency is requiring that these release tests and specifications be added to the CofA as a condition of approval, and applied to product already tested and released for launch and commercial distribution, patient access to and launch of this Breakthrough product could be delayed by over 3 months.

Portola proposes the following to mitigate this situation:

* Initiate assay validation for (b) (4) (b) (4), mannitol, sucrose and Polysorbate 80 prior to approval, complete assay validation, generate interim specifications, and add the new assays and acceptance criteria to the CofA by 31 October as part of a post-approval commitment. The interim specifications will be set to reflect both assay variability and process capability, and will be re-evaluated after (b) (4) batches or (b) (4) post licensure, whichever comes first. In the meantime, we propose to release product with the current controls and the current CofA.

* (b) (4) - Provide the Agency with our description of "conforms to reference" and an

example of the graphical output from this assay by 01 August. As noted in prior communications, this method is not sufficiently robust to support validation or quantitation of potential product (b) (4)

(b) (4). Therefore, peptide mapping is retained as a characterization method and will not be validated. We are developing a new robust method by which we can generate a specification. We are also evaluating the use of the new (b) (4) assay to measure extent of (b) (4). We will propose options for this and possible release specifications (if feasible) by the October 31, 2016 deadline.

* (b) (4) - Provide the Agency with the (b) (4) characterization data from (b) (4) lots generated using a non-validated method by 01 August.

* (b) (4) - Provide the Agency with characterization data generated by the current non-validated method by 01 August. A release specification for (b) (4) is dependent on a (b) (4) method that is being optimized for validation.

* Sucrose, mannitol, Polysorbate 80 - Validate the methods and generate release specifications for the drug product by the requested date of 31 October. In the interim we propose to provide tabulated batch record data denoting the specific amount of each excipient used during (b) (4) formulation by 01 August. Additionally, regarding sucrose and mannitol, we have a specification for (b) (4) which provides a surrogate for the (b) (4) in the formulation, and confirms consistency of formulation composition for batches that have been manufactured to date

Please let me know what time would be convenient for FDA. The following call-in information can be used.

1-877-668-4490 Call-in toll-free number (US/Canada)

(b) (4) Host access code

(b) (4) Attendee access code

Kind Regards,
Janice

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