MEMORANDUM

Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
Office of Blood Research and Review

To:	BLA STN 125586/0 & Thomas Maruna, OBRR/IOD/RPM Staff
From:	Andrey Sarafanov, PhD, OBRR/DHRR/LH
Applicant:	Portola Pharmaceuticals Inc.
Product:	Factor Xa Inhibitor Antidote (Andexanet alfa)
Indication	For patients treated with FXa inhibitor when reversal of anticoagulation is needed
Subject:	Chemistry, Manufacturing and Controls Review
Through:	Mark Weinstein, PhD, OBRR/IOD
	Basil Golding, MD, DHRR
CC:	Tim Lee, PhD, DHRR/LH & Mikhail Ovanesov, PhD, DHRR/LH

EXECUTIVE SUMMARY

This memorandum summarizes a review of product-related information in an original Biologics License Application (BLA) under STN 125586 submitted by Portola Pharmaceuticals Inc. for Factor Xa Inhibitor Antidote (Andexanet alfa). I reviewed information for Specifications and Extractable & Leachable in (b) (4) Drug Product (DP) (modules 3.2.S. and 3.2.P., respectively). Upon review of the data, I found them insufficient to support the application. I recommend revising the DP specifications by inclusion of additional parameters to ensure lot-to-lot consistency and efficacy of the product.

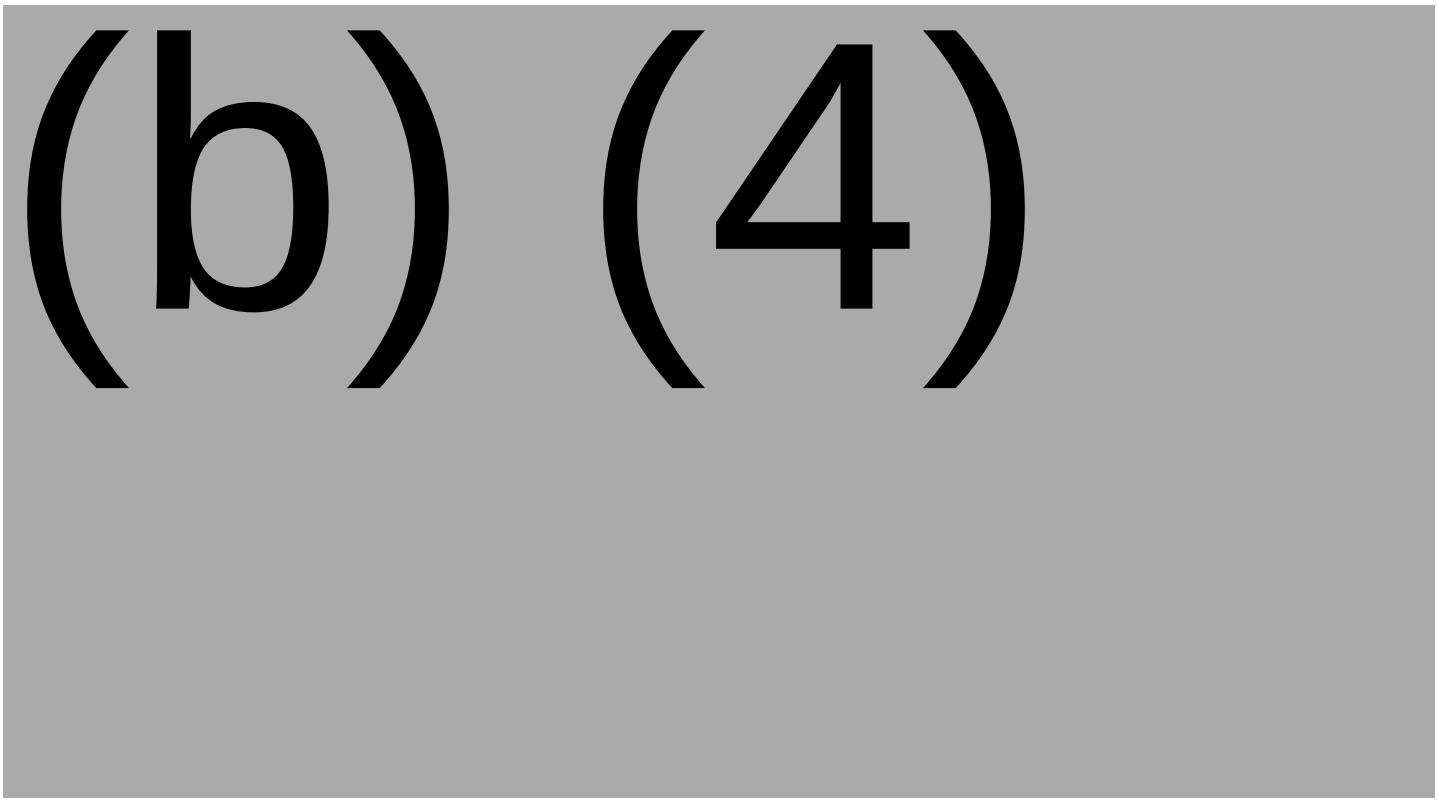
BACKGROUND

Andexanet alfa (Andexanet) is a recombinant mutated human factor Xa (FXa), which does not have procoagulant activity, but retains binding to FXa inhibitors. Andexanet acts by binding to FXa inhibitors, which restores activity of the intrinsic FXa. The lyophilized DP is to be reconstituted with 10.0 mL of sterile Water for Injection (WFI), which is not provided with the DP.

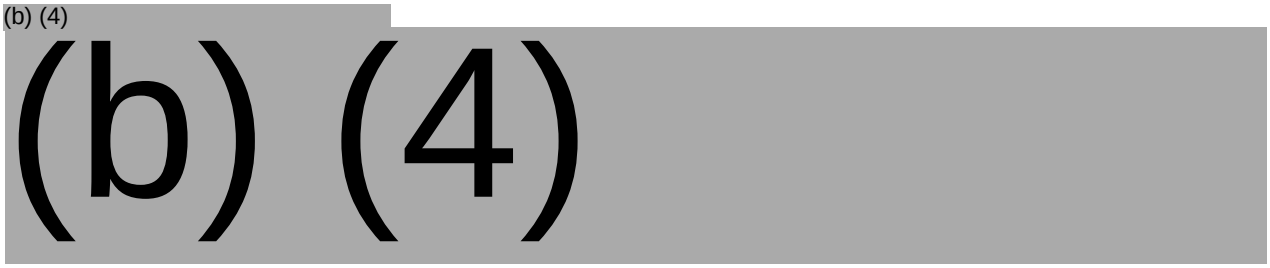
REVIEW SUMMARY

(b) (4)

(b) (4)



(b) (4)

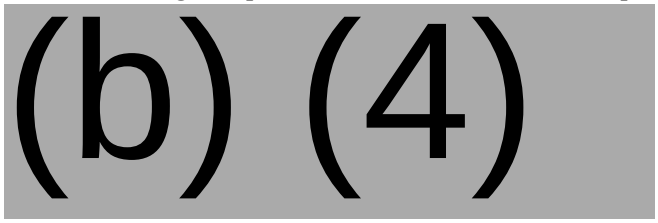


DRUG PRODUCT

3.2.P.2.3.1.7.2 Extractable and Leachable

The same principles and studies as those used for (b) (4) were applied to evaluate Extractable and Leachable in the DP (see above). Based on those, the contact materials considered to be high risk were the sterilizing filter, the (b) (4) and the vial and rubber stopper container closure.

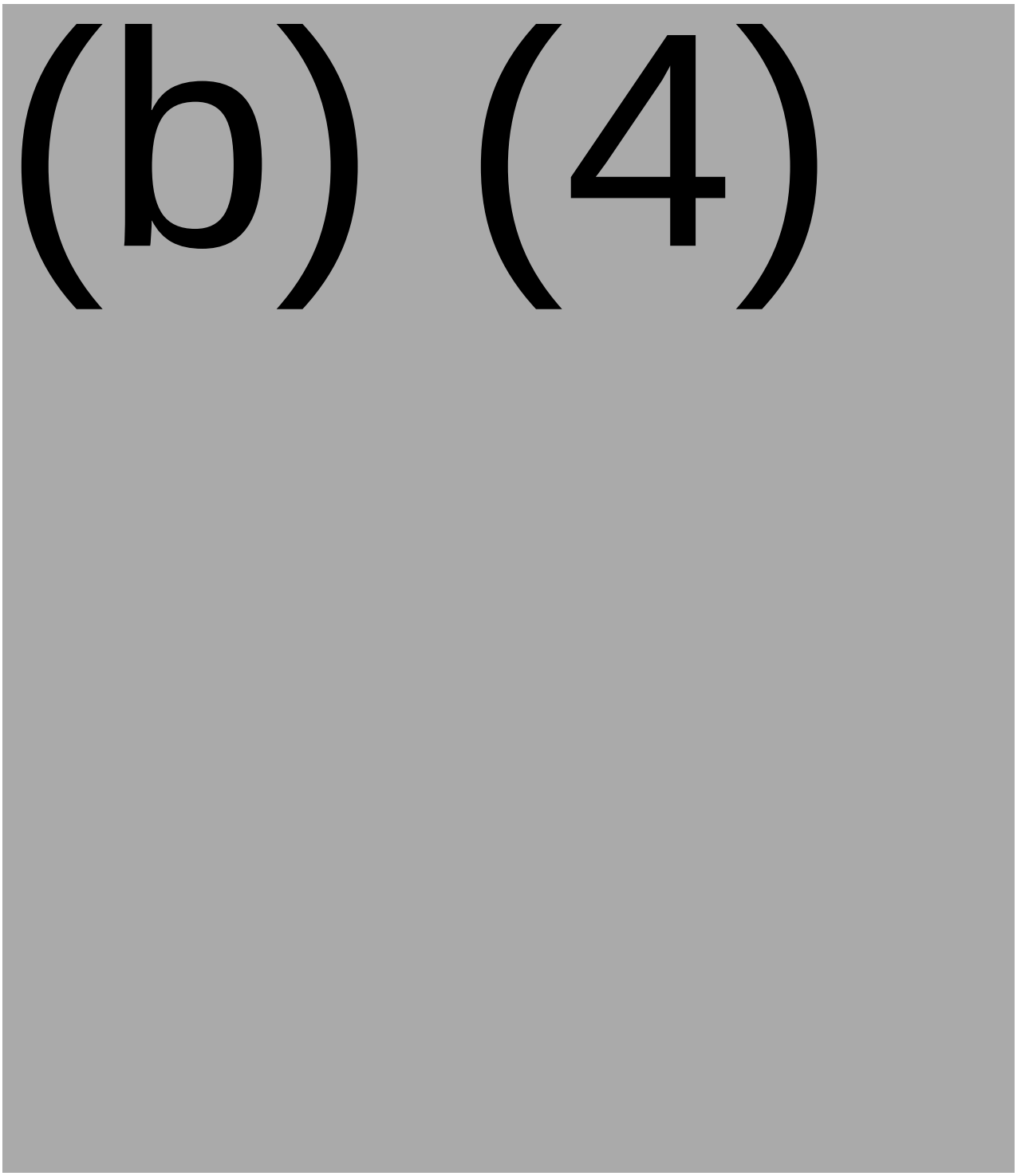
An Extractable study was performed for the above components, employing (b) (4) lot of the DP (b) (4) DP (b) (4) and (b) (4) lot of the DP (b) (4) DP (100 mg/vial), and using (b) (4) The samples were extracted with (b) (4) and analyzed by (b) (4) to provide semi-quantitative evaluation of volatile, semi- volatile, and non-volatile leachable. In all of these studies, all compounds detected were not toxic, and were not considered as potential leachable compounds needed to be monitored. However, the following compounds were still considered as potential leachables to be monitored in a stability study.



3.2.P.3.5. Process Validation and Evaluation

This section contains Report 15-3387-EXTT1-MPGLG (Extractable Test Validation Report for (b) (4) , which was reviewed above (Section 3.2.S.2.5.7.3).

Specifications for the (b) (4) *Drug Product*



Reviewer's Comment

- There are no parameters to control Identity by (b) (4) in the specifications. In particular, a (b) (4) control is required by (b) (4). These concerns were escalated further upon review of the DP specifications (see below).
- Reporting of Potency in relative units (percent) of a (b) (4) reference standard is not correct as it cannot support continuity of this parameter over time because of a decrease in the quality of the standard. An absolute value (Units of activity) is needed for these parameters.
- The potential impurity, (b) (4), was removed to the level below the limit of quantitation (b) (4) during the (b) (4) step, an early step of purification followed by several other steps. Thus, it is expected that residual (b) (4) in the DP will be at a very low level and not affect the safety of the product.

Potency

Direct Potency of Andexanet is determined by its ability to bind a direct FXa inhibitor (b) (4) (a low molecular weight inhibitor) and reverse the inhibition of human FXa in a mixture of human FXa and (b) (4). The restored human FXa activity is measured with an FXa-specific (b) (4) The potency of the Andexanet sample is compared to a reference standard and reported as relative potency (section 3.2.S.4.2.4).

Indirect Potency of Andexanet is determined by its ability to reverse the inhibition of human FXa by the indirect inhibitor Enoxaparin sodium (based on heparin) by binding to the antithrombin III-Enoxaparin complex. Test samples of Andexanet and controls are (b) (4) (b) (4) FXa is added and its activity is measured with an FXa-specific (b) (4). The potency of the Andexanet sample is compared to a reference standard and reported as relative potency (section 3.2.S.4.2.5).

Both methods to determine Direct and Indirect Potency were reviewed by Dr. Mikhail Ovanesov.

3.2.S.4.5 Justification of Specification

The proposed specifications were based on data from (b) (4) lots used in nonclinical toxicology studies, clinical studies, stability testing, process validation and relevant manufacture process development studies. The company stated that the manufacturing experience, pharmacopeial standards and respective methods capabilities were also considered to develop the specifications. The respective limits were set using data from statistical analysis (95% of the results with 99% confidence) of the results, bridging data from testing the lots (Reports AD-2015-001-007 V.3 and NC-15-0607-R0002) and the methods validation studies.

The developed specifications parameters are controlled by respective analytical methods, of which validation information is provided under Section 3.2.S.4.3 (reviewed by Dr. Mikhail Ovanesov). Justification for the limits of each parameter is provided. In particular, the limit for Endotoxin was established in accordance with (b) (4) with a limit of exposure (b) (4) corresponding to a maximum dose of (b) (4) of Andexanet.

The Identity parameter was controlled by (b) (4) during product development. However, the method was found not to be robust enough to support quantitation of potential product (b) (4) (b) (4) The company stated that (b) (4) would be retained as a characterization method. The company states that the specifications will be reassessed upon manufacture of (b) (4) commercial lots of (b) (4)

DRUG PRODUCT

3.2.P.1 Description and Composition

The lyophilized DP is to be reconstituted with 10.0 mL of sterile Water for Injection (WFI), which is not provided with the DP. The reconstituted DP contains 100 mg of Andexanet at a concentration of 10 mg/mL. The content of each vial of the lyophilized DP is shown below.

Composition of Drug Product (lyophilized) per vial.

Ingre	Quality	Function	Amount per Vial
andexanet alfa	In house	Active agent	(b) (4)
Tromethamine (Tris)	(b) (4)		
L-Arginine Hydrochloride			
Sucrose			
Mannitol			
Polysorbate 80			
(b) (4)			
(b) (4)			

3.2.P.4.1. & 3.2.P.4.4 Specifications and their justification for Excipients

The selection of excipients and their respective content was established according to the compendial standards.

3.2.P.5.6 Justification of Specifications

The proposed specifications were based on data from DP lots used in nonclinical toxicology studies, clinical studies, stability testing, process validation and relevant development studies. Manufacturing experience, pharmacopeial standards and method capability were also considered. For (b) (4) (b) (4) and the (b) (4) (indirect inhibitor potency), results from analysis of (b) (4) batches were used for setting specifications for the DP due to limited data set available for the DP batches. The non-compendial methods (b) (4) and (b) (4) (direct inhibitor potency, indirect inhibitor potency) were used throughout the development program for release and stability testing, with specifications set in alignment with their qualitative capabilities. Afterwards, these methods were optimized to be quantitative and used for setting of commercial specifications. Both Direct and Indirect Potency are determined by comparing the test sample response to the response of an Andexanet reference standard and reported as relative potency.

In advance of the process performance qualification (PPQ) campaign, specifications were set using data from statistical analysis (95% of the results with 99% confidence) of method bridging, data from testing of lots (Report NC-15-0607-R0002), and the methods validation studies. For each parameter, justification of its limits is provided as reviewed for the (b) (4) specifications. In particular, for Identity, the (b) (4) is considered to be qualitative and retained as a characterization method. The company states that the specifications will be reassessed upon manufacture of (b) (4) commercial lots of (b) (4).

3.2.P.5.1 Specifications of the Drug Product

Test Attribute	Test Method	Stability Assay	Acceptance Criteria
Tests Performed on Lyophilized Product:			
Characteristics	Visual Appearance	Yes	White to off-white lyophilized cake
	Reconstitution Time	Yes	(b) (4)
Purity	Moisture Content per (b) (4)	Yes	
	Sterility [1] per (b) (4)	Yes	Sterile
	Endotoxin per (b) (4)	No	(b) (4)
Tests Performed on Product After Reconstitution with 10.0 mL Sterile Water for Injection (SWFI):			
Characteristics	Appearance after Reconstitution	Yes	Clear, colorless to slightly yellow solution, essentially free of visible particulates.
	pH (b) (4)	Yes	7.8 (b) (4)
	(b) (4)	No	(b) (4)
Identity and Potency	Direct Potency	Yes	(b) (4)
Potency	Indirect Potency	Yes	
	Protein Concentration by (b) (4)	Yes	
Purity	Purity by (b) (4) (b) (4)	Yes	
	(b) (4)	Yes	
	(b) (4)	Yes	
	(b) (4)	Yes	
	Particulate Matter per (b) (4) (b) (4)	Yes	

(b) (4)
(b) (4)
[1] Container closure integrity testing per (b) (4) is performed instead of the (b) (4) sterility test during stability studies.

Reviewer's Comment

The comments are similar to those made for the (b) (4) specifications. In addition, no specifications are provided for essential excipients: Sucrose, Mannitol and Polysorbate 80.

INFORMATION REQUESTS AND COMMENTS

On April 6, 2016, FDA sent an information request (IR) to the company, further communicated as follows.

1. (Question 8). In the specifications of the (b) (4) and Drug Product (DP), you have not provided a parameter(s) to monitor (b) (4) of the protein. Your data for characterization of andexanet alfa (section 3.2.S.3.1) indicate that the protein has at least (b) (4) at (b) (4), which are (b) (4), respectively (Table 3.2.S.3.1-7). Therefore, the theoretical (b) (4) of the protein to (b) (4) However, in Table 3.2.S.3.1-8, you reported a (b) (4) indicating that (b) (4) of the (b) (4) of the protein is incomplete. In addition, the information provided in Figure 3.2.S.3.1.1-3 is not consistent with your analytical data because it does not show (b) (4), but does show (b) (4) at the (b) (4) and only (b) (4) on the molecule. Therefore, please correct Figure 3.2.S.3.1.1-3 to show all (b) (4) with the respective (b) (4) and provide a clear assessment of the (b) (4) (b) (4) of the (b) (4) on the protein in the eCTD file.

Response (sent on April 20, 2016, Amendment 25)
The company explained that the theoretical (b) (4) with Andexanet is (b) (4) However, the actual (b) (4) determined by (b) (4), resulted in the number of (b) (4)

Comment
The response is acceptable. The data show that the (b) (4) of Andexanet is (b) (4)

2. (Question 9). The proposed release specifications of (b) (4) DP for identity, (b) (4) (b) (4) and excipients are deficient. Andexanet alfa is a mutated coagulation factor product manufactured at large scale, formulated at high concentration and administered at high doses. To provide assurance of consistent product quality and to compensate for the limited manufacturing experience, please develop new (b) (4) DP release assays and propose release specifications to control the following parameters.

a. Identity by (b) (4), e.g., the (b) (4) method described under Justification of Specification section 3.2.S.4.5.2.6;
b. (b) (4)
c. Identity and quantity of excipients - sucrose, mannitol and Polysorbate 80.

Response (sent on April 20, 2016, Amendment 25)
a. The company explained that the (b) (4) method used for the product development (Section 3.2.S.4.5.2.6) is not sufficiently robust, and recognized the need of this method for the product Identity testing. They stated that a new (b) (4) method to be used for the DP lot release is under development, and the update of the status will be provided in October 2016.

Comment
The response is not acceptable. The company should include Identity by (b) (4) parameter in the (b) (4) DP Specifications before the BLA approval.

The following IR was submitted on June 22, 2016.
Your proposal to develop specifications and validate new (b) (4) method after October 2016 is not acceptable because this will preclude the FDA from reviewing the information before the goal date. We recommend you to continue to develop your current (b) (4) method which is already partially validated. Please introduce release specifications for identity by (b) (4) (b) (4) using your current (b) (4) method; and submit the specifications and justifications to the BLA by 01 August 2016. Please also commit to completing the validation

studies of this method by 31 October 2016; and re-evaluate the release specifications after you have obtained data from (b) (4) batches of (b) (4) drug product; or one year post licensure, whichever comes first.

Response (sent on July 08, 2016, Amendment 54)
The company stated that the new method will be validated by 31 October, 2016 and the release specification for Identity by (b) (4) using the validated method will be established after testing (b) (4) lots of Andexanet. The company also stated that they will provide the Agency with an example of the graphical output from this assay by August 1, 2016.

Additional Response (sent on July 29, 2016, Amendment 65)
The company provided examples of the graphical outputs from the (b) (4) and a tabulated summary of data for a reference standard and a test sample.

Comment
The responses are not acceptable. . The company failed to establish specification limits for Identity by (b) (4) by August 01, 2016, i. e. before the regulatory action due date. For the BLA approval, this parameter needs to be specified.

b. The company stated that during the (b) (4) risk assessment, (b) (4) was determined to not be a Critical Quality Attribute (CQA). The (b) (4) content is also not thought to affect the PK/PD of andexanet.

Comment
The response is not acceptable. The (b) (4) content, in particular, (b) (4), is known to affect PK of proteins, which may, in turn, affect efficacy of the DP. The (b) (4) content parameter should be controlled in the release specifications of the DP; otherwise the company should provide data that the asialated or not sufficiently (b) (4) protein has the same clinical efficacy.

The following IR was submitted on June 22, 2016.
We disagree with your statement that (b) (4) content is also not thought to affect the PK/PD of andexanet". Please use the available data obtained with the assays of your choice to introduce release specifications for the (b) (4) by 01 August 2016. Please also commit to completing the validation studies of these methods by 31 October 2016 and re-evaluate the release specifications after you have obtained data from (b) (4) batches of either (b) (4) drug product; or one year post licensure, whichever comes first.

Response (sent on July 08, 2016, Amendment 54)
Portola plans to initiate validation of the assay for (b) (4) content prior to approval and complete the validation and generate the interim specification limits by 31 October, 2016, as a part of post-approval commitment. The interim specifications will be re-evaluated after production of (b) (4) lots of the DP or one year post licensure, whichever comes first. In the meantime, Portola proposes to release the DP with the current specifications. Portola plans to provide the Agency with the (b) (4) characterization data from (b) (4) lots generated using a non-validated method by 01 August, 2016. For (b) (4), Portola plans to provide FDA with the data generated by the current non-validated method by 01 August, 2016.

Response (sent on July 29, 2016, Amendment 65)
The company provided interim data for (b) (4) content for (b) (4) lots using a non-validated method. These data showed that the (b) (4) content (b) (4)

The company also provided data for (b) (4) for (b) (4) lots using a non-validated (b) (4) method. These data showed that the average content of the (b) (4) (b) (4)

The company confirmed their commitment to initiate validation of methods for (b) (4) content and (b) (4) prior to approval and complete validation of these methods and introduce interim specifications limits by October 1, 2016, and re-evaluate the specifications parameters after (b) (4) batches or one year post licensure. In the meantime, the company proposed to release the product with the current controls.

Comment
The responses are not acceptable. The company failed to establish specification limits for (b) (4) content by August 01, 2016, i. e. before the regulatory action due date. For the BLA approval, these parameters need to be specified.

c. The company explained that assessment of excipients, in particular, mannitol and sucrose, in the DP by a surrogate assay, such as currently used (b) (4) testing, is appropriate. The company also stated that a method for detection and quantitation of Polysorbate 80 in Andexanet (b) (4) DP is currently under development, and the update of the status will be provided in October 2016.

Comment
The response is not acceptable. The company should develop actual, not surrogate, respective methods for controlling each excipient, Sucrose, Mannitol and Polysorbate 80, in the DP, and establish respective specifications parameters.

The following IR was submitted on June 22, 2016.
We disagree with your proposal to monitor the concentrations of excipients with the in-process control and surrogate assays. Andexanet is administered at high doses, which poses concerns of potential toxicity in patients who are sensitive to sucrose and mannitol. Please introduce specifications for sucrose and mannitol by August 01, 2016. Please also commit to completing the validation studies of these methods by October 31, 2016; and re-evaluate the release specifications after you have obtained data from (b) (4) batches of drug product; or one year post licensure, whichever comes first.

Response (sent on July 08, 2016, Amendment 54)
The company provided risk assessment for sucrose and mannitol use in patients as follows. In the Phase 1-3 studies in healthy volunteers and in more than 100 bleeding patients treated with ANNEXA-4, there was no sensitivity issue linked to the tolerability of sucrose or mannitol. Based on the literature, there is no concern in regard of using respective amounts of sucrose and mannitol at the highest possible dosages. The company stated that they plan to validate the sucrose and mannitol (as well as polysorbate 80) methods and generate the release specifications by the requested date of October 31, 2016.

Comment
The risk assessment of sucrose and mannitol is acceptable. However, the company ignored FDA request to include the specifications for sucrose and mannitol by 01 August 2016, which is not acceptable. For the BLA approval, sucrose and mannitol are required to be specified in the DP.

Additional IR was submitted on June 28, 2016
On 20 April, 2016, you indicated that you are developing a method for detection and quantitation of Polysorbate 80 in Andexanet. In addition to our request for sucrose and mannitol, submitted on June 22, 2016, please include specifications limits for Polysorbate 80 in the drug product by August 01, 2016, and commit to complete the method validation by October 31, 2016 and re-evaluate the limits after you have obtained data from (b) (4) batches of drug product or one year post licensure, whichever comes first.

Response (sent on July 08 11, 2016, Amendment 54)
The company stated that they plan to initiate validation of the assay for mannitol, sucrose, and Polysorbate 80 prior to approval and complete the validation and generate the interim specification limits by 31 October, 2016, as a part of post-approval commitment. The interim specifications will be re-evaluated after production of (b) (4) lots of the DP or one year post licensure, whichever comes first. In the meantime, Portola proposes to release the DP with the current specifications.

Comment
The response is not acceptable. For the BLA approval, mannitol, sucrose, and polysorbate 80 parameters need to be specified.

Response (sent on July 29, 2016, Amendment 65)
The company confirmed their plans to initiate assay validation for (b) (4) mannitol, sucrose, and Polysorbate 80 prior to approval, and complete assay validation, generate interim specifications, and add the new assays and acceptance criteria to the specification by October 31, 2016, as part of a post-approval commitment.

The company provided theoretical (calculated) values of mannitol, sucrose, and Polysorbate 80 content in the DP.

Comment
The response is not acceptable. Instead of establishing (interim) specifications for mannitol, sucrose, and polysorbate 80 in the DP, and providing actual data of analyses of DP lots to justify the limits, the company provided just assumed (theoretical) values. By this, the company still failed to establish specification limits for the components listed above, i. e. (b) (4) (b) (4), sucrose, mannitol and Polysorbate 80, by August 01, 2016, i. e. before the regulatory action due date. For the BLA approval, mannitol, sucrose, and Polysorbate 80 parameters need to be specified.

3. (Question 10). In the specifications of the (b) (4) DP (e.g., section 3.2.P.5.1), the Direct and Indirect Potencies are expressed in percentage units relative to a reference standard. However, the use of percentage unit is not suitable for the evaluation of the stability of the product because the stability of the reference standard is not established. To establish a reliable reference standard throughout the life-cycle of the product, please develop a potency unit that is traceable to international reference preparations distributed by the (b) (4) and the (b) (4). In this case, the potency unit could be defined as follows: (b) (4) Please update the specifications of the (b) (4) DP accordingly.

Response (sent on April 20, 2016, Amendment 25)
The company stated that they appreciate the FDA suggestion to develop a potency unit traceable to international reference preparations distributed by the (b) (4). They stated that it may be difficult (or impractical) to use a single potency unit for both direct and indirect inhibitors. In addition, unlike heparin or low molecular weight heparin, the potency of direct FXa inhibitors is usually expressed as a percentage, not as units. The company proposed to explore (b) (4) different assays for this purpose, with different units for direct and indirect inhibitors. The company committed to develop and validate a potency unit assessment method, based on the reference units of FXa activity, and bridge the current assay results to that.

Comment
The response is not acceptable as the respective corrections of the specifications should be performed before the regulatory action due date.

The following IR was submitted on June 22, 2016.

We acknowledge your commitment to "develop and validate a potency unit based on the reference units of FXa activity" and "will perform feasibility studies by modifications of the assays currently used for direct and indirect FXa inhibitors". However, it is imperative to introduce a product-specific unit prior to product licensure because as we have noted in the Information Request dated 06 April 2016, the use of percentage unit is not suitable for the evaluation of the stability of the product because the stability of the reference standard is not established. Therefore, we disagree with your proposal to delay characterization of the reference standards. By August 01, 2016, please assign a direct potency and an indirect potency of your primary product-specific standard. It can be arbitrarily assigned as (b) (4), respectively; and this unitage can then be used to set your release specifications accordingly. In addition, please apply this unitage to evaluate the potencies of all of your reference standards - primary, secondary or working - in direct and indirect units in side-by-side studies by 31 October 2016.

Response (sent on July 08, 2016, Amendment 54)

The company agreed to assign in-house units for Direct and Indirect Potency for the current Reference Standard Lot (b) (4) by August 01, 2016. This lot will be considered to have (b) (4) (b) (4) The acceptance criteria for these parameters will be modified as follows.

- Direct Potency must be between (b) (4)
- Indirect Potency must be between (b) (4)

The definition of (b) (4) direct or indirect potency units will be equivalent to (b) (4) (b) (4) The company stated that they would evaluate the respective reference standards and DP lots by October 31, 2016.

Response (sent on July 29, 2016, Amendment 65)

The company stated that they will not be able to revise the test methods and the DP specifications for Direct and Indirect potency to report results as Potency Units/mL by August 01, 2016, and intend to do it by September 15, 2016.

Comment

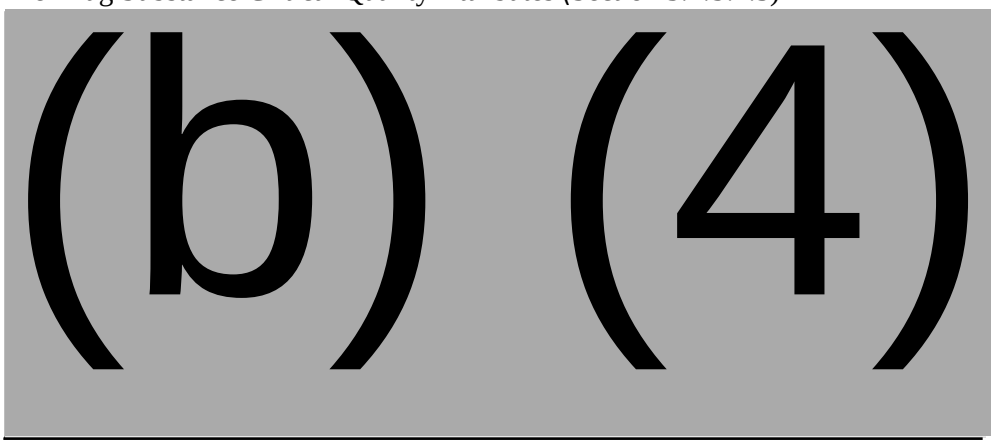
The response is not acceptable. The company failed to establish specification limits for Direct and Indirect potency to report results as Potency Units/mL by August 01, 2016, i. e. before the regulatory action due day. For the BLA approval, these parameters need to be specified in units but not in percent.

4. (Question 11). In the Justification of Specifications of the (b) (4) DP (sections 3.2.S.4.5 and 3.2.P.5.6, respectively), you have not provided an assessment of the critical quality attributes (CQA) of the product and their relative importance (such as arbitrary scores) for the product's safety and efficacy. Considering our comments above (1-3), please provide these data and update the eCTD file accordingly.

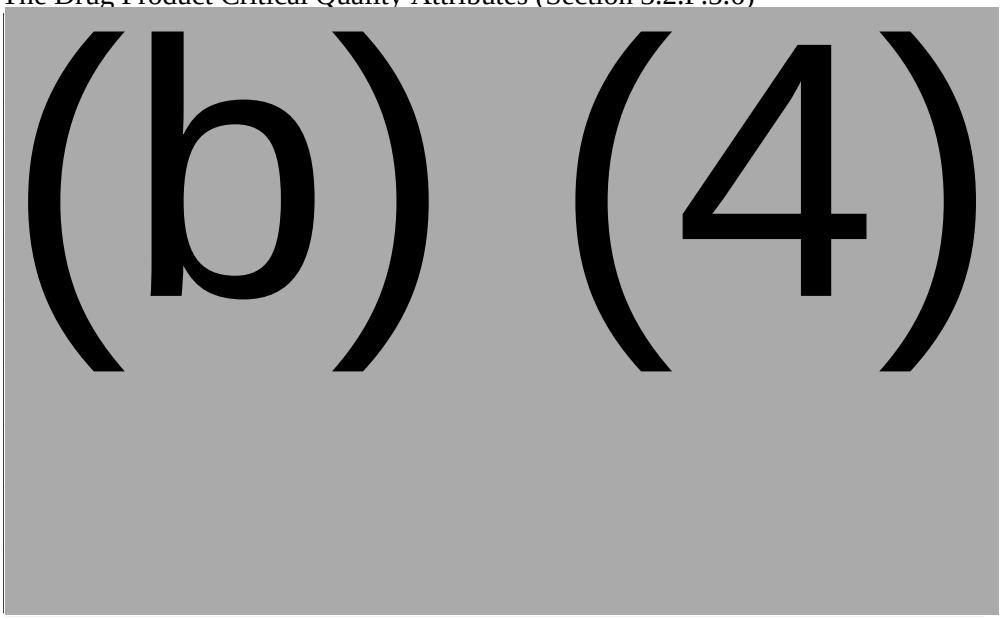
Response (sent on April 20, 2016, Amendment 25)

The company explained that Andexanet alfa (b) (4) quality attributes were identified using information from the literature for FXa, coagulation proteins, knowledge obtained from small-scale experiments, at-scale production process, and analytical understanding. Risk scoring of the quality attributes was performed according to their potential impact on safety and efficacy, and uncertainty around the impact scoring. Criticality of a quality attribute was determined by multiplying the impact and the uncertainty scores. Attributes with a criticality scoring of (b) (4) or greater were considered as critical (CQAs). According to this information, Sections 3.2.S.4.5 (DS) and 3.2.P.5.6 (DP) of the eCTD file were revised to include the following information.

The Drug Substance Critical Quality Attributes (Section 3.2.S.4.5)



The Drug Product Critical Quality Attributes (Section 3.2.P.5.6)



Comment
The response is acceptable.

5. (Question 12). In the specifications of the DP (section 3.2.P.5.1), please clarify which compound corresponds to the parameter "Concentration by (b) (4) Please revise this parameter to "Protein Concentration by (b) (4)

Response (April 20, 2016, Amendment 25)
The company revised the DP specifications to correct the parameter naming accordingly, and updated the eCTD file.

Comment
The response is acceptable.

6. (Question 13). In the specifications for the (b) (4) DP under "Test/Test Method" for compendial methods, please refer to the specific chapters of the compendia (e.g., (b) (4) for (b) (4) , etc.).

Response (sent on April 20, 2016, Amendment 25)
The company revised the DP specifications to refer to the specific chapters of the compendia when appropriate, and updated the eCTD file.

Comment. The response is acceptable.

REVIEW CONCLUSION

The proposed release specifications for the Drug Product are deficient in that they lack the following parameters.

- Identity by (b) (4)
- (b) (4)
- (b) (4)
- Sucrose Content
- Mannitol Content
- Polysorbate 80 Content

The specification limits for Potency are expressed in percent but not in units' scale that does not ensure continuity of reliable Potency controlling during long period of time. All the above characteristics of the Drug Product are important for controlling its lot-to-lot consistency, and thus for its safety and efficacy. The company failed to correct these deficiencies by the regulatory action due date, as FDA requested during the review process. Therefore, approval of the BLA is not recommended.

I recommended requesting the company to correct the above deficiencies. I recommend the following letter-ready questions.

Question 1.
With reference to our IRs dated 07 April, 2016 and your responses on 20 April, 08 July and 29 July, 2016, which we deem incomplete, please validate the (b) (4) assay as an identity test for andexanet alfa, and the methods used for determining the (b) (4) content.

Question 2.
With reference to our IR dated 07 April 2016 and your responses on 20 April, 08 July and 29 July 2016, which we deem incomplete, please validate analytical methods and establish release specifications for the excipients mannitol, sucrose, and Polysorbate 80. Please also qualify all compendial analytical methods used for the release of raw materials intended for FDP formulation. ANDEXXA is administered in large doses in the current regimen and you also plan to increase the number of doses in future studies. This poses concerns of potential toxicity in patients sensitive to sucrose and mannitol.

Question 3.
With reference to our IR dated 07 April 2016 and your responses of 20 April, 08 July and 29 July 2016, which we deem incomplete, please develop and validate potency units for ANDEXXA to replace the current unit of "*percent of a reference standard*." The proposed percentage approach is not suitable for the evaluation of the stability of the product because the stability of the reference standard is not established. The potency units of a standard(s) should be traceable to international reference preparations distributed by the (b) (4) for example, (b) (4) (b) (4) The units could be defined as follows: (b) (4) (b) (4) (b) (4) Please apply this unitage to evaluate the potencies of all of your reference standards - primary, secondary or working - in direct and indirect units in side-by-side comparative studies.