DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food & Drug Administration
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To	STN 125586/0
Through	William M. McCormick, Director, DBSQC/OCBQ
Product	FXa inhibitor antidote, ANDEXXA (Andexanet Alfa)
Sponsor	Portola Pharmaceuticals, Inc.
Subject	Addendum/Final Review Memo for Biological License Application for Quality Control Lot-Release Test Methods for the (b) (4) Drug Product for ANDEXXA (Andexanet Alfa)

Summary of Review

A new Biologics License Application (BLA) for Andexanet Alfa was submitted by Portola Pharmaceuticals. The product is intended to bind and reverse the anti-coagulant effects of factor Xa inhibitors including Apixaban, (b) (4) Rivaroxaban. This document constitutes the Addendum (Final) Review memo from DBSQC for the following analytical methods and their validations as used for the lot release of the Drug Product:

1. Direct Potency Assay
2. Indirect Potency Assay
3. (b) (4) Purity by (b) (4)
4. Moisture Content by (b) (4) Method

There are outstanding issues for the method numbers 1-3 mentioned above, which were not resolved during the review cycle. All other test methods, including the assay for moisture content, reviewed by LACBRP/DBSQC are found to be adequately described and validated for lot-release testing (this memo and the Primary Discipline Review memo, dated 20 June 2016). The review committee has decided to issue a Complete Response (CR) Letter for this BLA.

Background

Andexanet Alfa is proposed for urgent reversal of anticoagulation in patients administered with either direct or indirect FXa inhibitors, who require surgery or suffer a severe bleeding episode.

Andexanet Alfa is a recombinant protein expressed in Chinese Hamster Ovary cells. It retains the ability to bind direct and indirect inhibitors; however, it has no intrinsic activity.

FXa inhibitors bind and inhibit the activity of FXa. Andexanet Alfa binds to the FXa inhibitor with high affinity and prevents the FXa inhibitor from binding to FXa. Thus the native FXa activity is restored and the FXa inhibitor is sequestered. (b) (4) . Andexanet Alfa is proposed to be administered intravenously as a single bolus, followed by a longer infusion, dose-dependent on the amount of FXa inhibitor the patient is receiving.

Submitted Information Reviewed

This is a rolling electronic submission. Information submitted and reviewed includes:

- 125586/0.1 - 3.2.P.5.1 Specification(s)
- 125586/0.1 - 3.2.P.5.2.14 - Doc. VAL-60474-05 - (b) (4) Method
- 125586/0.45 – 1.11.1 Quality Information Amendment; received on 28 June 2016.
- 125586/0.57 – 1.11.1 Quality Information Amendment; received on 14 July 2016.
- 125586/0.65 – 1.11.1 Quality Information Amendment; received on 1 August 2016.

Review Narrative

1. Direct and Indirect Potency Assays

The Direct Potency Assay is a (b) (4) method that measures the ability of Andexanet Alfa (b) (4) Drug Product (DP) to reverse the inhibition of FXa by the inhibitor (b) (4). The proposed specification for this method is (b) (4).

The Indirect Potency Assay is also a (b) (4) method that measures the ability of Andexanet Alfa (b) (4) DP to reverse the inhibition of FXa by the indirect inhibitor Enoxaparin, through binding of (b) (4). The specification (b) (4) .

The following information request was submitted to the sponsor on 13 June 2016. The response was received on 28 June 2016. The review of the response was not addressed in the Primary Discipline Review Memo.

> With respect to your response received on 7 June 2016, we fail to see how the specificity data provides any information on the qualification of your standard. Since both assays are based on relative potency determinations, the data referred to in Table 4 of both documents you submitted gives information on the potency of the current standard relative to the previous standard. It is therefore imperative that you provide information on the

qualification of your primary standard, Lot (b) (4), and how the potency value of this standard was established.

Review of the Response: The sponsor explained (Amendment 45) that the potency of the Reference Standard, lot (b) (4), was assigned using the (b) (4) assay, described in the document, (b) (4). The method is similar to the Direct Potency assay however it differs in how the (b) (4) is calculated. In the (b) (4), it is calculated as:

(b) (4)

Since the Direct and Indirect potency assays are both relative potency assays, the sponsor stated that a single crossover determination was proposed to be used to determine the potency of the new Reference Standard. However, sponsor's justification is not acceptable since these are two different assays. Furthermore, the sponsor did not provide any data for the qualification of Lot (b) (4) as RS, nor did they provide the qualification protocol to establish a new RS, as requested. The same request was also submitted twice before, as part of the second (submitted on 4 May 2016) and third (submitted on 23 May 2014) IRs (see the Primary Discipline Review Memo, dated 20 June 2016). Consequently, a few questions remained unanswered.

a. Was the determination done from single or multiple replicates? How many replicates?

b. Is the number of replicates adequate (Give adequate statistical power for data analysis)?

c. What material was used as the standard? Was the previous RS used as the standard or a Primary RS was established against which the subsequent RS lots are qualified?

In spite of three IRs, we did not get clear answers to our questions. The following IR was submitted again on 6 July 2016.

i. You stated that the potency of the first reference standard was assigned using the (b) (4) and that for the subsequent standards will be determined using the Direct and Indirect Potency assays, using the first standard. However, based on the information you provided, it is not clear to us how you will qualify and establish subsequent reference standards. It is not acceptable if you continue to establish reference standard using the previous reference standard lot because that contributes to significant deviation in potency due to propagation of error. You should qualify and establish (b) (4) lot of your product as the Primary standard, which should be linked to your clinical outcome. You should qualify all of your subsequent lots using this Primary standard as the standard. In addition, you should

perform adequate number of replicate analyses so that the potency of the subsequent standard can be assigned with an acceptable statistical power. Please provide your reference standard qualification protocol to qualify subsequent standards for review.

ii. Please explain how qualifying your standard using the Direct Potency assay allows you to assign the potency for the Indirect Potency Assay as these two assays work via completely different mechanisms and are not mutually related. Please provide data in support of your explanation.

These IRs were not addressed within the review cycle and has been included in the CR Letter.

Conclusion: The method is clearly written. However, we are unable to conclude if the Direct and the Indirect Potency Assay methods are acceptable for quality control lot release in the absence of qualification data and qualification protocol to establish a new RS. Furthermore, the RS used in the Indirect Potency assay was not qualified by the assay method. A CR Letter should be issued. Related IRs will be included in the CR Letter (see later).

(b) (4)

The specifications are (b) (4). There is no specification for (b) (4). However, the results are to be reported.

The method is adequately described and validated. The sponsor reported (b) (4) from Andexanet Alfa (b) (4) DP, in addition to the (b) (4), by this method. The results were confirmed by the DBSQC lab during in support testing. However, when Andexanet Alfa DP lots were tested in the DBSQC lab during in-support testing, we found (b) (4) of which are (b) (4), in addition to (b) (4) (memo from Hsiaoling Wang and Alfred Del Grosso, dated 12 August 2016). The sponsor needs to investigate identity of the (b) (4).

Conclusion: A CR Letter should be issued. Related IRs will be included in the CR Letter requesting the sponsor to identify the (b) (4) seen under the altered assay condition (using a different (b) (4) agent) in the DBSQC laboratory (see later).

3. Moisture Content by (b) (4) Method

The water content by (b) (4) method for testing lyophilized Andexanet alfa DP samples is determined with a (b) (4) following (b) (4). The release specification is moisture (b) (4). This is acceptable.

The following IR was submitted to the sponsor on 1 June 2016. The complete response was received on 1 August 2016 (Amendment 65).

We do not agree that your Moisture by (b) (4) method can be considered a compendial method for your product as the cited method, (b) (4), is not described in sufficient detail to allow replication and there is no monograph for your product in USP/NF. In addition to the data you provided in validation report VAL-60150-03 and in Amendment 33 (dated May 26, 2016), please provide accuracy data, as we requested in our previous IR dated 12 May 2016.

Review of Response: In response, the sponsor provided representative system suitability data as well as results from spike recovery studies as requested in the IR.

System suitability check using a NIST traceable water standard is performed by (b) (4) (contract laboratory) as part of the routine execution of the test method. Results from triplicate measurements of (b) (4) lots of the standard show mean water content to be (b) (4) for both. The results are consistent with the certificate values for both lots. The maximum error was found to be within (b) (4), which is acceptable.

(b) (4)

Conclusion: The method is clearly written and adequately validated, and can be approved for quality control lot-release testing.

CR Letter Issues

The following issues are included in the CR Letter.

- (b) (4)
- Provide your reference standard qualification protocol for review.
- Qualify and establish one lot of Andexanet alfa as the Primary Reference Standard and ensure that your Working Reference Standards are qualified against this Primary standard over the product life-cycle. Your Primary reference standard should be established in such a way as to link to your clinical and safety outcomes as a surrogate. In addition, you should perform adequate number of replicate analyses to qualify reference standards so that the potency can be assigned with sufficient statistical power.

- Qualify the reference standards independently for both the Direct and the Indirect potency assays.