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To STN 125586/0

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Product FXa inhibitor antidote, ANDEXXA (Andexanet Alfa)

Sponsor Portola Pharmaceuticals, Inc.

Subject Primary Discipline Review Memo for Biological License Application for Quality Control Lot-Release Test Methods for the Drug Substance and 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), Enoxaparin, and Rivaroxaban. This document constitutes the Primary Discipline 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. Purity by (b) (4)
4. Purity by (b) (4)
5. Visual Examination
6. Reconstitution Time
7. (b) (4)
8. pH
9. Moisture Content
10. Protein Concentration by (b) (4)

The methods are clearly written. However, there are outstanding IRs for the validations of both potency assays and moisture which should be addressed prior to approval of these methods.

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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. Andexanet Alfa also binds to indirect FXa inhibitors which complex with antithrombin III. 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:

- 125586/0.0 – 2.3.S.5 Reference Standards or Materials
- 125586/0.1 – 3.2.S.4.2 Analytical Procedures
 - 3.2.S.4.2.4 Analytical Procedure Summary for Direct Potency Assay
 - 3.2.S.4.2.5 Analytical Procedure Summary for Indirect Potency Assay
- 125586/0.1 – 3.2.S.4.3 Validation of Analytical Procedures
 - 3.2.S.4.3.1.1 Validation of Analytical Procedures Summary for Direct Potency Assay
 - 3.2.S.4.3.1.2 Validation of Analytical Procedures Summary for Indirect Potency Assay
- 125586/0.1 - 3.2.S.5 Reference Standards or Materials
- 125586/0.1 - 3.2.R Regional Information
 - 3.2.R.2 VAL-60580-02 TME-0580, (b) (4) – Direct Potency Assay Validation Report
 - 3.2.R.2 VAL-60583-02 TME-0583 – Indirect Potency Assay Validation Report
- 125586/0.1 - 3.2.P.5.1 Specification(s)
- 125586/0.1 - 3.2.P.5.2 Method Description-Analytical procedures
 - 3.2.P.5.2.11 - Purity by (b) (4)
 - 3.2.P.5.2.14 - (b) (4)
 - 3.2.P.5.2.1 - Visual Appearance
 - 3.2.P.5.2.2 - Reconstitution Time
 - 3.2.P.5.2.7 - (b) (4)
 - 3.2.P.5.2.6 – pH
 - 3.2.P.5.2.3 – Moisture Content
 - 3.2.P.5.2.10 – Concentration by (b) (4)
- 125586/0.3 - 3.2.P.5.3 Validation of Analytical Procedures
 - 3.2.P.5.3.1.3 - Concentration by (b) (4)
 - 3.2.P.5.3.1.4 - Purity by (b) (4)
 - 3.2.P.5.3.1.7 - Purity by (b) (4)
 - 3.2.P.5.3.3.1 – Visual Appearance
 - 3.2.P.5.3.3.2 – pH

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- 3.2.P.5.3.3.3 – (b) (4)
- 3.2.P.5.3.3.6 – Moisture Content
- Doc. VAL-60131-27 – Concentration by (b) (4)
- Doc. VAL-60584-02 - (b) (4)
- Doc. VAL-60474-05 - (b) (4)
- Doc. VAL-60007-01 – Visual Appearance
- Doc. VAL-60004-04 - pH
- Doc. VAL-60008-05 - (b) (4)
- 125586/0.7 –1.2 Cover Letters
 - Cover Letter 20160222 – Information Request
- 125586/0.7- 3.2.S.4.2 Analytical Procedures
 - Doc. VAL-60580-02 - Direct Potency Assay
 - Doc. VAL-60583-02 - Indirect Potency Assay
- 125586/0.32-1.11 Quality Information Amendment
 - 1.11.1 Quality Information Amendment
- 125586/0.32-3.2.R Regional Information
 - 3.2.R.2 (b) (4)-VAL-60580-02.1: Addendum Direct Potency
 - 3.2.R.2 (b) (4)-VAL60583-02.1: Addendum Indirect Potency
- 125586/0.33-1.11 Quality Information Amendment
 - 1.11.1 Quality Information Amendment
- 125586/0.36 – Quality Information Amendment
 - 1.11.1 Quality Information Amendment

Review Narrative

1. Direct Potency Assay

This (b) (4) method measures the ability of Andexanet Alfa (b) (4) Drug Product to reverse the inhibition of FXa by the inhibitor (b) (4). The proposed dose formulation is 100 mg/vial. The proposed specification is (b) (4) of (b) (4). The sponsor provided an analytical procedure summary (3.2.S.4.2.4), a validation of analytical procedures summary (3.2.S.4.3.1.1), and a validation report (VAL-60580-02). The SOP was not provided with the original submission (125586/0.0), and this was requested in an IR (see 1.a below).

Method

The Direct Potency assay measures the ability of Andexanet Alfa to reverse the inhibition of FXa by binding to the FXa inhibitor, (b) (4)

(b) (4)

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(b) (4)

[Redacted text block]

Method Validation

This is a quantitative method. The validation report contained evaluation of the following characteristics: (b) (4)

[Redacted text block]

(b) (4)

[Redacted text block]

(b) (4)

[Redacted text block]

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(b) (4) [Redacted]

First Information Request and Review

The following IRs were submitted to the sponsor on 12 February 2016. The responses were received on 22 February 2016 as Amendment 7. The IR questions, the response of the sponsor and review of the responses are discussed below:

1. Please submit the current SOPs for the following assays:
 - a. Direct Potency (3.2.S.4.2.4), TME-0580, (b) (4) : Direct Inhibitor Potency Assay

Review of Response: The sponsor provided the standard operating procedure. It was clearly written and provided sufficient details. This is adequate.

2. Direct Potency Assay (3.2.S.4.2.4)

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- i. Please provide the names/descriptions of the materials used as Reference standard and Assay Control in the assay (Table 3.2.S.4.2-2). Are they in-house materials, commercially available from a US source or International Standard (IS) from (b) (4). If they are available from a US source, please provide the name(s) of the supplier(s) and catalog/part numbers. If the standard is an IS, please provide the code number.

Review of Response: The sponsor provided information on the reference standard, assay control and inhibitor used in the assay and referenced the SOP TME-0580 for further descriptions. This is adequate.

- ii. Are Control Sample and Assay Control mentioned in the section 3.2.S.4.2.4 the same material? If not, please provide the name/description and source of the Control Sample.

Review of Response: The sponsor confirmed the control sample and assay control were the same and referred to the SOP TME-0580 for clarification. This response is satisfactory.

- iii. Please provide the description and source of FXa used in this assay. If it is not an in-house material, please provide the source, including the name of the supplier and catalog/part/code number.

Review of Response: The sponsor clarified the Human FXa is purchased from (b) (4). This is adequate.

- iv. Please indicate the incubation temperature for the assay.

Review of Response: The sponsor indicated that the assay incubation temperature is (b) (4). This is sufficient.

- v. With reference to the System Suitability section of Table 3.2.S.4.2-2, please clarify what is meant by “All valid data points must have a (b) (4)”. What regression analysis is used to calculate the results (e.g., linear, quadratic, etc.)? What it being described by the term “The calculated ratio of the Assay Window (A-D) values”.

Review of Response: The sponsor clarified that the (b) (4) is between (b) (4), and explained that the regression analysis is a 4-parameter fit and referred to the SOP, TME-0580 for further details. This is adequate.

- vi. Please explain how the potency is determined, specifically how the (b) (4) of the standards, controls and test samples are calculated, and what is meant by the terms “(b) (4)” and “Target Potency” mentioned in your validity report.

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Review of Response: The sponsor referred to the SOP, TME-0580 for clarification on how potency was calculated. The SOP provided sufficient details. This is adequate.

Second Information Request and Review

The following IRs were submitted to the sponsor on 4 May 2016. The responses were received on 19 May 2016 as Amendment 32. The IR questions, the response of the sponsor and review of the responses are discussed below:

3. Analytical Method Validation Report, VAL-60580-02

- i. You have stated in section 2.3.S.5.2 that Andexanet alfa (b) (4) lot # (b) (4) (Portola Lot# (b) (4)) was developed as the reference standard for this assay. Please explain how this Reference Standard was qualified and provide a representative set of qualification data.

Review of Response: The sponsor stated that the Reference Standard, Lot (b) (4), was characterized as per release testing for the following attributes: (b) (4) assays and cited 3.2.S.5 Reference Standards or Materials for further information. It was not clear what standard the relative potency of the standard was qualified against. Furthermore, the sponsor also provided information on the primary standard, Lot (b) (4). No information was provided as to how the potency of the primary standard in the Direct and Indirect potency assays was established. This led to another IR (see 4.i below).

- ii. Please describe how the (b) (4) is prepared.

Review of Response: The sponsor stated that the (b) (4) was prepared by keeping a sample of Lot (b) (4). This is adequate.

- iii. You have measured linearity by plotting the calculated % relative potency against the target % relative potency. This is a measure of accuracy. Please clarify what sample was measured in the linearity study presented in Figure 3. Please provide response curves plotted against log nominal potency for your reference standard and drug product, including results of the parametric fit analyses and regression coefficients for the curves.

Review of Response: The sponsor provided an Addendum to their Validation Report, VAL-60580-02.1 (b) (4) – Direct Inhibitor Potency Assay Validation Report – Addendum, which provided the data for the 4-parameter fit analysis. Comparison of the slopes between Reference Standard and Test Sample were between (b) (4), which met the acceptance criterion of (b) (4). The R² values of the curves were between (b) (4), which met the acceptance criteria of (b) (4). This is adequate.

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Third Information Request and Review

Review of the Information Requests generated an additional request for information:

The following IR was submitted to the sponsor on 23 May 2016. The response was received on 7 May 2016 as Amendment 36. The IR question, the response of the sponsor and review of the response are discussed below:

What standard was used to determine the relative potency of Reference Standard, Lot (b) (4) ? How is the potency of the primary standard established? Please provide data demonstrating how the potency of the primary standard was established for both assays.

Review of Response: The sponsor stated that the Reference Standard was compared to the previous Reference Standard and cited their specificity studies in the respective validation reports which were used to determine the new Reference Standard potency. The response is not satisfactory because the potency determination of (b) (4) lot of the standard is based on the potency of the previous lot of the standard. However, no information was provided about how the potency of the primary standard was determined, and how it was qualified. This led to the generation of an additional IR (see 5 below).

Fourth Information Request and Review

Review of the Information Requests generated an additional request for information:

The following IR was submitted to the sponsor on 13 June 2016.

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.

Conclusion: The method is clearly written. There is one outstanding IR regarding the qualification of the Reference Standard for the validation, which should be addressed prior to approval of this method.

2. Indirect Potency Assay

This (b) (4) method measures the ability of Andexanet Alfa (b) (4) Drug Product to reverse the inhibition of FXa by the indirect inhibitor (b) (4) , through binding of Andexanet Alfa to the (b) (4) complex. The specification is (b) (4) of (b) (4) . The sponsor provided an analytical procedure summary (3.2.S.4.2.5), a validation of analytical procedures summary (3.2.S.4.3.1.2), and a validation report (VAL-

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60583-02). The manufacturer did not provide the SOP, TME-0583, and this led to an IR (see 1.a below).

Method

The Indirect Potency assay measures the binding of Andexanet Alfa to the indirect FXa inhibitor (b) (4) to reverse the inhibition of FXa in a mixture containing Andexanet Alfa, FXa, (b) (4). The released FXa activity is measured by (b) (4), producing a colored product which is measured at (b) (4).

(b) (4)

[Redacted text block]

Method Validation

This is a quantitative method. The validation report contained evaluation of the following characteristics: (b) (4)

[Redacted text block]

(b) (4)

[Redacted text block]

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(b) (4)

(b) (4)

The critical reagents will be further monitored for establishing expiration dates.

Information Request and Review

The following IRs were submitted to the sponsor on 12 February 2016. The responses were received on 22 February 2016 as Amendment 7. The IR questions, the response of the sponsor and review of the responses are discussed below:

1. Please submit the current SOPs for the following assays:
 - a. Indirect Inhibitor Potency (3.2.S.4.2.5), TME-0583, (b) (4): Indirect Inhibitor Potency Assay

Review of Response: The sponsor provided the relevant SOP. It was clearly written and provided sufficient detail. This is sufficient.

2. Indirect Potency Assay (3.2.S.4.2.5)
 - i. Please provide the name/description of the material used as Reference standard and Assay Control in the assay (Table 3.2.S.4.2-3). Please clarify if they are in-house materials, commercially available from a US source or International Standard (IS) from (b) (4). If they are available from a US source, please provide the name(s) of the supplier(s) and catalog/part numbers. If the standard is an IS, please provide the code number.

Review of Response: The sponsor clarified the source of the Reference Standard and Control and referred to the SOP for further information. This is sufficient.

- ii. Please provide the description and source of FXa used in this assay. If it is not an in-house material, please provide the source, including the name of the supplier and catalog/part/code number.

Review of Response: The sponsor indicated that the source of FXa was from (b) (4). This is sufficient.

- iii. Please indicate the incubation temperature for the assay.

Review of Response: The sponsor stated that the assay is carried out at (b) (4). This is sufficient.

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- iv. In the System Suitability section (Table 3.2.S.4.2-3), please clarify what is meant by “All valid data points must have a (b) (4)”. What regression analysis is used to calculate the results (e.g., linear, quadratic, etc.)? What it being described by the term “The calculated ratio of the Assay Window (D-A) values”.

Review of Response: The sponsor clarified that the (b) (4) is between (b) (4) measurements, and confirmed that the regression analysis is a 4-parameter fit and referred to the SOP, TME-0583 for further details. This is adequate.

- v. Please explain how the potency is determined, specifically how the (b) (4) of the standards, controls and test samples are calculated, and what is meant by the terms “(b) (4)” and “Target Potency” mentioned in your validation report.

Review of Response: The sponsor referred to the SOP, TME-0583 for clarification on how potency was calculated. The SOP provided sufficient details. This is adequate.

Second Information Request and Review

The following IRs were submitted to the sponsor on 4 May 2016. The responses were received on 19 May 2016 as Amendment 32. The IR questions, the response of the sponsor and review of the responses are discussed below:

3. Analytical Method Validation Report, VAL-60583-02

- i. In your validation report, VAL-60583-02, in Table 2: Sample Descriptions, it is listed that sample (b) (4) Drug Product, Lot number (b) (4) and sample (b) (4), Lot number (b) (4). However, in your validation report for the Direct Inhibitor Potency assay, VAL-60580-02, sample (b) (4) Drug Product, (b) (4), while sample (b) (4), Lot (b) (4). Please explain this discrepancy.

Review of Response: The sponsor stated that there had been a typographical error in the validation report VAL-60583-02, such that the lot numbers for the drug product (b) (4) had been switched. (b) (4) is the drug product, Lot (b) (4), while (b) (4) is the (b) (4), Lot (b) (4). This is satisfactory.

- ii. You have measured linearity by plotting the calculated % relative potency against the target % relative potency. This is a measure of accuracy. Please clarify what sample was measured in the linearity study presented in Figure 3. Please provide response curves plotted against log nominal potency for your reference standard and drug product, including results of the parametric fit analyses and regression coefficients for the curves.

Review of Response: The sponsor provided an Addendum to their Validation Report, VAL-60583-02.1 (b) (4) – Indirect Inhibitor Potency Assay Validation Report – Addendum, which

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provided the data for the 4-parameter fit analysis. Comparison of the slopes between Reference Standard and Test Sample were between (b) (4), which met the acceptance criterion of (b) (4). The R^2 values of the curves were (b) (4), which met the acceptance criteria of (b) (4). This is adequate.

Third Information Request and Review

Review of the Information Requests generated an additional request for information:

The following IR was submitted to the sponsor on 23 May 2016. The response was received on 7 May 2016 as Amendment 36. The IR question, the response of the sponsor and review of the response are discussed below:

What standard was used to determine the relative potency of Reference Standard, Lot (b) (4)? How is the potency of the primary standard established? Please provide data demonstrating how the potency of the primary standard was established for both assays.

Review of Response: The sponsor stated that the Reference Standard was compared to the previous Reference Standard and cited their specificity studies in the respective validation reports which were used to determine the new Reference Standard potency. The response is not satisfactory because the potency determination of one lot of the standard is based on the potency of the previous lot of the standard. However, no information was provided about how the potency of the primary standard was determined, and how it was qualified. This led to the generation of an additional IR (see 5 below).

Fourth Information Request and Review

Review of the Information Requests generated an additional request for information:

The following IR was submitted to the sponsor on 13 June 2016.

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.

Conclusion: The method was clearly written and provided sufficient details. However, since the same standard is used for the Direct and Indirect potency assays, and as there are issues regarding the qualification of the standard, this should be addressed prior to approval of this method.

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3. Purity by (b) (4)

(b) (4) separates molecules based on (b) (4). Assay specifications are (b) (4).

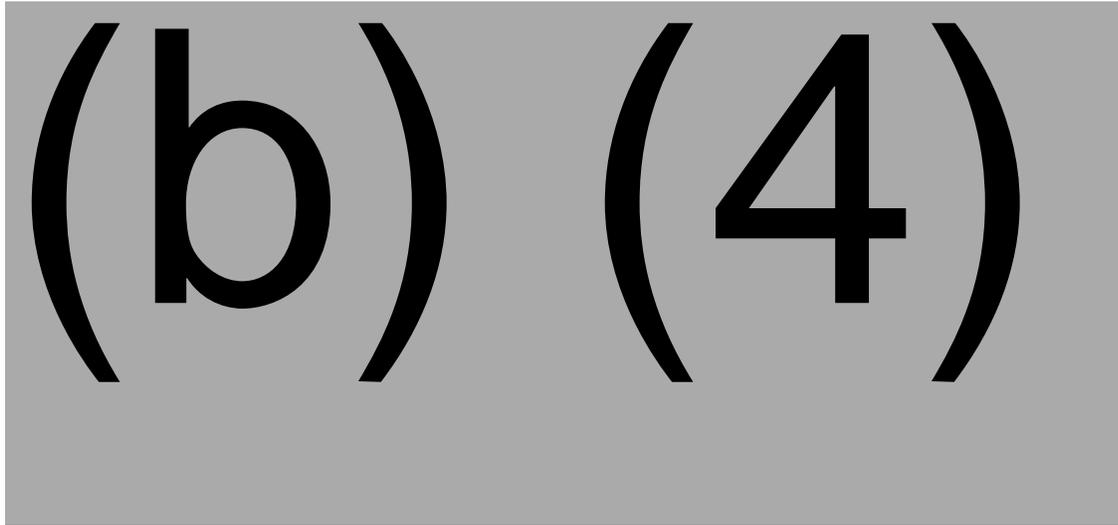
Method

(b) (4)

(b) (4)

The Analytical Procedure for the test method was requested via an IR.

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Method Validation

The following characteristics were studied to validate the method: (b) (4) [redacted]

(b) (4) [redacted]

(b) (4) [redacted]

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(b) (4)

First Information Request and Review

The following IRs were submitted to the sponsor on 12 February 2016. The responses were received on 22 February 2016 as Amendment 7. The IR questions, the response of the sponsor and review of the responses are discussed below:

1. Please submit the current SOPs for the following assays:
 - c. Purity by (b) (4) (3.2.S.4.2.7)

Review of Response: The sponsor provided the standard operating procedure. It was clearly written and provided sufficient details. This is adequate.

- i. Please provide description of the (b) (4) and (b) (4) (if any), including information regarding its supplier and catalog/part number

Review of Response: (b) (4)

No (b) (4) was used in the assay. This is acceptable.

- ii. Please provide the name/description of the material used as the standard in this assay. Please clarify if it is an in-house standard or commercially available from a US source. If it is commercially available from a US source, please provide the name of the supplier and catalog/part number

Review of Response: The reference standard is derived from (b) (4)-produced (b) (4) lot # (b) (4). The CoA was submitted. This response is satisfactory.

- iii. Please provide a representative (b) (4) of the drug product, identifying (b) (4)

Review of Response: The sponsor referred to Figure 2 in TME-0584 (previously submitted) for a representative (b) (4) of the drug product. This is adequate.

- iv. It is not clear to us what “the reference percent (b) (4)” (in the system

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(b) (4) [Redacted]

(b) (4) [Redacted]

(b) (4) [Redacted]

First Information Request and Review

The following IRs were submitted to the sponsor on 12 February 2016. The responses were received on 22 February 2016 as Amendment 7. The IR questions, the response of the sponsor and review of the responses are discussed below:

- 2. Please submit the current SOPs for the following assays:
 - d. (b) (4) assay (3.2.S.4.2.10)

Review of Response: The sponsor provided the standard operating procedure. It was clearly

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written and provided sufficient details. This is adequate.

- i. Is a (b) (4) used with the (b) (4)? If so, please provide information on the (b) (4) used, including supplier and catalog/part number.

Review of Response: No (b) (4) was used in the assay. This is acceptable.

- ii. Please provide the name of the supplier and catalog/part number of the (b) (4) standard used in the (b) (4) assay. This is acceptable.

Review of Response: (b) (4) standard, cat # (b) (4). This is acceptable.

- iii. Please provide the names/descriptions, including compositions, of the preparations used as reference standard and the suitability standard used in the assay. Please clarify if they are in-house standard or commercially available from a US source. If they are available from a US source, please provide the name(s) of the supplier(s) and catalog/part numbers.

Review of Response: (b) (4) Reference Standard is the quality standard for the reference material used. It is derived from (b) (4) -produced (b) (4) lot # (b) (4). This is acceptable.

Conclusion: The method is sufficiently validated and can be approved for its intended use

5. Visual Examination

The Visual Appearance method for testing Andexanet alfa in DP samples met both (b) (4) and (b) (4) and (b) (4) requirements. The method is (b) (4) compliant for clarity determination and (b) (4) compliant for visible particles and degree of coloration. The appearance of reconstituted solution is examined by visual inspection to be clear and without particulates. Analysts are qualified to perform the method through training. This training includes a near vision acuity test, a visual inspection exam, and a demonstration of performance by acceptable inspection of a series of test samples. The specifications are that the reconstituted product is a clear, colorless to slightly yellow solution and visible particles are to be reported. This is acceptable.

6. Reconstitution Time

The amount of time required for the drug product powder to dissolve in Water for Injection is measured. Only method repeatability was studied by (b) (4) replicate measurements of (b) (4) lots each of (b) (4). The RSD of measurements of individual lots are 9-21%. The specification is reconstitution time (b) (4). This is acceptable.

7. pH

The determination of pH method for testing Andexanet alfa in DP samples is compliant with (b) (4). Verification of the compendial method was examined by obtaining a pH reading of test samples on different days by (b) (4) different analysts. The absolute difference in

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readings was (b) (4) pH units, which met the criterion of (b) (4) pH units. The specification is pH of 7.8(b) (4). This is acceptable.

8. (b) (4)

(b) (4)
[Redacted]
[Redacted]
[Redacted]
[Redacted]
[Redacted]
[Redacted]
[Redacted] This is acceptable.

9. Moisture

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

First Information Request and Review

The following IR was submitted to the sponsor on 12 February 2016. The responses were received on 22 February 2016 as Amendment 7. The IR questions, the response of the sponsor and review of the responses are discussed below:

1a. Moisture Content (3.2.P.5.2.3)

Please confirm if the procedures described in the above mentioned sections of your submission represent final test procedures, as described in your respective SOPs. If they are not, please submit the current, working SOPs.

Review of Response: The procedures described in the BLA for the Moisture Content SOP (3.2.P.5.2.3) are consistent with the current test method TME-0150. This is acceptable.

Second Information Request and Review

The following IR was submitted to the sponsor on 12 May 2016. The responses were received on 27 May 2016 as Amendment 33. The IR questions, the response of the sponsor and review of the responses are discussed below:

In your validation of the Moisture by (b) (4) (3.2.P.5.2.3) you did not determine the accuracy of the method. Please evaluate the accuracy of the method and submit for review.

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Review of Response: The sponsor claimed that verification was not needed as the method is (b) (4) compendial. This is unacceptable.

Third Information Request and Review

The following IR was submitted to the sponsor on 1 June 2016. The response was received on 15 June 2016 in an email.

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 (b) (4). 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: (b) (4) runs a water check solution traceable to (b) (4) Standards to determine system suitability and accuracy of the (b) (4) instrument. (b) (4) standards from different lots were analyzed in (b) (4). Mean water content measured was (b) (4) for one and (b) (4) for the other. This met the acceptance criterion of (b) (4) water with a maximum error of (b) (4). However, the results were obtained with water standard only. The response did not provide results for accuracy determination using the drug product. Thus, the results do not address our IR completely.

CBER received the following e-mail from the sponsor (e-mail from Janice Castillo, Senior Vice President, Regulatory Affairs and Quality Assurance, Portola Pharmaceuticals, Inc. to Thomas Maruna and cc to M. Ovanesov, L. Bhattacharyya, E. Raptis-Zarou and Y. Zagorin) on 15 June 2016.

Since (b) (4) conducts drug product testing for Portola, the RFI below was forwarded to them for reply. We have received accuracy data from (b) (4), however, I am concerned that it might not be what FDA is asking for. The raw data we received are for the (b) (4) samples each for assays (b) (4) as originally delineated in the validation report VAL-60150-03 in Amendment 33. Please let me know if these accuracy data address FDA's request or if additional data are needed.

Thank you in advance for your help.

In response, L. Bhattacharyya sent the following e-mail:

I looked through your results. It is in the right direction. However, you have generated your data using the standard. It partially satisfies the data we need to have. Please provide similar data by (b) (4) drug product and provide (b) (4). Please provide the data from (b) (4) measurements and submit via the formal secured system. One additional clarification. Please do your best to keep the water content in the (b) (4) samples within or as close as possible to the upper limit of the proposed specification for water content.

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Conclusion: The method is clearly written. There is one outstanding IR regarding the accuracy of the method that must be addressed prior to approval of this method.

10. Protein by (b) (4)

The determination of protein content in samples of Andexanet alfa is by (b) (4) [redacted]. Assay specifications are (b) (4) [redacted].

Method

(b) (4) [redacted]
[redacted]
[redacted]
[redacted]
[redacted]
[redacted]

Validation of the method

The following were examined: (b) (4) [redacted]
[redacted]

(b) (4) [redacted]
[redacted]

(b) (4) [redacted]
[redacted]
[redacted]
[redacted]
[redacted]
[redacted]
[redacted]
[redacted]
[redacted]
[redacted]

(b) (4) [redacted]
[redacted]
[redacted]
[redacted]

DBSQC

(b) (4)

(b) (4)

(b) (4)

First Information Request and Review

The following IR was submitted to the sponsor on 12 February 2016. The responses were received on 22 February 2016 as Amendment 7. The IR questions, the response of the sponsor and review of the responses are discussed below:

Please confirm if the procedures described in the above mentioned sections of your submission represent final test procedures, as described in your respective SOPs. If they are not, please submit the current, working SOPs.

Review of Response: The procedure described in the BLA for the Protein Concentration by (b) (4) SOP (3.2.S.4.2.6) is consistent with the current test method, TME-0131.

Second Information Request and Review

The following IR was submitted to the sponsor on 12 May 2016. The responses were received on 27 May 2016 as Amendment 33. The IR questions, the response of the sponsor and review of the responses are discussed below:

In your validation of the Protein Concentration by (b) (4) (3.2.S.4.2.6) your robustness study is insufficient. Please evaluate robustness of your assay method by varying critical operating parameters of your procedure and submit for review.

Review of Response: Allowing a sample to sit at (b) (4) for (b) (4) and at (b) (4) for (b) (4) altered the measured protein concentration by (b) (4), respectively, when compared to the overall mean concentration determined in the intermediate precision study. The most critical operating parameter is the (b) (4). While it is controlled by instrument calibration and maintenance, the absorbance profile of Andexanet alfa between (b) (4) is essentially (b) (4) (little change). This is acceptable.

Conclusion: The method is adequately described and validated.