To: File (STN 125586/0) & Jean Gildner

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Subject: Final Review of Portola's Stability Studies in the Biologics License Application for coagulation factor Xa (Recombinant), inactivated--zhzo [ANDEXXA]

Contents

1. Executive Summary 1
2. Stability Studies for the Bulk Drug Substance 3
3. Stability Studies for the Final Drug Product 7
4. Out-Of-Specification (OOS) Results 12
5. Response to FDA Information Request 12
6. Conclusions 13

1. Executive Summary

This memorandum is an addendum to my Chemistry, Manufacturing and Controls (CMC) review dated 17 August 2016 for Portola Pharmaceuticals Inc. (Portola)'s original biologics license application (BLA) STN 125586/0 for *coagulation factor Xa (recombinant), inactivated--zhzo* with the proprietary name ANDEXXA, and International Nonproprietary Name (INN) *andexanet alfa.* The purpose of this memorandum is to summarize my review of Portola's 3 August 2017 responses to the FDA Complete Response Letter (CRL), and associated amendments.

ANDEXXA is presented as a lyophilized cake for intravenous administration after reconstitution with sterile Water for Injection. ANDEXXA is presented in one dosage strength of 100 mg per vial. ANDEXXA is indicated for patients treated with rivaroxaban and apixaban, when reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding.

I reviewed the stability data for the bulk drug substance (BDS) and final drug product (FDP) provided in the BLA resubmission and amendments 76, 95, 99, 100 and 107 dated August 4, November 29, December 22 and 26 of 2017; and January 25 of 2018, respectively.

Per ICH Q1A *"Stability Testing of New Drug Substances and Products"* and ICH Q5C *"Stability Testing of Biotechnological/Biological Products,* stability studies for ANDEXXA BDS and FDP are performed as follows:

- BDS: (b) (4)
  (b) (4)
- FDP: long-term storage condition (2-8°C) for up to (b) (4) months, accelerated storage condition (b) (4) for up to (b) months, and (b) (4) storage condition (b) (4) for up to (b) months.

The stability batches are manufactured by (b) (4) processes, a commercial scale ANDEXXA process denoted as (b) (4) and the previous (b) (4) The most significant changes from BDS (b) (4) are the introduction of the (b) (4). BDS (b) (4) also incorporates the final (b) (4) steps using the FDP (b) (4) instead of it being part of the FDP process. The FDP of (b) (4) uses the same formulation as (b) (4) but is manufactured at an approximately (b) (4) in scale than (b) (4) at the new FDP contract manufacturer, (b) (4).

Stability data for (b) (4) BDS lots are included in this BLA. (b) (4) of them are primary stability lots and the remaining (b) (4) lots are included as additional support. The (b) (4) primary stability lots are BDS (b) (4) Process Performance Qualification (PPQ) lots. The (b) (4) supportive stability lots are (b) (4) lots and (b) (4) lots. For all (b) (4) primary stability lots, (b) (4) (b) (4) data are available. For supportive stability lots, up to (b) (4) (b) (4) data are available.

Stability data for (b) (4) FDP lots are included in this BLA. (b) (4) primary stability lots are FDP (b) (4) PPQ lots. The other (b) (4) lots are pre-PPQ lots provided as additional support, and include (b) (4) lots and (b) (4) lots. The primary stability lots have up to 24 months of data under long-term storage condition. All (b) (4) primary lots have (b) months of data under accelerated storage condition, and (b) months of data under (b) (4) storage condition. Supportive stability lots have up to (b) (4) months of stability data under long-term storage condition, (b) months of data under accelerated storage condition, and up to (b) months of data under (b) (4) storage condition.

In addition, (b) (4) studies were performed on the BDS.

Two categories of methods were used in the stability studies, qualitative and quantitative methods:

- BDS qualitative methods: (b) (4)
  (b) (4)
- BDS quantitative methods: (b) (4),
  (b) (4) -
  (b) (4));
- FDP qualitative methods: appearance (lyophilized product and after reconstitution), identity by
  (b) (4)
  (b) (4)
- FDP quantitative methods: moisture, reconstitution time, pH, concentration by (b) (4) particulate matter, direct potency, indirect potency, (b) (4), purity by (b) (4)
  (b) (4)
  (b) (4)

Of these methods, five were added to the stability testing program after the initiation of the studies for both (b) (4) FDP primary stability lots: direct potency, indirect potency, purity by (b) (4) (b) (4)). The acceptance

criteria for these five methods were revised in 2017, and data for all lots tested by these methods were reassessed against the revised acceptance criteria. (b) (4) (b) (4) Tissue Factor Pathway Inhibitor (TFPI) inhibition method was implemented for stability only recently, and stability data are not yet available .

All BDS and FDP stability data for each method were discussed and trending plots were provided. In addition, statistical analysis for stability indicating methods was applied to predicted the shelf life for each method.

Conclusions:

My review of the stability studies confirmed that the manufacturing process is sufficiently established to manufacture the ANDEXXA product of consistent quality. Under the proposed storage conditions, there is no negative impact on the strength, purity and quality of ANDEXXA BDS and FDP within the proposed shelf-life. I, therefore, conclude that the stability data for BDS and FDP support the proposed shelf-life and storage conditions as follows:

- **BDS stored at (b) (4) .**
- **FDP stored at 2-8 °C for 24 months.**

2. Stability Studies for the Bulk Drug Substance

a) Materials

Stability data for (b) (4) BDS lots are included in this marketing application. The (b) (4) primary stability Lots (b) (4) are BDS (b) (4) PPQ lots. The (b) (4) supportive stability lots are (b) (4) Lots (b) (4), and (b) (4) Lots (b) (4).

All primary stability lots for (b) (4) data were provided. For supportive stability lots, (b) (4) (b) (4) data were provided. In addition, (b) (4) studies were performed on the BDS.

b) Stability Parameters and Specifications:

In the CSRL response, Portola presented new and revised methods for the release and stability studies of the BDS. These validated methods have been used for the analysis of primary stability lots of BDS. The specifications for ANDEXXA BDS are listed in Table 1.

(b) (4)

(b) (4)

c) BDS Storage Conditions:

The following storage conditions were investigated to evaluate the stability profile of ANDEXXA BDS.

(b) (4)

d) Primary BDS Stability Study Results:

2 pages determined to be not releasable: (b)(4)

(b) (4)

e) Predicted BDS Expiration Dates Through Statistical Analysis:

Statistical analysis was performed to evaluate the stability data for quantitative product attributed of (b) (4) primary stability lots using statistical software. A summary of the methods used to predict the expiration period, and the predicted expiration periods are shown in Table 2.

(b) (4)

Reviewer's Comments: *The statistical analysis demonstrated that the BDS is stable for* (b) (4) (b) (4) *supporting the proposed shelf-life of BDS of* (b) (4) *These studies indicate that the shelf-life of ANDEXXA FDP can be limited by a* (b) (4).

f) Post-Approval Stability Commitment

(b) (4) will be placed on stability (b) (4) for up to (b) (4) and the stability data will be provided in Annual Reports.

3. Stability Studies for the Final Drug Product

a) Materials

A total of (b) (4) lots were included in the FDP stability studies. (b) (4) primary stability lots ((b) (4) (b) (4)) were (b) (4) PPQ lots. The other (b) (4) were pre-PPQ lots included (b) (4) Lots

(b) (4)) provided as supportive stability study.

The primary stability Lots (b) (4) have up to 24 months of data under long-term storage condition. All (b) (4) primary lots have (b) months of data under accelerated storage condition, and (b) months of data under (b) (4) storage condition. Supportive stability Lots (b) (4) have 24 months of stability data under long-term storage condition, (b) months of data under accelerated storage condition, and up to (b) months of data under (b) (4) storage condition. Supportive stability Lots (b) (4) (b) (4) have up to (b) (4) months of stability under long-term storage condition and (b) months of stability data under accelerated storage condition.

b) Specifications for FDP:

In the CSRL response, Portola presented new and revised methods for the release and stability studies of the FDP. These validated methods have been used for the analysis of primary stability lots of FDP ((b) lots) manufactured by the proposed commercial process. The specifications for stability study of ANDEXXA FDP are listed in Table 3.

Table 3. Specifications for stability study of ANDEXXA alfa FDP

Test Attribute	Test Method	Acceptance Criteria
Tests Performed on Lyophilized Product:		
Characteristics	Visual Appearance	White to off-white lyophilized cake
	Reconstitution Time	(b) (4)
Purity	Moisture Content	(b) (4)
Tests Performed on Product After Reconstitution with 10.0 mL Sterile Water for Injection (SWFI):		
Characteristics	Appearance after Reconstitution	Clear, colorless to slightly yellow solution, essentially free from visible particulates
	pH	(b) (4)
Identity and Potency	Direct Potency	Identity confirmed (b) (4)
Potency	Indirect Potency	(b) (4)
	(b) (4) TFPI Inhibition	(b) (4)
	Protein Concentration by (b) (4)	(b) (4)
Purity	Sterility	Sterile
	Purity by (b) (4)	(b) (4)
	(b) (4)	(b) (4)

Test Attribute	Test Method	Acceptance Criteria
	(b) (4)	(b) (4)
	(b) (4)	
	(b) (4)	
	Particulate Matter	
	Purity by (b) (4)	

(b) (4) .

** (b) (4) *tissue factor pathway inhibitor (TFPI) inhibition method data was implemented for stability currently, but the specification criteria were not yet updated.*

c) FDP Storage Conditions

The following storage conditions were investigated to evaluate the stability profile of ANDEXXA FDP:

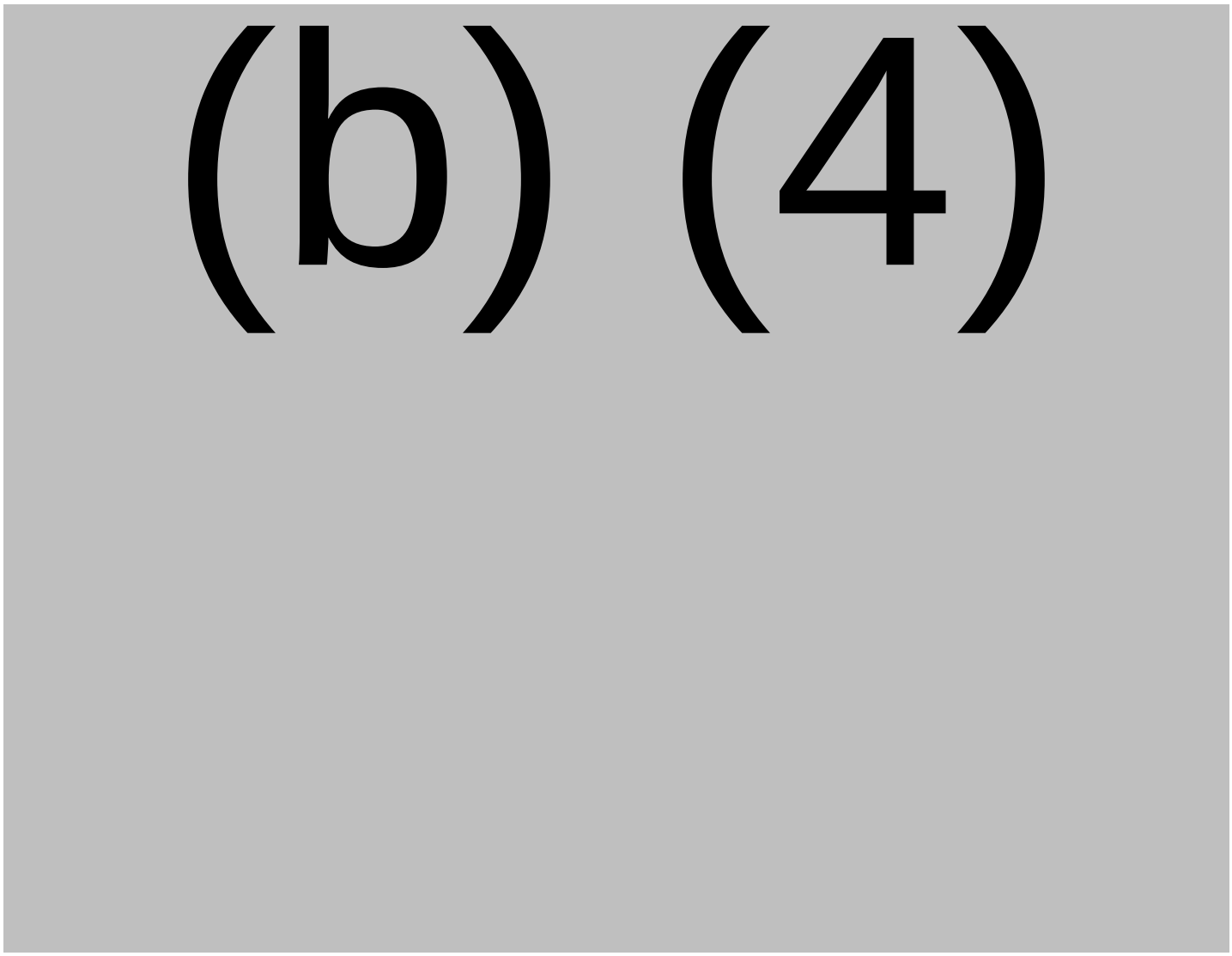
- Long-Term Condition: 2 to 8°C/ (b) (4)
- Accelerated Condition: 25°/ (b) (4)
- (b) (4) Condition: (b) (4)

d) FDP Stability Study Results:

- **Long-Term Condition: 2 to 8°C/** (b) (4)

(b) (4)

1 page determined to be not releasable: (b)(4)



Reviewer's Comments: *No significant changes were observed in appearance (lyophilized product), (b) (4) for up to (b) (4) months under long-term condition, after (b) months under accelerated condition and after (b) months under (b) (4) storage condition. For the quantitative methods, such as moisture, reconstitution time, pH, concentration by (b) (4) particulate matter, direct potency, indirect potency, (b) (4), purity by (b) (4) (b) (4) (b) (4), all the parameters data were within the specification accept criteria.*

e) Comparability Study Between FDP (b) (4) (b) (4) (b) (4)

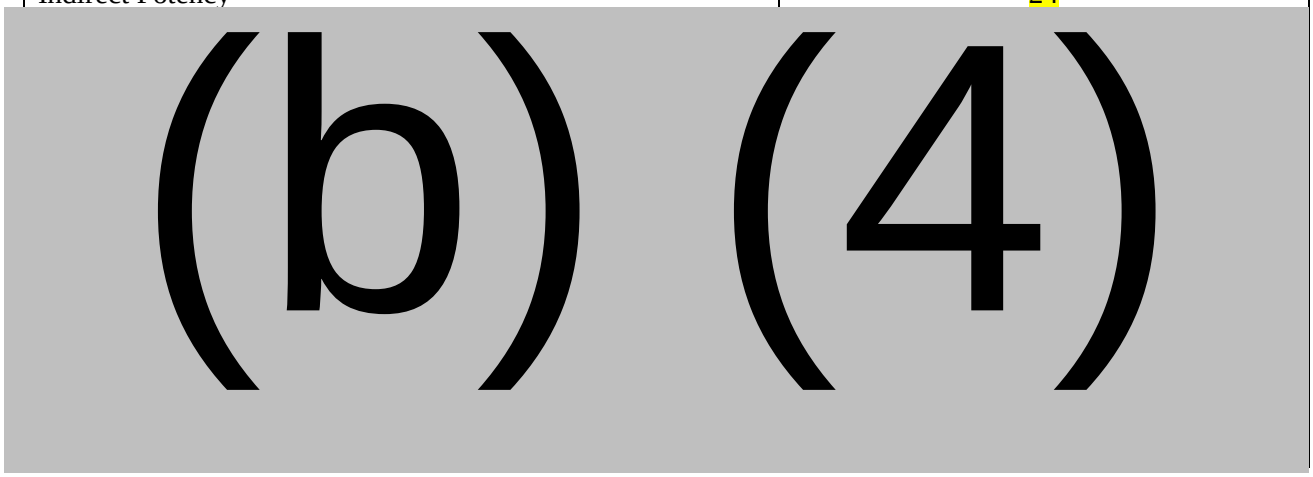
Comparability study between (b) (4) of FDP lots has been performed. (b) (4) FDP lots ((b) (4) from (b) (4) and (b) (4) from (b) (4)) were included in the comparability study, and four categories of testing were used for the analyses: release testing, supplemental characterization testing, side-by-side stability testing at long-term storage conditions (2 to 8°C), and side-by-side stability testing under (b) (4) (b) (4) storage conditions. Three months of data for the side-by-side stability testing at long-term storage condition were analyzed. (b) (4) months of data for the side-by-side stability testing at (b) (4) storage conditions were analyzed. All the results remained within the specifications demonstrating comparable stability trends between (b) (4) materials.

f) Predicted Expiration periods through statistical analysis:

Statistical analysis was performed to evaluate the stability data for quantitative methods of three primary stability lots using statistical software, see Table 4.

Table 4. Summary of stability indicating methods and predicted shelf life

Method	Predicted Intersection of 95% Confidence Interval and Acceptance Criteria (Months)
Direct Potency	(b) (4)
Indirect Potency	24



Reviewer's Comments: *The statistical analysis demonstrated that the FDP is stable for up to 24 months under long-term real-time storage condition, supporting the proposed shelf-life of FDP of 24 months when stored at 2-8 °C. These studies indicate that the shelf-life of ANDEXXA FDP can be limited by the* (b) (4) (b) (4) .

g) Post-Approval Stability Commitment

At least one commercial lot manufactured per year will be placed on stability under long-term (2-8°C) storage condition for up to (b) (4) months.

4. Out-Of-Specification (OOS) Results

(b) (4) ((b) (4) of BDS had an OOS under long-term storage condition, which was discussed on the next section question 3.

5. Response to FDA Information Request

Below is my review summary of Portola's December 26, 2017 response to the FDA's December 7, 2017 information request. The responses were provided in Amendment 100.

FDA Question 1

Regarding sections 3.2.S.7.2 and 3.2.P.8.2, and your post-approval stability protocol and stability commitment for commercial lots to place (b) (4) *Bulk Drug Substance (BDS)* (b) (4) *and at least one Final Drug*

Product (FDP) lot (b) (4) *on stability study, please revise the protocols to include the following time-points: 3, 6, and* (b) (4) *months.*

Portola's Response
Portola has revised the post-approval stability protocols for commercial (b) (4) FDP to include the requested 3, 6, and (b) (4)-month time points. Section 3.2.S.7.2 and Section 3.2.P.8.2 have also been updated accordingly.

Reviewer's Comment: *The response is acceptable.*

FDA Question 2
Please provide updated results from the ongoing stability studies, which should include 24 months of data for BDS lots (b) (4) *; and FDP lots* (b) (4) *. If there are out-of-specification (OOS) results, please provide the reasons for the OOS.*

Portola's Response
The 24 months of stability data for BDS Lots (b) (4) FDP Lots (b) (4) (b) (4) are provided in revised Section 3.2.S.7.3 and Section 3.2.P.8.3 respectively. Currently, only 18 months of stability data is available for FDP Lot (b) (4) The 24-month stability time point for Lot (b) (4) occurred on 13 December 2017, and as such testing for this time point is currently in progress. All the results for these lots data were remained within specification. ***Reviewer's***

Comment: *The response is acceptable.*

FDA Question 3
Please provide the investigation reports for the two OOS results in (b) (4) (b) (4) *months under long-term storage* (b) (4) *conditions.*

Portola's Response
Portola has provided the QC Laboratory Investigation Report (LIR-793), the notification of an expected OOS Result, and (b) (4) Complaint-007 for the two OOS results for (b) (4) - (b) (4) months under long-term storage (b) (4) conditions. The investigation reports concluded that the OOS stability results at (b) (4) for BDS lot (b) (4) were a consequence of the (b) (4) eta variant in this lot at the time of release combined with a stability acceptance criteria of (b) (4) and a method precision (CV) for (b) (4) Stability data confirmed this conclusion in that the (b) (4) has remained a (b) (4) for the subsequent (b) (4) time points and did not trend upwards. Although the BDS lot (b) (4) was used to manufacture the FDP lot (b) (4) the FDP lot was never released for clinical use and was only used to support stability. It should be noted that current revise version the commercial (b) (4) release and stability acceptance criteria is (b) (4)

Reviewer's Comment: *The response is reasonable and acceptable.*

6. Conclusions

The data from the stability studies for BDS and FDP are acceptable, and support the proposed shelf-life as follows:

For BDS: (b) (4)

- There were no significant changes, except for a (b) (4) (b) (4) in primary and supportive stability studies.

For FDP: 24 months at 2 to 8°C

- There were no significant changes, except for a (b) (4), under long-term storage condition for up to 24 months in the primary and supportive stability studies.
- The comparability between the FDP (b) (4) (b) (4) (b) (4) established from the stability perspective.