**FOOD AND DRUG ADMINISTRATION**
CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

MEMORANDUM

**To:** File (STN 125586/0) & Thomas Maruna

**From:** Yideng Liang, PhD, Staff Fellow, Laboratory of Hemostasis (LH), Division of Hematology Research & Review (DHRR)/OBRR

**Through:** Mikhail V. Ovanesov, PhD, Research Biologist, LH/DHRR/OBRR

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**Subject:** Final Review of Portola's Stability Studies in the Biologics License Application for Coagulation Factor Xa (Recombinant), Inactivated [ANDEXXA]

**Contents**



## 1. Executive Summary

Portola Pharmaceuticals, Inc. (Portola) submitted an original biologics license application (BLA) for Coagulation Factor Xa (Recombinant), Inactivated, on 17 December 2015. ANDEXXA is the proposed proprietary name and *andexanet alfa* is the International Nonproprietary Name (INN) of this product.

Andexanet alfa is a recombinant modified human factor Xa (fXa) protein. Portola's proposed indication is urgent reversal of anticoagulation in patients treated with direct or indirect fXa inhibitors.

I reviewed the stability data for the bulk drug substance (BDS) and final drug product (FDP) provided in the original BLA and amendments 23, 25, 38 and 49 dated April 18, April 20, June 14 and June 30, 2016, respectively. The proposed BDS and FDP shelf-life and investigated storage conditions, investigation methods and parameters are as follows:

- For BDS: (b) (4)
- For FDP: 24 months at 2 to 8°C at a concentration of 10 mg/mL in a vial that contains 100 mg of andexanet alfa.

The following storage conditions were investigated:

- BDS: (b) (4)
- FDP: stability data at 2 to 8°C (proposed real-time storage condition) for 24 months, (b) (4) (proposed real-time storage condition) for (b) (4) months, (b) (4) (accelerated storage condition) for (b) (4) months.

The proposed commercial BDS shelf-life acceptance criteria are the same as the release acceptance criteria with the exception of (b) (4). However, stability studies initiated before the summer of 2015 were based on the previous version of non-quantitative release assays. The (b) (4) new methods are: (b) (4)

*Reviewer's note:* It is not clear why the product is treated with (b) (4) before (b) (4). The treatment will (b) (4), and in turn gives a better result, which is not representative of the actual composition of the product.

To date, (b) (4) of accelerated and (b) (4) of (b) (4) data have been collected using these (b) (4) additional methods, but there are less than (b) (4) months of real-time stability data available for the complete set of proposed release specifications. Under long-term storage conditions, no significant changes have been observed on any (b) (4) FDP batch at the proposed storage conditions with the exception of a trend of an increase in the (b) (4). Accelerated conditions demonstrated stability indicating changes in the following methods:

- (b) (4)
- (b) (4)
- (b) (4)
- Direct potency
- Indirect potency.

Because (b) (4) stability data are significantly shorter than the proposed shelf-life duration, Portola presented additional stability data obtained from (b) (4) batches. These data were obtained with old release methods. The use of (b) (4) data was based on the results of comparability studies which demonstrated general comparability of the (b) (4) batches with the notable exception in the (b) (4), which were found at higher levels in (b) (4) batches. The significance of the increase in the (b) (4) is under investigation. In two amendments dated 30 June and 14 July 2016, Portola indicated that the (b) (4) increase may be related to a (b) (4) impurity which is yet to be identified. Therefore, the comparability of the (b) (4) materials remains not confirmed.

**Conclusions and Recommendation:**

The key stability-indicating parametrs/methods for andexanet alfa (b) (4) FDP were identified as (b) (4), purity by (b) (4)

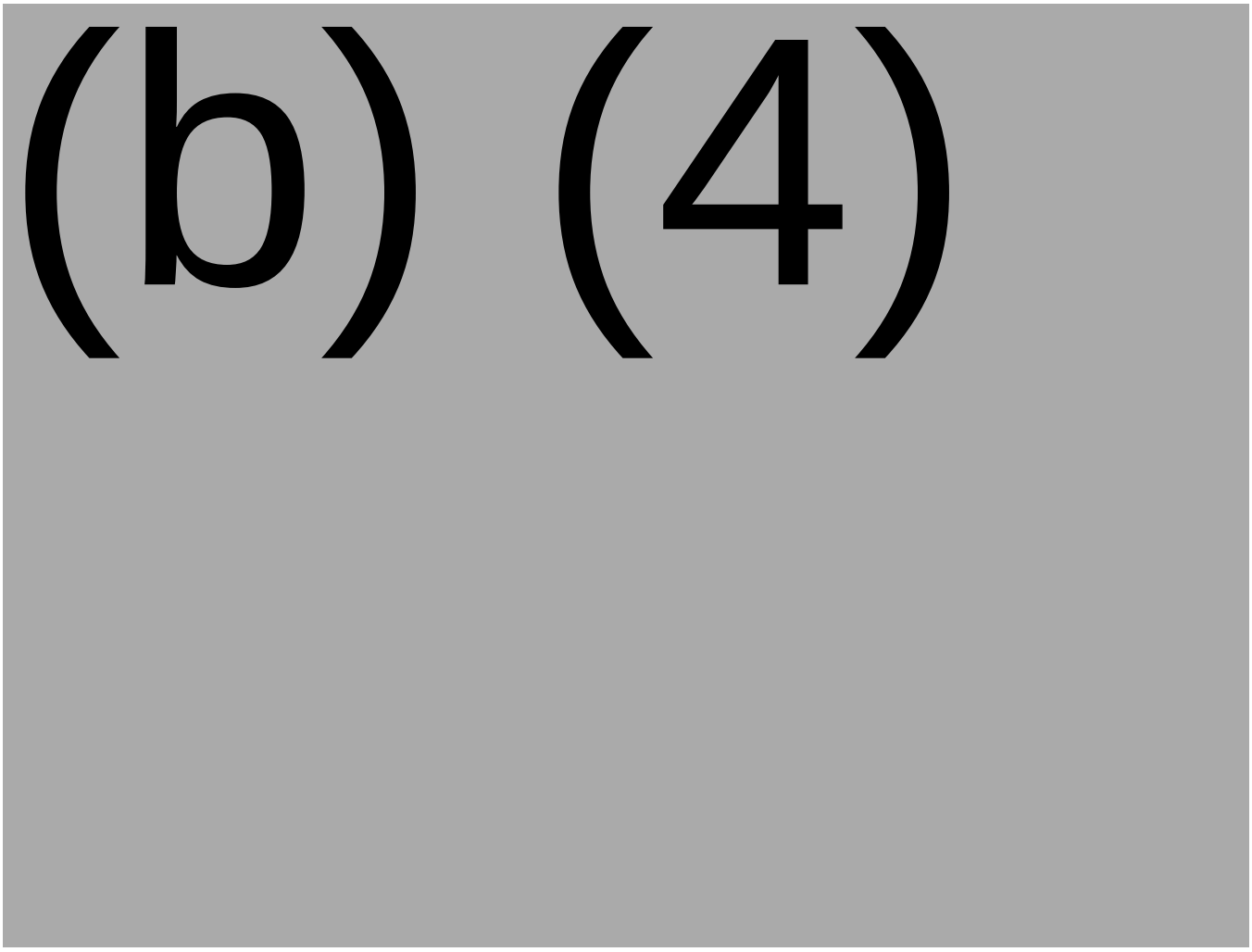
(b) (4)
, direct potency and indirect potency. Among these (b) (4) methods, (b) (4) were introduced after the summer of 2015. However, the data obtained with the old methods cannot be used to support the stability conclusions because Portola claims that the old methods are too variable.

In addition, there are only 6 months of stability data available for the proposed commercial (b) (4) materials. Portola's proposal to use stability data obtained with the (b) (4) batches in support of (b) (4) batches stability is not acceptable because comparability of these (b) (4) processes has yet to be established. Because review of comparability studies was outside the scope of my review, I defer to the CMC chair to make final conclusions about the shelf-lives of ANDEXXA BDS and FDP.

**2. Stability Studies for the Bulk Drug Substance**

**a) Materials**

A total of (b) (4) batches of Andexanet alfa (b) (4) were included in the stability study, which included clinical batches manufactured by (b) (4) and the commercial scale batches manufactured by (b) (4). The history of (b) (4) batches is listed in Table 1.



3 pages have been determined to be not releasable: (b)(4)

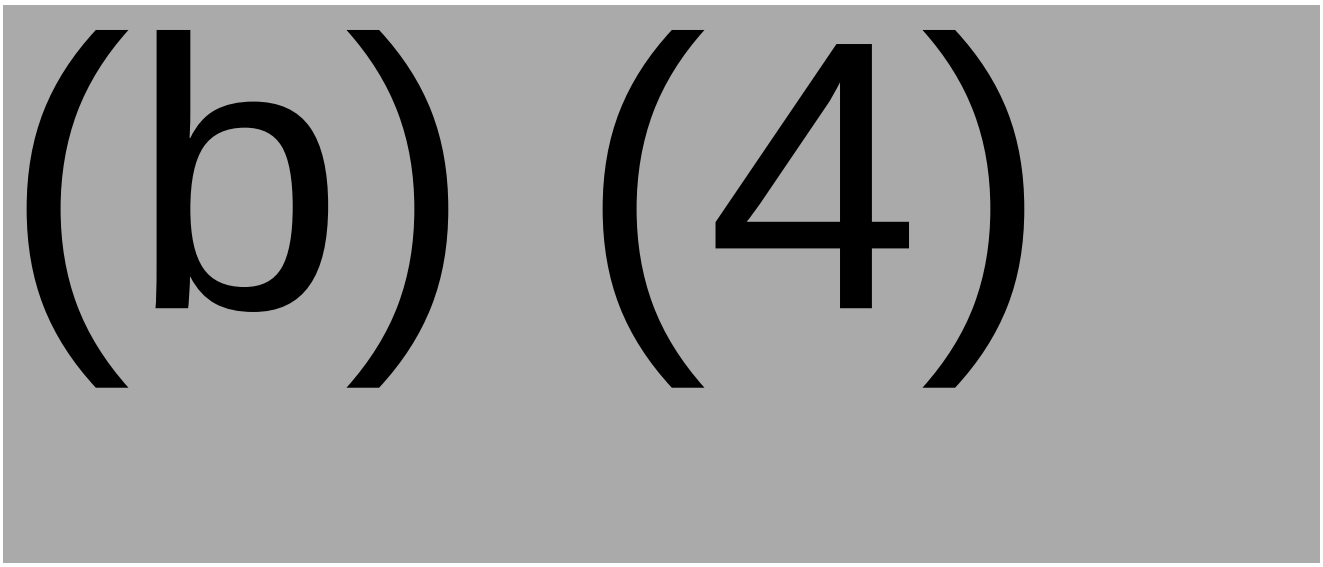
**c) BDS Storage Conditions:**

- (b) (4)
- (b) (4)
- (b) (4)
- (b) (4)

**d) BDS Stability Study Results:**

Table 3 summarizes the use of new and old stability indicating parameters/methods under real time stability conditions.

Table 3: Summary of BDS stability-indicating parameters/methods and tested sample history (months) stored at (b) (4)




The representative stability trending results are presented in the following figures (Fig. 1-12). (b) (4) new methods were introduced after the summer of 2015: (b) (4) . These methods were introduced to replace the previously established old methods (b) (4) . Portola claimed that the old versions of these methods were too variable and not quantitative.

- (b) (4)

Results using the old methods:

3 pages have been determined to be not releasable: (b)(4)

Portola claimed that the OOS results under accelerated and (b) (4) storage conditions are expected and acceptable, because the BDS will not be stored at these conditions.

**e) Post-Approval Stability Commitment**

The ongoing stability studies will be continued to completion. All OOS results and significant stability (b) (4) excursions will be investigated according to the appropriate SOPs.

(b) (4) lot will be placed on stability annually according to the protocol.

### 3. Stability Studies for the Final Drug Product

#### a) Materials

A total of (b) (4) batches were used in the FDP stability studies. (b) (4) batches of FDP (b) (4) ((b) (4) of 10 mg/mL, 100 mg/vial) manufactured by (b) (4) and (b) (4) batches of FDP (b) (4) ((b) (4) of 10 mg/mL, (b) (4) ) manufactured for Portola by (b) (4) . (b) (4) FDP have the same formulation composition. The FDP batch history is provided in Table 4.

**Table 4: Andexanet Alfa FDP Batch History.**

| Portola Lot # | Process | vial strength (Fill volume) | Date of Manufacture or Release | Batch Designation/Use | BDS lots [e] | Out-of-specification in | Release method [a] | Stability methods [a] | Notes | Real-Time Stability |
|---|---|---|---|---|---|---|---|---|---|---|
| (b) (4) | | | | Clinical Ph 1&2 Nonclin | (b) (4) | | Old | Old | | (b) (4): 24mo |
| | | | | R & D | Development | Accel. stab. Increase in the total (b) (4) | Old | Old | | 5C: 24mo (b) (4):24mo |
| | | | | Clinical Ph 1&2 | (b) (4) | | Old | Old | | 5C: 24mo (b) (4): 6mo |
| | | | | Clinical Ph 3 | (b) (4) | | Old | Old | Pivotal Ph. 3 clin. trials | 5C: 24mo (b) (4): 6mo |
| | | | | Clinical Ph 3 & 3b/4 | (b) (4) | | Old | Old | Pivotal Ph. 3 clin. trials | 5C: 12mo (b) (4): 6mo |
| | | | | Clinical Ph 3 | | | Old | | | |
| | | | | Clinical Ph 3b/4 | | | Old | | | |
| | | | | Clinical Ph 3b/4 | | | Old | | | |
| | | | | Clinical Ph 3b/4 | | | Old | | | |
| | | | | Clinical Ph 3b/4 | | | Old | | | |
| | | | | R & D | | Accel. stab. Increase in (b) (4) | | | | 6mo |

| Portola Lot # | Process | vial strength (Fill volume) | Date of Manufacture or Release | Batch Designation/Use | BDS lots [e] | Out-of-specification in | Release method [a] | Stability methods [a] | Notes | Real-Time Stability |
|---|---|---|---|---|---|---|---|---|---|---|
| (b) (4) | | 100 mg (b) (4) | (b) (4) | Clinical, CBER lot release [d] Stability | (b) (4) | | Old | Old New? | (b) (4) | 5C: 9 mo (b) (4): 6mo |
| | | 100 mg (b) (4) | | Clinical, CBER lot release [d] Stability | | | Old | New | | 6mo |
| | | 100 mg (b) (4) | | PPQ1 Clinical Ph 3b/4 | | | New | New old? | | 6mo |
| | | 100 mg (b) (4) | | PPQ2 | | | New | New | | 3mo |
| | | 100 mg (b) (4) | | PPQ3 | | | New | New | | 3mo |

a) The (b) (4) new methods are: Direct Potency, Indirect Potency, (b) (4) .

b) Stability samples were labeled as 10 mg/vial in the stability data sheet, which should be 100 mg/vial or 10 mg/mL.

c) Batch was produced using a non-validated (b) (4) . All subsequent batches were manufactured using a (b) (4) container. The (b) (4) is classified as a key operating equipment because it is used to determine the validated batch volume.

**b) Specifications for FDP:**

The proposed commercial release acceptance criteria and shelf-life specifications are the same for FDP, see Table 5.

Table 5. Commercial Release and Shelf-Life Specifications for 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) |

| | | |
|---|---|---|
| | Sterility [1] | Sterile |
| **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, free of visible particulates.* |
| | pH | 7.8 (b) (4) |
| Identity and Potency | Direct Potency | (b) (4) |
| Potency | Indirect Potency | |
| | Protein Concentration by (b) (4) | |
| Purity | Purity by (b) (4) | |
| | (b) (4) | |
| | (b) (4) | |
| | (b) (4) | |
| | Particulate Matter | |

(b) (4)

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

*Reviewer's note: "*essentially free of visible particulates*" is not acceptable. The specifications should read "*free of visible particles*".

**c) FDP Storage Conditions**

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

**d) FDP Stability Study Results:**

Table 6 summarizes the use of the new and old methods to measure the stability-indicating parameters under real-time stability conditions.

Table 6. Summary of FDP stability indicating methods and tested sample history (months) stored at 2-8 °C

| Lot # | (b) (4) |
|---|---|

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Process # | 3 | 3 | 3 | 3 | 3 | 3 | 2 | 2 | 2 | 2 |
| Old Method | (b) (4) | 9 | 6 | 6 | 3 | 3 | 6 | 24 | 24 | 18 | 24 |
| | (b) (4) | 9 | 6 | 6 | 3 | 3 | | 24 | 24 | 18 | 24 |
| | (b) (4) ) | 9 | 6 | 6 | 3 | 3 | | 24 | 24 | 18 | 24 |
| | (b) (4) | 9 | 6 | 6 | 3 | 3 | 6 | 24 | 24 | 18 | 24 |
| New Method | (b) (4) | | 6 | 6 | 3 | 3 | 6 | | | | |
| | Direct Potency | | 6 | 6 | 3 | 3 | 6 | | | | |
| | Indirect Potency | | 6 | 6 | 3 | 3 | 6 | | | | |
| | (b) (4) ) | | 6 | 6 | 3 | 3 | 6 | | | | |
| | (b) (4) ) | | 6 | 6 | 3 | 3 | 6 | | | | |

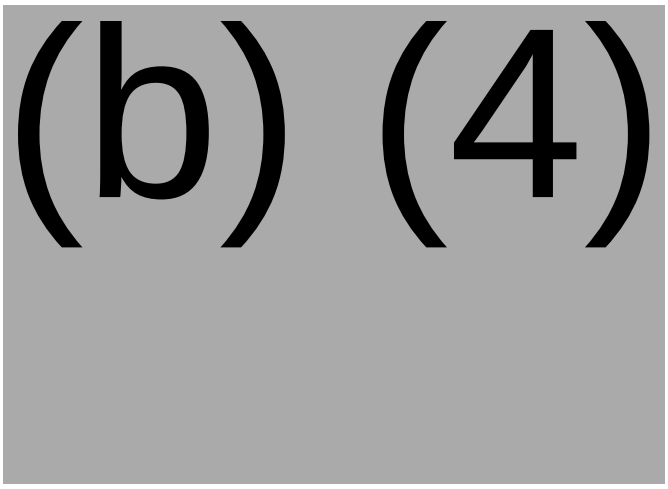
- Long-Term Condition: 2 to 8°C (b) (4)
  Results using the old methods

(b) (4)

Result using the new methods

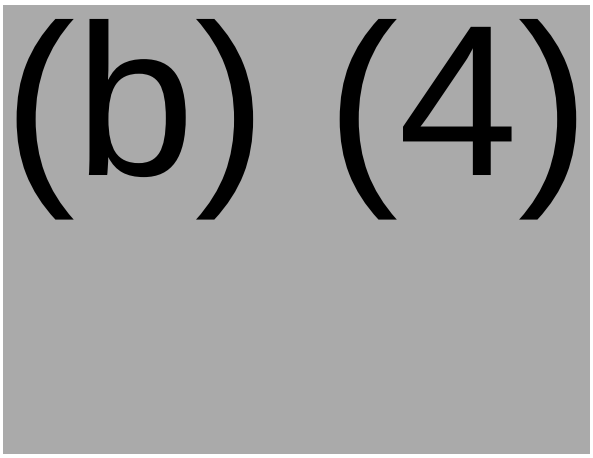
(b) (4)

All stability data were within specification by the old and new methods, there were no significant trend observed for FDP when stored at 2-8 °C with the exception of the (b) (4) trends for batch (b) (4), see figure below.

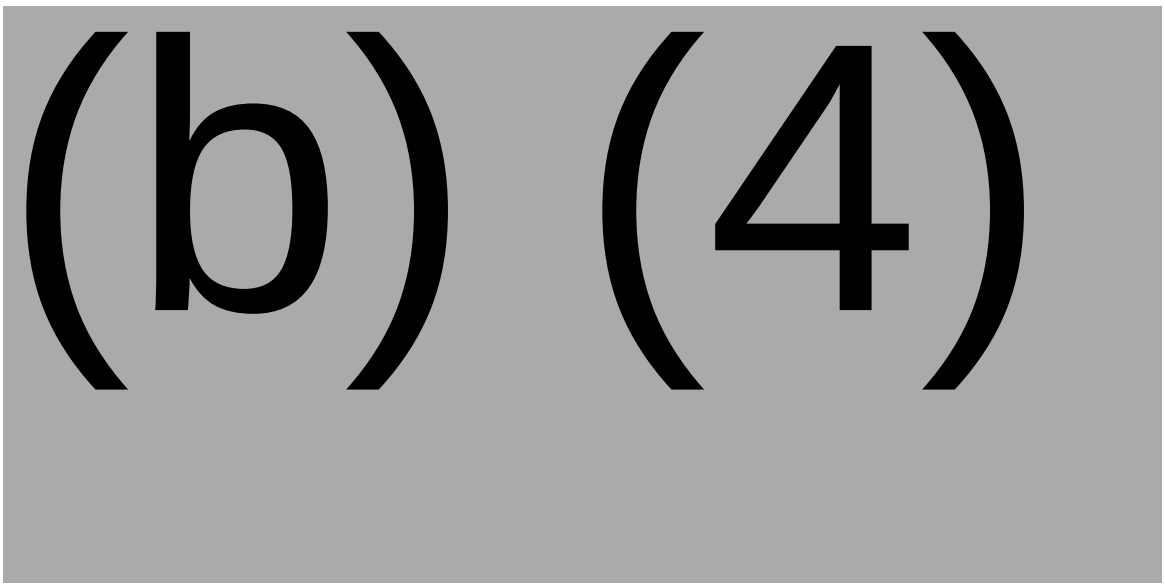


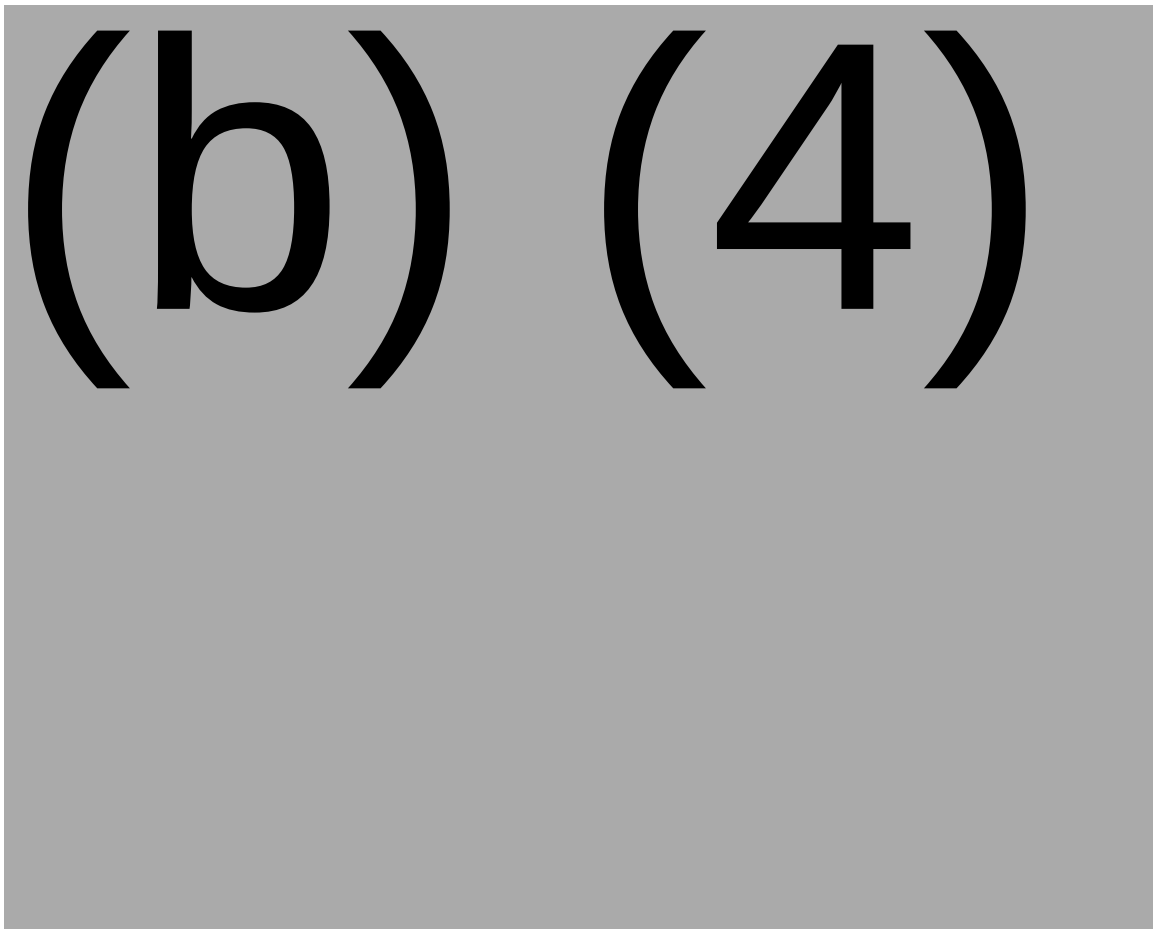

- Accelerated Condition: (b) (4) , Upright

Results using old methods:




Results using new methods:






Under accelerated and (b) (4) storage conditions, there was an (b) (4) . In addition, there was (b) (4) .

Reviewer's Comments:

I noted wrong sample labeling in 3.2.P.8.3 Stability Data, Table 3.2.P.8.3-3 to Table 3.2.P.8.3-16: FDP stability samples (fill quantity column) were labeled as (b) (4) in many stability data tables. These samples should have been 100 mg/vial or 10 mg/mL.

**Out-Of-Specification (OOS) Results**

For the BDS, under long-term storage conditions, no significant changes have been observed on any batches at the intended storage condition of (b) (4) with the exception of an increase in the (b) (4) which resulted in at least one trend investigation for batch (b) (4) .

I noted a discrepancy between the submitted stability data and the OOS I found during the pre-license inspection (PLI) of (b) (4) facility in (b) (4) . During the inspection, there was one OOS for BDS Lot # (b) (4) sample stored at (b) (4) for (b) (4) . The direct inhibitor

potency assay result was (b) (4) which was OOS (the acceptable activity: (b) (4)), the date of occurrence was July 30, 2015. On the same day, the investigation was started and the deviation investigation was closed on (b) (4). (b) (4) summary for this OOS investigation was: "*It is possible that sample could have been* (b) (4), *resulting in an artificially* (b) (4). *However, since there were no clear laboratory errors that would justify invalidating the original results. The results will be reported as is*". However, this OOS was not reported in the stability section of the BLA submission.

### 4. History of Changes in Specification Criteria

I noted that Portola has submitted three revisions of specifications for the BDS, and two revisions of specifications for the FDP. The history of changes in specifications is listed in Table 7.

Table 7. History of changes in specifications in BLA submission

| **a) History of changes in specification for BDS** | | |
|---|---|---|
| Version | Amendment # | Date of submission |
| Initial | 01 | Dec 17, 2015 |
| 2nd | 23 | April 15, 2016 |
| 3rd | 25 | April 20, 2016 |
| b) **History of changes in specification for FDP** | | |
| Version | Amendment # | Date of submission |
| Initial | 01 | Dec 17, 2015 |
| 2nd | 23 | April 15, 2016 |

## 5. Conclusion & Recommendation

- For (b) (4) FDP, the key stability-indicating parameters/methods are: (b) (4), direct potency and indirect potency.
- Among these (b) (4) methods, (b) (4) were introduced after the summer of 2015. So far, only (b) (4) batches of (b) (4) FDP for up to 6 months stability were tested by the new methods.
- I noted that one OOS result was not reported in the BLA.

The results and information on andexanet alfa stability are not sufficient to support the proposed shelf-life for andexanet alfa (b) (4) FDP because:

(i) The comparability of the (b) (4) and (b) (4) materials has yet to be established;

(ii) Empirical data on batches for (b) (4) processes are limited and insufficient because the critical analytical methods used to monitor the identity, purity and potency of the (b) (4) were introduced shortly after (b) (4) introduction. In addition, only the old methods continue to be used in the already initiated stability studies,

(iii) Data obtained with the previous versions of these methods were not trended quantitatively and therefore the linkage between the data from old and new methods is not well established.