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**To:** File: 125586/0.77

**Through:** Lokesh Bhattacharyya, Lab Chief, DBSQC/OCBQ/CBER  
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**Subject:** Review Memo for the Response (Amendment 77) to Complete Response Letter – AndexXa™ [Andexanet Alfa]

**Recommendation:** Approval

### Summary of Review

A new BLA was submitted by Portola for AndexXa™, STN: 125586. The review of the BLA showed major deficiency for the purity assay for the (b) (4) the final drug product (FDP) using (b) (4) method. The deficiency was summarized in the Complete Response (CR) Letter, dated 17 August 2016. The sponsor provided response as Amendment 77, received on 3 August 2017. This memo is the final review memo for the procedure used for the lot-release and stability testing. The procedure is found to be approvable for the intended use.

### Background of Submission

A new BLA was submitted by Portola for AndexXa™ [Andexanet Alfa], STN: 125586. The submission received a CR Letter, on 17 August 2016. The deficiency item 7 in the CR Letter is related to the purity assay for the (b) (4) FDP by (b) (4), which determines the percentages of (b) (4), and percentages of (b) (4) as (b) (4). On 3 August 2017, the sponsor provided a full response to the deficiencies listed in the CR Letter as Amendment 77.

This memo constitutes the review memo of the information provided by the sponsor in Amendment 77 for the SEC assay (the deficiency item 7).

### Submitted Information and Documents:

This is an electronic submission. Information submitted and reviewed includes:

Amendment 77, received 3 August 2017

- Cover letter
- 3.2.S.3.1 Elucidation of structure and other characteristics

- 2.3.S.3 Characterization
- 3.2.S.4.2 Analytical procedures
- 3.2.S.4.3 Validation of analytical procedures
- 3.2.S.5 Reference standards and materials
- 3.2.S.4.1 Specification
- 3.2.P.5.2 Analytical procedures
- 3.2.P.5.3 Validation of analytical procedures
- 3.2.P.5.1 Specification(s)

## Review Narrative

### Question 7. (b) (4) and (b) (4) by (b) (4)

The following comment was included in the CR Letter:

(b) (4) of your FDP (b) (4) samples, including (b) (4) batches of lyophilized drug product, (b) (4) lot of pre-lyophilized solution and the “reference standard”, which we analyzed by (b) (4) using a (b) (4) all show (b) (4), in addition to (b) (4) for (b) (4), when (b) (4) is replaced by (b) (4) in the (b) (4). Please identify the proteins in these (b) (4).

### Review of the Response:

The details of the (b) (4) method developed by FDA were provided to the sponsor. The sponsor repeated the method in their lab and obtained (b) (4) that contains (b) (4) from AndexXa samples in their lab for FDP, as was obtained in the FDA/CBER laboratory. The sponsor identified the (b) (4) as variants of AndexXa by (b) (4) analysis. They are: (b) (4)

(b) (4), respectively. All variants are active pharmaceutical ingredients (APIs) of AndexXa. These variants (b) (4) as a (b) (4) under the (b) (4) condition proposed by the sponsor in the BLA submission.

The sponsor pointed out that the primary objective of the (b) (4) method is to measure (b) (4) in AndexXa for characterization, release testing, and stability assessment. The variants are assessed quantitatively by other proposed analytical methods, including (b) (4)

(b) (4) and its validation were reviewed by DBSQC. They were

concluded to be appropriate methods for their intended use (detailed memo dated June 20, 2016). (b) (4) method and its validation were reviewed by DPPT and were found to be acceptable. “(b) (4)” is being reviewed by DPPT/OTAT Dr. Mikhail Ovanesov.

The results (Table 1) from both (b) (4) and (b) (4) are comparable for (b) (4) values.

(b) (4)

Method validation of the (b) (4) method was reviewed and found to be acceptable before (memo dated June 20, 2016).

Though the proposed (b) (4) method does not provide any (b) (4) of the variants of AndexXa, its purpose, monitoring (b) (4), in FDP (b) (4) is fulfilled. AndexXa variants are assessed by (b) (4). Therefore, it is not necessary to assess them by the (b) (4) method.

Conclusion:

The new experimental data provided sufficient information to allow approval of this test method for the determination of (b) (4) in the drug product.