M E M O R A N D U M

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

To: File (STN 125586/0)
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Subject: Final review of Adventitious Agents Safety Information in Portola's original BLA for Coagulation Factor Xa (Recombinant), Inactivated

Cc: Mikhail V. Ovanesov, PhD, Committee Chair, OBRR/DHRR/LH

Executive Summary

This memorandum summarizes the review of Adventitious Agents Safety Information in an original Biologics License Application (BLA) under STN 125586/0 submitted by Portola Pharmaceuticals, Inc. (Portola) for Coagulation Factor Xa (Recombinant), Inactivated. The proposed proprietary name of this product is *ANDEXXA*. As described below, the measures taken by Portola to control adventitious agents in the manufacture of *ANDEXXA* drug product are acceptable; therefore, I recommend approval of the BLA under STN 125586/0.

Evaluation of safety regarding adventitious agents

For the non-viral adventitious agents including bacteria, fungi, and mycoplasma, the potential of contamination of these agents is well controlled through the use of: (1) appropriate environmental control monitoring in the manufacturing process; (2) in-process controls, e.g., (b) (4) ; and (3) filtration steps including (b) (4) sterile filtration. The potential of *ANDEXXA* to be contaminated with non-viral adventitious agents is further reduced by testing the final product for sterility, and endotoxins. Portola manufactures *ANDEXXA* according to GMP regulations.

No human or animal derived raw materials are used in the manufacture of *ANDEXXA*. No raw materials or ingredients of human or animal origin are used in the formulation of

ANDEXXA final drug product. Thus, the potential risk of contaminating adventitious viruses or transmissible spongiform encephalopathy agents is minimized.

The potential of contamination by infectious viruses in cell culture is well controlled in the manufacture of *ANDEXXA*, which is produced in a genetically modified Chinese hamster ovary (CHO) cell line. (b) (4) for Portola performed viral tests on the (b) (4) for *ANDEXXA* that are consistent with the International Conference on Harmonisation (ICH) Q5A(R1) guideline. All test results for endogenous and adventitious viruses were negative except for (b) (4)

Additionally, the potential risk of viral contamination of *ANDEXXA* is further mitigated through two dedicated, (b) (4) viral clearance steps: (b) (4)

Portola has evaluated these viral clearance steps in relevant down-scale studies using model viruses. (b) (4) I find that these results support the proposal that viral clearance is effective in the manufacture of *ANDEXXA*.

Background

The active ingredient in *ANDEXXA* is a modified recombinant human Coagulation Factor Xa (rFXa) protein that lacks the coagulation activity of native FXa, but retains the high binding affinity for both direct and indirect FXa inhibitors. This product loses proteolytic activity (pro-coagulant activity) after the replacement of the active site serine residue with alanine at position (b) (4) of the (b) (4). The γ-carboxyglutamic acid domain was removed to eliminate the ability of this product to assemble into the prothrombinase complex (anti-coagulant activity). Additionally, this product is directly expressed as an activated FXa derivative rather than a FX precursor in CHO cells to skip the need for

FVIIa or FIXa activation in circulation. *ANDEXXA* is formulated as a sterile, non-pyrogenic, white to off-white lyophilized powder for intravenous injection only. When reconstituted with 10 mL of sterile Water for Injection, each container of *ANDEXXA* final product contains nominally 100 mg of rFXa, Inactivated.

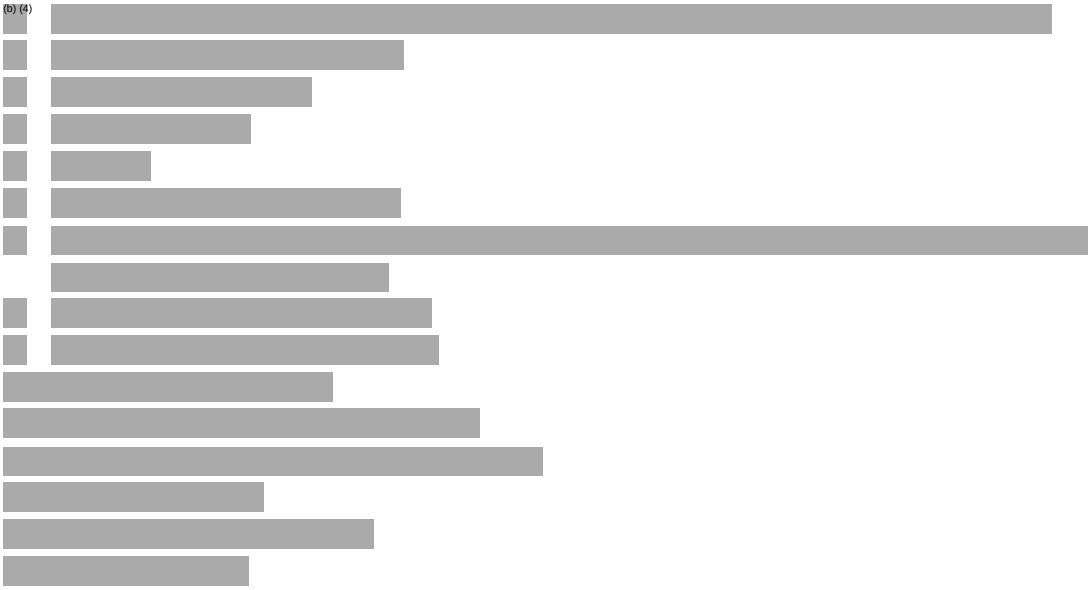
The manufacturing process of *ANDEXXA* includes two dedicated, (b) (4) viral clearance steps: (b) (4) Furthermore, no raw materials or ingredients of human or animal origin are used in the manufacturing process, which further mitigates the potential of viral contamination.

Summary of Review

Flow chart of the manufacturing process of ANDEXXA

The flow chart of the manufacturing process of *ANDEXXA* includes the following steps:

ANDEXXA drug substance



ANDEXXA drug product

(b) (4)

18. Sterile filtration
19. Aseptic filling and partial stoppering
20. Lyophilization

21. Capping and 100% inspection
22. Labeling and packaging
23. Drug product

Product reviewer's comment: Bolded in the above flow chart are the two dedicated viral inactivation/removal steps. (b) (4) The validation reports for these viral clearance steps were reviewed, and the results demonstrate that these steps are capable of either inactivating or removing viruses, thus lowering the potential of viral contamination.

Evaluation of safety of adventitious agents

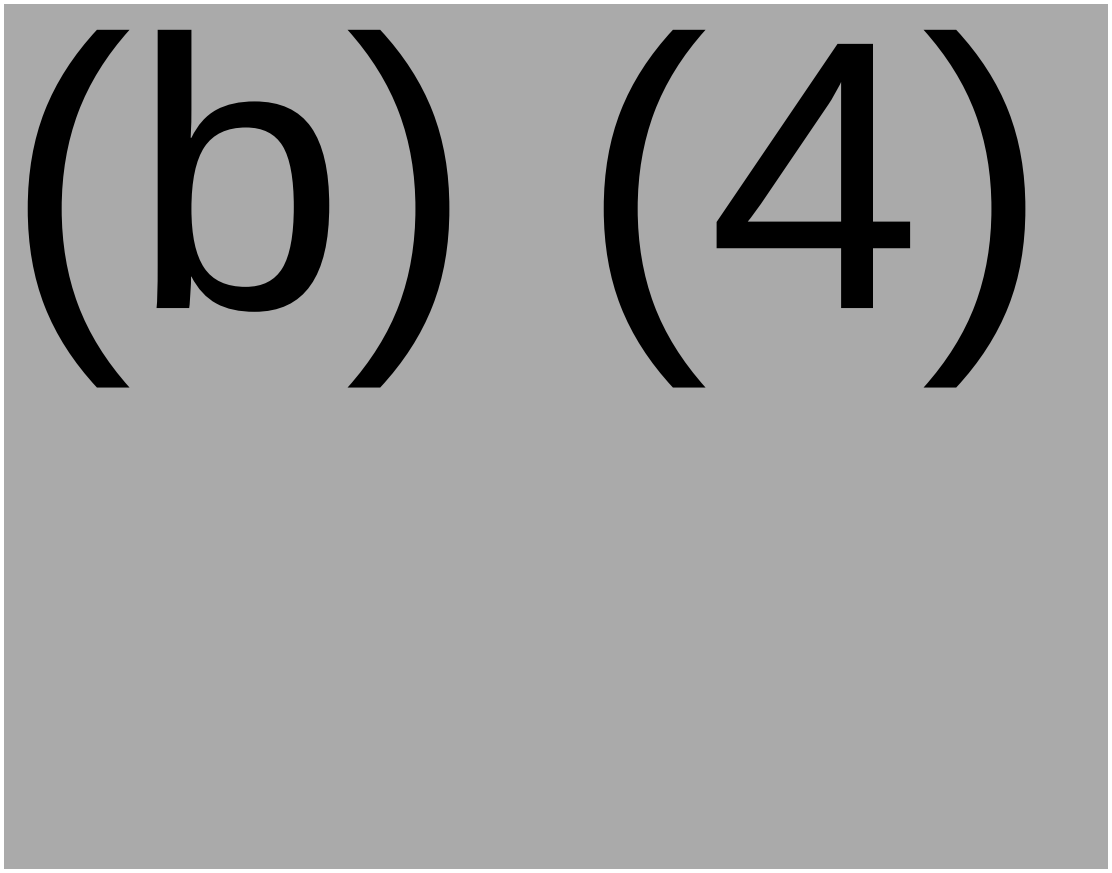
1. Control of non-viral adventitious agents

   For the non-viral adventitious agents including bacteria, fungi, and mycoplasma, the potential of contamination of these agents is well controlled through the use of: (1) appropriate environmental control monitoring in the manufacturing process; (2) in-process controls, e.g., (b) (4) ; and (3) filtration steps including (b) (4) sterile filtration. The potential of *ANDEXXA* to be contaminated with non-viral adventitious agents is further reduced by testing the final product for sterility, and endotoxins. Portola manufactures *ANDEXXA* according to GMP regulations.

2. Testing of (b) (4) for the absence of infectious viruses

(b) (4)

(b) (4)



(b) (4)

3. Control of materials used in the manufacturing process

No human or animal derived raw materials are used in the manufacture of *ANDEXXA*. No raw materials or ingredients of human or animal origin are used in the formulation of *ANDEXXA* final drug product. Additionally, routine cleaning procedures in the manufacturing process of *ANDEXXA* include sanitization of equipment with (b) (4) . Thus, the potential risk of contaminating adventitious viruses is minimized.

4. Testing the capacity of the *ANDEXXA* purification process to clear viruses

There are two dedicated, (b) (4) steps for viral clearance in the manufacturing process of *ANDEXXA*, which are (b) (4) . (b) (4) in the process also contribute to virus removal. (b) (4)

1) (b) (4)

(b) (4)

(b) (4)

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

(b) (4)

(b) (4)

5) Virus reduction factors

The viral clearance data from the abovementioned down-scale studies are summarized as follows:

(b) (4)

Product reviewer's Comment: Virus selection in the down-scale studies is consistent with the FDA recommendation regarding the biological drug products derived from cell lines of human or animal origin. The qualification of the down-scale systems used for viral clearance is acceptable, and the viral clearance data derived from these down-scale systems are sufficient to support the effectiveness of viral clearance in the commercial manufacturing process.

The mechanism for viral clearance between the (b) (4) steps are similar. To avoid overestimating its viral clearance capacity, I used the data generated from (b) (4) for the calculation of the total log reduction factors. Down-scale studies on the relevant steps resulted in at least the following overall log reduction factors, in parentheses, for these viruses: (b) (4)

Recommendation

The process assuring the safety from non-viral adventitious agents including bacteria, fungi, and mycoplasma is well controlled through the use of validated cleaning/sanitization procedures, in-process controls, filtration steps including (b) (4) sterile filtration, and release tests of sterility and endotoxins in the final product. The safety of the product from contamination with adventitious viruses is enhanced through complete viral tests of the (b) (4) . Furthermore, no human or animal derived raw materials are used in the manufacture of *ANDEXXA*. Additionally, viral safety is further enhanced by two dedicated viral clearance steps: (b) (4) The measures taken by Portola to control adventitious agents in the manufacture of *ANDEXXA* are acceptable. Therefore, I recommend approval of the BLA under STN 125586/0.