



MEMORANDUM

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

To: File (STN 125591/0)
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Through: Mark Weinstein, PhD, Assoc. Dep. Dir. for Science, OBRR/IOD
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Subject: Final review of Adventitious Agents Safety Information in CSL Behring's original BLA for Antihemophilic Factor (Recombinant), Single Chain

Cc: Alexey. Khrenov, 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 125591/0 submitted by CSL Behring (CSLB) for Antihemophilic Factor (Recombinant), Single Chain (rFVIII). The proposed proprietary name of this product is *AFSTYLA*. As described below, the measures taken by CSLB to control adventitious agents in the manufacture of *AFSTYLA* drug product are acceptable; therefore, I recommend approval of the BLA under STN 125591/0.

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., testing for bioburden and mycoplasma in (b) (4) [REDACTED]. The potential of *AFSTYLA* to be contaminated with non-viral adventitious agents is further reduced by testing the final product for sterility, endotoxins, and particulate matter. CSLB manufactures *AFSTYLA* according to GMP regulations.

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

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

The potential of contamination by infectious viruses in cell culture is well controlled in the manufacture of *AFSTYLA*, which is produced in a genetically modified Chinese hamster ovary (CHO) cell line. CSLB performed viral tests on the Master Cell Bank (MCB) for *AFSTYLA* 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 a positive result of (b) (4) and the presence of (b) (4) found through (b) (4) on MCB. The positive result of (b) (4) appears to be associated with the presence of (b) (4) that are considered to be non-pathogenic. Furthermore, all viral tests were negative except for (b) (4). CSLB routinely tests cell cultures used in the manufacturing process for adventitious viruses to ensure that viruses are below their detectable levels.

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

step in the manufacturing process also contributes to virus removal.

CSLB has evaluated these viral clearance steps in relevant down-scale studies using model viruses. The viruses selected for the studies include (b) (4)

The wide range of physico-chemical properties of these model viruses demonstrates the ability of the manufacturing process to reduce potential viral contamination from *AFSTYLA*. Down-scale studies on the relevant steps resulted in the following overall log reduction factors, in parenthesis, for these viruses: (b) (4). I find these results support the proposal that viral clearance is effective in the manufacture of *AFSTYLA*.

Background

The active ingredient in *AFSTYLA* is a single-chain recombinant Antihemophilic Factor with a truncated B domain and 4 amino acids of the adjacent acidic a3 domain (amino acids 765 to 1652 of full-length FVIII), which is produced in CHO cells. *AFSTYLA* is formulated as a sterile, non-pyrogenic, lyophilized powder for intravenous injection only. When reconstituted with its diluent, sterile Water for Injection (sWFI), each container of *AFSTYLA* final product contains nominally 250, 500, 1000, 2000 or 3000 IU of rFVIII.

The manufacturing process of *AFSTYLA* includes two dedicated, orthogonal viral clearance steps: (b) (4)

[redacted] step in the process also contributes to virus removal. 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 AFSTYLA

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

AFSTYLA drug substance

(b) (4)



AFSTYLA drug product

- (b) (4) . Formulation and sterile filtration
- (b) (4) . Aseptic filling
- (b) (4) . Lyophilization
- (b) (4) . Capping and crimping
- (b) (4) . Labeling and packaging
- (b) (4) . Drug product

Product reviewer's comment: Bolded in the above flow chart are the two dedicated viral inactivation/removal steps. (b) (4)

[redacted] also contribute to viral clearance. The validation

reports for these 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 (Section 3.2.A.2)

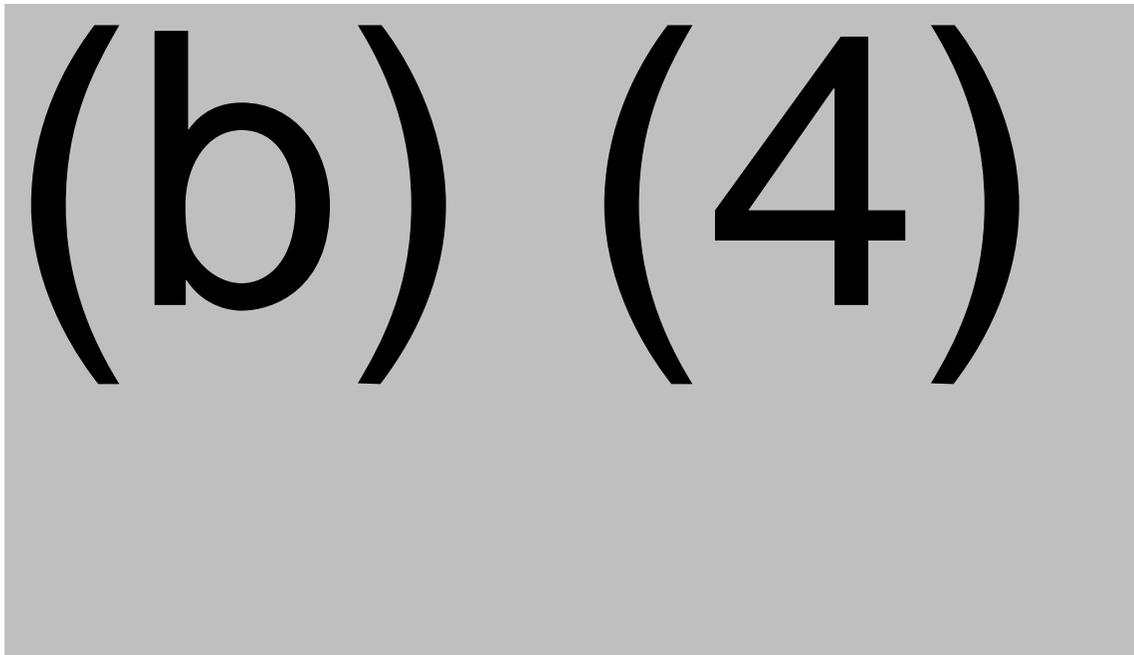
1. Control of non-viral adventitious agents

For the non-viral adventitious agents including bacteria, fungi, and mycoplasma, the potential of contamination of these agents is well controlled by: (1) using appropriate environmental control monitoring in the manufacturing process; (2) in-process controls, e.g., testing for bioburden and mycoplasma (b) (4)

The potential of *AFSTYLA* to be contaminated with non-viral adventitious agents is further reduced by testing the final product for sterility, endotoxins, and particulate matter. CSLB manufactures *AFSTYLA* according to GMP regulations.

2. Testing of all mammalian cell banks for the absence of infectious viruses

Master cell bank (MCB) used for the production of *AFSTYLA* is well controlled regarding the potential of viral contamination. The MCB named CSL627 MCB (b) (4) has been tested for viruses according to ICH Q5A(R1). All viral tests were found negative except for a positive result of (b) (4) and the presence of (b) (4). This MCB was also found to be absent of mycoplasma, bacteria, and fungi. Furthermore, (b) (4) were tested, and found negative for mycoplasma, bacteria, fungi, and adventitious viruses other than (b) (4). These data are summarized as follows:



(b) (4)

Product reviewer's comment: The tests performed on the MCB are consistent with ICH Q5A(R1) guidance. All test results for endogenous and adventitious viruses were negative except for a positive result of (b) (4) and the presence of (b) (4) that were found through (b) (4). The positive result of (b) (4) appears to be associated with the presence of (b) (4) that are considered to be non-pathogenic. Moreover, there are two dedicated virus inactivation/removal steps in the manufacturing process. These steps are used to reduce the potential of the DP to be contaminated with endogenous or adventitious viruses.

According to the ICH guidance Q5A, the full tests for viral safety are not required to be performed on the WCB if these tests are performed on the MCB: viral safety should be evaluated at least (b) (4). The data shown above provided further assurance that the manufacturing process is not prone to be contaminated by potential adventitious viruses. Therefore, these data are considered to be sufficient to support both MCB and WCB used for the manufacture of *AFSTYLA*.

3. Control of materials used in the manufacturing process

No human or animal derived raw materials are used in the manufacture of *AFSTYLA*. However, (b) (4)

(b) (4)

[Redacted]

No raw materials or ingredients of human or animal origin are used in the formulation of *AFSTYLA* final drug product. Additionally, routine cleaning procedures in the manufacturing process of *AFSTYLA* include sanitization of equipment with (b) (4) for the removal and/or inactivation of potential contaminations of viruses or TSE agents. Thus, the potential risk of contaminating adventitious viruses or TSE agents is minimized.

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

There are two dedicated steps for viral clearance in the manufacturing process of *AFSTYLA*, which are (b) (4)

[Redacted]

in the manufacturing process also contributes to virus removal. The viruses selected for the studies include (b) (4)

[Redacted]

Virus inactivation and/or removal by the respective step(s) were tested at least (b) (4)

Product reviewer's comment: Regarding the non-enveloped viruses, CSLB only provided clearance studies on (b) (4). After consultation with Dr. Mahmood Farshid, our resident expert on viral clearance in the Division of Hematology Research and Review, we conclude that this design is still acceptable considering that the manufacturing process includes a (b) (4), which is very effective for non-enveloped virus clearance.

(b) (4)

[Redacted]

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

(b) (4)

(b) (4)

(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.

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, (b) (4) 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 MCB (b) (4)

Furthermore, no human or animal derived raw materials are used in the manufacture of *AFSTYLA*. Additionally, viral safety is further enhanced by two dedicated viral clearance steps: (b) (4) step in the manufacturing process also contributes to viral clearance. The measures taken by CSLB to control adventitious agents in the manufacture of *AFSTYLA* are acceptable. Therefore, I recommend approval of the BLA under STN 125591/0.