



MEMORANDUM

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

To: File (STN 125582/0)
Thomas Maruna, Regulatory Project Manager, OBRR/IOD/RPM Staff

From: Ze Peng, PhD, OBRR/DHRR/LH

Through: Mark Weinstein, PhD, Assoc. Dep. Dir. for Science, OBRR/IOD
Basil Golding, MD, Division Director, OBRR/DHRR

Subject: Final review of Adventitious Agents Safety Information in CSL Behring's
Original BLA for Coagulation Factor IX (Recombinant), Albumin Fusion
Protein

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 125582/0 submitted by CSL Behring (CSLB) for Coagulation Factor IX (Recombinant), Albumin Fusion Protein. The proposed proprietary name of this product is *IDELVION*. As described below, the measures taken by CSLB to control adventitious agents in the manufacture of *IDELVION* drug product are acceptable; therefore, we recommend approval of the BLA under STN 125582/0.

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 endotoxins and mycoplasma (b) (4); and (3) filtration steps including (b) (4) sterile filtration. The potential of *IDELVION* to be contaminated with non-viral adventitious agents is further reduced by testing the final product for sterility and endotoxins. CSLB manufactures *IDELVION* according to GMP regulations.

No human or animal derived raw materials are used in the manufacture of *IDELVION*. No raw materials or ingredients of human or animal origin are used in the formulation of *IDELVION* 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 *IDELVION*, which is produced in a genetically modified Chinese hamster ovary (CHO) cell line. CSLB performed viral tests on the Master Cell Bank (MCB) for *IDELVION* that are consistent with the International Conference on Harmonisation (ICH) Q5A(R1) guideline. Moreover, all viral tests were negative except for the presence of (b) (4) and a positive result of (b) (4) that were at the limit of the established (b) (4) used for production. The positive result of (b) (4) appears to be associated with the presence of (b) (4) that are considered to be non-pathogenic. 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 *IDELVION* is further mitigated through two dedicated, orthogonal viral clearance steps: Solvent/Detergent (S/D) treatment (b) (4) 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 these 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 of *IDELVION*. Down-scale studies on the relevant steps resulted in the following overall log reduction factors, in parenthesis, for these viruses: (b) (4). We find that these results support the proposal that viral clearance is effective in the manufacture of *IDELVION*.

Background

The active ingredient in *IDELVION* is a recombinant fusion protein linking coagulation factor IX with human albumin (rIX-FP), which is produced in CHO cells. *IDELVION* is formulated as a sterile, non-pyrogenic, lyophilized powder for intravenous injection only. When reconstituted with its diluent, sterile Water for Injection, each container of *IDELVION* final product contains nominally 250, 500, 1000, or 2000 IU of rFIX.

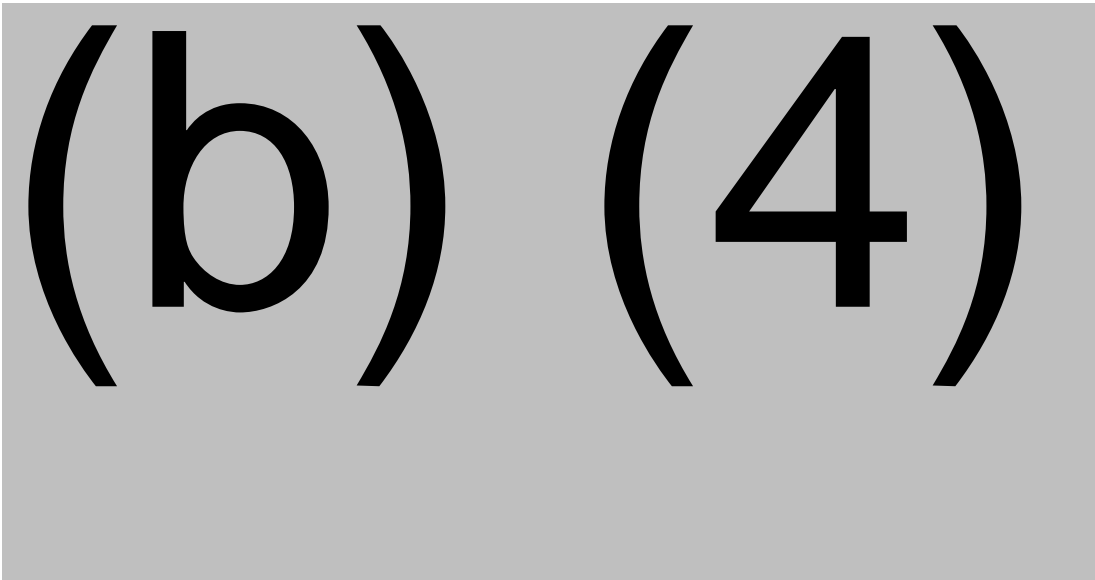
The manufacturing process of *IDELVION* includes two dedicated, (b) (4) clearance steps: S/D treatment (b) (4)

in the manufacturing 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 IDELVION

IDELVION drug substance



IDELVION drug product

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

Product reviewer's comment: Regarding the manufacture of *IDELVION*, CSLB did not include (b) (4) of S/D reagents to be critical process parameters at the step of solvent-detergent virus inactivation (with reference to page 3 of 9 in Section 3.2.S.2.4.1 *Control of Critical Steps*). As the data in the viral clearance studies indicate, these two parameters are also critical for virus inactivation.

We requested CSLB to add these parameters with their acceptance limits to Table
3.2.S.2.4.1-1 Critical Process Parameters for the manufacture of the drug substance.

This information request (IR) was sent to CSLB on 22 May 2015, and they responded in an amendment on 30 June 2015. Their response is summarized as follows:

(b) (4)

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(b) (4)

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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) employing in-process controls, e.g., testing for endotoxins and mycoplasma in (b) (4) sterile filtration. The potential of *IDELVION* to be contaminated with non-viral adventitious agents is further reduced by testing the final product for sterility and endotoxins. CSLB manufactures *IDELVION* 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 *IDELVION* is well controlled regarding the potential of viral contamination. The MCB named CSL654 MCB has been tested for viruses according to ICH Q5A(R1). All the tests were found negative for the presence of viruses except for the expected presence of non-infectious endogenous (b) (4). This MCB is 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). The data are summarized as follows:

(b) (4)

(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 the presence of (b) (4) that were found through (b) (4) 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 once on the cells at the limit of *in vitro* cell age used for production. All viral tests were negative except for (b) (4) found through (b) (4) and a positive result of (b) (4) used for production. The positive result of (b) (4) appears to be associated with the presence of (b) (4) that are considered to be non-pathogenic. 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 IDELVION.

3. Control of materials used in the manufacturing process

No human or animal derived raw materials are used in the manufacture of IDELVION. However, (b) (4) under the same conditions as those collected for human consumption. The manufacturer certifies that this raw material is compliant with the *Note for guidance on minimizing the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products* (EMA/410/01). No raw materials or ingredients of human or animal origin are used in the formulation of IDELVION final drug product. Additionally, routine cleaning procedures in the manufacturing process of IDELVION include sanitization of product contact equipment with (b) (4) for the removal and/or inactivation of potential contaminations of viruses or prions. Thus, the potential risk of adventitious viruses or TSE agents contamination is minimized.

4. Testing the capacity of the IDELVION purification process to clear viruses

There are two dedicated steps for viral clearance in the manufacturing process of *IDELVION*, which are S/D treatment (b) (4)

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

(b) (4) samples collected at relevant manufacturing steps. Virus inactivation and/or removal by the respective step(s) were tested at (b) (4).

Product reviewer's comment: Regarding the non-enveloped viruses, CSLB only provided clearance studies on (b) (4). We considered MVM is a relevant non-enveloped virus to the CHO cell line used for the production of *IDELVION*, and asked CSLB to expand their validation studies to include MVM regarding the capability of the manufacturing process for viral clearance, such as (b) (4) steps.

This IR was sent to CSLB on 22 May 2015. They requested to discuss this issue with FDA in their email dated 18 June 2015. They stated that the manufacturing process has a sufficient reduction capacity for parvoviruses including (b) (4) and additional studies using (b) (4) instead of (b) (4) would not lead to a changed assessment of viral safety. After we re-evaluated the viral validation studies with Dr. Mahmood Farshid, we concluded that the existing data are sufficient to ensure the safety of the product. Therefore, we conveyed the following information to CSLB on 19 June 2015 by email: Although CSLB is encouraged to include MVM in the future studies, these studies would not be required to support this original BLA. CSLB accepted this comment in the amendment dated 30 June 2015. Thus, this IR can be closed.

1) Solvent/Detergent treatment

(b) (4)

(b) (4)

(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 MCB and cells (b) (4) used for production. Furthermore, no human or animal derived raw materials are used in the manufacture of *IDELVION*. Additionally, viral safety is further enhanced by two dedicated viral clearance steps: S/D treatment at (b) (4) (b) (4). The step (b) (4) also contributes to viral clearance. The measures taken by CSLB to control adventitious agents in the manufacture of *IDELVION* are acceptable. Therefore, we recommend approval of the BLA under STN 125582/0.