



MEMORANDUM

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

To: File of STN 125446/0
Edward Thompson, RPMB/DBA/OBRR

From: Ze Peng, Ph.D., LH/DH/OBRR

Through: Mark Weinstein, Ph.D., Assoc. Dep. Dir. for Science, OBRR

Subject: Final Review of Adventitious Agents Safety information in Baxter's original BLA for Coagulation Factor IX (Recombinant)

Cc: Mikhail Ovanesov, Ph.D., Committee Chair, LH/DH/OBRR

Executive Summary

This memorandum summarizes the review of Adventitious Agents Safety Evaluation (Section 3.2.A.2) in an original Biologics License Application (BLA) under STN 125446 submitted by Baxter for Coagulation Factor IX (Recombinant) (rFIX). The proposed proprietary name of this product is RIXUBIS. In general, the measures taken by Baxter to control adventitious agents in the manufacture of RIXUBIS are acceptable; therefore, I recommend approval of the BLA under STN 125446/0.

Evaluation of Safety regarding Adventitious Agents

Baxter manufactures the RIXUBIS drug product according to GMP regulations. The use of validated cleaning/sanitization procedures, in-process ----b(4)-----, and testing of the RIXUBIS final product for sterility and endotoxins, reduces the potential risk of contamination from non-viral adventitious agents such as bacteria, fungi, and mycoplasma.

Additionally, the potential risk of contaminating adventitious viruses or transmissible spongiform encephalopathy agents is minimized because there are no raw materials or ingredients of human or animal origin included in the manufacturing process or in the formulation of the product.

RIXUBIS is produced by a Chinese Hamster Ovary (CHO) cell line. Baxter performed tests for viruses on the ---b(4)----- for RIXUBIS that were consistent with International Conference on Harmonisation (ICH) Q5A(R1) guidance. All results from viral testing were negative except for the presence of -b(4)- particles found by ---b(4)----- particles are retrovirus-like particles,

and are considered to be nonpathogenic. Moreover, the viral tests, including -b(4)- and the ---b(4)-----, for retro- and adventitious viruses, were negative on cells that were at the limit of the *in vitro* cell age used for production (--b(4)-----). In addition, Baxter routinely tests -b(4)----- used in the manufacturing process for adventitious viruses to ensure that the viruses are below detectable levels. These data demonstrate that the potential of contamination by infectious viruses is well controlled for up to -b(4)-

Additionally, Baxter employs two dedicated viral clearance steps, Solvent/Detergent (S/D) treatment (--b(4)-----), and 15 nm nanofiltration to mitigate the potential viral contamination of RIXUBIS. Baxter has evaluated these viral clearance steps in -b(4)----- studies using -b(4)------. The viruses selected for these studies include ---b(4)-----

----- The wide range of physico-chemical properties of these -b(4)----- tests the ability of the manufacturing process to eliminate viruses from RIXUBIS.

--b(4)----- studies on the relevant steps resulted in the following overall log reduction factors, in parenthesis, for these viruses: --b(4)-- -----
----- I find these results to be acceptable to support the proposal that viral clearance is effective in the manufacture of RIXUBIS.

Background

RIXUBIS is a purified rFIX protein produced in a genetically engineered CHO cell line. It has a primary amino acid sequence which is identical to the Ala-148 allelic form of plasma-derived FIX, and has structural and functional characteristics similar to those of endogenous FIX. RIXUBIS is formulated as a sterile, non-pyrogenic, white or off-white lyophilized powder for intravenous injection only. When reconstituted with its diluent, Sterile Water for Injection, RIXUBIS contains 250, 500, 1000, 2000 or 3000 IU of rFIX per vial.

Baxter manufactures RIXUBIS bulk drug substance (BDS) at its -b(4)- facility (-b(4)---), and the final drug product (FDP) at its -b(4)------. The manufacturing process of RIXUBIS includes two dedicated viral clearance steps: solvent/detergent treatment, and 15 nm nanofiltration. In addition, no raw materials or ingredients of human or animal origin are included in the manufacturing process or in the formulation of the product, which further mitigates the potential of viral contamination.

Summary of Review

Flow chart of the manufacturing process of RIXUBIS

[b(4)]

[b(4)]

FDA comment: As highlighted in the above flow diagram, there are two dedicated viral inactivation/removal steps. These steps are considered to lower the potential of viral contamination, provided that these steps are validated for viral clearance.

Evaluation of safety for non-viral adventitious agents

Baxter manufactures the RIXUBIS drug product according to GMP regulations. 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 validated cleaning/sanitization procedures, in-process controls (e.g., sterility testing and freedom from mycoplasma at the -----b(4)-----). The potential of RIXUBIS to be contaminated with non-viral adventitious agents is further reduced by testing the final product for sterility and endotoxins. Therefore, the measures taken by Baxter to control non-viral adventitious agents in the manufacture of RIXUBIS are acceptable.

Testing of all -b(4)- for the absence of infectious viruses

1. -b(4)-

Baxter -b(4)- for the production of rFIX. Although the CHO cell line is widely used in multiple licensed biological products, and the risk of adventitious agents has been found to be relatively low, Baxter and -b(4)- (a contract company) performed a series of viral safety tests on the -b(4)-. The results are summarized below:

[b(4)]

FDA comment: The tests performed on the b(4) are consistent with ICH Q5A(R1) guidance. All test results for endogenous and adventitious viruses were negative except for –b(4)- particles that were found in ---b(4)----- . Although –b(4)- particles are retrovirus-like particles, they are considered to be nonpathogenic. Moreover, there are two dedicated virus inactivation/removal steps in the manufacturing process. These steps are used to reduce the potential of the final drug product to be contaminated with endogenous and adventitious viruses.

2. –b(4)----- and cells at the –b(4)----- used for production

Baxter did not perform the abovementioned tests on the –b(4)----- . Instead, they established an in-process control for –b(4)----- testing of adventitious viruses in the routine manufacturing process.

FDA comment: According to the ICH guidance Q5A, the full tests for viral safety are not required to be performed on the b(4) if these tests are performed on the b(4) viral safety should be evaluated at least b(4) on the cells at the –b(4)----- -- ---- used for production. This information will provide further assurance that the manufacturing process is not prone to contamination by adventitious viruses. After discussion with Dr.'s Tim Lee, Roman T. Drews, and Mahmood Farshid, FDA sent the following information request to Baxter on 5 February 2013.

With reference to the FDA Guidance for Industry, Q5A viral safety evaluation of biotechnology products derived from cell lines of human or animal origin, please provide assurance that the production process is not prone to contamination by adventitious virus by performing in vivo tests at least once on cells at the limit of in vitro cell age used for production, i.e., end-of-production cells.

Baxter responded in an amendment on 12 February 2013. Their response is summarized as follows:

The viral safety tests were performed on the cells at the limit of –b(4)----- used for production (--b(4)-----, which serve as the –b(4)----- generation number for routine production), which were originally expanded from the –b(4)----- . The viral tests include *in vivo* assays for adventitious viruses in suckling mice, adult mice, embryonated eggs, and guinea pigs. The relevant data for these tests are provided in this amendment.

FDA comment: The *in vivo* tests for detecting contamination by adventitious viruses have been performed on the cells at the –b(4)----- used for production by the contract company, --b(4)----- . Moreover, the viral tests, including ----b(4)-----, for retro- and adventitious viruses were negative on cells at the limit of –b(4)----- used for production (--b(4)-----). In addition, --b(4)----- in the manufacturing process are routinely tested to be negative for adventitious viruses. These data demonstrate that the potential of contamination by infectious viruses is well controlled for up to –b(4)-----.

Human or animal-derived component exposure in the manufacture of RIXUBIS

There are no raw materials or ingredients of human or animal origin included in the RIXUBIS manufacturing process or in the formulation of the product, which minimizes the potential risk of adventitious viruses and transmissible spongiform encephalopathy agents.

Please note that Baxter used –b(4)----- in the CHO cell line development (i.e., --b(4)-----). The b(4) provided by –b(4)----- was sourced from either -----b(4)-----

FDA comment: The viral tests for the b(4) used in the development of –b(4)--- comply with CFR 9 Part 113.53. Moreover, the b(4) is not used in the b(4) and routine manufacturing process of RIXUBIS. The viral screening tests performed in b(4) and --b(4)----- used for production also indicate the absence of infectious viruses. Together with the viral clearance capacity of the manufacturing process, viral safety margin of the RIXUBIS FDP is high.

Viral clearance

There are two dedicated steps for viral clearance in the manufacturing process: S/D treatment (--b(4)-----); and 15 nm nanofiltration. Baxter has evaluated all of these steps in –b(4)----- studies. The viruses selected in these studies include ---b(4)-----

---b(4)-----
These viruses resemble viruses which may contaminate the RIXUBIS drug product, and represent a wide range of physico-chemical properties that tests the ability of the manufacturing process to eliminate viruses.

1. Solvent/Detergent treatment

1) Qualification of the -b(4)----- system used for viral clearance

To evaluate the capacity of S/D treatment to clear viruses, Baxter did a validation study (*Study No. reg706e*) on the -b(4)----- system. In this study, the test results of -b(4)-----
----- . These data support the qualification of the system -b(4)----- . Thus, the viral clearance data derived from the -b(4)----- system can be used for evaluating the viral clearance capacity of S/D treatment at -b(4)----- . To demonstrate the robustness of the system for viral clearance, Baxter -b(4)----- of the S/D treatment, and used the -b(4)----- of S/D components in the relevant viral clearance studies. The details of these parameters are listed as follows:

[b(4)]

2) Viral clearance study

The following data support the conclusion that S/D treatment is an effective step to inactivate enveloped viruses. The samples used for the virus clearance study were obtained from the -b(4)-, and all samples are tested for toxicity and interference with -b(4)----- . The -b(4)----- viral clearance data on S/D treatment are summarized below:

[b(4)]

[b(4)]

As shown above, no infectivity was detected after -b(4)- of S/D treatment for all referenced enveloped viruses, even under the worst case scenario, i.e., --b(4)-

The viral reduction factor for -b(4)- S/D treatment at -b(4)- was changed from -b(4)- as shown on the above table (with reference to Study No. *reg706e*) -b(4)- based on an additional viral clearance study No. -b(4)-

As shown below, S/D treatment effectively inactivated -b(4)-. Thus, I agree with Baxter that the mean viral reduction factor for -b(4)- at the S/D treatment step can be changed from -b(4)- as determined using a more sensitive assay.

[b(4)]

2. Nanofiltration

1) Qualification of the -b(4)- system used for viral clearance

The nanofilters used in nanofiltration are manufactured by -b(4)- with a pore size of 15 nm, and a -b(4)-. To evaluate the capacity of nanofiltration (-b(4)-) to clear viruses, Baxter did a validation study (*Study No.*

reg701e) on a –b(4)----- system. In this study, the test results on critical parameters such as –b(4)----- nanofiltration were found to be comparable between –b(4)----- . The rFIX test results for concentration, before and after nanofiltration are listed below:

[b(4)]

These data support the qualification of the system –b(4)----- . Thus, the viral clearance data derived from the –b(4)----- system can be used for evaluating the viral clearance capacity of nanofiltration at –b(4)-----

To demonstrate its robustness in the following viral clearance study, Baxter selected the load to filter area, and the –b(4)----- to be set to or beyond the range of limits specified at –b(4)----- . The details are listed as follows:

[b(4)]

2) Viral clearance study

The samples (lots –b(4)-----) used for virus clearance studies were obtained from the –b(4)---- . All samples were tested for toxicity and interference with virus –b(4)---- assays. –b(4)-- independent runs were used for each virus in the study. Viruses selected include two enveloped viruses, –b(4)-----, and two non-enveloped viruses, --b(4)----- . As the data show in the following table, nanofiltration can result in at least a –b(4)----- of both non-enveloped and enveloped viruses.

[b(4)]

[b(4)]

3. Virus reduction factors

The viral clearance data from the abovementioned --b(4)----- studies are summarized as follows:

Manufacturing steps	--b(4)-----				
	--b(4)-----			--b(4)-----	
	--b(4)---	--b(4)---	--b(4)---	--b(4)---	--b(4)---
Solvent/Detergent treatment	--b(4)---	--b(4)---	--b(4)---	--b(4)---	--b(4)---
Nanofiltration	--b(4)---	--b(4)---	--b(4)---	--b(4)---	--b(4)---
--b(4)-----	--b(4)---	--b(4)---	--b(4)---	--b(4)---	--b(4)---

FDA Comment: Virus selection in the --b(4)----- 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 --b(4)----- systems are sufficient to support the effectiveness of viral clearance in the commercial manufacturing process.

Recommendation

The safety of 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)-----, and release tests of sterility and endotoxins in final product. The safety of the product from contamination with adventitious viruses is enhanced through complete viral tests of the b(4) and cells at the --b(4)----- used for production. No raw materials or ingredients of human or animal origin are included in the manufacturing process or in the formulation of the product. Additionally, the viral safety is further enhanced by two dedicated viral clearance steps: S/D treatment, and 15 nm nanofiltration. The measures taken by Baxter to control adventitious agents in the manufacture of RIXUBIS are acceptable. Therefore, I recommend approval of the BLA under STN 125446/0.