



**FOOD AND DRUG ADMINISTRATION**  
CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

MEMORANDUM

Final CMC review

**To:** File (STN BL 125446/0) & Edward Thompson

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**Subject:** Final CMC Review of Baxter's original BLA application for Coagulation Factor IX (Recombinant)

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## 1. Executive Summary

### Background

Baxter Healthcare Corporation (Baxter) submitted a biologics license application (BLA) for Coagulation Factor IX (Recombinant), under the proprietary name RIXUBIS™, for the following proposed indications in adults with hemophilia B: (1) control and prevention of bleeding episodes, (2) peri-operative management, and (3) routine prophylaxis to prevent or reduce the frequency of bleeding episodes. The product is currently not licensed or authorized to be marketed in any countries.

The recombinant Coagulation Factor IX (rFIX) is expressed in Chinese Hamster Ovary (CHO) cells, and purified using a process that includes two validated viral inactivation/reduction steps, namely solvent/detergent treatment and nanofiltration. No human or animal materials are employed in the manufacture of RIXUBIS™.

RIXUBIS was developed for the U.S. market under IND 14488 for replacement therapy, per-operative management and prophylaxis for adults with hemophilia B. The investigational code of Baxter for this product is BAX 326.

Currently, one rFIX product (BeneFIX®, Wyeth/Pfizer) and several plasma-derived FIX concentrates and FIX-containing prothrombin complex concentrates (PCC) are licensed in the U.S. and elsewhere for the treatment of patients with hemophilia B. The protein structure, function and impurity profile of RIXUBIS™ are similar, but not identical, to those of BeneFIX. Although both products are expressed in CHO cells, the manufacturing processes are different. Like other FIX-containing products, RIXUBIS™ vials are labeled with the actual FIX potency as measured by a one-stage clotting assay in units traceable to the 4<sup>th</sup> World Health Organization (WHO) International Standard for FIX concentrate, which is a plasma-derived preparation.

**CMC review summary:**

**a) Product Manufacture and Product Quality**

The Bulk Drug Substance (BDS) is manufactured at Baxter's multi-product facility in –b(4)-----  
RIXUBIS™ is manufactured without the use of any animal- or human-derived components. The process includes two validated virus inactivation/removal steps, namely solvent/detergent treatment with a mixture of -----b(4)-----  
-----; and nanofiltration through a 15-nm –b(4)----- filter.

The rFIX is secreted by a CHO cell line--b(4)-----  
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The rFIX is purified by a process of chromatographic steps. –b(4)--- -----  
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The RIXUBIS™ Final Drug Product (FDP) is a lyophilized powder manufactured at Baxter's multi-product facility in –b(4)-----, where the -----b(4)-----  
appropriate strength, formulated, distributed to vials and lyophilized.

The manufacturing process is well developed and controlled as evidenced by:

- An established design space within which the manufacturing process is robust in delivering product of consistent yield, purity and potency. This was demonstrated in a series of small-scale and commercial scale product runs utilizing the *Design of Experiments* concept.
- Identification, validation and control of critical steps and intermediates throughout the manufacturing process.
- Consistency among over ---b(4)-----  
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- A subset of representative conformance batches that has been fully characterized by an extensive battery of tests described below.
- Appropriately chosen and validated in-process and lot release tests and their specifications.

Although *Quality by Design* (QbD) elements were used in developing the manufacturing process, the CMC sections of the BLA are presented as a traditional process validation exercise, and Baxter has not proposed any QbD-associated regulatory approach. For example, the quality of the RIXUBIS™ is controlled with a comprehensive panel of lot release tests that is comparable to that of currently licensed recombinant coagulation factor products.

#### *Control of Starting Materials*

Most of the chemicals used are of –b(4)--- grade, and purchased from reliable sources. Quality control testing of raw materials not listed in pharmacopeia is performed either by the raw material manufacturer, Baxter or contractors except for identity testing, which is carried out in Baxter laboratories. USP-grade purified water is produced –b(4)------. All materials used in the cell culture media are manufactured from raw materials that contain no animal parts, products or by-products. The safety of the genetically-engineered CHO cell line used to develop the RIXUBIS™ --b(4)----- was extensively characterized –b(4)----- for RIXUBIS. -----b(4)----- ADVATE and RECOMBIMATE.

#### *Final Drug Product*

RIXUBIS™ is supplied as a lyophilized powder in 10-mL glass vials of five nominal dosage strengths: 250, 500, 1000, 2000, and 3000 IU per vial. Each vial and carton is labeled with the actual FIX potency as measured with a validated one-stage clotting assay in units traceable to the 4<sup>th</sup> World Health Organization (WHO) International Standard for Factor IX concentrate, which is a plasma-derived preparation.

Recombinant FIX FDP is formulated as a sterile, nonpyrogenic, white or off-white, lyophilized powder preparation for intravenous injection and is stabilized with a mixture of sugars and salts. Drug product composition: rFIX (Active Ingredient); 20 mM L-Histidine (-b(4)--); 60 mM NaCl (as ---b(4)-----); 4 mM CaCl<sub>2</sub> (as ---b(4)-----); 110 mM Mannitol and 35 mM Sucrose (as ----b(4)-----); and 0.005% Polysorbate 80 --b(4)-----

For all dosage presentations, each carton contains a 5-mL vial of sterile water for injection (--b(4)---) and a BAXJECT II NTD device (Baxter). The needle-less BAXJECT device is for the transfer of sWFI to the drug vial, and withdrawal of the reconstituted product into a syringe for intravenous administration.

#### *Characterization of rFIX Structure and Function*

RIXUBIS™ is a purified protein that has –b(4)- amino acids in a—b(4)--polypeptide chain. It has a -b(4)--- amino acid sequence that is identical to the Ala 148 allelic form of plasma-derived (pd) Factor IX with -----b(4)-----

The rFIX characterization program utilized an extensive panel of analytical methods to evaluate the structure and function of the product, and showed that RIXUBIS is comparable in purity and characteristics to licensed pd and recombinant FIX products. It also demonstrated the consistency of the manufacturing process and quality of various conformance lots derived from ---b(4)-----

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#### *Evaluation of Safety regarding Adventitious Agents*

Baxter manufactures RIXUBIS™ according to cGMP regulations. For non-viral adventitious agents such as bacteria, fungi, and mycoplasma, the potential contamination of these agents is well controlled through the use of validated cleaning/sanitization procedures, and ---b(4)-----

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The RIXUBIS™ FDP is further guaranteed to be free of non-viral adventitious agents by the testing of Sterility and Endotoxins.

There are no raw materials or ingredients of human or animal origin included in the manufacturing process or in the formulation of the product, which minimizes the potential risk of adventitious viruses and transmissible spongiform encephalopathy agents. The safety margins of the CHO cell line used for the production of RIXUBIS™ are supported by the virus safety risk assessment.

Viral tests on the -b(4)----- for RIXUBIS™ are consistent with International Conference on Harmonisation (ICH) Q5A(R1) guideline. All results for viral testing were negative except for the -b(4)-- particles found on -b(4)----- The -b(4)- particles are retrovirus-like particles, and are considered to be nonpathogenic. Moreover, the viral tests, including -b(4)-----, for retro- and adventitious viruses were negative at the limit of *in vitro* cell age used for production (-b(4)-----). In addition, cell cultures in the manufacturing process are routinely tested negative for adventitious viruses. These data demonstrate that the potential of contamination by infectious viruses is well controlled for up to -b(4)-----.

Additionally, the potential of viral contamination of RIXUBIS™ is mitigated by two dedicated viral clearance steps: Solvent/Detergent (S/D) treatment (---b(4)-----), and 15 nm nanofiltration. Baxter has evaluated these and other manufacture steps in -b(4)---- studies. The viruses selected in these studies include ---b(4)---

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----- These model viruses resemble viruses which may have the potential to contaminate the RIXUBIS™ drug product, and represent a wide range of physico-chemical properties in evaluating the ability of the manufacturing process to inactivate or remove viruses. ---b(4)-----

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----- These results are sufficient to support the effectiveness of viral clearance in the commercial manufacturing process.

#### *Impurities*

The levels of impurities in the product are found to be acceptable and not likely to affect its safety and efficacy as demonstrated in clinical studies. A summary of product evaluation and process validation studies regarding impurity levels is provided in the table below:

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#### *Specifications*

The methods and established specifications are comparable to those of licensed FIX products; however, direct comparison of limits is difficult due to differences in assay conditions.

RIXUBIS FDP release methods and specifications are presented in the table below:

Test method	Specification
---b(4)-----	---b(4)-----
Appearance – Reconstituted Solution	Clear solution, practically free from foreign particles
---b(4)-----	---b(4)-----
---b(4)-----	---b(4)-----
---b(4)-----	---b(4)-----
Sterility – ---b(4)-----	Sterile
Total Protein	---b(4)----- -----
rFIX Activity – Clotting method <sup>#</sup>	---b(4)----- ---b(4)----- ---b(4)----- ---b(4)----- ---b(4)----- -----b(4)----- ----- ----- -----
Specific Activity of rFIX – Calculation <sup>1</sup>	≥ 200 IU/mg of protein
rFIXa Activity – ---b(4)-----	---b(4)----- -----
rFIX Pre-activation – Calculation <sup>1</sup>	≤ 0.03%
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---b(4)-----	---b(4)-----
---b(4)-----	---b(4)-----
---b(4)----- -----	---b(4)----- ---b(4)-----
---b(4)-----	---b(4)-----
---b(4)-----	---b(4)-----
Polysorbate-80 ---b(4)----- -----	---b(4)-----
--b(4)-----	---b(4)-----
---b(4)-----	---b(4)-----
--b(4)-----	---b(4)-----
Sucrose – ---b(4)-----	---b(4)-----
Mannitol ----b(4)-----	---b(4)-----
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After discussions with FDA, Baxter agreed to --b(4)--the specifications for rFIX pre-activation and rFIX potency based on the available manufacturing data. Furthermore, Baxter conducted additional evaluation of the rFIX pre-activation specification. Activated FIX (FIXa) is a potentially thrombogenic product-related impurity which is found in all FIX-containing products. The level of FIXa is usually controlled at release of FDP with --b(4)----- for activated coagulation factors, -b(4)---. For the release of RIXUBIS™, Baxter developed a --b(4)-----  
----- Using this and other assays, including the --b(4)-----, lower levels of FIXa were found in RIXUBIS™ lots in comparison to licensed FIX-containing products. In addition, analysis of the available pharmacovigilance data supported comparable safety profiles between RIXUBIS™ and licensed pd FIX-containing products.

The quality of RIXUBIS™ is further assured by the comprehensive testing panel of BDS release assays. Compared to the FDP, the BDS testing panel evaluates the following additional process-related impurities: --b(4)----- . Although process validation studies demonstrated consistent removal of --b(4)---, Baxter agreed to add --b(4)--- as a BDS release test in response to the development of --b(4)--- antibodies in subjects in clinical trials. It should be stated that the ---b(4)----- antibodies were low, and their presence has not been associated with any adverse reactions. In addition, similar rates of --b(4)----- antibodies were observed in some patients before RIXUBIS™ administration as well as in a population of normal healthy individuals. Please refer to the clinical review section of this memorandum for further information on antibody development.

#### *Stability*

The available stability data indicate no critical trends during the observed long-term storage period. The data support the proposed shelf-life of RIXUBIS™ for 18 months at  $5 \pm 3^\circ\text{C}$ . The data also support storage at room temperature (i.e.,  $25^\circ\text{C}$  or  $30^\circ\text{C}$ ) for 6 months. The reconstituted product is stable for 3 hours at controlled room temperature.

Stability studies are ongoing and Baxter has committed to placing one commercial lot on stability annually rotating among different dosage strengths.

It is noteworthy that Baxter observed multiple out-of-specification (OOS) results in potency in the ongoing stability studies during the BLA review. The root cause for these OOS results was identified as poor robustness of the potency assay. Retesting using a revalidated potency assay showed that the OOS results were incorrect and that all product lots met stability specifications during stability testing. Adequate performance of the revalidated potency assay has been demonstrated through a series of intra- and inter-laboratory studies.

Using the revalidated assay, Baxter retested potency of all available FDP batches used in the pre-clinical and clinical investigations and found that the assay deficiencies had no impact on the outcomes of the clinical investigations, stability studies and manufacturing validation studies. In addition, Baxter used the re-tested potency data for analyses of all the pharmacokinetic data.

#### **b) Exemption from CBER Lot Release**



Since RIXUBIS™ is a well-characterized recombinant DNA-derived product, alternatives to official lot release are allowed under the provision described in Federal Register 58:38771-38773. Furthermore, in the Federal Register Notice (60 FR 63048) published on 8 December 1995, the Director of CBER announced that routine lot-by-lot release by CBER is no longer required for licensure of this class of products. The exemption of RIXUBIS™ from lot-by-lot release by CBER is further supported by Baxter's ability to adequately control the manufacturing process and produce a product of established quality.

As part of the review of the BLA, conformance lots of RIXUBIS™ representing the --b(4)----- approach) were assayed by CBER for the following parameters: --b(4)-----, reconstitution time, --b(4)-----, and Factor IX potency (clotting assay). The testing results from CBER met specifications and are consistent with those from Baxter.

CBER lot testing revealed that evaluation of RIXUBIS™' FIX activity can be affected by the type of aPTT reagent and reference standard used in the assay. A multi-laboratory study conducted by Baxter, which include CBER's Lot Release, Baxter's Lot Release at --b(4)----- Baxter's Plasma Products Lot Release at --b(4)----- and Baxter's R&D laboratories, has demonstrated up to 40% higher potencies than those on the RIXUBIS™ label when conformance lots were tested using aPTT reagents used by CBER laboratory and plasma-derived FIX activity standard, the 4<sup>th</sup> WHO International Standard for FIX Concentrate (NIBSC code 07/182). However, results from all four laboratories met specifications for RIXUBIS™ potency when either the aPTT reagent validated by Baxter's potency assay or the RIXUBIS™-derived potency standard were used.

To inform RIXUBIS™ users of possible discrepancy due to variation in assay conditions, the following statement has been added to the package insert: *"Factor IX potency results can be affected by the type of aPTT reagent and reference standard used in the assay; differences of up to 40% have been observed."*

This statement and findings are consistent with the previously reported variations in the measurements of coagulation factor activity in licensed and investigational recombinant Coagulation Factor IX and VIII products. For example, the current labeling for BeneFIX includes the following statement: *"Dosing of BeneFIX may differ from that of plasma-derived factor IX products [see Clinical Pharmacology (12)]. Subjects at the low end of the observed factor IX recovery may require upward dosage adjustment of BeneFIX to as much as two times (2X) the initial empirically calculated dose in order to achieve the intended rise in circulating factor IX activity."*

**c) Post-marketing commitment:**

Baxter agreed to provide additional validation for the lot release method "--b(4)-----" within 6 months of the BLA approval date. Stability studies are ongoing and Baxter proposed placing one commercial lot on stability annually rotating among different potencies.

**d) Conclusion & Recommendation**

The quality and purity of RIXUBIS are acceptable and comparable to the licensed recombinant FIX product. The manufacturing process is sufficiently validated and well controlled. We did not identify any CMC issue that may prevent approval, and recommend approval from a CMC perspective.

**2. Bulk Drug Substance**

**2.1. Manufacturing process**

**2.1.1. Manufacturing sites and laboratories**

BAX 326 Bulk Drug Substance (BDS) is manufactured by --b(4)----- at the address listed in Table 1. The license holder is Baxter Healthcare Corporation (Baxter), One Baxter Way, Westlake Village, CA 91362.

**Table. BAX 326 BDS Manufacturing Facility Names and Responsibilities**

Manufacturing Step	Manufacturing Site
--b(4)-----	--b(4)-----
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Testing laboratories:

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CBER conducted an inspection at Baxter ---b(4)-----  
----- on January 21-25, and 28-29, 2013. On January 29, 2013, a Form FDA 483 was issued to  
Baxter containing 11 objectionable observations. Baxter's responses to the FDA 483 observations  
were reviewed, and we found the deficiencies adequately addressed.

## 2.1.2. Manufacturing process and controls

### 2.1.2.1. Overview

Generally, the BDS manufacturing process is relatively standard for recombinant plasma protein and meets or exceeds the quality standards implemented in the manufacture of other licensed recombinant coagulation factor products. The process is well established and well controlled as was demonstrated by the development history, process validation exercises, batch records (over b(4) BDS batches) and pre-approval inspection. My review did not identify objectionable findings with the exception of poor robustness of the –b(4)----- which was demonstrated to have no effect on the process validation studies (discussed in the section entitled Deficiencies resolved during review cycle).

Recombinant FIX is expressed in a Chinese Hamster Ovary (CHO) cell line that secretes the ---  
b(4)-----  
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During the pre-approval inspection of the-b(4)---- facility, the inspection team observed critical activities related to BDS manufacture, which included –b(4)-----.

The manufacturing in the production---b(4)---- -----  
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A flow diagram representing an overview of the manufacturing process for the rFIX BDS is attached in Figure 1 below.

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The In-Process Controls performed on the different production steps are listed in the table below. The suitability and extent of these controls were identified during the course of process development and subsequently confirmed during the process validation studies. An out-of-specification (OOS) result may have two outcomes:

1. “Nonconformity” means that an investigation will be initiated and the batch can be accepted or rejected based on the results of the investigation. This outcome is assigned to most of critical parameters.
2. “Terminate” means that if investigation confirms results, the batch will be rejected or the production run will be terminated. Only three parameters with definite negative effect on product quality and safety are included in this category:
  - Cell viability
  - Presence of adventitious agents
  - Maximum time of cells in culture

**Table. In process controls**

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#### **BATCH AND SCALE DEFINITION**

One production campaign is defined as a --b(4)-----  
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#### **2.1.2.2. Cell culture**

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#### **2.1.2.4.Reprocessing**

Reprocessing is not performed or planned for the manufacture of rFIX BDS.

#### **2.1.2.5.Filling, storage and shipping**

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#### **2.1.3. Control of materials**

The quality of raw materials used for the manufacture of RIXUBIS is adequately assured through the utilization of several key components listed below:

1. Baxter Corporation has extensive knowledge base and established corporate-wide procedures for control of raw materials.

2. Materials are centrally purchased, qualified, stored, labeled and distributed by Baxter's dedicated divisions, e.g., Warehouses and Quality.
3. Quantity and quality information (e.g., Certificates of Analysis) on raw materials is stored on central computerized systems.
4. Suppliers are selected based upon their ability to supply materials that consistently meet specifications. In some cases, materials are developed and manufactured exclusively for Baxter, e.g., cell culture media base.
5. The supplier qualification program is supported by regular audits performed according to written procedures.
6. After a supplier has been qualified, the raw material may be accepted based upon a review of the Certificate of Analysis.
7. Baxter laboratories conduct specified abbreviated confirmatory testing, e.g., at a minimum, identity.
8. Specifications have been established for each raw material used in the manufacture of rFIX BDS.
9. The decision to release or reject a lot is made by Quality based on the incoming documentation and the results of the analysis. Quality completes the required documentation to modify the status of the material from quarantined to "released" or "rejected" and applies the proper status tag on the material.

#### **2.1.3.1. Control of materials – listed in pharmacopeia**

Compendial materials are tested in accordance to the specified pharmacopeia monographs. Where available, Baxter meets the strictest requirements described in either the US or European Pharmacopeias.

#### **2.1.3.2. Control of Non-biological materials not listed in pharmacopeia**

Tests are performed either by the manufacturer, by Baxter, or by contractors except identity testing, which is carried out in Baxter laboratories.

#### **2.1.3.3. Raw Materials of Human/Animal Origin**

##### **2.1.3.3.1. Background**

No materials of human or animal origin are utilized in the manufacture of rFIX with the exception of the host cell line, which is described in this section.

Baxter has evaluated the safety margins of the rFIX product, which are based on the strict control over the CHO cell line expressing rFIX and several manufacturing process features, e.g., --b(4)--- --

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steps. In addition, testing for adventitious viruses is performed on the --b(4)-- -----  
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##### **2.1.3.3.2. SOURCE, HISTORY, AND GENERATION OF THE --b(4)-----**

According to ICH guideline Q5D, Baxter provided a summary of the source, history and generation of the rFIX --b(4)-----

3 pages determined to be not releasable: b(4)

#### 2.1.4. Controls of critical steps and intermediates

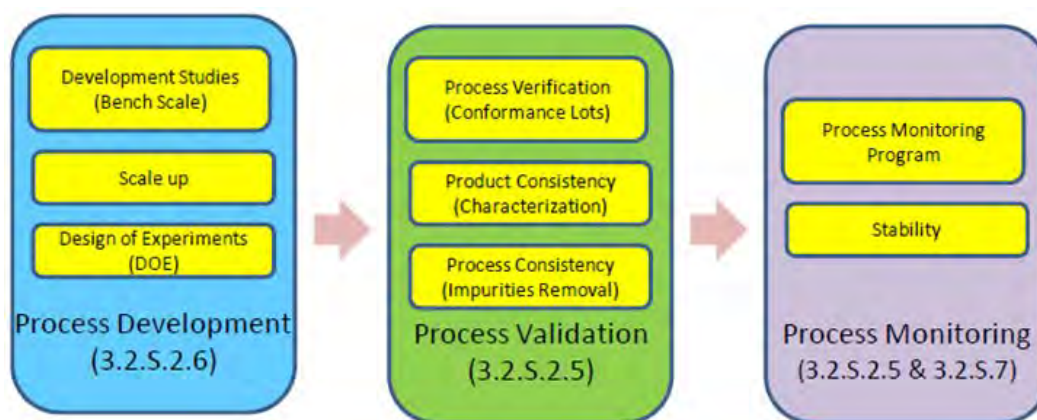
Controls performed at critical steps (Step numbers and descriptions see section 3.2.S.2.2 Description of Manufacturing Process and Process Controls) of the manufacturing process and on intermediates (including starting materials) for rFIX are listed in Table 1 of the section 2.1.2. *Manufacturing process and controls* above.

#### 2.1.5. Process validation and evaluation

I agree with Baxter's conclusion that the process and equipment are suitable for consistent manufacturing of the BDS.

The process validation studies are adequate, which is demonstrated by

1. The utilization of the elements of the Quality by Design approach to develop a robust process that is specifically optimized for robustness, yield and low impurity profile.
2. The management of the life-cycle of the process through a Process Monitoring program and Process Control strategy (see the chart below).
3. The development of the process at the ----- -b(4)-) followed by validated -b(4)---- (-b(4)-----).
4. Process validation at commercial scale demonstrated process consistency and robustness with conformance batches meeting pre-defined specifications.
5. The utilization of FDA guidance, e.g., conformance batches were selected to represent the different stages of the -b(4)-----) following the particular design that was recommended by the FDA in the Pre-BLA communication. In addition, -b(4)-----BDS batches were used per pre-defined validation plan for the validation exercises, i.e., there was no evidence that "bad" batches were intentionally skipped and excluded from the analysis.



Adequacy of process validation was further verified by additional details obtained during the Pre-Approval Inspection when the following elements were reviewed and discussed with Baxter responsible personnel:

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Finally, in accordance with the 2011 FDA guidance on Process Validation: General Principles and Practices, Baxter created and established a division-wide procedure toward “Continuous Process Monitoring”. Subsequently, this division-wide procedure was customized for the b(4) Facility. The main components of the Process Monitoring program involves identification of process parameters to monitor, a statistically based algorithm to analyze and trend the data, periodic review by technical experts and quality management, and, finally, actions that are taken, if necessary, under existing Quality Systems.

#### **2.1.5.1. Overview of process validation**

A summary of validation reports is provided in the table below:

**Table. Manufacturing Process Validation Reports**

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Process validation was performed to demonstrate the following:

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4. -b(4)-----
  - -b(4)-----

2 Pages determined to be not releasable: b(4)

[ b(4) ]

I agree with Baxter’s conclusion that process and quality attributes data from –b(4)-----  
----- demonstrated  
manufacturing process robustness and consistency.

#### **2.1.5.2. Characterization**

The intra-campaign and inter-campaign consistency was demonstrated through structural and functional characterization studies with RIXUBIS –b(4)- conformance samples, RIXUBIS FDP samples along with samples from a licensed rFIX product. See Characterization section below.

#### **2.1.5.3. Impurity removal**

The ability of the purification process to consistently remove process-related impurities was assessed in –b(4)--- production runs, see the table below.

[ b(4) ]

#### **2.1.6. Manufacturing process development**

Baxter utilized Design of Experiments approach in the development of the manufacturing process (summarized in the table below). Although this approach provides additional assurance of process



robustness, Baxter's submission is not a Quality by Design submission. Process development started with the understanding of the structural properties of rFIX, which served as the basis for process design.

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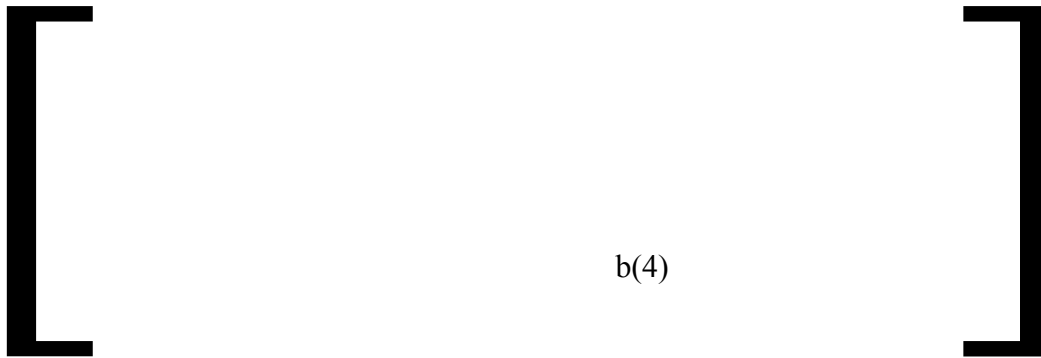
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## 2.2.Characterization

### 2.2.1.Elucidation of structure and function

The structural and functional characteristics of RIXUBIS were found comparable to those of endogenous FIX and the licensed recombinant FIX product BeneFIX. The purity and functional activity of RIXUBIS is comparable to those of BeneFIX. The amino acid sequences of RIXUBIS and BeneFIX are –b(4)---. The post-translational modifications are comparable.

#### 2.2.1.1.Factor IX structure and function



RIXUBIS as well as Human coagulation factor IX (hFIX) is a –b(4)----- that belongs to the class of –b(4)---- proteases. Maturation of FIX requires the ---b(4)----- giving rise to the –b(4)----- amino acids and a molecular weight of approximately -b(4)- including the –b(4)----- . The –b(4)-----, from where it is –b(4)-----, - -----b(4)----- . A schematic structure of the RIXUBIS molecule is given in Figure 1 above.

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#### ***2.2.1.1.1.RIXUBIS structure***

The structure of RIXUBIS was investigated by a number of analytical methods focusing on the elucidation of the primary structure, posttranslational modifications, three-dimensional structures and biological activity. A selected set of b(4) Conformance samples representing the --b(4)-----, as well as samples representing the --b(4)----- were used. Furthermore, FDP clinical samples representing different potencies and licensed

recombinant FIX product BeneFIX (a Comparator FDP) samples with different potencies were also included in the characterization exercise.

- The protein content of RIXUBIS was determined by --b(4)--  
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**Conclusion:**

I agree with Baxter's conclusion that acceptable comparability has been established between the BDS conformance samples and FDP clinical samples, and the licensed rFIX product. Specifically,

- The primary structure of RIXUBIS was found to be correct and consistent. --b(4)----- analysis showed that RIXUBIS is a highly --b(4)----- protein and the CHO cells express this protein with a consistent --b(4)----- pattern. Characterization of ---b(4)----- showed the expected structures. Protein composition proved that RIXUBIS is expressed as a stable protein with a relatively low amount of degradation products. All other posttranslational modifications were also found to be consistent.
- No significant differences between samples from the ---b(4)----- of a production campaign were noticed throughout this characterization exercise. No significant difference between samples from the --b(4)----- production campaign and a sample representing --b(4)- with the ---b(4)----- production campaign were noticed. No significant differences among samples from --b(4)----- production campaigns were noticed suggesting consistent manufacturing.

**2.2.1.1.2.RIXUBIS function**

In this study, conformance batches of RIXUBIS (--b(4)-----) were characterized with respect to their hemostatic potency, the efficiency of activation by ---b(4)----- . In addition, the functional properties of RIXUBIS were compared to three batches of the licensed rFIX product with different potencies.

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In summary, there were no relevant differences found among the various –b(4)-- batches from ---b(4)-----and RIXUBIS FDP conformance batches with respect to their hemostatic potency, the efficiency of activation by –b(4)----- in the presence of –b(4)-----, and the capacity to ---b(4)-----

### **2.2.2.Impurities**

The levels of impurities in the product are found to be acceptable and not likely to affect its safety and efficacy. I agree with Baxter that consistent removal of impurities is assured because

1. Profiles of process- and product-related impurities were evaluated and found to be consistent with the well-characterized impurities in licensed coagulation factor products; no new impurities were identified.
2. Side-by-side comparison between RIXUBIS and licensed products demonstrated comparable or improved impurity profile in RIXUBIS.
3. Purification process has been developed specifically to clear the process- and product-related impurities.
4. Design space for the critical impurity-determining process parameters has been established.
5. Adequate capability of the process to remove and reduce the levels of impurities has been demonstrated through process validation studies.
6. Consistent purity of the b(4) batches has been demonstrated through the process validation exercises and scale-comparability exercises.
7. Impurities are controlled at ---b(4)----- and FDP; meaningful specifications were developed.
8. Batch analyses are available for over –b(4)--- batches. Consistent removal of impurities is demonstrated.

## **2.3.Control of Drug Substance**

### **2.3.1.Specifications and Analytical procedures**

In general, Baxter proposed an adequate panel of analytical methods to assess the –b(4)-----, and quality attributes of RIXUBIS BDS. The analytical methods and proposed acceptance limits were based on the data obtained from the developmental studies and manufacturing experience.

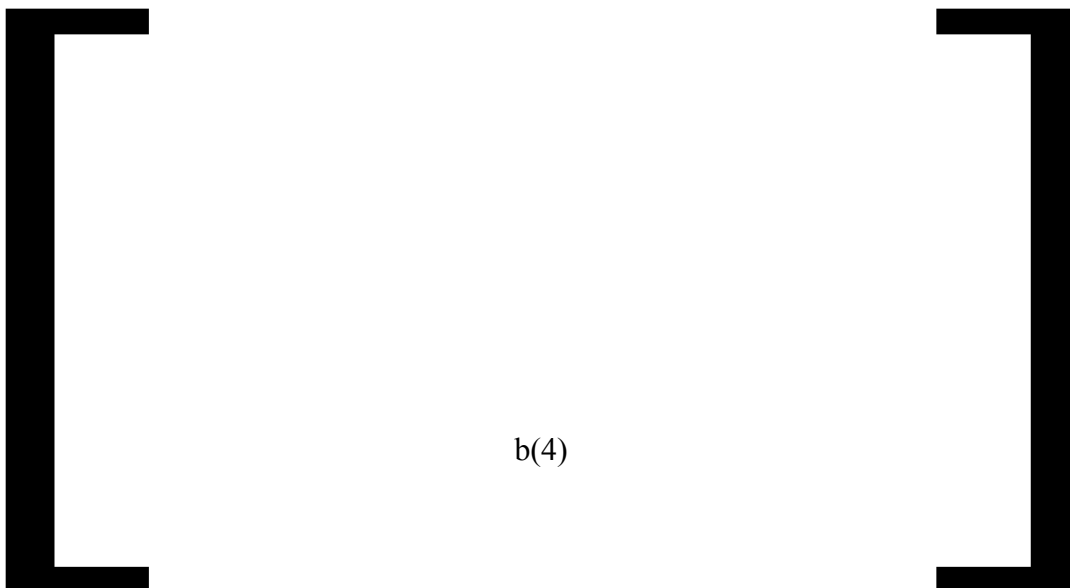
The suitability of the panel of analytical methods is also supported by the analysis of comparability to other products:



1. The methods and established specifications are generally comparable to those of licensed plasma-derived and recombinant FIX products. When possible, Baxter attempted to formalize the method outcomes by providing quantitative rather than qualitative measures. This is not typical but is highly recommended.
2. Dr. Nancy Kirschbaum (OBRR/DH/LH) conducted a direct comparison of BDS method panels for several licensed and investigational recombinant coagulation factor products. RIXUBIS's panel was one of the most extensive in the number of assays used. However, direct comparison of acceptance limits is difficult due to differences in assay conditions.
3. Baxter used several lot release assays for comparative evaluation of RIXUBIS and licensed plasma-derived and recombinant FIX products as part of the RIXUBIS characterization program. RIXUBIS quality assessed by the lot release assays was comparable to the quality of licensed products.

RIXUBIS BDS release methods and specifications are presented in the table below:

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Baxter's QC operations at --b(4)----- were a subject of the January 2013 Pre-Approval Inspection. My general impression was that the laboratory is well managed, the staff is well trained and the operations are well controlled. I was specifically interested in observing two methods, --b(4)----- which is a thrombogenic product-related impurity found in licensed FIX products. Both assays are used for control of in-process samples and as release for BDS and FDP. I had the opportunities to meet with many members of the laboratory units during the inspection and also during the review of the validation reports that were presented to me on each day of the inspection. Baxter's approach is to have responsible employees assigned to each assay at each stage of the assay life cycle, i.e., assay development, validation, transfer and routine use. This approach ensures that a highly trained and experienced employee is personally responsible for each of the methods, as was evidenced by multiple presentations given to me by different individuals, each of them is responsible for the following assays: --b(4)----- -----

### **2.3.2.Validation of analytical procedures**

The method validation studies submitted by Baxter demonstrate that analytical assays used for routine release of RIXUBIS BDS are suitable for their intended use, i.e., they are adequate to assess quality attributes of the product and to confirm consistency of the released lots.

Assay validation reports have been reviewed by CBER's Lot Release Branch at the Laboratory of Analytical Chemistry and Blood Related Products of the Division of Biological Standards and

Quality Control, by Dr. Lokesh Bhattacharyya and Dr. Hsiaoling Wang. Deficiency in compliance with the ICH guideline was found in some of the validation reports. Baxter resolved these deficiencies successfully without making changes to the method procedures and release specifications.

In addition to reviewing the method validation reports, I was able to review Baxter's validation records during the Pre-Approval Inspection.

Specifically, validation of the --b(4)----- and related standards has been a subject of my inspection investigation and discussions with Baxter employees. This method has not been originally included in the lot release specifications for the b(4) or FDP but it was used for process validation and, specifically, the demonstration of the removal of impurities. Moreover, the development of anti-Furin antibodies in several patients treated with rFIX product was an important observation during clinical trials. Therefore, control of the Furin impurity and proper validation and maintenance of assay were considered to be of special importance during the FDA mid-cycle meeting in January 2013.

I found that Baxter had acquired extensive knowledge on the Furin molecule and assays for its monitoring. For example, the standard that is used in the assay has been --b(4)----- at Baxter by --b(4)----- Furin. Only the --b(4)----- is found  
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### **2.3.3.Batch analysis**

Batch analyses were reviewed by Dr. Yideng Liang. She concluded that there were no adverse trends within and among different manufacturing campaigns. I support her conclusion that the available batch data demonstrate that the BDS manufacturing process is robust.

### **2.3.4.Justification of specification**

In general, the panel of analytical methods proposed by Baxter is adequate to assess the --b(4)-----, and quality attributes of RIXUBIS BDS. The analytical methods and proposed acceptance limits were based on the data obtained from the developmental studies and manufacturing experience.

## **2.4.Reference standards and materials**

In-house FIX reference material lot --b(4)----- has been established from b(4) of the released b(4) batches for the following FIX drug substance and drug product test methods:

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- --b(4)-----

- ---b(4)-----

The suitability of the reference material has been established through stability studies, potency assignment exercises and extensive structure/function studies.

The suitability of –b(4)----- for FDP potency assignment has been confirmed during conformance lot testing by CBER Lot Release Laboratory.

Similarly, Baxter’s internal SOPs ensure that all standards used in all analytical methods are

- Suitable for the intended purpose
- Well characterized
- Stable
- Consistent such that the assay remains unchanged when standard preparations are changed

Baxter maintains a –b(4)----- master calibration plan for all primary and secondary standards. Standards are calibrated using current validated bioassays, b(4) assays are performed each time and the confidence interval for these assays should be b(4) Loss of activity during storage may lead to potency reassignment in –b(4)-- intervals but this was not needed for FIX-related standards. Potency is retested every –b(4)-----.

## **2.5.Container closure system**

--b(4)-- ----- is used as the container closure system for the storage of BDS. The b(4) body is made of ---b(4)-- -----  
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was qualified for its intended use per Baxter’s procedures governing the qualification of materials used in manufacturing processes.

## **2.6.Stability**

### **2.6.1.Stability summary and conclusions**

Stability studies have been reviewed by Dr. Yideng Liang.

The stability of –b(4)- commercial scale batches of rFIX BDS supports the shelf life of –b(4)-----.  
The batches on –b(4)----- and accelerated storage conditions -----b(4)-----  
--- are scheduled to be monitored through –b(4)----- to provide data to justify the –b(4)----- of the shelf-life.

### **2.6.2.Post-approval Stability Commitment**

Baxter proposed a commitment to place one commercial BDS batch on stability per year. The annually selected batch will have been manufactured during that year.

## 1. Final drug product

### 1.1. Description and composition of the drug product

The FDP consists of a lyophilized powder for solution for injection. The proposed nominal dosage strengths are 250, 500, 1000, 2000 and 3000 IU/vial. Each dosage strength is reconstituted using Sterile Water for Injection and mixed prior to intravenous injection. Irrespective of the nominal potency, each vial of rFIX FDP is reconstituted with sWFI with a nominal volume of 5 mL and a minimum extractable volume of 5 mL. There are no formulation overages used for the FDP.

The composition of the finished drug product and relevant reference standards is provided in the table below.

Name of Constituent	Unit of Measure (Nominal Dosage Strength)	Function	Reference to Standards
Quantity rFIX /Vial	250, 500,1000, 2000 or 3000 IU/vial	Active Ingredient	
Concentration rFIX		Active Ingredient	
L-Histidine	20 mM		
NaCl	60 mM		
CaCl <sub>2</sub>	4 mM		
Mannitol	110 mM		
Sucrose	35 mM		
Polysorbate 80			
b(4)	0.005% wt		

The BAXJECT II Needle-less Transfer Device is designed for transferring and mixing drugs contained in two vials, and then withdrawing the reconstituted product into a syringe. Each BAXJECT II NTD has a two vial holder, a two-sided siliconized piercing plastic spike for penetration into the rubber stoppers of the two vials, a stopcock with an embedded filter, and a female port designed for connection to a syringe.

The BAXJECT II NTD is a Class II medical device and is classified under the regulation for Intravascular Administration Sets (21 CFR § 880.5440). The device complies with the applicable elements of the FDA Guidance, “Guidance on Premarket Notifications for Intravascular Administration Sets”, October 12, 2000. The BAXJECT II NTD is manufactured by Baxter Healthcare at a facility located in ---b(4)----- (FDA Establishment Registration Number –b(4)-----).

### 1.2. Pharmaceutical development

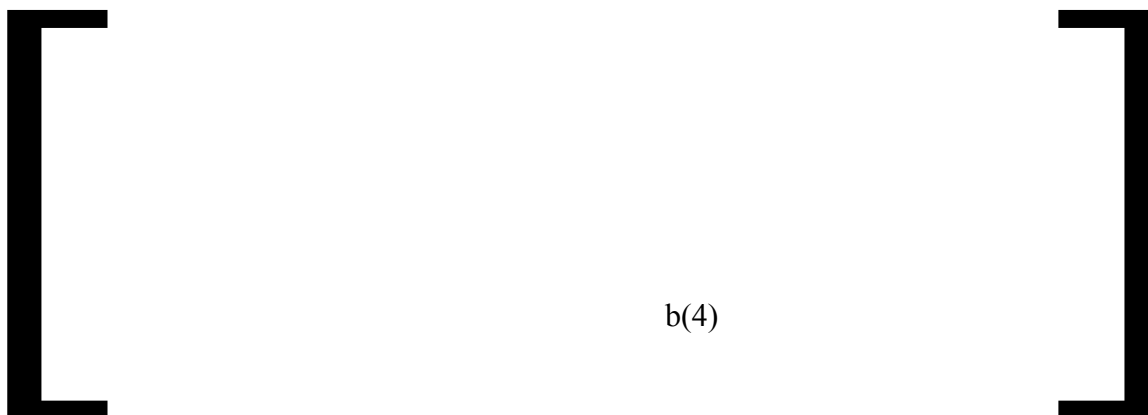
The formulation development for rFIX was focused on optimization of potency and stability indicative parameters under normal and stress conditions. I found no deficiencies during review of the optimization and validation studies. Similarly to BDS process development, a Design of

Experiments approach has been used extensively for the optimization of FDP lyophilization process.

The rFIX FDP process development took a systematic, stepwise approach. The –b(4)- steps, as outlined in the figure below were:

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**Figure. Overview of Drug Product Process Development**



To verify the safety profile of the container closure system, the vials and stoppers were examined per relevant International Pharmacopoeial test procedures and additional delamination and extractables studies.

The functionality of the container closure system for use with RIXUBIS FDP was also addressed.

Finally, the compatibility of RIXUBIS with BAXJECT II device was demonstrated at the lowest and highest potencies (250 IU and 3000 IU).

### 3.3.Manufacture

#### 3.3.1.Manufacturers

The thawing, formulation, filling, lyophilization, labeling and packaging operations are performed at Baxter Healthcare Corporation, --b(4)-----

#### Testing Laboratories

<b>In-Process Control of Bulk Drug Product</b>	<b>Testing Site</b>
--b(4)----- --- --b(4)----- ---	--b(4)--- ----- -----
<b>Final Container Testing of the Final Drug Product</b>	<b>Testing Site</b>
All lot release tests	--b(4)--- ----- -----

#### Sterile Water for Injection (sWFI)

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#### 3.3.2.Batch formula

The batch formulae for the products are based on the manufacture of typical batch sizes of --b(4)---  
The exact batch size is dependent upon the potency of the rFIX BDS and the quantity of the BDS removed from the containers received from the drug substance manufacturer. The entire content of a --b(4)-- of BDS is --b(4)------. The buffer composition is identical for each dosage strength of RIXUBIS.

#### 3.3.3.Description of manufacturing process and process controls

The RIXUBIS BDS produced at the --b(4)- facility is shipped to the --b(4)----- facility  
--b(4)-- -----  
----- are performed (see the figure below). The process is comparable to other licensed

recombinant coagulation factor products manufactured by Baxter. The FDP manufacturing at the --b(4)----- facility has good compliance history.

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b(4)

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#### **3.3.4.Controls of critical steps and intermediates**

I agree with Baxter that appropriate and typical in-process controls have been identified and are monitored to control the manufacture of RIXUBIS FDP.



### 2.1.7. Process validation and evaluation

The consistency and robustness of full-scale manufacturing was demonstrated through process verification exercises carried out during the conformance lots manufacture. This was accomplished using a bracketing approach as shown in the table below.

Description	Nominal Potency (IU/Vial)	Number of Lots	Targeted Batch Volume (L)
Lowest Potency	250	b(4)	b(4)
		b(4)	b(4)
Highest Potency	3000	b(4)	b(4)
		b(4)	b(4)
Intermediate Potencies	500	b(4)	b(4)
	1000	b(4)	b(4)
	2000	b(4)	b(4)

The life-cycle of the process is managed through Baxter's corporate Process Monitoring program and Process Controls strategy.

Process validation studies included the following important elements:

- Process Parameters
- Product Parameters
- Manufacturing Process Homogeneity
- Manufacturing Process Maximum and Minimum Load Validation
- Manufacturing Process Hold Times Validation

## 2.2. Control of excipient

The excipients used in the pharmaceutical production of RIXUBIS FDP are listed in the table below. In all cases the quality of the raw materials is controlled with appropriate compendial methods.

**Table. Excipients**

Excipient Description	Excipient Citation
L-Histidine	b(4)
Calcium Chloride	b(4)
Sodium Chloride	b(4)
Mannitol	b(4)
b(4) (Polysorbate 80)	b(4)
Sucrose	b(4)
Water for Injections b(4)	b(4)

### 3.5.1. Specifications

## Specification for Recombinant Factor IX (rFIX) Drug Product

Potency (IU/vial)		250	500	1000	2000	3000
Parameters	Test Methods	Acceptance Criteria				
b(4)	Visual	b(4)				
Appearance (reconstituted solution)		Clear solution, substantially free from foreign particles				
Reconstitution time	Time					
b(4)	b(4)	b(4)				
Endotoxins						
Sterility	b(4)	Sterile				
Total protein		b(4)				
rFIX Activity <sup>4</sup>	Clotting	b(4)				
Specific rFIX Activity	Calculation <sup>1</sup>	≥ 200 IU/mg				
b(4)	b(4)	b(4)				
rFIX preactivation	Calculation <sup>1</sup>	≤ 0.03 %				
b(4)	b(4)	b(4)				
b(4)	b(4)	b(4)				
b(4)						
b(4)						
Polysorbate-80	b(4)	b(4)				
b(4)						
b(4)						
Sucrose						
Mannitol						
b(4)						

After discussions with CBER, Baxter agreed to –b(4)- the specifications for rFIX pre-activation (from –b(4)-- to < 0.03%) and rFIX potency (from –b(4)----- IU per vial to –b(4)----- based on the available manufacturing data.

The diluent for the lyophilized rFIX FDP, Sterile Water for Injection (SWFI), is manufactured by --b(4)----- (5 mL size). The test parameters, test methods and release specifications for the SWFI produced at –b(4)----- are provided in the table below.

**Specifications for 5 mL Sterile Water for Injection (Diluent) produced at –b(4)-----**  
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[ b(4) ]

### **3.5.1. Analytical procedures and method validation**

The method validation studies submitted by Baxter demonstrate that analytical assays used for the routine release of RIXUBIS FDP are suitable for their intended use, i.e., they are adequate to assess quality attributes of product and to confirm consistency of the released lots.

Some BDS methods are also used for release of FDP, although the specifications and validation exercises are different and independent of each other.

Assay validation reports have been reviewed by the CBER's Lot Release Branch. In addition, CBER's Lot Release Branch conducted testing of three conformance batches using a subset of FDP release assays. In all cases, the tested batches met Baxter's release specifications.

### **3.5.2. Batch analysis**

A summary of batch analysis data of b(4) lots of rFIX drug product (b(4) lots of 250 IU, b(4) lots of 500 IU, b(4) lots of 1000 IU, b(4) lots of 2000 IU, and b(4) lots of 3000 IU,) manufactured at Baxter facility

located in –b(4)----- were reviewed by Dr. Yideng Liang. I support her conclusion that the available batch data demonstrate that BDS manufacturing process is robust.

### **3.6.Reference standards and materials**

The FDP standard, --b(4)----- is described above in Section 2. Bulk Drug Substance , 2.4. Reference Materials. The suitability of –b(4)----- standard for FDP potency assignment has been established through Baxter’s qualification studies and confirmed during conformance lot testing by CBER Lot Release laboratory.

### **3.7.Container closure system**

The rFIX drug product is filled in a ---b(4)----- glass vial with a nominal capacity of 10 mL. The vial is closed with a –b(4)-- rubber stopper with an inert coating, and sealed with an -b(4)----- overseal and tamper proof snap-off plastic cap. The vials conform to –b(4)----- requirements for hydrolytic resistance.

### **3.8.Stability**

The proposed shelf life of rFIX drug product is 18 months when stored at  $5 \pm 3^{\circ}\text{C}$ , with a 6 month storage time at room temperature ( $\leq 30^{\circ}\text{C}$ ) within this 18 month storage period. Once removed from  $5^{\circ}\text{C}$  storage, the recombinant Factor IX product cannot be returned to refrigerated storage.

The reconstituted product is stable for –b(4)---- at  $25^{\circ}\text{C} \pm 2^{\circ}\text{C}$  (room temperature). Baxter recommends using the reconstituted product within 3 hours to avoid the risk of microbial contamination. In addition, -----b(4)-----

----- The activities of rFIX and rFIXa are within the acceptance criteria (80-120% of the control samples). All other parameters including Appearance, Reconstitution Time, b(4), rFIX pre-activation, Total Protein, Specific Activity, --b(4)---, and –b(4)----- remained within acceptance criteria throughout the photo stability stress testing. Therefore, the rFIX drug product is found to be stable under these study conditions.

Stability data have been reviewed by Dr. Yideng Liang. She found that stability data are supportive of the proposed shelf life and storage conditions.

## 4.Validation of Bioanalytical and Immunogenicity Testing Procedures

Baxter validated bioanalytical and immunogenicity testing procedures used during the preclinical (method summary is presented in Table 4-1 below) and clinical (Table 4-2) development programs. Each validation exercise utilized either animal or human plasma spiked with RIXUBIS and, in most validations, a comparator rFIX product. Acceptable recovery of spiked activity, assay accuracy, repeatability, intermediate precision, robustness and range of linearity were established for each assay. It was demonstrated that the respective assay results are not influenced by –b(4)---freezing and thawing of plasma (depending on the assay, no more thanb(4)cycles).

**Table 4-1. Preclinical program assays**

Assay Type	Parameter Measured	Method Validation Report
FIX 1-stage clotting assay in rat, cynomolgus monkey and human FIX-deficient plasma	FIX activity	RD_VB_020902
FIX chromogenic assay	FIX activity	RD_VB_050903
FIX antigen ELISA in cynomolgus monkey plasma	FIX antigen	RD_PPD_010904_R1
FIX antigen ELISA in rat plasma	FIX antigen	RD_PPD_060805
FIX antigen ELISA in FIX-deficient mouse plasma	FIX antigen	RD_PPD_060804

**Table 4-2. Assays used in clinical trials**

Assay Type	Parameter Measured	Method Validation Report	Validated by
FIX 1-stage clotting assay	FIX activity	VAL2010-029.001	--b(4)----- -----
FIX antigen ELISA	FIX antigen	VAL-2010-016.001	--b(4)----- -----
FIX inhibitory antibodies (--b(4)-----)	Inhibitory antibodies against FIX activity	Validation 300680.003	--b(4)----- -----
Binding antibodies to FIX	Total Ig binding antibodies to FIX	QR 2010_01	--b(4)----- -----
Binding antibodies to Furin	Total Ig binding antibodies to Furin	QR 071001_02	--b(4)----- -----
Binding antibodies to CHO protein	Total Ig binding antibodies to CHO protein	QR 071001_01	--b(4)----- -----

Preclinical methods were validated at Baxter's Preclinical R&D according to Baxter's internal standard operating procedures for method validation. I agree with Baxter that these methods are suitable for their intended use.

During the pre-approval inspection I was able to discuss with Baxter the validations of analytical methods used in clinical studies. Clinical sample testing and respective method validation exercises have been contracted out to well-established contractors –b(4)----- (FIX's activity, ELISA and inhibitory antibodies) and ---b(4)----- (binding antibodies to FIX, CHO protein and Furin). FIX activity and FIX inhibitory antibody methods were conducted according to commonly used clinical laboratory practices. Specifically, FIX activity in patient plasma samples was measured using the one-stage activated partial thromboplastin time test (APTT) against the plasma standard of FIX (traceable to the respective international standard). The FIX inhibitory antibodies were tested using a standard --b(4)----- . These methods are representative of the clinical use of FIX-containing products

In addition, Baxter conducted a multi-laboratory study to establish the comparability of the FIX clotting activity methods which are used for potency assignment (i.e., product labeling by Baxter's QC laboratories) and the clinical sample testing (conducted by the contractor laboratory). Both methods were comparable in the evaluation of FIX activity of RIXUBIS and a licensed comparator rFIX product.

In summary, my review did not identify issues with the pre-clinical and clinical method validations reports.

## **5.Adventitious agents safety evaluation**

Adventitious agents safety evaluation has been reviewed by Dr. Ze Peng. He found that the data provided by Baxter are acceptable.

The potential of contamination by infectious viruses is well controlled. For non-viral adventitious agents such as bacteria, fungi, and mycoplasma, the potential contamination of these agents is well controlled through the use of validated cleaning/sanitization procedures, and –b(4)----- . Additionally, the potential of viral contamination of RIXUBIS™ is mitigated by two dedicated viral clearance steps: Solvent/Detergent (S/D) treatment –b(4)----- and 15 nm nanofiltration.

## **6.Deficiencies resolved during review cycle**

The following deficiencies were resolved successfully in the course of the review cycle.

### *1. DH/OBRR:*

- a. The company agreed to introduce lot release assays to demonstrate consistent removal of process-related impurities (S/D mixture components and Furin). This was warranted by the review of clinical data (antibodies to Furin, see Clinical Review conducted by Dr. Stephannie Omokaro, M.D.) and harmonization with the specifications for similar products reviewed by our laboratory (S/D components).
  - b. Specifications for FIX pre-activation and FIX potency were tightened based on the available manufacturing history. Initial specifications were too wide and not sufficiently supported with data.
  - c. In addition, specification for FIX pre-activation was justified with extensive analysis of the safety and analytical data for RIXUBIS and relevant comparator FIX-containing products.
  - d. In November/December of 2012, the company identified problems with the performance of the FIX potency assay dating back to 2008. The potency assay has been revalidated in January of 2013. Adequate assay performance has been demonstrated through a series of intra- and inter-laboratory studies. Re-evaluation of prior test results (including retests of all available batches used in pre-clinical and clinical investigations) demonstrated that the prior deficiencies in potency assay had no impact on the outcomes of clinical investigations, stability studies and manufacturing validation studies.
2. *DMPQ/OCBQ (Facilities):*
- a. The company improved the segregation of manufacturing process steps before and after viral inactivation.
3. *DBSQ/OCBQ (Lot Release Laboratory):*
- a. Deficiencies with certain lot release assay validations were successfully corrected through additional studies and one Post Marketing Commitment (see below). In all cases, the validation deficiencies were found to be minor because no change in method procedures or relevant specifications was needed to address the reviewer's concerns.
  - b. The initial assessment of potency of three conformance lots measured by the FDA Lot Release Laboratory revealed 30% higher values than those on the RIXUBIS label. Subsequent investigation conducted by Baxter's and FDA Lot Release laboratories revealed an up to 40% difference in potency when different aPTT reagents and reference standards were used in the assay. Use of reagents validated by Baxter or substitution of plasma-derived potency standard for RIXUBIS-derived potency standard resolves discrepancies in potency assignment. This observation is described in the package insert to inform users of possible discrepancy due to variation in assay conditions. In addition, Baxter established adequate comparability of the FDP potency release assay to the FIX activity assay used in clinical trials for assessment of pharmacokinetic parameters.

## 7. Post-approval commitments

Two post-marketing commitments were made by Baxter:

1. Baxter commits to provide validation data to support the *Precision (Repeatability and Intermediate Precision)*, *Linearity* and *Range* for the test method, *Method No.* ---b(4)-----, used to determine the ---b(4)----- in RIXUBIS. Baxter will apply an approach similar to that used for ---b(4)-----determination in validation report ---b(4)-----, and will submit the final report to the FDA by 30 November 2013.
2. Baxter commits to place at least one RIXUBIS lot on the stability program annually, rotating among different dose strengths.

## 8. Conclusions and recommendation

The quality and purity of RIXUBIS are generally acceptable and comparable to the licensed recombinant FIX product. The manufacturing process is sufficiently established and reasonably controlled. No major CMC issues were identified that can prevent approval. I recommend approval.