

MEMORANDUM



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



To: Administrative File (STN 125574/0)
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Subject: Final Review of the CMC Information in the Original Biologics License
Application from Bayer HealthCare LLC for Antihemophilic Factor
(Recombinant) [KOVALTRY]

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INTRODUCTION

Bayer HealthCare LLC (Bayer) submitted an original Biologics License Application (BLA) to seek U.S. licensure for Antihemophilic Factor (Recombinant). The proprietary name of the product to be marketed in the U.S. is KOVALTRY.

KOVALTRY is indicated for use in adults and children with hemophilia A for:

- On-demand treatment and control of bleeding episodes;
- Perioperative management of bleeding;
- Routine prophylaxis to reduce the frequency of bleeding episodes.

KOVALTRY is not indicated for the treatment of von Willebrand disease.

BACKGROUND

Hemophilia A is a rare hereditary hematologic disorder caused by deficiency or dysfunction of Coagulation Factor VIII (FVIII, historically referred to as Antihemophilic Factor), resulting in bleeding secondary to abnormal clot formation. Hemophilia A has an X-linked, recessive inheritance pattern affecting 1 in 5,000 male births with rare occurrence in females. The clinical manifestation of hemophilia A includes hemorrhages into joints and muscles, and also bleeds into the digestive system and brain. Patients with hemophilia A are treated to replace the deficient FVIII by intravenous administration of plasma-derived or recombinant FVIII products. Several full-length (RECOMBINATE, Kogenate FS, ADVATE, ADYNOVATE) and B-domain-deleted (XYNTHA, Novoeight, ELOCTATE, and NUWIQ) recombinant FVIII products are currently licensed in the U.S. Bayer's licensed product, Kogenate FS, was one of the first recombinant FVIII products approved by the FDA in 1993 under STN 103332.

The rationale for KOVALTRY development was to improve the manufacturing process licensed for Kogenate FS. Similar to Kogenate FS, KOVALTRY is an unmodified full-length recombinant FVIII (rFVIII) glycoprotein comprising the human derived amino acid sequence and is formulated with sucrose. It is produced in genetically engineered Baby Hamster Kidney (BHK) cells, with the following key improvements to the manufacturing process:

- The establishment of a new, higher producing cell bank based on a BHK cell line co-expressing rFVIII and human heat-shock protein 70 (HSP70)
- Optimization of downstream purification process
- Introduction of a (b) (4) 20N nanofiltration step for virus removal, in addition to detergent treatment for virus inactivation
- Removal of human and animal derived raw materials from the cell culture (b) (4) (b) (4) .

To support licensure for the proposed indications, the clinical development program for KOVALTRY included data from:

- A two-part, randomized, cross-over of potency assignment, open-label trial to evaluate the pharmacokinetics, efficacy, and safety profile of plasma protein- free recombinant FVIII formulated with sucrose in previously treated subjects (PTPs) with severe hemophilia A under prophylaxis therapy and during surgery,
- A randomized, cross-over of potency assignment, open label trial to demonstrate superiority of prophylaxis over on-demand therapy in PTPs,
- An uncontrolled open-label trial to evaluate safety and efficacy of KOVALTRY in children with severe hemophilia A under prophylaxis therapy,
- An optional 1-year extension for the collection of additional safety and efficacy data, including surgery.

The safety and efficacy of KOVALTRY was evaluated in prospective, open-label, multicenter clinical trials of 193 subjects with hemophilia A conducted under Investigational New Drug (IND) application, IND 14035.

KOVALTRY has recently received approval for commercial distribution from the European Medicines Agency (February 22, 2016); in addition to FDA, this product is also currently under review for marketing authorization by the Japan's Pharmaceuticals and Medical Devices Agency.

Regulatory History

The BLA was received by FDA on December 16, 2014 and was reviewed under the standard (12-month) review schedule of the PDUFA V program and included the milestones listed in Table 1. This product does not have orphan designation.

During review of the clinical data and in light of Bioresearch Monitoring inspectional findings, FDA requested that Bayer submit monitoring reports from the selected clinical sites for the Leopold I and II studies, which were critical for assessment of safety and efficacy of KOVALTRY in hemophilia A patients. On September 25, 2015, Bayer submitted this information in amendment 33, which was classified as a *Major Amendment*, and the action due date was extended to March 16, 2016 (Table 1).

The scope of this review included evaluation of process validation studies for the commercial scale production of drug substance (DS) and drug product (DP); control of source materials (cell bank system) and other raw materials; characterization of rFVIII; justification of Specifications

for DS and DP; batch analyses; stability studies; and evaluation of safety of KOVALTRY with regard to adventitious agents. In addition, this reviewer participated in the Team Biologics Inspection of the Bayer's (b) (4)

The development of the manufacturing processes for DS and DP and establishment of process parameters and in-process control tests to provide adequate control over the manufacturing process were evaluated by Dr. Nancy Kirschbaum (LH/DHRR/OBRR) and the conclusions are summarized in her review memorandum.

Analytical methods used to control the quality of intermediates, DS, and DP and their validation were reviewed by Dr. Alexey Khrenov (OBRR/DHRR/LH) and Drs. Lokesh Bhattacharyya, Alfred Del Grosso and Claire H. Wernly (OCBQ/DBSQC/LACBRP). The suitability of the methods for their intended use as release tests for DP is summarized in their review memoranda.

Table 1: Review Milestones

Milestone	Date
Received	December 16, 2014
Filed	February 9, 2015
Mid-Cycle Communication	June 11, 2015
Blood Products Advisory Committee	Waived
PeRC Meeting	October 7, 2015
Late-Cycle Meeting	October 8, 2015
Major Amendment	October 16, 2015
Action Due Date	March 16, 2016

EXECUTIVE SUMMARY

1. The manufacturing processes for KOVALTRY DS and DP are validated in accordance with ICH Guidelines Q7A, Q8 and Q11. The validation studies were performed at Bayer's (b) (4) facility, the intended commercial site, under prospective process validation protocols. (b) (4) conformance DP lots covering all nominal potencies were manufactured from DS conformance batches originating from (b) (4) stages of (b) (4) cell culture campaigns. All process and quality controls complied with pre-defined acceptance criteria stated in validation protocols, and the results of release testing were within specifications; thereby, fulfilling the requirements for process validation. Process validation data were supplemented with data for phase 3 clinical lots manufactured using the same process in the same facility thus being representative of the commercial process.

As requested by the FDA, Bayer added quality control tests for increased control of the (b) (4) process (b) (4), and revised stability program for this (b) (4). Bayer also submitted Interim reports from concurrent full scale validation studies which adequately established the lifetimes of (b) (4) based on the number of commercial runs performed, which will be followed in commercial production.

The manufacturing process for DS allows a (b) (4) step in the event of the (b) (4) test failure. Per the FDA request, Bayer provided results from (b) (4) studies and (b) (4) commercial run performed under worst-case conditions where the reprocessed material was evaluated by major quality attributes and full release testing, extended characterization and stability performance of DS and DP. No adverse impact on product quality due to (b) (4) was shown that justified the (b) (4)

Bayer has a program for continued process verification, consistent with the life cycle approach recommended in *FDA Guidance for Industry: Process Validation: General Principles and Practices*.

2. The data in the BLA demonstrate that the cell bank system is adequately controlled, and the safety and productivity of the cell culture is ensured for up to (b) (4) used in commercial production. Characterization of the cell bank system was performed in accordance with ICH Guideline Q5D and included analyses for (b) (4). Evaluation of the cell bank system for safety with regard to adventitious viruses was performed in accordance with ICH Guideline Q5A(R1). Genetic characterization in accordance with ICH Guideline Q5B confirmed the correct nucleotide sequence of the rFVIII construct, the same rFVIII integration patterns and integrity of the rFVIII coding region in genomic DNA isolated from master cell bank, working cell bank and end-of-production cells, and comparable gene copy numbers. The same methodologies were used to demonstrate sequence fidelity, consistent integration status and genetic stability of the HSP70 construct in (b) (4) cell banks. Per the FDA request, the stability program for cell banks was expanded to include (b) (4) and is acceptable.
3. The characterization program for KOVALTRY used an extensive panel of (b) (4) analytical methods to evaluate the structure and function of the rFVIII protein. The amino acid sequence, post-translational modifications (N-linked and O-linked glycosylation and tyrosine sulfation patterns), and the subunit structure of rFVIII were found to be consistent with the expected structure of FVIII and comparable to Kogenate FS. The rFVIII in KOVALTRY has (b) (4) important for the normal lifecycle of FVIII. The functional characterization demonstrated expected (b) (4) (b) (4) of rFVIII, its (b) (4), and biological activity in the chromogenic substrate and one-stage clotting assays. Per the FDA request, Bayer adequately justified the use of (b) (4) assay for assessing two post-translational modifications – glycosylation profile and sialylation capping.
4. The specifications for DS and DP are established in accordance with ICH Guideline Q6B. The parameters are selected from critical quality attributes determined in the process development studies and risk assessments. Acceptance ranges/limits are established

based on statistical analyses of the manufacturing data, regulatory requirements, experience with the licensed predecessor product, Kogenate FS, and clinical outcome. In the course of review, a number of parameters were added or their acceptance criteria were revised. Bayer adequately justified the choice of potency assay for product labeling. While Kogenate FS has been labeled with a one-stage clotting assay, potency of KOVALTRY will be assigned using a chromogenic substrate assay. This was supported by acceptable agreement between the results from both assays during release testing of drug product, comparable performance of both assays in measuring the recovery of KOVALTRY in plasma samples in a field study, and comparable clinical outcome in cross-over clinical studies. The current specifications for (b) (4) DP are adequate to control the identity, purity, potency, and safety of KOVALTRY.

5. The results of Batch Analyses encompass (b) (4) DS and (b) (4) DP commercial-scale batches (conformance and clinical) and support consistent performance of the manufacturing process to produce a product that meets pre-determined quality specifications. As a well-characterized recombinant product, KOVALTRY is exempted from routine lot-by-lot release by CBER. In-support testing by CBER confirmed the results of batch analyses for conformance DP lots reported in the BLA and the suitability of critical quality-defining methods for their intended use as lot release tests. In amendment 36 dated October 20, 2016, Bayer committed to validating a (b) (4) assay.
6. The stability data and projections for conformance lots support the proposed shelf-life of 30 months for KOVALTRY final container when stored at 2 – 8°C (36 – 48°F). Within this period, KOVALTRY may be stored for a single period of up to 12 months at temperatures up to +25°C or 77°F. The proposed shelf-life is further supported by satisfactory stability data for clinical lots throughout and above the claimed period. The real-time stability data for DS support its shelf-life of (b) (4). The in-use stability data support the labeling claim that the reconstituted product is stable for up to (b) (4) at ambient temperature.
7. The safety of the product with regard to adventitious viruses is ensured by the inclusion of (b) (4) viral clearance steps in the purification process: treatment with (b) (4) for virus inactivation and 20 nm nanofiltration for virus removal. Bayer has evaluated these steps in relevant down-scale systems using (b) (4) and demonstrated acceptable log reduction factors achieved with these two steps: (b) (4). Bayer also demonstrated additional contribution of other manufacturing steps to virus removal.

RECOMMENDATION

The Applicant has provided sufficient data and comprehensive information on Chemistry, Manufacturing and Controls in the BLA, and has adequately addressed the requests from all CMC reviewers in amendments 8, 19, 22, 24, 31, 34, 36, 38, 48, and 50. The Applicant also

fulfilled all agreements from the pre-BLA stage. Issues resolved during the review process are discussed in respective sections of this memorandum.

The manufacturing process for KOVALTRY*, Antihemophilic Factor (Recombinant), is considered to be adequately validated at the commercial scale and is sufficiently controlled to assure consistent manufacture of the commercial product that meets the acceptable release specifications. The manufacturing process provides acceptable safety margins regarding adventitious agents.

I and other CMC reviewers from the Division of Hematology Research and Review, OBRR, recommend **APPROVAL** of the BLA for Antihemophilic Factor (Recombinant) [KOVALTRY] with the following Post Marketing Commitment:

- Bayer commits to validating a (b) (4) assay and submitting the result in a Changes Being Effected in 30 Days (CBE-30) Supplement.

Final Report Submission: June 30, 2016

The Clinical reviewer concluded that the submitted clinical data demonstrate the safety and efficacy of KOVALTRY for the proposed indications. The performed sensitivity analysis of the clinical data based on CBER review of monitoring reports did not reveal an impact on the overall results and confirmed product's safety and efficacy.

**In the review, the proprietary name KOVALTRY is used interchangeably with the company's development code for this product, BAY 81-8973, where the references to Bayer's documents are given.*

MANUFACTURING FACILITIES

Table 2: Manufacturing and Testing Facilities for KOVALTRY

Facility	Manufacturing Operations
Bayer Healthcare LLC (b) (4)	Drug Substance Manufacturing In-Process Control and Quality Control Release Testing for Drug Substance Stability Storage and Testing for Drug Substance Drug Product Manufacturing Drug Product Release Testing Drug Product Labeling Finished Goods Packaging Authorization of Finished Goods for Distribution Stability Storage and Testing for Drug Product
(b) (4)	Manufacture of 3 mL and 5 mL pre-filled diluent syringe with Sterile Water For Injection and Release Testing

MANUFACTURING PROCESS DESCRIPTION

KOVALTRY is manufactured at Bayer HealthCare LLC facility in (b) (4). The manufacturing process for KOVALTRY was developed based on the process for Kogenate FS. Drug substance (DS) manufacture proceeds through (b) (4)

(b) (4)

(b) (4)

Manufacture of Drug Product

The drug product (DP) manufacturing process remains unchanged compared to Kogenate FS and consists of (b) (4) of DS batches, dilution to appropriate target potency, sterile filtration through (b) (4) sterile filters, filling into vials, lyophilization, and packaging. One minor adjustment is that Polysorbate 80 (b) (4)

(b) (4), as for Kogenate FS that simplified the DP manufacturing process. In amendment 34, Bayer clarified that in-process control testing for *Potency* is performed on (b) (4)

(b) (4) to achieve target FVIII potency, and the remaining volume of the formulation (b) (4)

(b) (4). The detailed assessment of the lyophilization, filling and packaging steps is provided in the memorandum of the DMPQ reviewer (Lori Peters).

SOURCE MATERIAL QUALITY AND CONTROL


Cell Bank System

Source, history and generation of the cell substrate and cell banking system, characterization, and testing are described in Module 3.2.S.2.3, Control of Materials in the BLA.

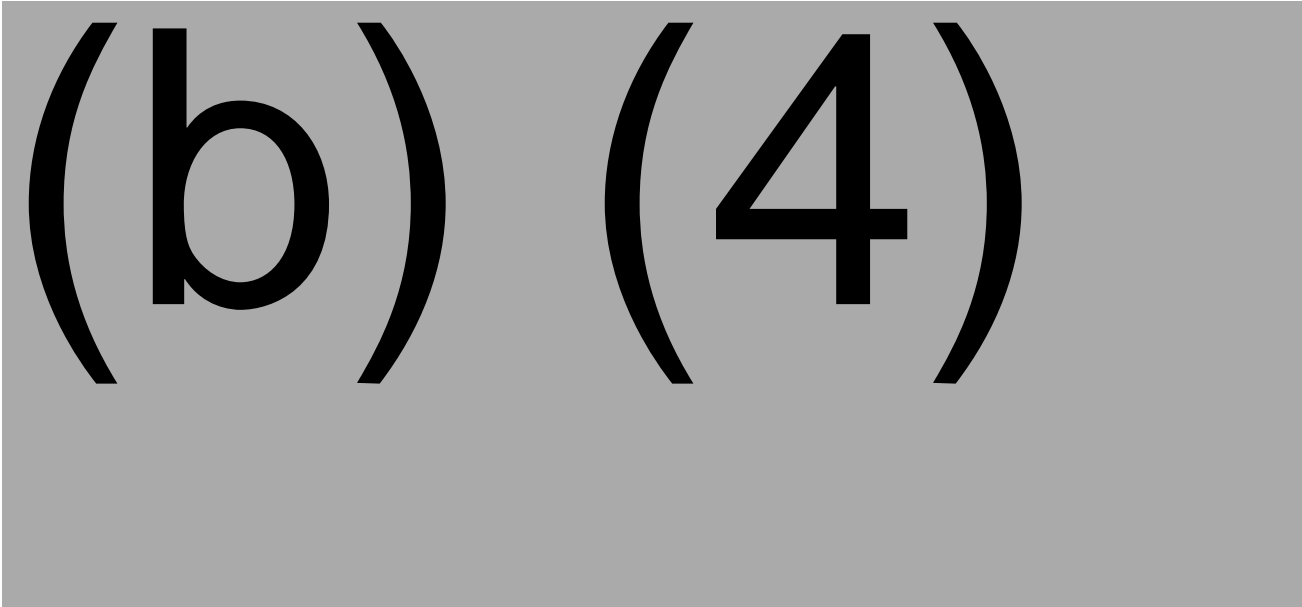
(b) (4)

(b) (4)



(b) (4)

- (b) (4)
- 

(b) (4)



(b) (4)



Other Raw Materials

All raw materials used in the production of KOVALTRY are sourced from approved suppliers, compliant with (b) (4) and released against approved specifications. No animal- or human-derived raw materials are used in the manufacturing process for KOVALTRY. All raw materials used in the manufacture of rFVIII DS were evaluated in risk assessments in accordance with ICH Guideline Q9 “*Quality Risk*”

Management”. For those raw materials that were identified as raw material critical quality attributes based on toxicity assessments, robust clearance by the purification process below the limit of quantification and significantly below the Daily Permitted Exposure limits was adequately demonstrated. Sucrose and polysorbate 80 are DP specification parameters which are tested for lot release. The information on ingredients used in the manufacture of KOVALTRY was captured in the CBER BITS-ABC system.

IN-PROCESS CONTROLS

The process (critical process parameters) and quality (in-process control tests) controls in the manufacture of DS are described in Modules 3.2.S.2.4, Control of Critical Steps and Intermediates, and 3.2.S.2.6, Manufacturing Process Development. These aspects were reviewed by Dr. Nancy Kirschbaum and detailed in her memorandum.

In summary, Bayer integrated risk assessment, experimental evaluation and manufacturing experience as the basis for establishing manufacturing process controls. Critical quality attributes were established based on extensive experience and prior knowledge of the Kogenate FS commercial product, KOVALTRY product and process understanding, and regulatory guidelines. The operational ranges for the DS manufacture were initially determined in (b) (4) factor studies for each unit operation, and were verified during clinical manufacturing campaigns (total (b) (4) DS batches) based on results of in-process control and release testing. Per FDA request, Bayer provided extensive comparative data and source documents that adequately justified (b) (4) developmental studies to be representative of the intended commercial process in establishing process controls. Bayer also provided definitions for their criticality assessments that were found consistent with definitions in the ICH Guideline Q8. Bayer’s development strategy was designed with the upfront intent that no significant manufacturing or scale-up changes were made between clinical and commercial manufacturing in order for clinical material to be representative of the commercial manufacturing process.

Definitions provided by Bayer in amendment 22:

Process Parameter (Operational Parameter or Process Inputs) is defined as a parameter that can be directly manipulated. Process Parameters are segregated into three categories:

1. Critical Process Parameter (CPP): a process parameter which variability has an impact on a critical quality attribute and therefore is controlled by Operating Range to ensure the process produces the desired product quality.
2. Key Process Parameter: a non-critical process parameter that, when varied within the Characterization Range, has a significant impact on process consistency or on a performance attribute. Characterization Range is expected to be greater than Operating Range.
3. Non-Critical Process Parameter: a process parameter that, when varied within the Characterization Range, will not have a significant impact on either process consistency or product quality.

Process Performance Attribute (PPA, also Process Performance Parameter or Process Outputs) is defined as an in-process measurement that is used to evaluate the performance of the process.

PPAs are segregated into three categories:

1. Critical Performance Attribute (CPA): a direct measure of the functionality or objective of a step especially as it relates to product quality. Critical Quality Attribute (CQA): a physical, chemical, biological or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality.
2. Key Performance Attribute: an attribute that is used to assess process consistency for a particular process step or stage.
3. Non-Key Performance Attribute: an attribute that is not a direct measure of process consistency or performance of a particular step or is considered redundant with other measures of process consistency/performance.

Per FDA request, Bayer added (b) (4) tests to the specification for the (b) (4), which originally had included only (b) (4). The intended stability claim for the (b) (4) was clarified and the stability program was revised according to FDA recommendations to add accelerated conditions, and to perform (b) (4) testing at the final stability time point (amendment 22).

(b) (4) studies did not support the claimed lifetimes of (b) (4) and (b) (4). As requested by the FDA, Bayer submitted Interim reports from concurrent full scale validation studies which established the lifetimes (b) (4) based on the number of commercial runs performed, which will be followed in commercial production (discussed under Validation).

The suitability of the current licensed process for Kogenate FS for commercial manufacture of KOVALTRY DP was evaluated in (b) (4) scaled-down process evaluation studies and during clinical development and was supported by release and stability results meeting specifications in place. In conclusion, established process parameters and in-process control tests provide adequate control of the manufacturing process.

VALIDATION OF MANUFACTURING PROCESS FOR DRUG SUBSTANCE

(b) (4)

(b) (4)

VALIDATION OF MANUFACTURING PROCESS FOR DRUG PRODUCT

Validation of the DP manufacturing process for KOVALTRY is described in Module 3.2.P.3.5. A (b) (4) approach was used, which included manufacturing DP (b) (4) conformance batches derived from (b) (4) DP lots, (b) (4) DP lots, and (b) (4) DP lots stages of the (b) (4) to confirm acceptable process performance throughout (b) (4). DP conformance lots covered all dosage strengths – 250 international units (IU), 500 IU, 1000 IU, 2000 IU, and 3000 IU (Table 9). Process and quality controls for DP conformance lots complied with the prospectively defined acceptance criteria and the results of release testing were within specifications thus fulfilling the requirements for a successful process validation.

DP conformance lots were manufactured using the same process in the same facility and the same primary container closure system that were used in the manufacture of the phase 3 clinical DP lots. All process parameters in the manufacture of clinical and conformance DS batches, from which DP lots originated, remained unchanged. Therefore, data from clinical production were included to supplement process validation data, consistent with the life cycle approach recommended in *FDA Guidance for Industry: Process Validation: General Principles and Practices*.

Section 3.2.P.5.4, Batch Analyses contains results of release testing of (b) (4) DP lots (b) (4) conformance and (b) (4) clinical lots) covering all dosage strengths and representing different cell age. The results for all batches are within DP release specifications.

In conclusion, based on the evaluation of the manufacturing and testing data for clinical and conformance lots of DS and DP, the manufacturing process for KOVALTRY was found to be sufficiently controlled and adequately validated to consistently produce DS batches and DP lots of the required quality at full manufacturing scale at Bayer's (b) (4) facility.

Table 9. Drug Product Conformance Lot Information

Dosage strength	Cell Culture (b) (4) Stage (DoM)*	Cell Culture (b) (4) Stage (DoM)	Cell Culture (b) (4) Stage (DoM)
250 IU	(b) (4)	(b) (4)	(b) (4)
	(b) (4)		
500 IU	(b) (4)		
1000 IU	(b) (4)		
	(b) (4)		
2000 IU		(b) (4)	(b) (4)
			(b) (4)
3000 IU		(b) (4)	(b) (4)
			(b) (4)
			(b) (4)

*Date of Manufacture

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

(b) (4)

Reviewer's comments

Bayer's characterization program was comprehensive and utilized an extensive panel of analytical methods to evaluate the structure of the rFVIII product. Results from identity and (b) (4) demonstrated the expected (b) (4)

Compared to Kogenate FS, KOVALTRY has (b) (4)

(b) (4)

(b) (4)

1 page determined to be not releasable: (b)(4)

(b) (4)

CHARACTERIZATION: BIOLOGICAL ACTIVITY

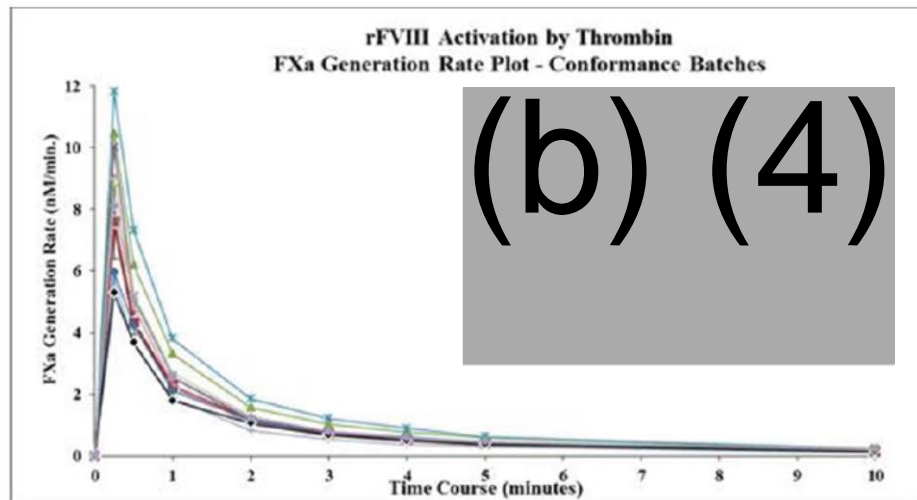
Biochemical characterization

(b) (4)

Functional Characterization

The biological potency of rFVIII was demonstrated by its ability to support FX activation in the chromogenic substrate (CS) assay and to promote blood clotting in FVIII-deficient plasma in the one-stage clotting (OC) assay. Although Kogenate FS is labeled using the OC assay, Bayer sought to label KOVALTRY using the CS assay. Therefore, analytical characterization included a comparison of the CS and OC assays tested under a variety of conditions. While the initial studies (conducted with 3 lots of Kogenate FS and 4 lots of BAY 81-8973) determined the CS/OC ratio of potency results as (b) (4), further testing over the years, using a product-specific standard in both assays and assigning its potency against the WHO IS, indicated that the CS assay gives approximately (b) (4) higher potency values compared to the OC assay (discussed in detail under Drug Product Specification).

Figure 12. Thrombin Activation Rates from FXa Generation Chromogenic Substrate Assay for Conformance Batches



Note a rapid initial FXa generation rate peaking at 0.25 minutes followed by a declining rate through the 10 minute interval.

(b) (4)

Thus, the results of the characterization studies confirmed the expected structure and functional properties of rFVIII and demonstrated comparability of KOVALTRY to its predecessor product, Kogenate FS. The comparability of structural and functional characteristics of rFVIII across

clinical and conformance batches of DS and DP support consistent performance of the manufacturing process and justify the use of clinical data in process validation.

IMPURITIES

Product- and process-related impurities were identified and characterized in clinical and conformance (b) (4) batches. Robust removal of product- and process-related impurities by the purification process was demonstrated during clinical production and in (b) (4) studies, and was confirmed during the validation of the commercial process. For each impurity, a risk assessment was performed in accordance with ICH Guideline Q9; for all impurities, the final levels in (b) (4) were significantly below the Permitted Daily Exposure values according to WHO and ICH guidelines, and typically below the method Quantitation Limit.

According to the provided data for all clinical and conformance runs, (b) (4) is cleared by the (b) (4)

. Therefore, I concur with Bayer that testing for these process-related impurities can be discontinued for the commercial production.

Residual levels of critical process-related impurities, such as (b) (4), are controlled to acceptable limits as (b) (4) specification parameters. HSP70 levels were consistently below the method detection limit, and the (b) (4) studies confirmed (b) (4) of HSP70 by the (b) (4) steps. The risk of immune response and hypersensitivity reactions to HCP or HSP70 was evaluated in clinical studies and is considered low. In clinical studies, the majority of patients were negative for anti-BHK HCP or anti-HSP70 antibodies throughout the study. Those patients, who tested positive or borderline positive, were either positive at baseline, or showed fluctuations in antibody titers with no trending pattern or clinical manifestation.

Product-related impurities, (b) (4), are controlled to acceptable levels through release testing of (b) (4) DP. Due to (b) (4), KOVALTRY has a significantly lower level of (b) (4) compared to its predecessor Kogenate FS.

SPECIFICATION FOR DRUG SUBSTANCE (MODULE 3.2.S.4.1)

(b) (4)

(b) (4)

DESCRIPTION AND COMPOSITION OF DRUG PRODUCT

KOVALTRY is available as a sterile, non-pyrogenic, white to slightly yellow lyophilized powder in single-use glass vials containing nominally 250 international units (IU), 500 IU, 1000 IU, 2000 IU, or 3000 IU of rFVIII potency per vial. The final product does not contain any preservative. Each vial of KOVALTRY is labeled with actual rFVIII potency expressed in IU determined by a chromogenic substrate assay. This potency assignment employs a Factor VIII concentrate standard that is referenced to the current World Health Organization (WHO) International Standard (IS) for Factor VIII concentrate, and is characterized by appropriate methodologies to ensure accuracy of the results.

The reconstituted product is indicated for intravenous administration. KOVALTRY is formulated with the following excipients: 2.2% glycine, 1% sucrose, 30 mM sodium chloride, 2.5 mM calcium chloride, 20 mM histidine and 80 ppm polysorbate 80. Intravenous administration of sucrose contained in KOVALTRY will not affect blood glucose level.

Container and Closure

The container closure system for KOVALTRY consists of a vial, stopper, and overseal. The DP is filled into 10 mL, (b) (4) Type I glass vials (supplied by (b) (4)), and vials are sealed with 20 mm grey bromobutyl rubber, (b) (4) stoppers (supplied by (b) (4)). There are two options for the overseal to provide for product reconstitution: (1) BIO-SET reconstitution cap integrated with the product vial, or (2) (b) (4) aluminum seal with plastic flip-off top for the vial; this configuration is provided with a stand-alone vial adapter with 15-micrometer filter. Both needleless reconstitution systems have been marketed with Kogenate FS. The BIO-SET reconstitution cap is manufactured by Baxter LTD/Biodome and is pre-sterilized by (b) (4). Container-closure integrity of both configurations was demonstrated by (b) (4) testing and all acceptance criteria in the study were met. The vial adapter is a 510(K)-cleared device (clearance number (b) (4)) manufactured by (b) (4) that allows for transfer of fluids between the diluent syringe and DP vial. Labeling of the container closure system is performed by Bayer at their facility in (b) (4).

Both container closure configurations are designed to connect with the sterile water for injection (SWFI), prefilled diluent syringe. Diluent-prefilled syringes are manufactured by (b) (4) and consist of a (b) (4) glass, Type I barrel, and the plunger stopper and tip cap stopper made of grey bromobutyl rubber. There are two sizes of syringe barrel: a 3 mL barrel syringe is prefilled with 2.5 mL of SWFI and is used for

reconstitution of 250 – 1000 IU vials; and a 5 mL barrel syringe is prefilled with 5 mL of SWFI and is used for reconstitution of 2000 and 3000 IU vials. Container closure integrity was assessed by (b) (4) testing of both the 3 mL and 5 mL syringe sizes. The results of the (b) (4) test for both syringe sizes met the acceptance criteria in the study.

An infusion set for intravenous administration is also provided; two options are available – manufactured by (b) (4) – and both are 510(K) cleared: the 510(k) clearance (b) (4) and (b) (4) , respectively. The Division of Manufacturing and Product Quality (CBER) and the Center for Devices and Radiological Health found the design control documentation and verification activities for the container closure components sufficient. The detailed assessment of the container closure components is provided in the memoranda of the DMPQ reviewer (Lori Peters) and the CDRH consult reviewer (Ryan McGowan).

SPECIFICATIONS FOR DRUG PRODUCT (MODULE 3.2.P.5.1)

Bayer's approach and principles for establishing the release specifications for DP are described in Module 3.2.P.5.6. The specification parameters are selected from critical quality attributes determined in the process development studies and risk assessments. The acceptance ranges and limits are based on either regulatory requirements (b) (4) or statistical analysis of manufacturing data obtained from both clinical (250 IU: 4 batches, 500 IU: 4 batches, 1000 IU: 7 batches, 2000 IU: 2 batches) and conformance (250 IU: 3 batches, 500 IU: 1 batches, 1000 IU: 2 batches, 2000 IU: 3 batches, 3000 IU: 4 batches) lot testing. Statistical analyses were carried out using each individual test result, and stability data were considered, where applicable. For certain chemistry-based assays (pH, Appearance, Clarity, Color, and Moisture) experience with the licensed Kogenate FS product, which has the same formulation and container closure, was also considered.

Table 12: Drug Product Specification

Attribute	Parameter	Method	Specification
Physical and Chemical	Appearance	Visual inspection (b) (4)	Pre-reconstitution: White to slightly yellow solid Post-reconstitution: Liquid is clear, colorless with no particles present
	Clarity	(b) (4)	(b) (4)
	Color	(b) (4)	(b) (4)
	Residual Moisture	(b) (4)	(b) (4)
	Reconstitution Time	(b) (4)	(b) (4)
	pH	(b) (4)	6.6 to 7.0
	(b) (4)	(b) (4)	(b) (4)
	(b) (4)	(b) (4)	(b) (4)

Attribute	Parameter	Method	Specification
Identity	Identity (b) (4)	(b) (4)	(b) (4)
	(b) (4)	(b) (4)	(b) (4)
Purity / Impurities	Purity (b) (4)	(b) (4)	(b) (4)
	(b) (4)	(b) (4)	(b) (4)
	(b) (4)	(b) (4)	(b) (4)
	(b) (4)	(b) (4)	(b) (4)
	(b) (4)	(b) (4)	(b) (4)
Potency	FVIII Activity (b) (4) (concentration after reconstitution in 2.5 mL for 250 – 1000 IU or 5.0 mL for 2000 and 3000 IU vials)	CS assay (b) (4)	250 IU: (b) (4) 500 IU: (b) (4) 1000 IU: (b) (4) 2000 IU: (b) (4) 3000 IU: (b) (4)
	Specific Activity, U/mg	Calculation based on the CS assay and Protein Concentration	(b) (4)
	Total Protein (concentration)	(b) (4)	250 IU: (b) (4) 500 IU: (b) (4) 1000 IU: (b) (4) 2000 IU: (b) (4) 3000 IU: (b) (4)
Safety	Sterility	(b) (4)	Must comply: Negative – no evidence of microbial growth within (b) (4) of incubation
	Endotoxin	(b) (4)	(b) (4)
Excipients	Sodium	(b) (4)	(b) (4)
	Calcium	(b) (4)	(b) (4)
	Glycine	(b) (4)	(b) (4)
	Histidine	(b) (4)	(b) (4)
	Sucrose	(b) (4)	(b) (4)

Attribute	Parameter	Method	Specification
	Polysorbate 80	(b) (4)	(b) (4)

*Revisions made in the course of review are presented in blue.

Reviewer's Comments

Similar to DS, the original communication of justifications of Specifications for the KOVALTRY DP was found deficient. In response to FDA requests, Bayer provided results of statistical analyses of manufacturing data (with data distribution) for the clinical and conformance lots of KOVALTRY DP that were used to derive the proposed specifications. The following review issues were resolved (amendments 8, 19, 22, 24, 34, 36, 38 and 48):

Review Issue Resolved: Potency Assignment for KOVALTRY Drug Product

A significant review issue was the choice of assay for potency assignment of KOVALTRY which was discussed with the Applicant through information requests and at the Late-Cycle Meeting. KOVALTRY's licensed predecessor product, Kogenate FS, is labeled using an OC assay, whereas Bayer sought to label KOVALTRY using a CS assay. Comparative potency data for KOVALTRY provided in the BLA indicated approximately (b) (4) consistently higher values obtained with the CS assay compared to the OC assay. FDA expressed concerns that switching from OC to CS assay would break the continuity of protein fill when transitioning from Kogenate FS to KOVALTRY; specifically, a potential for approximately (b) (4) less FVIII protein filled per vial. This concern was supported by results from comparative protein determination for Kogenate FS versus KOVALTRY of the same nominal potencies provided in amendment 36. Addressing FDA concerns in the course of review, Bayer provided additional information to justify the use of the CS assay for *Potency* labeling (amendments 8, 19, 22, 24, 36, 38).

• Release Testing

Over the course of development, the ratio of the CS to the OC assays during DP release testing has improved from the original ratio of (b) (4) to the current ratio of (b) (4). This improvement was a result of using the same standard, calibrated against the WHO IS, for both assays and subsequent establishment of product-specific standard calibrated against the current WHO IS (Tables 13). For the two post-validation launch lots, (b) (4), the CS/OC ratio is (b) (4) and (b) (4), respectively.

Table 13. Results of the Chromogenic Substrate and One-Stage Clotting Assays Over Time

Lots Tested	CS Assay Standard	OC Assay Standard	CS/OC Ratio
Initial CS/OC Ratio (n=3 Kogenate-FS n=4 Kovaltry)	(b) (4) (Kogenate-FS) WHO (b) (4) IS	(b) (4)	(b) (4)
Improved CS/OS Ratio Clinical Lots (n=5)	(b) (4) (Kogenate-FS) WHO (b) (4) IS	(b) (4) (Kogenate-FS) WHO (b) (4) IS	(b) (4)
Improved CS/OS Ratio Special Study	(b) (4) (Kovaltry) WHO (b) (4) IS	(b) (4) (Kovaltry) WHO (b) (4) IS	(b) (4)

Conformance Lots (n=9)			
Improved CS/OS Ratio Launch Lot (1000 IU)	(b) (4) (Kovaltry) WHO (b) (4) IS	(b) (4) (Kovaltry) WHO (b) (4) IS	(b) (4)
Improved CS/OS Ratio Launch Lot (2000 IU)	(b) (4) (Kovaltry) WHO (b) (4) IS	(b) (4) (Kovaltry) WHO (b) (4) IS	(b) (4)

(b) (4)

- Field Study KINE 140146 for Measuring Recoveries

Based on the FDA feedback from the pre-BLA stage, Bayer performed a field study involving 41 clinical laboratories from around the world where comparative recoveries of KOVALTRY spiked into hemophilic plasma were measured with methodologies, reference standards and reagents routinely used in clinical laboratories. The study report provided in amendment 24 demonstrated good agreements of recovery values from both assays compared to nominal target values, and between recovery values from the OC and CS assays (b) (4) difference). The FVIII recoveries versus target values and the CS/OC ratios for KOVALTRY were comparable to the reference full-length product ADVATE which potency is also assigned by the CS assay. The results indicated that the FVIII activity of KOVALTRY can be adequately measured in plasma using either an OC or CS assay according to routine methods of the testing laboratory (Table 15).

Table 15. Summary Results from the Field Study KINE 140146

FVIII Recovery by One-Stage Clotting Assay					
Concentration	Ratio for KOVALTRY		ADVATE		PLASMA
	vs nominal target	vs measured target*	vs nominal target	vs measured target	vs nominal target
Low: 0.043 IU/mL	107%	115%	119%	109%	
Medium: 0.375 IU/mL	92%	100%	104%	96%	
High: 0.865 IU/mL	88%	97%	97%	89%	
Plasma control: 0.960 IU/mL					95%
FVIII Recovery by Chromogenic Assay					
Concentration	Ratio for KOVALTRY		ADVATE		PLASMA
	vs nominal target	vs measured target	vs nominal target	vs measured target	vs nominal target
Low: 0.043 IU/mL	102%	110%	114%	104%	
Medium: 0.375 IU/mL	98%	106%	112%	102%	
High: 0.865 IU/mL	97%	107%	114%	105%	
Plasma control: 0.960 IU/mL					95%
CS/OC Ratio for KOVALTRY			CS/OC Ratio for ADVATE		
Low: 0.043 IU/mL	Medium: 0.375 IU/mL	High: 0.865 IU/mL	Low: 0.043 IU/mL	Medium: 0.375 IU/mL	High: 0.865 IU/mL
0.95 ^a	1.06	1.10	0.96	1.07	1.18
1.04 ^b	1.04	1.14	1.02	1.07	1.21
1.14 ^c	1.10	1.06	1.12	1.17	1.17

^a CS/OC ratio based on analysis of full dataset

^b CS/OC ratio based on analysis of selected dataset (laboratories that performed both assays)

^c CS/OC ratio based on test results in Bayer's lab

- Clinical Studies

In the Leopold I and Leopold II clinical cross-over studies, dosing patients based on the CS assay was as effective during prophylaxis or on-demand treatment as dosing with approximately 20% more KOVALTRY based on the original CS/OC ratio of 1.23 (discussed in the memorandum of the Clinical reviewer).

- Introduction of Total Protein Specification Parameter

Per FDA request, the parameter *Total Protein* with adequately established acceptance ranges was added to the DP specification to allow control of vial fill consistency in commercial manufacture.

The acceptance ranges for *Total Protein Content* were initially calculated as extreme values from the specifications limits at each fill size for *Specific Activity* and *Potency* (b) (4) of nominal potency). The calculation method was used due to limited data for each fill size currently available. This approach was found unacceptable considering that the established range for *Specific Activity* already reflects variability of manufacturing data for both *Potency* and *Total Protein*. Per my request, Bayer re-calculated the acceptance ranges for each fill size for *Total Protein* using nominal values for *Potency* and the lower and upper limits for *Specific Activity* which is a more stringent approach. Clinical and conformance DP release test results ranged from (b) (4) for (b) (4) batches of 250 IU, (b) (4) for (b) (4) batches of 500 IU, (b) (4) for (b) (4) batches of 1000 IU and were all within respective specification limits.

Based on the totality of the data provided by Bayer and CBER results from in-support testing of DP lots (with the CS/OC ratio in the range of (b) (4) FDA has concurred with Bayer's request for use of the CS assay for potency assignment of KOVALTRY.

Other Specification Parameters

The release acceptance limit for *Potency* (by the CS assay) is based on (b) (4) of the nominal target potency. This value reflects manufacturing experience and clinical stability data for end of shelf-life potency expectations (95% confidence interval around regression of the stability trend) and is acceptable. Clinical and conformance DP release test results for *Potency* ranged from (b) (4)

(b) (4)

The specification range for *Specific Activity* (b) (4) was set as Mean (b) (4) (N=31) based on statistical analysis of clinical and conformance DP test results (individuals) which ranged from (b) (4). As this parameter is not dependent on fill size, the combined data were used to establish the specification range and such approach is justified. This range for KOVALTRY is comparable to the ranges for other approved FVIII products (b) (4) for XYNTHA; (b) (4) for ADVATE; (b) (4) for Kogenate FS; and (b) (4) for Novoeight).

(b) (4)

- (b) (4)

The specification for *Purity* was tightened (NLT (b) (4)) relative to that used during clinical release (b) (4) and is the same for (b) (4) DP as no purity changes are expected to occur between (b) (4) DP stages. The specification is based on Mean (b) (4) of clinical and conformance (b) (4) DP data. Clinical and conformance DP purity test results ranged from (b) (4).

The specification for (b) (4)

The specification for *Moisture Content* is equivalent to that for the licensed Kogenate FS (b) (4). Bayer proposes the (b) (4) method as the primary method for testing KOVALTRY which is justified by the established equivalency between the (b) (4) method and the (b) (4) method (used for Kogenate-FS). The (b) (4) method is included as an alternative method that will only be implemented under change control ahead of testing if the (b) (4) method is replaced.

The release specifications for excipients were all tightened relative to the limits employed for clinical release. The ranges are now based on Mean (b) (4) (N=62) data from the clinical and conformance DP lots and cover all vial fill sizes. Under CRMTS #9108 and in the BLA, Bayer requested to remove the requirement for Chloride excipient release testing for commercial manufacture of Kovaltry. Testing for Chloride, which is introduced in the formulation with Calcium Chloride and Sodium Chloride, had been performed during development and clinical production. Bayer fulfilled their commitment under CRMTS #9108 and provided test results for (b) (4) DP conformance lots in all dosage strengths in the BLA in section 3.2.P.5.4, Batch Analyses. Considering that all results for Chloride in all lots are within the acceptance ranges and that DP lots will continue to be release tested for Calcium and Sodium, Bayer's request to remove Chloride testing from lot release testing for commercial manufacture of KOVALTRY appears justified.

The specification for (b) (4) was set based on the Mean (b) (4) (b) (4). The specification for *Endotoxin* is set at (b) (4) and is the same as for (b) (4). Clinical and conformance DP endotoxin test results were (b) (4).

DP Specifications submitted in amendment 48 (summarized in Table 12) are acceptable.

ANALYTICAL METHODS

Analytical methods used to control the quality of (b) (4) DP and their validation were reviewed by Dr. Alexey Khrenov (OBRR/DHRR/LH) and Drs. Lokesh Bhattacharyya, Alfred Del Grosso and Claire H. Wernly (OCBQ/DBSQ/LACBRP). The suitability of the methods for their intended use as release tests for DP is summarized in their review memoranda.

In summary, the design of the validation protocols and analysis of validation data was found appropriate and statistically sound. No substantive issues were identified during the review except for the method for (b) (4)

[REDACTED]

[REDACTED] Bayer committed to validating a (b) (4) assay and submitting the validation report in a Changes Being Effected in 30 Days (CBE-30) Supplement by June 30, 2016. Based on FDA advice, the method for (b) (4) was partially re-validated.

An acceptable reference standard qualification and maintenance program has been established. Two in-house product-specific reference standards have been qualified for routine analytical testing of commercial (b) (4) DP. Working Potency Standard is intended for potency testing. The potency value of Clinical Working Potency Standard STD (b) (4), used for testing clinical lots, was assigned against the WHO (b) (4) IS and represented Kogenate FS material. The currently used Working Potency Standard (including process validation studies) is product-specific, i.e., represents KOVALTRY material, and its potency value was assigned against the WHO (b) (4) IS. These standards were qualified by meeting the acceptance criteria of the release specification; the current potency standard will be tested (b) (4) against the WHO IS to confirm potency stability. Product Reference Standard is intended to be used in other analytical procedures requiring reference standard. It was qualified by release and extended characterization methods and amino acid analysis.

As a result of our review, all test methods for (b) (4) DP are sufficiently described in their respective SOPs, adequately validated in accordance with ICH Guideline Q2(R1) and can be considered suitable for their intended use.

EXEMPTION FROM CBER LOT RELEASE

The Laboratories of the Division of Biological Standards and Quality Control (DBSQC) in the Office of Compliance and Biological Quality (OCBQ), CBER, FDA, performed in-support testing of five conformance DP lots of KOVALTRY representing 250 IU, 1000 IU and 3000 IU dosage strengths for the following parameters:

- Appearance pre- and post-reconstitution
- Reconstitution Time and pH
- Color and Clarity
- Residual Moisture by (b) (4)
- FVIII Potency by the OC and CS assays
- Endotoxin by the (b) (4)

In all assays, the acceptance criteria for the assay performance and assay validity characteristics were satisfied. The DBSQC results for KOVALTRY samples in all tests were within the proposed DP specifications and comparable to the results reported by Bayer. In particular, the potency values obtained by the DBSQC using the CS and OC assays and the current in-house Potency Standard calibrated against the (b) (4) WHO IS were close, with the CS/OC ratio being in the range of (b) (4).

Under the provision described in Federal Register (FR) 58:38771-38773 and the 60 FR 63048-63049 publication (December 8, 1995), routine lot-by-lot release by CBER is not required for KOVALTRY because it is a well-characterized recombinant product. The in-support testing by CBER confirmed suitability of critical quality-defining methods for their intended use as lot release specification tests. Exemption of KOVALTRY from CBER Lot Release is justified.

STABILITY

The stability program for KOVALTRY DS included studies under proposed long-term storage conditions of (b) (4) and an alternative storage condition of (b) (4), as well as studies under accelerated (b) (4) condition. The study design included evaluation of DS (b) (4) conformance batches (b) (4) as well as in commercial (b) (4) conformance batch (b) (4) which was (b) (4). The (b) (4) is considered representative of the commercial scale (b) (4) because the materials are identical. Evaluation of DS stability included assessment of (b) (4)

The stability program for KOVALTRY DP included studies under two proposed long-term storage conditions – at 2 – 8°C and the cycle conditions (stored at 2-8°C for a planned time period and then transferred to the 25°C storage condition for the remainder of the stability study), as well as under accelerated (b) (4) conditions. The studies were performed on DP lots representative of the intended commercial manufacturing process (b) (4) conformance and (b) (4) clinical lots) and encompassed all fill sizes – (b) (4) 250 IU, (b) (4) 500 IU, (b) (4) 1000 IU, (b) (4) 2000 IU, and (b) (4) 3000 IU lots. The inclusion of stability data for clinical lots is justified considering that they were manufactured by the same process in the same facility and use the same container closure system.

Reviewer's comments

In the course of review, per FDA request, the applicant provided up-to-date stability data for the conformance DS batches (b) (4) for long-term storage conditions, and performed analysis of all critical quality attributes for trends which was not presented in the original submission due to limited data being available (amendment 34).

Drug Substance Stability

(b) (4)

Drug Product Stability

The stability studies for the clinical DP lots are completed and cover (b) (4) months at 2-8°C, (b) (4) months at cycling conditions, and 30 months at (b) (4), with data meeting specifications for all parameters throughout storage periods.

The 18-month stability data for conformance lots revealed no negative trends during the observed periods for all storage conditions (potency, (b) (4), and purity by (b) (4)). The data and projections support the proposed shelf-life of 30 months for KOVALTRY final container when stored at 2 – 8°C (36 – 48°F). Within this period, KOVALTRY may be stored for a single period of up to 12 months at temperatures up to +25°C or 77°F. The proposed shelf-life is further supported by satisfactory stability data for clinical lots throughout and above the claimed period and therefore can be granted. The photo-stability data indicate that KOVALTRY is sensitive to extreme light, and that the secondary packaging provides adequate protection to the product from photo-degradation. Therefore, the product should be stored in the original carton to protect it from light.

For clinical and conformance batches, the post-reconstitution testing was performed at the beginning and the end of the stability program. The in-use stability data support the stability of the reconstituted product for up to four hours at ambient temperature; the labeling states a more conservative, three hour claim for the reconstituted product. The storage conditions and handling of reconstituted KOVALTRY are accurately described in the labeling. The established stability protocol provides sufficient control of DP stability post-approval. Bayer commits to placing (b) (4) representative batch per fill size of KOVALTRY DP on stability (b) (4)

EVALUATION OF SAFETY REGARDING ADVENTITIOUS AGENTS

Non-Viral Pathogen Safety

The safety with regard to non-viral adventitious agents such as bacteria, fungi, and mycoplasma is ensured through the control of bioburden in source materials, adherence to current good manufacturing practice, in-process control monitoring, validated sterile filtration and aseptic filling processes, and release and stability testing for sterility and endotoxin.

Viral Safety

Recombinant FVIII is produced in a transfected BHK cell line. All cell banks (MCB and WCB) and EOP cells have been tested in accordance with ICH Guidelines Q5A(R1) and Q5D and demonstrated to be free of infectious viruses in both *in vitro* and *in vivo* tests. The tests only revealed the expected presence of endogenous (b) (4) -like particles detected in (b) (4) which have been proven non-infectious in relevant co-cultivation assays. The (b) (4) from every cell production campaign is directly tested for adventitious viruses in relevant *in vitro* assays.

The risk of virus contamination is further mitigated by the inclusion of two (b) (4) viral clearance steps in the purification process: treatment with (b) (4) for virus inactivation and 20 nm nanofiltration for virus removal. Bayer has evaluated these steps in relevant down-scale systems representative of the cGMP manufacturing steps using (b) (4)

The virus clearance capability of each process step was determined by measuring the (b) (4) for viral infectivity. Virus infectivity was determined using (b) (4) assays to compare the amount of model virus introduced before the process step to the remaining amount of virus after the process step.

(b) (4)

Per my consultation with Dr. Mahmood Farshid, the current position of FDA is that only (b) (4) methods representing different mechanisms of viral clearance can be considered for the calculation of total (b) (4) (e.g., viral inactivation treatment, viral removal by nanofiltration, and any one additional manufacturing step that contributes to viral clearance), and this position was conveyed to Bayer. Bayer reasoned that the (b) (4) and (b) (4) steps are based on different modes of FVIII binding (b) (4) and were included in the calculations of total (b) (4) as representing different mechanisms.

Further discussion was found unnecessary because even without additional steps, the log reduction factors achieved with two main clearance steps are acceptable: (b) (4). These model viruses represent a wide range of size and physico-chemical properties and the results support the effectiveness of the manufacturing process to clear viruses from KOVALTRY. Total (b) (4) are not included in the labeling for recombinant products and remain internal information.

In addition, to avoid carry-over of impurities from one manufacturing step to the next one, strict process segregation has been implemented by separating upstream cell culture from downstream purification areas, using (b) (4) for the (b) (4) to maintain closed process systems, and streamlining the (b) (4) into a (b) (4) area.

CONCLUSION

The Applicant has provided sufficient data and comprehensive information on Chemistry, Manufacturing and Controls in the BLA and has adequately addressed the requests from all CMC reviewers in amendments 8, 19, 22, 24, 31, 34, 36, 38, 48, and 50. The manufacturing process for KOVALTRY, Antihemophilic Factor (Recombinant), is considered to be adequately validated and sufficiently controlled to ensure consistent manufacture of the commercial product that meets the justified release specifications. The implemented control strategy for the cell bank system and the developed manufacturing processes for the (b) (4) DP provide acceptable safety margins with regard to adventitious agents. The analytical methods are adequately validated and are suitable for their intended use as lot release tests.

Bayer has a program for continued process verification (CPV) as the third stage of process validation (amendment 38). The CPV program is governed by a standard operating procedure and is performed under pre-approved protocols to periodically analyze the data collected for CQAs and CPPs for in-process intermediates, DS, and DP, and perform statistical trend analyses and assessment of process stability and capability.

Thus, the information on Chemistry, Manufacturing, and Controls is sufficient and satisfactory, and I recommend **APPROVAL** of Bayer's BLA for KOVALTRY. This recommendation is shared by all members of the review committee.

APPENDIX: HISTORY OF INFORMATION REQUESTS

Date of Information Request	Communicated Review Issues from FDA or Additional Information from Bayer	Amendment/ Date of Response
May 11, 2015	Justification of DS and DP Specifications; Additional parameters to be included in DS Specifications; Justification of equivalency of (b) (4) analyses as tests for <i>Identity</i> ; Justification of <i>Chromogenic Substrate Assay</i> as release test for potency assignment.	Amendment 8 June 1, 2015
June 29, 2015	Control of critical steps and intermediates (process parameters and in-process tests); Specifications for (b) (4); Information on raw materials identified as raw material CQAs, and their removal by the manufacturing process; Revisions to Stability Program for Cell Banks; Request for Interim Reports from concurrent full-scale validation of lifetimes of (b) (4), and further recommendations; Assessment of viral clearance capacity of the manufacturing process; Clarification on standards used in comparative studies of the CS and OC assays, and request for potency results for post-validation DP lots by both assays.	Amendment 19 July 31, 2015
July 10, 2015	Storage stability of (b) (4) process (b) (4); Definitions and actions relating to control strategy terms; Request for reports from small-scale studies for establishing operations ranges for CPPs, and justification of small-scale studies as representative of intended commercial process; Request for small-scale studies reports and justification of claimed lifetimes of (b) (4) and (b) (4); Justification of (b) (4) through the (b) (4) step; Comparability report for clinical and process validation manufacturing phases; Additional parameters for inclusion to DS Specifications.	Amendment 22 August 10, 2015
Fulfillment of Pre-BLA agreement	Final Study Report for Field Study KINE 140146 in support of the use of the CS assay for potency assignment.	Amendment 24 August 17, 2015
Addendum to responses in Amendment 19	Potency results from the CS and OC assays for two launch DP lots manufactured post-validation.	Amendment 31 September 11, 2015
September 15, 2015	Request for up-to-date stability data for conformance DS and DP lots with trend analyses; Request for the results of DP testing for the parameter <i>Total Protein</i> for ten latest lots of Kogenate FS and Kovaltry; Clarifications on the sequence of steps in DP manufacturing process; Revisions to DP Specification, and request to include the parameter <i>Total Protein</i> .	Amendment 34 October 2, 2015

Response to the LCM CMC questions	Justification of the CS assay as a release test for <i>Potency</i> ; Justification of (b) (4) at the (b) (4) step; Commitment to validating (b) (4).	Amendment 36 October 20, 2015
October 21, 2015	Questions relating to the (b) (4) study report for the (b) (4) lifetime; Request for the first 10-year Stability Reports for MCB and WCB; Recommendation to re-establish the acceptance ranges for <i>Total Protein</i> in DP Specification; Questions relating to continued process verification; Specifications and stability of (b) (4).	Amendment 38 November 6, 2015
February 12, 2016	Request to re-establish the acceptance ranges for <i>Total Protein</i> in DP Specification; Request to re-structure presentation of parameters within DP Specification into groups by categories.	Amendment 48 February 19, 2016
February 29, 2016	Information on off-site storage facility for cell banks	Amendment 50 March 4, 2016