<table>
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<th><strong>Summary Basis for Regulatory Action</strong></th>
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<td><strong>Date</strong></td>
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<td><strong>Orphan Designation</strong></td>
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<td><strong>Recommended Action</strong></td>
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**Signatory Authorities Action**

**Jay S. Epstein, MD**

*Office Signatory Authority:*

- [ ] I concur with the summary review
- [ ] I concur with the summary review and include a separate review or addendum to add further analysis
- [ ] I do not concur with the summary review and include a separate review or addendum

**Mary Malarkey**

*Office Signatory Authority:*

- [ ] I concur with the summary review
- [ ] I concur with the summary review and include a separate review or addendum to add further analysis
- [ ] I do not concur with the summary review and include a separate review or addendum
<table>
<thead>
<tr>
<th>Discipline</th>
<th>Reviewers and Consultants</th>
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<tbody>
<tr>
<td>Clinical</td>
<td>Megha Kaushal, MD, OBRR/DHCR/CRB</td>
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<tr>
<td>Clinical Pharmacology</td>
<td>Carl-Michael Staschen, MD, PhD</td>
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<td></td>
<td>Iftekhar Mahmood, PhD, OBRR/DHCR/HPRB</td>
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<tr>
<td>Bio-Statistics</td>
<td>Lin Huo, PhD, OBE/DB</td>
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<tr>
<td>Pharmacology/Toxicology</td>
<td>La’Nissa Brown-Baker, PhD, OBRR/DHCR/HPRB</td>
</tr>
<tr>
<td>CMC – Product</td>
<td>Natalya Ananyeva, PhD, OBRR/DHRR/LH</td>
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<td></td>
<td>Nancy Kirschbaum, PhD, OBRR/DHRR/LH</td>
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<tr>
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<td>Alexey Khrenov, PhD, OBRR/DHRR/LH</td>
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<tr>
<td>CMC – Facility</td>
<td>Lori Peters, CSO, OCBQ/DMPQ/BI</td>
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<tr>
<td>Bio-research Monitoring</td>
<td>Bhanumahti Kannan, MS, OCBQ/DIS/BMB</td>
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<tr>
<td>Labeling</td>
<td>Loan Nguyen, PharmD, OCBQ/DCM/APLB</td>
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<td></td>
<td>Kristine Khuc, PharmD, OCBQ/DCM/APLB</td>
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<tr>
<td>Epidemiology</td>
<td>Marthe Bryant-Genevier, MD, OBE/DE/AEB</td>
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<tr>
<td>Lot Release Testing Plan / In-Support Testing</td>
<td>Karen Campbell, OCBQ/DBSQC</td>
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<td></td>
<td>Lokesh Bhattacharyya, PhD, OCBQ/DBSQC/LACBRP</td>
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<td>Claire H. Wernly, PhD, OCBQ/DBSQC/LACBRP</td>
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<tr>
<td>Regulatory Project Manager</td>
<td>Pratibha Rana, MS, OBRR/IOD/RPMS</td>
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<tr>
<td>Advisory Committee</td>
<td>Product not presented to an advisory committee</td>
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### 1. Introduction

Bayer HealthCare LLC (Bayer) submitted an original biologics license application (BLA) to seek U.S. licensure for Antihemophilic Factor (Recombinant). The intended commercial product is a sterile lyophilized powder in single-use glass vials containing nominally 250, 500, 1000, 2000 or 3000 international units (IU) of Coagulation Factor VIII (FVIII) potency per vial. The product is reconstituted with the provided diluent (sterile Water for Injection, sWFI) for intravenous administration. 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.

### 2. 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, full-length and B-domain-deleted.
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 FVIII 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 the downstream purification process
- Introduction of a 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 and downstream purification steps.

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 study for the collection of additional safety and efficacy data, including use of KOVALTRY in 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 received approval for commercial distribution from Health Canada on February 3, 2016 and the European Commission on February 22, 2016; in addition to FDA’s review, this product is 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.

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<th>Milestone</th>
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<tr>
<td>Received</td>
<td>December 16, 2014</td>
</tr>
<tr>
<td>Filed</td>
<td>February 9, 2015</td>
</tr>
<tr>
<td>Mid-Cycle Communication</td>
<td>June 11, 2015</td>
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</table>
**Review Issues Resolved during BLA Review**

In the course of review, specific chemistry, manufacturing and controls (CMC) issues were raised and resolved via information requests. FDA requested that Bayer add quality control tests for increased control of the; revise the stability program for cell banks; validate lifetimes based on concurrent full-scale validation studies; provide additional data to justify step; revise the drug substance and drug product specifications; commit to validating a assay as a post-marketing study; and provide additional data to justify 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.

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). CBER review of monitoring reports led to the re-analysis of clinical data. A sensitivity analysis of the clinical data did not reveal an impact on the overall results of the Leopold I and II studies; the overall results had demonstrated the safety and efficacy of KOVALTRY for the proposed indications.

3. Chemistry, Manufacturing and Controls (CMC)

a) Product Quality

**Manufacturing Process**

KOVALTRY is manufactured at the Bayer HealthCare LLC facility in. The manufacturing process for KOVALTRY was developed based on the process for Kogenate FS. Drug substance (DS) manufacture proceeds through step; revise the...
The drug product (DP) manufacturing process remains unchanged compared to Kogenate FS and consists of (b) (4) of DS, dilution to appropriate target potency, sterile filtration, filling into vials, lyophilization, and packaging.

**Source Material Quality and Control**

**Cell Bank System**

The BHK cell line expressing the rFVIII active ingredient in KOVALTRY was established by introducing the human heat-shock protein 70 (HSP70) gene into the same cell line used for Kogenate FS using commercially available materials and biotechnological procedures. HSP70 is an intracellular protein that improves proper folding of the FVIII protein, provides resistance to programmed cell death and thereby increases rFVIII expression level. KOVALTRY will be the first licensed recombinant coagulation factor which is manufactured using a cell line co-expressing a heat-shock protein. The effective removal of this process-related impurity by the purification process has been adequately demonstrated, and the risk of immune response has been determined to be low (please refer to sections Impurities and Immunogenicity).

Characterization of the master cell bank (MCB), WCB and End-of-Production (EOP) cells was performed in accordance with ICH Guideline Q5D: Derivation and Characterization of Cell Substrates Used for Production of Biotechnological / Biological Products, 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): Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin. Genetic characterization was performed in accordance with ICH Guideline Q5B: Quality of Biotechnological Products: Analysis of the Expression Construct in Cells Used for Production of r-DNA Derived Protein Products. These studies confirmed the (b) (4)

The stability program for MCB and WCB is in place. As requested by the FDA, Bayer revised the protocol to include the (b) (4)

**Other Raw Materials**

All raw materials used in the production of KOVALTRY are sourced from approved suppliers, compliant with USP/NF, JP or Ph. Eur. monographs, and released against approved specifications. No animal- or human-derived raw materials are used in the manufacturing process or DP formulation.

**In-Process Controls**

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 manufacture were. Per the FDA request, Bayer provided extensive comparative data and source documents that adequately justified developmental studies to be representative of the intended commercial process in establishing process controls. 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.

Per the FDA request, Bayer added which originally had included only concentration. The intended stability claim for the was clarified, and the stability program was revised according to FDA recommendations to add accelerated conditions, and to perform testing at the final stability time point.

Small-scale studies did not adequately support the claimed lifetimes of As requested by the FDA, Bayer submitted Interim reports from concurrent full scale validation studies which established the initial lifetimes of based on the number of commercial runs performed, which will be followed in commercial production.

The suitability of the currently licensed process for Kogenate FS for commercial manufacture of KOVALTRY DP was evaluated 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.

**Process Validation**

Bayer’s validation strategy for the DS and DP manufacturing processes is consistent with the recommendations in ICH Guidelines Q7A, Q8 and Q11. The validation studies were performed at the Bayer’s facility, the intended commercial site, under prospective process validation protocols. The process validation studies for DS were designed to cover maximum duration and maximum capacity of production and were performed under nominal operating conditions. Conformance DP lots of all nominal potencies were manufactured from DS conformance batches originating from 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. Since phase 3 clinical lots were manufactured using the same process in the same facility, these data were considered applicable to supplement process validation data, consistent with the life cycle approach recommended in *FDA Guidance for Industry: Process Validation: General Principles and Practices*.

The manufacturing process for DS allows a. Per the FDA request, Bayer provided results from small-scale studies and commercial run of DS conformance lots) performed under worst-case conditions where the material was
evaluated by major quality attributes and full release testing, extended characterization and stability performance of DS and DP. The data showed no adverse impact on product quality due to (b) (4) that justified the (b) (4) . The established total purification processing time cannot be exceeded in the event of (b) (4)

Based on the evaluation of the manufacturing and testing data for clinical and conformance lots, the manufacturing process for KOVALTRY was found to be sufficiently controlled, consistent and adequately validated.

**Drug Product Composition and Presentation**

KOVALTRY is available as a sterile, non-pyrogenic, white to slightly yellow lyophilized powder in single-use glass vials containing nominally 250, 500, 1000, 2000, or 3000 international units (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 Bayer’s Factor VIII concentrate standard that has been calibrated against the current World Health Organization (WHO) International Standard 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 Closure System**

The container closure system for KOVALTRY consists of a vial, stopper, and overseal. The DP is filled into 10 mL, (b) (4), Type I, clear glass vials (supplied by (b) (4), and vials are sealed with 20 mm gray 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). The vial adapter is a 510(k)-cleared device manufactured by (b) (4) that allows for transfer of fluids between the diluent syringe and DP vial. Container closure integrity of both configurations was demonstrated by (b) (4) testing and all acceptance criteria in the study were met. 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 clear, colorless, (b) (4) glass, Type I barrel, and the plunger stopper and tip cap stopper made of gray 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 testing of both the 3 mL and 5 mL syringe sizes. The results of the test for both syringe sizes met the acceptance criteria in the study.

An infusion set for intravenous administration is also provided; are available – manufactured by are 510(k) cleared.

**Characterization of rFVIII Structure and Function**

The active ingredient in KOVALTRY is the unmodified full length recombinant FVIII glycoprotein comprising the human derived amino acid sequence with a molecular weight, including glycosylation, of 330 – 360 kDa. The structure of the rFVIII molecule is illustrated in Figure 1.

**Figure 1. Structure of Recombinant Factor VIII**

**Structural and Functional Characterization**

The characterization program used an extensive panel of analytical methods to evaluate both structure and function of the rFVIII protein. The structural characterization studies were performed on clinical and conformance batches in comparison with in-house Product Reference Standard and Kogenate FS. Physicochemical and functional characterization of the rFVIII molecule was carried out on DP lots. Results from identity, Post-translational modifications, including glycosylation sites, and tyrosine sulfation, important for the normal lifecycle of FVIII, were characterized using an extensive panel of approaches and were found consistent with the known structure of FVIII and between all lots tested. Contents of galactose-alpha-1,3-galactose (alpha-Gal) and N-glycolyl neuraminic acid (NGNA), that are not expressed in humans and are potentially immunogenic, were below the 1% limit of detection established for each analytical method. Other potential adverse modifications, such as . Results from these in vitro characterization studies supported comparability of KOVALTRY to Kogenate FS.
The potency of rFVIII was demonstrated by its ability to support Factor X 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. Results indicated that the CS assay gives approximately higher potency values compared to the OC assay.

**Impurities**

Product- and process-related impurities were identified and characterized in clinical and conformance batches. Robust removal of product- and process-related impurities by the purification process was demonstrated during clinical production and in 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. Residual levels of critical process-related impurities, such as host cell protein (HCP), are controlled to acceptable limits as specification parameters. HSP70 levels were consistently below the method detection limit, and the studies confirmed robust removal of HSP70 by the purification process. The risk of immune response and hypersensitivity reactions to HCP or HSP70 was evaluated in clinical studies and is considered to be low. Product-related impurities, are controlled to acceptable levels through release testing of DP. Due to removal of human- and animal-derived raw materials from the manufacturing process and the introduction of the nanofiltration step, KOVALTRY has a lower level of compared to its predecessor Kogenate FS.

**Analytical Methods**

Suitable analytical methods have been validated to support quality control testing throughout manufacture, final product release and stability monitoring. The design of the validation protocols and the analysis of validation data were appropriate and statistically sound. No substantive issues were identified during the review except for the method for quantification of HCP.

In response to FDA request, Bayer committed to validating a assay and submitting the validation report in a Changes Being Effected in 30 Days (CBE-30) Supplement by June 30, 2016. Based on the FDA advice, the method for 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 DS and DP. Working Potency Standard is intended for potency testing.
and is calibrated against the current WHO IS. Product Reference Standard is intended to be used in other analytical procedures requiring a reference standard.

As a result of our review, all test methods for DS and 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.

Drug Substance and Drug Product Release Specifications

The specifications for DS and DP were established in accordance with ICH Guideline Q6B. The parameters were selected from critical quality attributes determined in process development studies and risk assessments. Acceptance ranges/limits are established based on regulatory requirements, statistical analysis of the release manufacturing data for clinical and conformance batches/lots, clinical outcome, analytical variability, and stability data.

In response to the FDA requests, the following modifications were made to the DS specification:

- Over the course of development, the ratio of the CS to the OC potency values 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. For two post-validation launch lots, the difference in the CS and OC potency values is \((b)(4)\).

- A field study involving 41 clinical laboratories from around the world was performed to measure comparative recoveries of KOVALTRY, based on the FDA feedback from the pre-BLA stage. The study report provided during the BLA review demonstrated good...
agreement 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 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.

- In the clinical program, dosing patients based on the CS assay was as effective during prophylaxis or on-demand treatment as dosing with approximately more KOVALTRY based on the original CS/OC ratio of (b) (4) (discussed in clinical sections).

- 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.

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

The final DP release specification in Table 2 reflects revisions made per the FDA requests (in blue) and is considered adequate to control the identity, quality, purity, potency, and safety of KOVALTRY.

**TABLE 2: SPECIFICATION FOR DRUG PRODUCT**

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<tr>
<th>Attribute</th>
<th>Parameter</th>
<th>Method</th>
<th>Specification</th>
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</thead>
<tbody>
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<td>Physical and Chemical</td>
<td>Appearance</td>
<td>Visual inspection</td>
<td>Pre-reconstitution: White to slightly yellow solid</td>
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<td></td>
<td></td>
<td>(b) (4)</td>
<td>Post-reconstitution: Liquid is clear, colorless with no particles present</td>
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<tr>
<td></td>
<td>Clarity</td>
<td>(b) (4)</td>
<td>(b) (4)</td>
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<tr>
<td></td>
<td>Color</td>
<td>(b) (4)</td>
<td>(b) (4)</td>
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<tr>
<td></td>
<td>Residual Moisture</td>
<td>(b) (4)</td>
<td>(b) (4)</td>
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<tr>
<td></td>
<td>Reconstitution Time</td>
<td>Timer</td>
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<tr>
<td></td>
<td>pH</td>
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<td>6.6 to 7.0</td>
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<td>Identity</td>
<td>Identity</td>
<td>(b) (4)</td>
<td>Complies: (b) (4)</td>
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<td>(b) (4)</td>
<td>(b) (4)</td>
<td>(b) (4)</td>
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<td>Purity / Impurities</td>
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<td>(b) (4)</td>
<td>(b) (4)</td>
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<td>(b) (4)</td>
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STN 125574/0 Bayer’s BLA for KOVALTRY
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<th>Attribute</th>
<th>Parameter</th>
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<th>Specification</th>
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<tr>
<td>Potency</td>
<td>FVIII Potency</td>
<td>CS assay</td>
<td>250 IU: (b) (4)</td>
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<td>(vial content; (b) (4) at release)</td>
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<td>500 IU: (b) (4)</td>
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<td></td>
<td>(concentration per mL after reconstitution in 2.5 mL for 250 – 1000 IU or 5.0 mL for 2000 and 3000 IU vials)</td>
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<td>1000 IU: (b) (4)</td>
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<td></td>
<td>Specific Activity</td>
<td>Calculation based on the CS Potency value and Protein Concentration</td>
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<td></td>
<td>Total Protein</td>
<td>(b) (4)</td>
<td>3000 IU: (b) (4)</td>
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<td></td>
<td>(vial content and concentration per mL)</td>
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<td>Must comply: Negative – no evidence of microbial growth within (b) (4) of incubation</td>
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<td>Safety</td>
<td>Sterility</td>
<td>Membrane filtration per (b) (4)</td>
<td>250 IU: (b) (4)</td>
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<td></td>
<td>Endotoxin</td>
<td>(b) (4)</td>
<td>500 IU: (b) (4)</td>
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<td>Excipients</td>
<td>Sodium</td>
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<td></td>
<td>Calcium</td>
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<td></td>
<td>Glycine</td>
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<td>Histidine</td>
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<td>Polysorbate 80</td>
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<td>Must comply: Negative – no evidence of microbial growth within (b) (4) of incubation</td>
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**Batch Analyses and In-Support Testing**

The BLA contains results of release analyses of commercial-scale DS batches conformance and clinical batches) and DP lots conformance and clinical lots. The results for all batches are within DS and DP release specifications.

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

The results met the acceptance criteria for the assay performance characteristics. In addition, the DBSQC test results for KOVALTRY samples were within the proposed DP specifications and
comparable to the results reported by Bayer. In particular, the potency values obtained by the DBSQC for the CS and OC assays, using the current in-house Potency Standard from Bayer which is calibrated against the WHO IS, were found to be acceptable. The CS/OC ratio are reported to be in the range of (b) (4) 

The in-support testing confirmed the suitability of critical test methods for their intended use as release specification tests.

**Stability Studies**

The stability program for KOVALTRY 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 commercial manufacturing process (both conformance and clinical lots) and encompassed all fill sizes – 250 IU, 500 IU, 1000 IU, 2000 IU, and 3000 IU lots.

The stability studies for the clinical lots are completed and cover at 2 – 8°C, at the cycle conditions, and 30 months at , with data meeting specifications for all parameters throughout storage periods.

In the course of review, per the FDA request, the applicant provided up-to-date stability data for the conformance lots (18 months for long-term storage conditions), and performed analysis of all critical quality attributes for trends (only limited data had been generated at the time of the original submission). The stability data for conformance lots revealed no negative trends in all evaluated parameters (potency, (b) (4), and purity by (b) (4)) during the observed periods for all storage conditions.

The data and projections support the proposed shelf-life of 30 months for KOVALTRY final container when stored at +2 °C to +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 stability 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.

The stability data for DS are sufficient to support its shelf-life of (b) (4) The established stability protocol is adequate to control DS stability post-approval.
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 - like particles detected in in vitro and in vivo tests, which have been proven non-infectious. In the commercial manufacture of KOVALTRY, every cell culture campaign includes in-process testing for adventitious viruses at specified time intervals.

The risk of virus contamination is further mitigated by the inclusion of two orthogonal viral clearance steps in the purification process: treatment with 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 steps and the filtration to virus removal. 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. In addition, strict process segregation has been implemented by separating upstream cell culture from downstream purification areas, using for the to maintain closed process systems, and streamlining the nanofiltrate into a post-viral filtration area.

b) Exemption from CBER Lot Release

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. Thus, exemption of KOVALTRY from CBER Lot Release is justified. CBER has performed in-support testing of commercial scale KOVALTRY DP lots of 250 IU, 1000 IU and 3000 IU nominal potencies. Test results were deemed consistent with the proposed commercial release specifications.

c) Review of Manufacturing Facilities and Inspections

Facility information and data provided in the BLA were reviewed by CBER and found to be sufficient and acceptable. The facilities involved in the manufacture of KOVALTRY are listed
in Table 3. The activities performed and inspectional histories are noted in the table and are further described in the paragraphs that follow.

### Table 3: Manufacturing Facilities for KOVALTRY

<table>
<thead>
<tr>
<th>Name/address</th>
<th>FEI number</th>
<th>Inspection/ waiver</th>
<th>Results/ Justification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sterile Diluent Manufacturer, Release Testing</td>
<td>(b) (4)</td>
<td>Waived</td>
<td>Team Biologics (b) (4) VAI</td>
</tr>
<tr>
<td></td>
<td>(b) (4)</td>
<td>Waived</td>
<td>CDER IOG (b) (4) NAI</td>
</tr>
<tr>
<td></td>
<td>(b) (4)</td>
<td>Waived</td>
<td>CDER IOG (b) (4) VAI</td>
</tr>
</tbody>
</table>

VAI – Voluntary Action Indicated  
NAI – No Action Indicated

Team Biologics conducted a surveillance inspection of Bayer Healthcare LLC from (b) (4). The inspection was classified as voluntary action indicated (VAI) and all inspectional 483 observations were resolved.

Team Biologics conducted a surveillance inspection of (b) (4). The inspection was classified as VAI and all inspectional 483 observations were resolved. Surveillance inspections of (b) (4) locations at (b) (4) were performed by CDER IOG. The inspection at the (b) (4) and was classified as no action indicated (NAI). The inspection at the (b) (4) site in (b) (4) was conducted from (b) (4) and was classified as VAI and all inspectional 483 observations were resolved.
d) Environmental Assessment

The BLA included a request for a categorical exclusion from an Environmental Assessment under 21 CFR § 25.31(c). The FDA concluded that this request is justified as the manufacturing of this product will not alter significantly the concentration and distribution of naturally occurring substances and no extraordinary circumstances exist that would require an environmental assessment.

e) Recommendation

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 acceptable release specifications. The manufacturing process provides acceptable safety margins regarding adventitious agents. The reviewers from the Division of Hematology Research and Review, OBRR, and the Division of Manufacturing and Product Quality and the Division of Biological Standards and Quality Control, OCBQ, conclude that Bayer Healthcare LLC has provided sufficient data and information on chemistry, manufacturing and controls to support the licensure of KOVALTRY.

4. Non-Clinical Pharmacology/Toxicology

a) General Considerations

The safety and effectiveness of KOVALTRY were characterized in a nonclinical program that included in vivo comparison of its effectiveness in hemostasis and induction of thrombogenesis with the Applicant’s predecessor recombinant Factor VIII (FVIII) product Kogenate FS, as well as in vivo pharmacokinetics, local tolerability, and single and repeat-dose toxicity studies in FVIII-deficient (hemophilic) mice, and in FVIII replete (i.e., wild-type) dogs, rats and rabbits. Studies were Good Laboratory Practices (GLP) compliant or non-compliant. A risk assessment of the potential extractable and leachable components present in the KOVALTRY drug substance, as per the ISO 10993 standards, was also completed.

Previous experience with similar recombinant and plasma-derived FVIII products has demonstrated that the toxicities of exogenously administered FVIII are extensions of its pharmacologic activity, i.e., hypercoagulability of blood, thrombosis, and thromboembolus formation in treated animals and patients. Additional expected findings in test animals are development of neutralizing and non-neutralizing antibodies directed against the human FVIII protein (i.e., immunogenicity), with the potential to cross-react and neutralize endogenous FVIII in wild-type animals.

b) Pharmacological/Toxicological Findings

**Pharmacology**

Nonclinical pharmacology studies with KOVALTRY were conducted in a rodent model of hemophilia A (i.e., mice with a naturally occurring mutation/deletion of FVIII function), and in normal, FVIII-replete (i.e., wild-type) rats, and in rabbits.
Hemophilic mice were dosed intravenously with KOVALTRY, or another approved recombinant human FVIII product in a cross-over study design. Dosing of hemophilic mice with KOVALTRY at doses approximately equivalent to the human starting dose restored the \textit{ex vivo} whole blood clotting time (WBCT) activity and activated partial thromboplastin times (aPTT) to within normal limits, and the results were comparable to those obtained following dosing with the predecessor FVIII product previously licensed and marketed by the Applicant. There were no effects of KOVALTRY or the other FVIII preparation on the hematology profiles in the mice as compared to prior to dosing (i.e., baseline), and no serious adverse effects or evidence of thrombogenicity were reported. In summary, animal studies with KOVALTRY showed the expected pro-coagulant pharmacologic activity in a rodent model of hemophilia A, and the results were similar to those obtained with another approved recombinant human FVIII product.

Secondary pharmacology studies with KOVALTRY in wild-type rats showed no elevations of \textit{ex vivo} biomarkers of thrombosis (i.e., thrombin, thrombin-anti-thrombin complex, D-dimer and prothrombin fragments 1+2 formation) at doses up to 5-fold greater than the maximum KOVALTRY clinical dose. Results for these biomarkers after KOVALTRY dosing were similar to those achieved in rats dosed with the comparator groups of either an approved recombinant human FVIII product, or a marketed human plasma-derived FVIII concentrate. No abnormal tissue pathology, and only sporadic evidence of \textit{in situ} thrombosis with no apparent relationship in the incidence or severity to the FVIII dose level were observed on microscopic examination of lung and other tissues from rats dosed with KOVALTRY at up to 5-fold greater doses than the maximum clinical dose of 40 to 50 IU/kg.

There was no evidence of undesirable \textit{in vivo} secondary pharmacologic activity, i.e., thrombogenesis, in FVIII-replete rats and FVIII-replete rabbits dosed with KOVALTRY at dose levels up to 8-fold greater than the equivalent human KOVALTRY starting dose. There were no effects of KOVALTRY or the other approved FVIII preparation on the hematology profiles in the rats or rabbits as compared to prior to dosing (i.e., baseline), and no serious adverse effects or evidence of thrombogenicity were reported.

These data were used as proof-of-concept to support the rationale for entering KOVALTRY into clinical trials, and to support the pharmacology section of the KOVALTRY BLA Package Insert (PI).

\textbf{Pharmacokinetics}

Pharmacokinetic (PK) studies with KOVALTRY were conducted concurrently with the pharmacology studies in Hemophilia A mice described above, and FVIII activity was measured by both the OC and CS assays. With both assays, the PK profiles from hemophilic mice dosed with KOVALTRY showed dose-dependent effects in all parameters measured, and were comparable to those obtained when the mice were dosed with the approved, human recombinant FVIII comparator. Similar PK profiles were obtained in FVIII-replete, wild-type rats dosed with KOVALTRY or an approved, human FVIII comparator product. A series of PK studies in FVIII-replete, wild-type rats and rabbits showed that the KOVALTRY product tested in the nonclinical safety program was comparable to those lots used in clinical trials, and that there were no meaningful changes in the critical PK parameters.

\textbf{Toxicology}

Overall, no unexpected findings or significant concerns were identified in toxicity studies conducted in wild-type, FVIII-replete rabbits and rats. Rabbits dosed with a single, intravenous
injection of KOVALTRY at doses up to 8-fold greater than the clinical starting dose demonstrated no systemic or tissue pathologies. A repeat-dose toxicity study with KOVALTRY was conducted in rabbits; animals were dosed daily for 5 days by bolus intravenous injection with KOVALTRY doses equal to, and up to 8-fold greater than the clinical starting dose. Although statistically significant differences in some measured parameters of toxicity were reported (e.g., hematology, prothrombin time and aPTT, serum chemistry and urinalysis), the findings were not consistent or dose-related between the KOVALTRY dose groups, and no corresponding histopathological findings were detected. The findings in the KOVALTRY dosed rabbits were comparable to those in rabbits receiving an equivalent dose of either an approved, recombinant human FVIII product or a human plasma-derived FVIII concentrate as comparators, suggesting that the safety profile of KOVALTRY is similar to that of other, approved FVIII products. In a repeat dose toxicity study with KOVALTRY in rats, the animals were dosed daily for 5 days by bolus intravenous injection with KOVALTRY doses equal to, and up to 20-fold greater than the clinical starting dose. Although statistically significant differences in some measured parameters of toxicity were reported (e.g., hematology, prothrombin time and aPTT, serum chemistry and urinalysis) and were consistent and dose-related between the KOVALTRY dose groups, no corresponding histopathological findings were detected and the findings were not considered toxicologically meaningful. The hematology findings in the toxicity studies in FVIII replete animals were expected and consistent with exaggerated pharmacologic effects of exogenous FVIII, which have previously been demonstrated in animal studies with other recombinant and plasma-derived FVIII products.

**Special Toxicology Studies**
A repeat-dose exploratory study in hemophilia A mice was conducted to compare the immunogenicity of KOVALTRY DP with Kogenate FS, the predecessor recombinant FVIII product previously licensed and marketed by the Applicant. No remarkable toxicities were reported in mice after once weekly intravenous dosing for 5 doses with either the Kogenate FS or KOVALTRY products, and there were no statistically significant differences in the incidence of immunogenicity in mice dosed with Kogenate FS compared to animals injected with KOVALTRY. Comparable exposures to human rFVIII, as measured by the Area Under the Concentration versus Time Curve, were demonstrated in PK studies in rats and rabbits after a single intravenous injection of either the Kogenate FS or KOVALTRY products. These nonclinical data suggest that the same doses of either recombinant FVIII product result in similar pharmacologic activity, toxicity, exposure and potential for immunogenicity in hemophilia A mice, and support the Applicant’s conclusion that the safety profile of KOVALTRY is comparable to that of their previously approved, recombinant FVIII product Kogenate FS.

**Toxicologic Risk Assessment Analysis**
A toxicological risk assessment analysis, providing identification and safety qualification of the extractable and potential leachable substances from the components used in the KOVALTRY manufacturing process, was also provided in this submission. The results of this risk analysis indicated that the levels of potential leachable or extractable impurities appear acceptable, as they were significantly lower than the maximally allowed daily exposure levels identified from extensive clinical and nonclinical experience. Additionally, the safety of these extractable and leachable compounds can be considered adequately qualified because several lots of KOVALTRY were used in the nonclinical toxicology testing, at daily doses of rFVIII exceeding the recommended clinical dose by up to 8-fold. The risk of the presence of these compounds, at the levels identified, to patients with hemophilia A receiving intravenous doses of KOVALTRY
is considered minimal and acceptable, considering the benefit of FVIII replacement therapy in this population.

There were no animal studies with KOVALTRY to assess carcinogenicity, in vitro or in vivo mutagenicity, fertility, reproductive toxicity or teratogenicity. KOVALTRY is a recombinant human protein, and animals receiving repeated doses of the product developed antibodies against FVIII that both accelerated clearance of the protein and, in some cases, neutralized its procoagulant activity. Therefore, long-term, repeat-dose toxicity studies, as well as the standard carcinogenicity bioassay (i.e., 2 years of daily KOVALTRY dosing in both rats and mice), were not feasible to conduct.

Because KOVALTRY is a protein, the standard battery of genotoxicity testing as recommended in the International Conference on Harmonization (ICH) S2 guidance documents would not provide information to address potential mutagenicity of the rFVIII, and as per the ICH S6 guidance on biotechnology-derived protein therapeutics, these studies were not required. The lack of carcinogenicity, mutagenicity and chronic toxicity data are addressed in the appropriate section of the package insert.

No nonclinical reproductive or developmental toxicity studies were conducted in support of this submission. Hemophilia A is an X-linked disorder and affects mostly male subjects; therefore, it is highly unlikely that a pregnant or lactating woman would receive KOVALTRY. KOVALTRY received a Pregnancy and Lactation designation in the labeling that includes statements that nonclinical reproductive and developmental toxicity studies with KOVALTRY have not been conducted, that the risks to the developing fetus are unknown, and that the product should be used in a pregnant woman only if clearly needed. This labeling is consistent with that included in prescribing information for other approved recombinant human coagulation factors for the treatment of hemophilia A or B.

c) Recommendation

The results from the nonclinical program, including the safety profile and hemostatic activity of KOVALTRY and the toxicological risk assessment support KOVALTRY’s use for the proposed indications.

5. Clinical Pharmacology

a) Mechanism of Action

KOVALTRY temporarily replaces the missing clotting Factor VIII that is needed for effective hemostasis. Upon activation by thrombin, rFVIIIa acts as a cofactor for activated Factor IX triggering a chain of biochemical reactions – activation of Factor X, which converts prothrombin into thrombin, and subsequent interaction of thrombin with fibrinogen results in the formation of the fibrin clot that stops the bleeding.

b) Pharmacodynamics

Plasma clotting time as measured by the activated partial thromboplastin time (aPTT) is prolonged in patients with hemophilia A. Treatment with KOVALTRY normalizes the aPTT.
c) Pharmacokinetics

The clinical pharmacology of KOVALTRY has been assessed in three submitted studies.

1. A randomized, cross-over, open-label trial to evaluate the pharmacokinetics, efficacy, and safety profile of plasma protein-free recombinant FVIII formulated with sucrose (KOVALTRY) in previously treated subjects with severe hemophilia A under prophylaxis therapy (Report # A62366; Leopold I)

This study consisted of 3 parts (A, B, C) and an optional extension phase. The primary objective of Part A was to assess the PK non-inferiority of KOVALTRY compared to Kogenate FS in subjects with severe hemophilia A. Part B assessed the safety, tolerability, and efficacy of prophylaxis treatment with KOVALTRY in subjects with severe hemophilia A over a 12 month treatment period. Only those subjects who participated in Part A were reassessed for KOVALTRY PK after 6 or 12 months of treatment in Part B. Part C was dedicated to major surgery only. The extension part was an optional continuation of the prophylaxis treatment for up to 12 additional months.

PK data were obtained in a randomized cross over study following a single dose of 50 IU/kg of KOVALTRY or Kogenate FS in 26 patients between the ages of 12 to 61 years with severe hemophilia A. The washout period between the 2 treatments was ≥3 days. Repeat PK study was conducted in 19 patients using a dose of 50 IU/kg KOVALTRY after 6 or 12 months of prophylaxis treatment. For all PK studies, 50 IU/kg of KOVALTRY or Kogenate FS was given as an IV-infusion over 10 min. Blood samples were collected at pre-injection, and at 0.25, 0.5, 1, 3, 6, 8, 24, 30, and 48 hours following the injection. FVIII plasma activity was determined by the OC and the CS assays in a central laboratory. PK parameters were calculated by non-compartmental analysis.

Using data from the OC and the CS assays, both analyses showed that the bioavailability of KOVALTRY was at least non-inferior to that of Kogenate FS. With both assays, the 90% CIs for AUCs were 1.13 to 1.25 (OC assay) and 1.11 to 1.28 (CS assay). Overall, the data demonstrated PK non-inferiority for KOVALTRY compared to Kogenate FS.

Based on the OC assay, the systemic clearance and half-life of KOVALTRY for adults (≥ 18 years) were 0.035 ± 0.012 dL/h per kg, and 14 ± 4 h, respectively. The systemic clearance and half-life of KOVALTRY for adolescents (12-17 years) were 0.053± 0.017 dL/h per kg and 12 ± 1 hours, respectively.

Based on the CS assay, the systemic clearance and half-life of KOVALTRY for adults (≥ 18 years) were 0.027 ± 0.01 dL/h per kg, and 14 ± 4 h, respectively. The systemic clearance and half-life of KOVALTRY for adolescents (12-17 years) were 0.034± 0.01 dL/h per kg and 14 ± 6 hours, respectively.

In the repeat PK study (n =19), the PK parameters following the first dose were comparable with the PK parameters following 6 months of prophylactic treatment.

2. A phase 2/3, randomized, cross-over, open-label trial to demonstrate superiority of prophylaxis over on-demand therapy in previously treated subjects with severe
hemophilia A treated with plasma protein-free recombinant FVIII (KOVALTRY) formulated with sucrose (Report # PH-37042; Leopold II).

PK study was only performed in subjects recruited at centers in Japan, and who were willing to participate in this optional investigation. Four subjects (35 to 51 years of age) participated in the PK study. The subjects received a dose of 50 IU/kg by IV-infusion over 10 min (1 subject over 30 min). FVIII activity levels were determined with the OC and the CS assays. The PK parameters were calculated using a non-compartmental method.

Based on the OC-assay, the systemic clearance and half-life of KOVALTRY were 0.033 ± 0.01 dL/h per kg and 12 ± 3 hours, respectively. Incremental in-vivo recovery was 2.1 ± 0.5 IU/dL per IU/kg. Based on the CS-assay, the systemic clearance and half-life KOVALTRY were 0.031 ± 0.01 dL/h per kg and 13 ± 3 hours, respectively. Incremental in-vivo recovery was 2.1 ± 0.5 IU/dL per IU/kg.

PK evaluation in this study was limited to the data of 4 subjects from Japan. Slightly lower concentrations were measured using the OC assay, but mean half-life values were comparable to the CS assay.

3. A multi-center phase 3, uncontrolled, open-label trial to evaluate safety and efficacy of KOVALTRY in children with severe hemophilia A under prophylaxis therapy (Report # A51496; Leopold Kids).

In this study, there were a total of 50 previously treated patients (PTPs) ≤ 12 years of age (25 subjects > 6 – 12 years and 25 subjects aged 0-6 years). Subjects were treated with 25 – 50 IU/kg at least twice per week, or more frequently. Blood samples were obtained at pre-injection and at 20-30 min, 4 h, and 24 h after the end of injection of study medication. In vivo recovery 20-30 min after the end of the injection was determined at baseline, months 1, 2 and 6 (or final visit). In vivo recovery was only measured when the subject was not actively bleeding. Activity levels of KOVALTRY were determined in a central laboratory with the CS assay. The PK parameters were calculated by non-compartmental analysis.

Based on the CS assay, the PK parameters of KOVALTRY were as follows.

- PTPs 2-6 years of age: systemic clearance CL = 0.037 (% CV = 25.1%) dL/h/kg, terminal half-life t1/2 = 12 (%CV = 27%) hours, incremental in-vivo recovery IVR = 2.1 ± 0.5 IU/dL per IU/kg.
- PTPs 6-12 years of age: systemic clearance CL = 0.043 (% CV = 34.8%) dL/h/kg, terminal half-life t1/2 = 12 (% CV = 16.6%) hours, incremental in-vivo recovery IVR = 2.1 ± 0.5 IU/dL per IU/kg.

Based on the CS assay, the clearance of KOVALTRY was 37% and 59% higher (body weight adjusted) in children 0 – < 6 years and 6 – 12 years of age, respectively, compared to adults.
d) Conclusions

The following conclusions can be drawn from clinical pharmacology studies:

- The PK profile of KOVALTRY after single-dose administration (50 IU/kg) was at least non-inferior to that of Kogenate FS.
- In the repeat PK study, the PK parameters following the first dose were comparable with the PK parameters following 6 months of prophylactic treatment.
- The PK study in Japanese subjects was limited to 4 subjects. Slightly lower concentrations were measured using the OC assay, but mean half-life values were comparable to the CS assay.
- Based on the CS assay, the clearance of KOVALTRY was 37% and 59% higher (body weight adjusted) in children 0 – < 6 years and 6 – 12 years of age, respectively, as compared to adult subjects.

6. Clinical/Statistical

a) Clinical Program

Summary of Clinical Studies

The completed and ongoing clinical trials to support licensure of KOVALTRY for the proposed indication are summarized in the Tables below adapted from BLA 125574/0 Clinical Overview. (BAY81-8973=KOVALTRY).
The safety and efficacy of KOVALTRY were evaluated in a total of 193 individual PTPs (62 PTPs from Leopold I Part B dosed at 20-50 IU/kg 2-3 times per week, 80 PTPs from Leopold II dosed on demand and 20-40 IU/kg 2-3 times per week, and 51 PTPs from Leopold Kids dosed 25-50 IU/kg at least 2x/week) with severe hemophilia A (FVIII less than 1% of normal), who received at least one dose of KOVALTRY in three multicenter, open label clinical studies. Study subjects consisted of adult and adolescents (n= 142 with ≥150 prior EDs) and pediatric PTPs (≤12 years of age with ≥50 prior EDs; n=51). Thirteen subjects (12 from Leopold Extension) discontinued the studies prematurely secondary to reasons such as withdrawal by the patient, withdrawn consent, and one for an AE, non-compliance, and investigator’s decision.

The ongoing safety and efficacy extension trial in pediatric PTPs (≤12 years of age) and the PUPs study were formalized as post marketing commitments and will include ongoing monitoring for inhibitor development, as well as non-inhibitor binding antibodies against the product, FVIII, and HSP-70 and BHK cell impurities.

Efficacy Analysis

Routine Prophylaxis to Reduce the Frequency of Bleeding Episodes
Leopold II was a phase 2/3, randomized, cross-over trial conducted at 30 centers in 11 countries. Demographic and baseline characteristics were relatively similar in both arms, as all subjects had received on-demand treatment with FVIII and no regular prophylaxis for ≥6 consecutive months in the previous 5 years and target joint bleeds were present in 90% of the subjects. Ten of the subjects were adolescents (14 to 16 years of age). An intra-individual cross-over between 2 potency periods (CS/EP or CS/ADJ) was part of the design. Subjects were randomized to one of 6 treatment groups: either on-demand therapy, low-dose (20 to 30 IU/kg, 2x/week) prophylaxis
therapy or high-dose (30 to 40 IU/kg, 3x/week) prophylaxis therapy, each with the sequence CS/EP → CS/ADJ or the sequence CS/ADJ → CS/EP. (Refer to the table of clinical studies above).

The full analysis set consisted of a total of 80 subjects assigned to either on-demand therapy with KOVALTRY (n=21) or one of the prophylaxis regimens (n=59). Eighty subjects received at least one injection of KOVALTRY. One patient in the on-demand group discontinued the study for non-compliance with documentation of dosing, but all 80 subjects comprised the ITT population.

Subjects in the combined low dose and high dose prophylaxis group were dosed at a median dose of 31.2 IU/kg (median low dose: 30.4 IU/kg, median high-dose: 37.4 IU/kg), not including the treatment for breakthrough bleeds. The on-demand arm subjects were dosed at a median of 22 IU/kg. The median Annualized Bleeding Rate (ABR) [Interquartile Range (IQR)] in the ITT population was 2 bleeds/year [0-7] in the combined prophylaxis group compared to a rate of 60 bleeds/year [42-76] in the on-demand arm. Comparison of the ABRs in an ANOVA resulted in p<0.0001. The bleeding rate in the high dose prophylaxis group was lower when compared to the low dose prophylaxis group, which was also significantly different (p<0.0001). The results show a substantial reduction in ABR with routine prophylaxis as compared to on-demand treatment. These data are summarized in the table below.

Table 4: Annualized Bleeding Rate by Treatment for ≥12 years of age (ITT population)

<table>
<thead>
<tr>
<th>Bleeding Etiology</th>
<th>Combined Low Dose and High Dose Prophylaxis Group</th>
<th>On-demand</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median</td>
<td>Median</td>
</tr>
<tr>
<td>All bleeds</td>
<td>2</td>
<td>60</td>
</tr>
<tr>
<td>Spontaneous</td>
<td>1</td>
<td>42</td>
</tr>
<tr>
<td>Trauma</td>
<td>0</td>
<td>8</td>
</tr>
<tr>
<td>Joint</td>
<td>2</td>
<td>39</td>
</tr>
</tbody>
</table>

Source: Adapted from Applicant’s Table 2-4, Summary of Clinical Efficacy

Separate comparisons of bleeding rates for both potency assignments consistently resulted in p values of <0.0001. No clinically relevant differences in ABR were seen between the potency assignments.

KOVALTRY was demonstrated to be effective for reducing the frequency of bleeding episodes in hemophilia A subjects. The medical reviewer concluded that KOVALTRY was effective in reducing bleeding compared to on-demand use when administered as routine prophylaxis in adolescent and adult subjects with hemophilia A.

**On-demand Treatment and Control of Bleeding Episodes**

A total of 241 bleeds and 154 bleeds were reported during the efficacy period in Leopold I, Part B and the extension study, respectively. Most of the bleeds were joint bleeds (79% and 78%). In Leopold I, Part B, 208 (86%) bleeds were treated successfully with ≤2 injections. In the extension study, 136 (88%) were treated successfully with ≤2 injections.

A total of 1497 bleeds were reported during the efficacy period in Leopold II. There were 293 bleeds in the 59 subjects of the combined prophylaxis group and 1204 bleeds in the 21 subjects...
of the on-demand group. Irrespective of the treatment regimen, most of the bleeds were joint bleeds (77.2% in the on-demand group and 87.0% in the prophylaxis group). Seventy-six percent of the on-demand bleeds required one injection and 82% of the combined prophylaxis arm required one injection; 20% in the on demand arm required 2 injections and 12% in the combined prophylaxis arm required two injections; 5% in the on demand arm required 3 or more injections and 4% in the combined prophylaxis arm required 3 or more injections. None of the subjects in the on demand group remained bleed free during the study. Sixteen subjects in the prophylaxis group remained bleed free during the study.

The majority (>85%) of the bleeds/subjects were controlled with ≤2 injections in both of the studies, as also seen in other FVIII products. The median number of injections for the treatment of bleeds was consistently a single one in all studies. The medical reviewer therefore concluded that KOVALTRY was effective in adults and adolescents for on-demand treatment and control of bleeding episodes.

**Perioperative Management of Bleeding**

A total of 13 major and 46 minor surgical procedures (elective or emergent) were performed in and Leopold I Part B, C, and Extension Study and Leopold II. Dosing with KOVALTRY perioperatively could be used only after at least 20 bleeding events had been assessed. The safety and efficacy of KOVALTRY in the surgical setting was evaluated throughout the trial by a Data Monitoring Committee (DMC) and a formal evaluation of surgical outcomes was performed at the conclusion of both studies.

Seven of the 13 major surgeries were orthopedic procedures while most of the minor procedures were tooth extractions. Blood transfusions were needed in three major surgical procedures: a single patient for removal of pseudotumor twice and another patient for knee prosthesis. The assessment of hemostatic control with KOVALTRY provided by the investigators/surgeons was “good” or “excellent” for all types of surgery. The median dose for major surgery was 801 IU/kg and the median dose for minor surgery was 103 IU/kg.

Since all of the assessments of hemostatic control had “good” or “excellent” ratings as evaluated by investigators/surgeons and by the DMC, the medical reviewer concluded that KOVALTRY was effective in adults and adolescents for perioperative management of bleeding and that these data could be extrapolated to perioperative use of KOVALTRY in children.

**Bioresearch Monitoring (BIMO) Inspections**

BIMO inspections of three clinical study sites were performed in support of the BLA and were conducted in accordance with FDA’s Compliance Program Guidance Manual (CPGM) 7348.811, Inspection Program for Clinical Investigators. The three selected sites represented 2% and 15% of the enrolled subjects in Leopold I and Leopold II studies, respectively.

<table>
<thead>
<tr>
<th>Study (Site Number)</th>
<th>Study Site</th>
<th>Location</th>
<th>Number of Enrolled Subjects</th>
<th>Form FDA 483 Issued</th>
<th>Final Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leopold-I (14006)</td>
<td>University of California-Davis Hemophilia</td>
<td>Sacramento, California</td>
<td>2</td>
<td>Yes</td>
<td>OAI*</td>
</tr>
<tr>
<td></td>
<td>Treatment Center</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
The inspections at clinical sites 82001 and 82002 did not reveal significant issues that would impact the validity of the clinical data submitted in the BLA. The inspection at site 14006 noted additional unreported adverse events and bleeds, incorrect study drug administration, protocol deviations, inadequate record keeping by the clinical investigator, and deficiencies in reporting research activities to the Institutional Review Board (IRB).

In addition, CBER reviewed the inspection results and the Applicant’s response for the European Medicines Agency (EMA) inspections of clinical sites 54005 and 54001 for the Leopold II study. The EMA findings and the Applicant’s response to the EMA raised concerns for CBER with regard to study conduct at these sites. CBER requested monitoring reports for selected clinical sites from the Leopold I and Leopold II studies to independently assess the monitors’ findings of the EMA-inspected sites and other sites that were not inspected by the FDA.

Due to substantial deviations from the study protocol and inadequacies in overall study conduct by the clinical investigators, the Bioresearch Monitoring Branch recommended exclusion of two subjects at site 14006, eight subjects at site 54005, and one subject at site 54001 from final analyses of clinical data. A sensitivity analysis performed excluding these subjects did not impact the overall results of the Leopold I and II studies; the overall results had demonstrated the safety and efficacy of KOVALTRY for the proposed indications.

**b) Pediatrics**

The safety, efficacy, and pharmacokinetic profiles of KOVALTRY were established in pediatric PTP subjects less than 12 years of age in Leopold Kids Part A. This trial was a multicenter, open label, uncontrolled study with a single treatment group conducted at 25 centers in 12 countries. A total of 51 subjects participated in the study: 25 PTP were <6 years of age and 26 PTPs were between 6 to 12 years of age. The treatment group was comprised of 51 subjects and all but 1 subject were included in the per protocol population, as this patient was erroneously diagnosed with hemophilia A.

Prior to the study, 11 subjects had received on-demand treatment and 40 subjects had regular prophylaxis. The frequency of prophylaxis treatment was ≤2x/week (21 subjects), >2x/week (30 subjects). Individual dosages were selected by the investigator within the allowed dose range of 25 – 50 IU/kg. The median dose per infusion for prophylaxis was 34 IU/kg. A total of 23 subjects remained completely bleed free during the 6-month treatment period.

The median ABR was 1.9 bleeds/year with a minimally higher ABR (2 bleeds/year) in the younger cohort. A total of 97 bleeds were reported, and the percentage of subjects who experienced at least 1 bleed was 54.9%. The majority (73%) were trauma bleeds. The majority of bleeds were successfully treated with ≤2 injections. A total of 17% of bleeds did not require any additional doses of KOVALTRY beyond routine prophylaxis.
The median annualized number of total bleeds during prophylaxis treatment was markedly below the mean number of 4.0 bleeds during the previous 12 months before enrollment and the majority of bleeds were successfully treated with ≤2 injections of KOVALTRY. Therefore, the medical reviewer concluded that KOVALTRY was effective in reducing bleeding when administered as routine prophylaxis and for on-demand treatment and control of bleeding episodes in children with hemophilia A.

c) Other Special Populations

Not applicable to this BLA.

d) Overall Comparability Assessment

The manufacturing process for KOVALTRY was developed based on the current commercial Kogenate FS manufacturing process, with improvements in the DS manufacturing. No significant manufacturing or process scale-up changes were made between pre-clinical, clinical and conformance material production, except for minor measures implemented to improve process efficiency. All clinical material was generated at full manufacturing scale in Bayer’s licensed commercial facilities intended for commercial manufacture.

The Applicant conducted characterization studies and provided sufficient data to demonstrate biochemical and functional comparability between KOVALTRY batches used in the nonclinical and clinical studies and the commercial product. The material used in the clinical trials is representative of that manufactured by the commercial manufacturing process.

Efficacy Conclusions

KOVALTRY is effective in adults and children for on-demand treatment and control of bleeding episodes, perioperative management of bleeding, and for routine prophylaxis to reduce the frequency of bleeding episodes. The dosing and frequency for routine prophylaxis shown to be effective is 20-40 IU/kg 2 or 3 times a week for adults and 25-50 IU/kg 2-3 times a week or every other day for children ≤12 years.

7. Safety

Safety Summary

Safety variables recorded in the three phase 1 to 3 clinical studies included medical and disease history, adverse events (AEs) (in terms of their seriousness, severity, and relationship to the study drug), safety laboratory evaluations (e.g., chemistry, hematology, coagulation parameters, urinalysis), inhibitor development, antibodies (anti-HSP70 antibody and BHK cell impurities antibodies), and vital signs. Bleeding was monitored and considered an efficacy outcome; subjects were also monitored for development of inhibitors that could predispose to bleeding.

Adverse Reactions

There were no deaths in any of the trials presented in the BLA.
Integrated Analysis of Safety

Across all trials there were 133/193 (69%) subjects who reported at least one AE. The most frequently reported adverse events were headache, pyrexia, and pruritus. There were a total of 27 SAEs reported. Only one serious adverse event was judged to be possibly related to KOVALTRY, a myocardial infarction (MI) in a 62 year old male with several risk factors for cardiovascular events. This event occurred 4 hours after administration of KOVALTRY. There was only one subject who discontinued treatment due to an AE. This discontinuation was a four year old boy with a device related infection judged by the investigator not to be drug related.

AEs of special interest included immunogenicity, thrombosis, and hemolysis. There was a single case of a confirmed inhibitor (see below under Immunogenicity), one case of a MI, and no cases of hemolysis.

Immunogenicity

The immunogenicity of KOVALTRY was evaluated with regard to antibody development against FVIII (inhibitors), HSP70, and hamster proteins (BHK/HCP) in PTPs.

The majority of subjects had detectable levels of anti-HSP70 antibodies, which were below the 95th percentile determined in normal controls and defined as cut-off for normal values. There were 13 subjects with values above the cut-off level for positivity at any time (screening/baseline or during the study). Two subjects entered positive and became negative; one patient entered positive and remained positive; five entered negative and became transiently positive, five entered negative and became and remained positive. There were no clinical consequences of the antibodies.

Anti-BHK-HCP antibodies were also tested. Five subjects tested positive. Two subjects tested positive prior to the start of the study and became negative; two subjects were positive prior to the study and then became transiently negative; one patient entered positive and had negative results throughout the study. There were no clinical consequences of these antibodies.

There was one 13 year old PTP who developed a low titer inhibitor of 0.6 BU/ml at ED550 during an episode of acute pneumonia. The patient continued the treatment with the study drug without any change in dosing. No FVIII inhibitors were detected in adults PTPs.

No patterns of abnormal vital signs or physical examination findings were noted.

The KOVALTRY safety analysis in PUPs includes data that were available, as of April 15, 2015, from the ongoing Leopold Kids Part B study. This study has a targeted enrollment of ≥25 children <6 years of age with ≥50 EDs to any FVIII concentrate. Enrolled subjects receive prophylaxis treatment with KOVALTRY. The available results from the Leopold Kids Part B study show that 6 of 14 PUPs have developed inhibitors to KOVALTRY. The expected prevalence of inhibitor development in hemophilia A patients is approximately 30% in severe disease and less in mild or moderate disease. The highest is in PUPs with severe disease (3-52%). Thus, the preliminary data suggest that the inhibitor rate in PUPs treated with KOVALTRY is within the expected range. Final conclusions regarding the safety of KOVALTRY in PUPs will be made after study completion.
Pharmacovigilance

No post marketing surveillance data were submitted for review because as of December 2015, KOVALTRY had not been approved in any country. The available data from clinical trials submitted by Bayer in support of this BLA permitted an evaluation of potential safety concerns for KOVALTRY.

The data submitted in support of this BLA do not identify safety issues in the use of KOVALTRY for the treatment of bleeding episodes, including for long-term use in children and adult PTPs with severe hemophilia A. Any potential safety issues were adequately addressed by Bayer in their risk management plan.

Safety Conclusions

KOVALTRY is well tolerated in adults and pediatric patients. There were no unexpected adverse events. No inhibitory antibodies to FVIII were detected in adult Hemophilia A patients. One pediatric PTP of 142 PTPs (0.7%) developed an inhibitor to FVIII. However, this is an accepted rate (<1.25%) of inhibitors for this safety population based on previous Blood Products Advisory Committee recommendations. PUPs are at the greatest risk for inhibitor development. The ongoing PUPs study has shown an inhibitor rate in the expected range. Final conclusions regarding the safety in PUPs will be made after study completion.

8. Advisory Committee Meeting

The Division of Hematology Research and Review and the Division of Hematology Clinical Review in the Office of Blood Research and Review reviewed the information in this application and determined that referral to the Blood Products Advisory Committee prior to product approval was not needed for the following reasons (FDAAA [HR 3580-138 SEC. 918: REFERRAL TO ADVISORY COMMITTEE]):

- The new molecular entity provision (NME) does not apply to KOVALTRY as this product does not represent a novel product class. Recombinant FVIII products have been licensed in the U.S. since 1992 and have been used to control and prevent bleeding in hemophilia A patients.

- The mechanism of action of FVIII and its function in blood coagulation is well studied and understood. Upon activation by thrombin, FVIIIa acts as a cofactor for activated Factor IX, triggering a chain of biochemical reactions – activation of Factor X, which converts prothrombin into thrombin, and subsequent interaction of thrombin with fibrinogen resulting in the formation of a fibrin clot that potentially stops bleeding. When infused into a patient with hemophilia A, FVIII products temporarily replace the missing endogenous FVIII.

- KOVALTRY is a recombinant analog of human unmodified full-length FVIII. The amino acid composition of KOVALTRY is consistent with that predicted from the cDNA sequence of the expression construct and is identical to that of Kogenate FS. The functional characteristics, in vitro potency in standard clotting assays and clinical hemostatic activity of KOVALTRY are consistent with those of other human
recombinant as well as plasma-derived FVIII products, and enable the formation of a fibrin clot via the intrinsic coagulation pathway.

- The manufacturing process for KOVALTRY includes two viral clearance steps – detergent treatment for virus inactivation and nanofiltration for virus removal, and no human or animal derived materials are used in the manufacture or formulation of KOVALTRY. Together, this assures product safety with regard to adventitious viruses.

- The proposed indication for KOVALTRY is similar to that of other U.S. licensed recombinant FVIII products for patients with hemophilia A.

- The design of the clinical studies to evaluate the safety and efficacy of KOVALTRY for the proposed indications was adequate and the efficacy and safety results of the studies did not raise any concerns.

- Review of information submitted in the BLA for KOVALTRY did not raise any controversial issues or pose unanswered scientific questions which would have benefited from Advisory Committee discussion and recommendations.

9. Other Relevant Regulatory Issues

The notable issues raised in the course of the review are described in the respective sections of this document, and they have been satisfactorily resolved through information requests and teleconferences. There were no other relevant regulatory issues.

10. Labeling

a) Proprietary Name

The proposed proprietary name, KOVALTRY, was reviewed by the Advertising and Promotional Labeling Branch (APLB), and was found to be acceptable on March 3, 2015. KOVALTRY was determined to be acceptable as the proprietary name for the product by the Agency on May 21, 2015.

b) Prescribing Information/Carton and Container Labels

The product labeling (i.e., prescribing information, patient package insert, and instructions for use) and the product package and container labels were reviewed, commented, and/or revised by the appropriate discipline reviewers and by the APLB from a promotional and comprehension perspective.

FDA comments regarding the product labeling were initially conveyed to the Applicant on November 4, 2015, and negotiated throughout months of December, 2015 and January – March, 2016. The final version of Full Prescribing Information (FPI) submitted on March 15, 2016 was determined to be acceptable. Carton and container labels submitted to the BLA on January 28, 2016 were considered acceptable. A copy of FPI is attached.
11. Recommendation and Benefit/Risk Assessment

a) Recommended Regulatory Action

The CBER review committee recommends APPROVAL of this BLA for Antihemophilic Factor (Recombinant), under the proprietary name KOVALTRY. The manufacturing process for KOVALTRY is considered adequately validated and controlled. Efficacy and safety clinical data for KOVALTRY support a favorable benefit/risk determination for use in adults and children with hemophilia A for the following indications:

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

b) Benefit/Risk Assessment

The benefits of KOVALTRY for the proposed indications are considered to outweigh the risks. Effective hemostasis in treatment and control of bleeding episodes, perioperative management of bleeding, and routine prophylaxis was demonstrated in children and adult subjects with severe hemophilia A. Efficacy of KOVALTRY for these indications appears comparable to that of licensed recombinant and plasma-derived Antihemophilic Factor (Human) products.

The safety concerns for this product are thrombogenicity and immunogenicity. There was one case of an MI possibly related to KOVALTRY. Regarding immunogenicity, KOVALTRY is produced in genetically engineered BHK cells, similar to its predecessor, Kogenate FS. Kogenate FS has been reported to have an increased inhibitor development rate in PTPs and PUP. The formation of FVIII inhibitors was observed in one pediatric PTP treated with KOVALTRY (n=51). In the ongoing PUPs trial, Leopold Kids Part B, the inhibitor rate is currently 42.9% (n=14). The final study report for this ongoing trial will provide further evidence and data in regard to the risk of immunogenicity in PUPs, as the ability to clearly define the risk for inhibitor development is limited by the current study size. Some PTPs developed anti-BHK and anti-HSP antibodies, but those patients were either positive at baseline, or showed fluctuations in antibody titers with no trending pattern. Those patients did not have any clinical sequelae attributed to the formation of these antibodies, and so these antibodies are considered to be of low risk.

c) Recommendation for Post Marketing Requirement Risk Management Activities

The available data do not suggest a safety concern that would necessitate either a Risk Evaluation and Mitigation Strategy (REMS) or a required post-marketing (PMR) study.

d) Recommendation for Post Marketing Activities

POSTMARKETING STUDIES SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

As stated in Amendment 47 dated February 18, 2016, Bayer commits to the following:
1. Bayer HealthCare LLC commits to collecting additional safety and efficacy information of KOVALTRY in patients with hemophilia A in a clinical study in 25 previously untreated patients under Protocol 13400 “A multi-center Phase III uncontrolled open-label trial to evaluate safety and efficacy of BAY 81-8973 (KOVALTRY) in children with severe haemophilia A under prophylaxis therapy”
   
   - Final protocol submission: December 20, 2010 (completed)
   - Study/Clinical trial completion: February 28, 2019
   - Final Report submission: August 31, 2019

2. Bayer HealthCare LLC commits to collecting additional safety and efficacy information of KOVALTRY in patients with hemophilia A in an extension clinical study under Protocol 13400 “A multicenter Phase III uncontrolled open-label trial to evaluate safety and efficacy of BAY 81-8973 (KOVALTRY) in children with severe haemophilia A under prophylaxis therapy”
   
   - Final protocol submission: December 20, 2010 (completed)
   - Study/Clinical trial completion: December 31, 2020
   - Final Report submission: June 30, 2021

**POSTMARKETING STUDIES NOT SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B**

As stated in Amendment 36 dated October 20, 2015, Bayer commits to the following:


   Final Report Submission: June 30, 2016