DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

Our STN: BL 125574/0 **BLA APPROVAL**

Bayer HealthCare LLC
Attention: Ms. Vicki Chen
100 Bayer Boulevard
PO Box 915
Whippany, NJ 07981-0915

Dear Ms. Chen:

Please refer to your Biologics License Application (BLA) for Antihemophilic Factor (Recombinant) dated December 16, 2014, received December 16, 2014, submitted under section 351(a) of the Public Health Service Act (PHS Act).

LICENSING

We have approved your biologics license application for Antihemophilic Factor (Recombinant) effective this date. You are hereby authorized to introduce or deliver for introduction into interstate commerce Antihemophilic Factor (Recombinant) under your existing Department of Health and Human Services U.S. License No. 0008. Antihemophilic Factor (Recombinant) is indicated for use in adults and children with hemophilia A for: (1) on-demand treatment and control of bleeding episodes; (2) perioperative management of bleeding; and (3) routine prophylaxis to reduce the frequency of bleeding episodes.

The review of this product was associated with the following National Clinical Trial (NCT) numbers: NCT01029340, NCT01233258, and NCT01311648.

MANUFACTURING LOCATIONS

Under this License, you are approved to manufacture Antihemophilic Factor (Recombinant) at the Bayer HealthCare LLC facility in [redacted] You may label your product with the proprietary name KOVALTRY and market it in single-use vials containing nominally 250 international units (IU), 500 IU, 1000 IU, 2000 IU, or 3000 IU of factor VIII potency per vial. The diluent (Sterile Water For Injection in pre-filled syringe) will be manufactured at the [redacted] facilities in [redacted]

ADVISORY COMMITTEE

We did not refer your application to the Food and Drug Administration Blood Products Advisory Committee because our review of information submitted in your biologics license application (BLA), including the clinical study design and trial results, did not raise concerns or controversial issues which would have benefited from an advisory committee discussion.

DATING PERIOD

The dating period for Antihemophilic Factor (Recombinant) drug product shall be 30 months from the date of manufacture when stored at +2°C to +8°C. During the dating period, drug product may be stored at temperatures up to +25°C for a single period of up to 12 months. The date of manufacture shall be defined as the date of final sterile filtration of the formulated drug product. Following the final sterile filtration, no reprocessing/reworking is allowed without prior approval from the Agency. The dating period for your drug substance shall be [redacted] when stored at [redacted]

FDA LOT RELEASE

You are not currently required to submit samples or protocols of future lots of Antihemophilic Factor (Recombinant) to the Center for Biologics Evaluation and Research (CBER) for release by the Director, CBER, under 21 CFR 610.2. We will continue to monitor compliance with 21 CFR 610.1 requiring completion of tests for conformity with standards applicable to each product prior to release of each lot.

BIOLOGICAL PRODUCT DEVIATIONS

You must submit reports of biological product deviations under 21 CFR 600.14. You should identify and investigate all manufacturing deviations promptly, including those associated with processing, testing, packing, labeling, storage, holding and distribution. If the deviation involves a distributed product, may affect the safety, purity, or potency of the product, and meets the other criteria in the regulation, you must submit a report on Form FDA-3486 to the Director, Office of Compliance and Biologics Quality, at the following address:

Food and Drug Administration
Center for Biologics Evaluation and Research
Document Control Center
10903 New Hampshire Ave
WO71-G112
Silver Spring, MD 20993-0002

MANUFACTURING CHANGES

You must submit information to your biologics license application for our review and written approval under 21 CFR 601.12 for any changes in, including but not limited to, the manufacturing, testing, packaging or labeling of Antihemophilic Factor (Recombinant), or in the manufacturing facilities.

LABELING

We hereby approve the draft package insert labeling submitted under amendment 52, dated March 15, 2016 and the draft carton and container labeling submitted under amendment 43, dated January 28, 2016.

Please provide your final content of labeling in Structured Product Labeling (SPL) format and include the carton and container labels. In addition, please submit three original paper copies for carton and container final printed labeling. All final labeling should be submitted as Product Correspondence to this BLA, STN BL 125574, at the time of use (prior to marketing) and include implementation information on FDA Form 356h.

In addition, please submit the final content of labeling (21 CFR 601.14) in SPL format via the FDA automated drug registration and listing system, (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Information on submitting SPL files using eLIST may be found in the guidance for industry titled, "*SPL Standard for Content of Labeling Technical Qs and As"* at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

You may submit two draft copies of the proposed introductory advertising and promotional labeling with an FDA Form 2253 to the Advertising and Promotional Labeling Branch at the following address:

Food and Drug Administration
Center for Biologics Evaluation and Research
Document Control Center
10903 New Hampshire Ave
WO71-G112
Silver Spring, MD 20993-0002

You must submit copies of your final advertisement and promotional labeling at the time of initial dissemination or publication, accompanied by Form FDA 2253 (21 CFR 601.12(f)(4)).

All promotional claims must be consistent with and not contrary to approved labeling. You should not make a comparative promotional claim or claim of superiority over other products unless you have substantial evidence or substantial clinical experience to support such claims (21 CFR 202.1(e)(6)).

ADVERSE EVENT REPORTING

You must submit adverse experience reports in accordance with the adverse experience reporting requirements for licensed biological products (21 CFR 600.80) and you must submit distribution reports as described in 21 CFR 600.81. For information on adverse experience reporting, please refer to the guidance for industry *Providing Submissions in Electronic Format —Postmarketing Safety Reports* at http://www.fda.gov/Drugs/DrugSafety/ucm400526.htm and FDA's Adverse

Event reporting System website http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm115894.htm. For information on distribution reporting, please refer to the guidance for industry *Electronic Submission of Lot Distribution Reports* at http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/PostMarketActivities/LotReleases/ucm061966.htm.

PEDIATRIC REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We note that you have fulfilled the pediatric study requirement for all relevant pediatric age groups for this application.

AGREED UPON POSTMARKETING COMMITMENTS

POSTMARKETING STUDIES SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We acknowledge your written commitments as described in your letter of February 18, 2016, as outlined below:

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

Please submit clinical protocols to your IND 14035, and a cross-reference letter to this BLA, STN BL 125574, explaining that these protocols were submitted to the IND. If the information in the final study report supports a change in the labeling, the final study report must be submitted as a supplement. Supplements in support of labeling changes based on a postmarketing study report may be subject to a user fee. Please use the following designators to prominently label all submissions, including supplements, relating to these postmarketing study commitments as appropriate:

- **Postmarketing Commitment – Protocol**
- **Postmarketing Commitment – Correspondence**
- **Postmarketing Commitment – Final Study Report**
- **Supplement contains Postmarketing Commitments – Final Study Report**

For each postmarketing study subject to the reporting requirements of 21 CFR 601.70, you must describe the status in an annual report on postmarketing studies for this product. Label your annual report an **Annual Status Report of Postmarketing Requirements/Commitments** and submit it to the FDA each year within 60 calendar days of the anniversary date of this letter until all Requirements and Commitments subject to the reporting requirements of section 506B of the FDCA are fulfilled or released. The status report for each study should include:

- the sequential number for each study as shown in this letter;
- information to identify and describe the postmarketing commitment,
- the original schedule for the commitment,
- the status of the commitment (i.e., pending, ongoing, delayed, terminated, or submitted), and
- an explanation of the status including, for clinical studies, the patient accrual rate (i.e., number enrolled to date and the total planned enrollment).

As described in 21 CFR 601.70(e), we may publicly disclose information regarding these postmarketing studies on our Web site at (http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Post-marketingPhaseIVCommitments/default.htm).

POSTMARKETING STUDIES NOT SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We acknowledge your written commitment as described in your letter of October 20, 2015, as outlined below:

3. Bayer HealthCare LLC commits to validating a [redacted] assay and submitting the results in a Changes Being Effected in 30 Days (CBE-30) Supplement by June 30, 2016.

    - Final Report Submission: June 30, 2016

We request that you submit information concerning nonclinical and chemistry, manufacturing, and control postmarketing commitments and final reports to your BLA, STN BL 125574. Please refer to the sequential number for each commitment.
Please use the following designators to label prominently all submissions, including supplements, relating to these postmarketing study commitments as appropriate:

- **Postmarketing Commitment – Status Update**
- **Postmarketing Commitment – Final Study Report**
- **Supplement contains Postmarketing Commitment – Final Study Report**

For each postmarketing commitment not subject to the reporting requirements of 21 CFR 601.70, you may report the status to FDA as a **Postmarketing Commitment – Status Update**. The status report for each commitment should include:

- the sequential number for each study as shown in this letter;
- the submission number associated with this letter;
- describe what has been accomplished to fulfill the non-section 506B PMC; and,
- summarize any data collected or issues with fulfilling the non-section 506B PMC.

When you have fulfilled your commitment, submit your final report as **Postmarketing Commitment – Final Study Report** or **Supplement contains Postmarketing Commitment – Final Study Report**.

PDUFA V APPLICANT INTERVIEW

FDA has contracted with Eastern Research Group, Inc. (ERG) to conduct an independent interim and final assessment of the Program for Enhanced Review Transparency and Communication for NME NDAs and Original BLAs under PDUFA V ('the Program'). The PDUFA V Commitment Letter states that these assessments will include interviews with applicants following FDA action on applications reviewed in the Program. For this purpose, first-cycle actions include approvals, complete responses, and withdrawals after filing. The purpose of the interview is to better understand applicant experiences with the Program and its ability to improve transparency and communication during FDA review.

ERG will contact you to schedule a PDUFA V applicant interview and provide specifics about the interview process. Your responses during the interview will be confidential with respect to the FDA review team. ERG has signed a non-disclosure agreement and will not disclose any identifying information to anyone outside their project team. They will report only anonymized results and findings in the interim and final assessments. Members of the FDA review team will be interviewed by ERG separately. While your participation in the interview is voluntary, your feedback will be helpful to these assessments.

Sincerely,

Jay S. Epstein, MD
Director
Office of Blood Research and Review
Center for Biologics Evaluation and Research