

# MEMORANDUM



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



**From:** Natalya Ananyeva, PhD, Committee Chair and Product Reviewer, Laboratory of Hemostasis (LH), Division of Hematology Research and Review (DHRR)/OBRR

**To:** Basil Golding, MD, Director, DHRR/OBRR  
Paul Mintz, MD, Director, Division of Hematology Clinical Review (DHCR)/OBRR

**Subject:** Designation of BLA STN 125574/0.33 as a Major Amendment

## **DESIGNATION OF AMENDMENT 125574/0.33 AS MAJOR**

Biologics License Application (BLA), STN 125574/0, for Antihemophilic Factor (Recombinant) with the proposed proprietary name KOVALTRY was submitted by Bayer HealthCare, LLC (Bayer) on 16 December 2014. The application is on a standard 12-month review schedule under the PDUFA V Program, with the Action Due Date (ADD) on 16 December 2015.

On 25 September 2015, Baxter submitted amendment STN 125574/0.33 containing monitoring reports from the requested clinical sites for the Leopold I and II studies which are the culmination of an ongoing dialogue between Bayer and the Agency regarding assessment of safety and efficacy of KOVALTRY in hemophilia patients. On behalf of the review committee for BLA STN 125574/0, and based on the initial recommendation from the Bioresearch Monitoring Branch (BMB)/Division of Inspections and Surveillance (DIS) (memo attached), I recommend designation of STN 125574/0.33 as a Major Amendment.

## **BACKGROUND**

FDA conducted a Bioresearch Monitoring (BIMO) inspection for the Leopold I study at the U.S. Clinical Site 14006 during August 17-21, 2015. The FDA investigator identified significant deviations from applicable FDA regulations in the study conduct as described in the memorandum from the BMB. Based on the review of the documents collected at the clinical site and Bayer's responses to the Form FDA-483 observations, the BMB recommended the exclusion of two subjects from analyses of safety and efficacy.

The findings of the European Medicine Agency (EMA) inspections of Chinese Clinical Sites 54005 and 54001 for the Leopold II study (submitted to CBER by the Applicant on 14 August 2015) identified substantial deviations from the study protocol and inadequate documentation of medical history. The EMA findings and the Applicant's response raised concern for FDA with regard to study conduct at these sites, and the BMB made a preliminary recommendation to exclude the nine subjects' data from our analyses (please refer to the memorandum from the BMB).

On 11 September 2015, CBER requested that the Applicant submit their monitoring reports for selected clinical sites from the Leopold I and Leopold II studies in order to independently assess the findings from the EMA inspection and study conduct at sites that were not inspected by the FDA. These reports were submitted on 25 September 2015 in Amendment 33.

### **JUSTIFICATION FOR MAJOR AMENDMENT DESIGNATION**

SOPP 8402 and the PDUFA V Program define a Major Amendment as a submission of information to a pending application that extends the review clock. According to section V.D. of SOPP 8402, an amendment may be qualified as major when it contains a substantial amount of new information and data not previously submitted to or reviewed by the Agency.

Amendment STN 125574/0.33 came to FDA within three (3) months before the ADD and contains:

- A substantial amount of new clinical information and data not previously submitted to or reviewed by the Agency. Specifically, the monitoring reports from Clinical Sites 14001, 39001 and 65001 for the Leopold I study and from Sites 54001, 54002, 54003, 54004 and 54005 for the Leopold II study which amount to a total of 3295 pages.
- This information will require review by the BMB/DIS/OCBQ to assess the monitoring reports for study conduct; may require additional review by the DHCR/OBRR Clinical reviewer to decide which subjects should be included in the analysis; and a possible subsequent re-analysis of the studies for safety and efficacy by the Clinical reviewer.
- The review of new information will require additional information and new analyses from the Applicant to be submitted in a future amendment as discussed at the Late-Cycle Meeting on 8 October 2015.
- Labeling review will depend on the outcome of the review and re-analysis of the clinical data.

STN 125574/0.33 meets the criteria of SOPP 8402 and the PDUFA V Program by the amount (3295 pages) and type of information (critical for assessment of safety and efficacy of KOVALTRY) and thus qualifies for a Major Amendment. In addition, Amendment 33 was received by the FDA at a late stage of the review process and is linked to a future projected amendment. Therefore, designation of Amendment 33 as major and extension of the review schedule are justified to allow adequate time for thorough multi-disciplinary reviews and new analyses of clinical data to assess safety and efficacy of KOVALTRY.

### **NEW ACTION DUE DATE**

According to section V.E.1.b. of SOPP 8402 and the PDUFA V Program, a Major Amendment extends the ADD of an original application by three (3) months. If the Major Amendment designation receives concurrence by the DHRR and DHCR Directors, the new ADD for BLA STN 125574/0 will be **16 March 2016**.