

# MEMORANDUM



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



**To:** Administrative File for BLA (STN 125574/0)  
Natalya Ananyeva, PhD, Chair, Laboratory of Hemostasis (LH)/ Division of Hematology Research and Review (DHRR)/OBRR  
Pratibha Rana, RPM, RPMS/IOD/OBRR

**From:** Alexey Khrenov, PhD, Senior Staff Fellow, LH/DHRR/OBRR

**Through:** Tim Lee, PhD, Acting Chief, LH/DHRR/OBRR  
Basil Golding, MD, Director, DHRR/OBRR

**Subject:** Final review of the *Validation of Analytical Procedures* in Bayer's original BLA for Antihemophilic Factor (Recombinant) [KOVALTRY]

## EXECUTIVE SUMMARY

This memorandum summarizes the review of the sections related to the *Validation of Analytical Procedures* of the original BLA under STN 125574/0 for Antihemophilic Factor (Recombinant), (Applicant – Bayer Healthcare LLC, USA; proposed proprietary name – KOVALTRY; company code BAY 81-8973). This review is for the analytical procedures used for the control of drug substance (DS) including the procedures used for both drug product (DP) and DS. Tests for (b) (4) in the DP were also reviewed by this reviewer.

The review of analytical procedures used exclusively in the control of the DP (except (b) (4) ), as well as methods for the control of bioburden and endotoxin (b) (4) was performed by reviewers from the Division of Biological Standards and Quality Control (DBSQC).

All analytical methods used for the characterization of the identity, purity, quality and safety of the (b) (4) have been adequately validated to support their intended use in the manufacture of KOVALTRY. Thus, the information on analytical methods supports the approval of the BLA.

## BACKGROUND

KOVALTRY is a recombinant analogue of human plasma-derived Factor VIII (pdFVIII), which has the identical domain structure - (b) (4) . Similar to pdFVIII, KOVALTRY is (b) (4)

The protein is

expressed in a Baby Hamster Kidney (BHK) cell line and the protein sequence and upstream manufacturing process is the same as those for Bayer's licensed product KOGENATE FS.

KOVALTRY is different from KOGENATE FS in that it is produced using a new cell substrate, which co-expresses the gene for human heat shock protein 70 (HSP70) that improves FVIII productivity. Also, a number of (b) (4) steps are performed using technologies different from those used in KOGENATE FS manufacturing. Unlike KOGENATE FS, which uses a one-stage clotting assay for potency assignment, KOVALTRY potency is assigned using a chromogenic substrate assay.

The proposed indications for KOVALTRY are: (1) on-demand treatment and control of bleeding episodes, (2) perioperative management of bleeding, and (3) routine prophylaxis to prevent or reduce the frequency of bleeding episodes, in adults and children with hemophilia A.

KOVALTRY DS and DP are manufactured at the Bayer Facility in (b) (4). KOVALTRY is supplied in single-use glass vials containing 250, 500, 1000, 2000, and 3000 International Units (IU). It is reconstituted with 2.5 mL sterile Water for Injection (sWFI) for the 250 IU, 500 IU and 1000 IU presentations, and with 5 mL sWFI for the 2000 IU and 3000 IU presentations. KOVALTRY is administered by intravenous injection after reconstitution.

## **REVIEW SUMMARY**

### **Modules reviewed (including relevant documents supplied in appendices and amendments):**

3.2.S.3.2 Impurities  
3.2.S.2.4 Control of Critical Steps and Intermediates  
3.2.S.4.2 Analytical Procedures  
3.2.S.4.3 Validation of Analytical Procedures  
3.2.S.5 Reference Standards or Materials

3.2.P.5.2 Analytical Procedures  
3.2.P.5.3 Validation of Analytical Procedures  
3.2.P.6 Reference Standards or Materials

3.2.R Regional Information (selected documents)

### **Review History**

The application was submitted on 16 December 2014. The BLA was reviewed under the standard schedule of the PDUFA V program. Amendment 125574/0.33 submitted on 25 September 2015 was classified as a *major amendment* on 16 October 2015 and the Action Due Date was extended from 16 December 2015 to 16 March 2016.

The only issue raised by this reviewer on the assay for (b) (4) was communicated to the company in the Late-Cycle Meeting Package sent on 25 September 2015.

Bayer responded to my comments in amendment 125574/0.36 and during the Late-Cycle Meeting.

### **Narrative:**

The descriptions of the analytical procedures and respective summary validation reports for (b) (4) DP was provided in sections 3.2.S and 3.2.P, including section 3.2.S.2.4 Control of Critical Steps and Intermediates. However, only summaries of the validation studies were provided in these sections and the original validation reports were provided in section 3.2.R. This practice was unconventional, but did not affect the review, as relevant documents were found and reviewed. The methods covered by this memorandum are listed in Table 1. Other analytical procedures used in the manufacture of KOVALTRY were reviewed by DBSQC (see respective memos).

**Table 1. Method validations/verifications reviewed.**

<b>Parameter</b>	<b>Method</b>	<b>Part of Specification for</b>
(b) (4)	(b) (4)	(b) (4)
pH	(b) (4)	(b) (4)
Color	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
Purity by (b) (4)	(b) (4)	(b) (4)/DP
(b) (4)	(b) (4)	(b) (4)/DP
(b) (4)	(b) (4)	(b) (4)/DP
Chromogenic Potency	Chromogenic Substrate assay	(b) (4)/DP
Specific Activity (Chromogenic Potency/Total Protein Content)	(b) (4)	(b) (4)/DP
Total Protein Content	(b) (4)	(b) (4)/DP
Identity by (b) (4)	(b) (4)	DP
(b) (4)	(b) (4)	DP
Potency: One-Stage Clotting assay	One-Stage Clotting assay	Not part of specifications

This memorandum outlines the issues raised during the review of the BLA and does not contain descriptive information which is found in the BLA. If the section of the BLA is not mentioned in the review, it is because no issues were identified.



## GENERAL COMMENTS

It must be noted that the KOVALTRY protein has the (b) (4) to that of the currently licensed KOGENATE FS. As such, analytical procedures used for the control of KOVALTRY are mostly the same as those used for KOGENATE FS. These procedures were established and validated a long time ago and successfully used for an extended period of time. However, validation/verification exercises were performed to confirm their performance in the analysis of KOVALTRY.

No issues were identified in the review of the validation of analytical procedures. All the test methods reviewed are sufficiently described in their respective SOPs and adequately validated in accordance with ICH Guideline Q2(R1). The validation exercises were adequate, and the validation reports were of sufficient detail. Of note, rigorous statistical data analysis was also performed during validations.

An acceptable reference standard qualification and maintenance program has been established. Two separate reference standards are used in the testing of (b) (4): *Working Potency Standard*, used for potency testing, and *Product Reference Standard*, utilized in other analytical procedures requiring a reference standard. The potency assignment of the *Clinical Working Potency Standard* used for the testing of clinical lots was performed using the WHO (b) (4) International Standard (IS); and that of the current *Working Potency Standard* was performed using the WHO (b) (4) IS.

(b) (4)



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

While the clinical significance of (b) (4) is not established, adequate control of this parameter is considered crucial both from the safety and process consistency standpoint. We consider the differences observed to be significant enough to request the development of a new (b) (4) assay, using the KOVALTRY-specific (b) (4), characterized in the BLA.

Bayer agreed to a Post-Marketing Commitment (PMC) to validate a (b) (4) assay and will submit the results in a Changes Being Effected in 30 Days (CBE-30) Supplement by June 30, 2016. As the current assay still allows for the control of the majority of (b) (4) in KOVALTRY, and (b) (4) in the manufacturing process was demonstrated, the risk of its continual use is minimal, and a PMC is acceptable.

## CONCLUSION

*Suitable analytical methods have been validated to support quality control testing throughout the manufacture and release of the drug substance of KOVALTRY. The design of the validation protocols and analysis of the validation data were appropriate and statistically sound.*

*I recommend approval of the BLA for KOVALTRY from the perspective of analytical methodology.*