

# 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 125566/0)  
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Research and Review (DHRR)/OBRR  
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**CC:** Tim Lee, PhD, Acting Chief, LH/DHRR/OBRR

**Subject:** Final consult review of the *Analytical Methods* sections in Baxter's original BLA for Antihemophilic Factor (Recombinant), PEGylated [ADYNOVATE]

## EXECUTIVE SUMMARY

This memorandum summarizes the consult review of the *Analytical Methods* sections of the original BLA under STN 125566/0 for Antihemophilic Factor (Recombinant), PEGylated (Applicant – Baxter International, USA; proposed proprietary name – ADYNOVATE; company code BAX855). This review is for the procedures used for control of drug substance only. The review of the analytical procedures used in control of drug product, as well as the methods for control of bioburden and endotoxin in (b) (4) was performed by the reviewers from the Division of Biological Standards and Quality Control.

All analytical methods used for the characterization of the (b) (4) of the drug substance have been adequately validated to support their intended use in the manufacture of ADYNOVATE. Thus, the information on analytical methods supports the approval of the BLA.

## BACKGROUND

ADYNOVATE is a recombinant analogue of human plasma-derived Factor VIII (pdFVIII), which has identical domain structure - A1-A2-B-A3-C1-C2. Similar to pdFVIII, ADYNOVATE is synthesized as a single chain and prior to its secretion is cleaved to the heavy chain (A1-A2-B) and light chain (A3-C1-C2) held together by a metal ion ( $\text{Ca}^{2+}$  or  $\text{Cu}^{2+}$ ) bridge. The protein is expressed in a CHO cell line and the protein sequence and upstream manufacturing process is the

same as for Baxter licensed product ADVATE. ADVATE and ADYNOVATE use the same bulk drug substance (BDS)

ADYNOVATE is different from ADVATE, in that during manufacture of ADYNOVATE, ADVATE BDS is chemically conjugated with 20 kDa branched polyethylene glycol (PEG) polymer, which is attached to the protein molecule through (b) (4) residues. Although full-length rFVIII contains (b) (4) residues, the reaction conditions are optimized to achieve the conjugation degree of (b) (4) moles of PEG per mole of protein.

The PEG moiety is conjugated to rFVIII in order to increase the plasma half-life through at least one known mechanism, the reduction of the receptor-mediated clearance of the FVIII molecule.

The proposed indication for ADYNOVATE is control and prevention of bleeding episodes and routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and adolescent patients with Hemophilia A.

In the manufacture of ADYNOVATE, the ADVATE BDS manufactured either at Baxter's (b) (4) facilities according to BLA 125063 is used. The BDS is shipped to the (b) (4) facility where PEG conjugation and following purification and formulation steps are performed, and ADYNOVATE (b) (4) BDS is produced. This BDS is then shipped to the (b) (4) facility where formulation, sterile filtration, aseptic filling into vials and lyophilization are performed. Four nominal dosage strengths of 250, 500, 1000, 2000 IU/vial are manufactured. Final labeling and secondary packaging is performed at Baxter's (b) (4) facility.

## **REVIEW SUMMARY**

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

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

### **Review History**

The application was submitted as on 25 November 2014. The BLA was reviewed under the normal schedule of the PDUFA V program.

An information request (IR) was sent on June 30, 2015 with questions regarding analytical procedures. The response to IR was received on July 16, 2015 as part of amendment 125566/0.19, which was reviewed and deemed mostly adequate. A follow-up IR was sent on July 17, 2015. The response to IR was received on July 29, 2015 as part of amendment

125566/0.24, which was reviewed and considered adequate. The texts of IR's sent are provided in the appendix.

**Narrative:**

**DRUG SUBSTANCE SPECIFICATION AND ANALYTICAL PROCEDURES**

**Table 1. ADYNOVATE BDS Specification**

(b) (4)

The specifications and analytical procedures for BDS control the physicochemical properties, (b) (4). The excipients are controlled at the DP stage.

The descriptions of the analytical procedures and their validation are provided in sections 3.2.S.4.2 Analytical Procedures, 3.2.S.4.3 Validation of Analytical Procedures and 3.2.S.5

Reference Standards or Materials, which are reviewed below (except for Bioburden and Endotoxin tests reviewed by DBSQC).

It must be noted that the specification of BDS is limited due to the fact that ADVATE BDS is used as starting material with a number of key quality attributes controlled at the release of ADVATE BDS. As such, the choice of analytical procedures and design of their respective validations are aligned to their intended purpose, which is the control of the effects of PEGylation and following steps in ADYNOVATE BDS manufacturing process from ADVATE starting material. This approach is acceptable.

#### **Procedures not requiring validation**

(b) (4)

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

(b) (4) .

14 pages determined not to be releasable

standard was documented through analytical method validation and documented in the analytical procedure.

*The company possesses a set of well-characterized reference standards suitable for characterization and commercial release of FBDS and DP.*

## **CONCLUSION**

*All analytical methods used for the characterization of (b) (4) of ADYNOVATE bulk drug substance have been adequately validated to support the control of the quality of the product and its specifications. The company possesses a set of well-characterized reference standards suitable for characterization and commercial release of the BDS.*

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

## **APPENDIX**

### **Information requests sent to the company.**

#### **IR sent on June 30, 2015.**

1. In regards to method validation report (b) (4)-65-09180 "Total PEG in Bax855 (b) (4)"
  - a. The range of the assay is not properly validated. While the range of the assay is claimed to be (b) (4) of total PEG, all the studies, except specificity, were performed by (b) (4) (b) (4) PEG in the analyzed samples. Please perform supplemental validation of the assay range; or alternatively, re-evaluate the current range and its suitability for the intended purpose of the assay.
  - b. Please provide details on how the data presented in Appendices 2 and 3 were calculated for each concentration point.
  - c. Please clarify when the PEG standard was spiked to (b) (4) - before or after the (b) (4).

2. In regards to method validation report (b) (4)-65-205Z “PEG Distribution in BAX855 (b) (4)
  - a. Please submit the development report (b) (4)-65-2052O, referenced in the validation report.
  - b. The conclusions regarding the robustness of the assay were made in the absence of pre-determined acceptance criteria. Please clarify how robustness was established.
  - c. The precision and intermediate precision of the assay were not established in regards to the (b) (4) steps. Please validate these parameters by performing the test using multiple (b) (4) of the same (b) (4) sample.
3. In regards to method validation report 2012-BAX855(b) (4)-RFPQ1 “Report of validation of the Method “DETERMINATION DE L’ACTIVITE DU FVIII RECOMBINANT (rAHF) (b) (4) ) A L’AIDE DU (b) (4) ” for the quantification of the BAX855 (b) (4) samples.”
  - a. The data for accuracy validation presented in section 7.3 of the report demonstrate significant dependence of the assay results from (b) (4) in all matrices. Thus, the assay results may be affected by changing (b) (4) within the established range (b) (4). Please control this factor by introducing into the test instruction the system suitability criteria for sample concentration.
  - b. The data for robustness validation presented in section 7.4 of the report demonstrate a significant (b) (4) trend for both matrices (the difference between the first and last sample in the series is (b) (4)). The acceptance criterion format (% CV from mean value) is not statistically appropriate under the circumstances. Thus, the assay results may be significantly affected by the elapsed time. Please control this factor by limiting the duration of analysis cycles in the test instruction.
  - c. The summary of deviation 7540 provided in the report is unclear. Please provide detailed information regarding deviation 7540.

**IR sent on July 17, 2015.**

With reference to your 16 July 2015 response to FDA Question 1b dated 30 June 2015, we take exception to the way you calculated the recoveries of total PEG. Table 1 of validation protocol (b) (4)-65-09180 demonstrates that the specificity samples were prepared by (b) (4)

However, the calculation scheme you presented does not reflect that. To account for the (b) (4) in the specificity sample, an adjustment needs to be made. In your example, your calculation for (b) (4) Total PEG is as follows:

(b) (4)

However, the (b) (4)

*Total PEG* should be:

((b) (4)

If our understanding of your sample preparation is correct, please re-calculate the data in Appendices 2 and 3, and re-evaluate the method performance in the validation report.