



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration  
Silver Spring MD 20993

Our STN: BL 125591/0

CSL Behring Recombinant Facility AG  
Attention: Mr. Kevin Darryl White, MBA, RAC  
c/o CSL Behring L.L.C.  
1020 First Avenue  
PO Box 61501  
King of Prussia, PA 19406

Dear Mr. White:

Please refer to your Biologic License Application (BLA) submitted under section 351(A) of the Public Health Service Act for Antihemophilic Factor (Recombinant), Single Chain [AFSTYLA], in vials containing 250, 500, 1000, 2000 or 3000 IU for intravenous injection after reconstitution.

Attached are our meeting materials, including our agenda, for the Late-Cycle Meeting (LCM) scheduled for February 18, 2016, 3:30 pm – 5:00 pm EST.

If you have any questions, please contact the Regulatory Project Manager, LT Thomas J. Maruna, MSc, MLS (ASCP)<sup>CM</sup>, CPH at (240) 402-8454 or [thomas.maruna@fda.hhs.gov](mailto:thomas.maruna@fda.hhs.gov).

Sincerely,

Basil Golding, MD  
Director  
Division of Hematology Research and Review  
Office of Blood Research and Review  
Center for Biologics Evaluation and Research

ENCLOSURE:  
Late-Cycle Meeting Materials

## **Late-Cycle Meeting Materials**

**Meeting Date and Time:** February 18, 2016, 3:30 pm – 5 pm EST

**Meeting Location:** Federal Research Center - Building 71, Room 1208  
10903 New Hampshire Avenue  
Silver Spring, MD 20993

**Application Number:** BL 125591/0

**Product Name:** Antihemophilic Factor (Recombinant), Single Chain [AFSTYLA]

**Indication:** In adults and children with hemophilia A (congenital Factor VIII deficiency) 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.

**Sponsor/Applicant Name:** CSL Behring Recombinant Facility AG (CSL)

## **INTRODUCTION**

The purpose of a Late-Cycle Meeting (LCM) is to share information and to discuss any substantive review issues that we have identified to date, Advisory Committee (AC) meeting plans (if scheduled), and our objectives for the remainder of the review. The application has not yet been fully reviewed by the signatory authorities, division directors, and application Chair. Therefore, the meeting will not address the final regulatory decision for the application. We are sharing this material to promote a collaborative and successful discussion at the meeting.

During the meeting, we may discuss additional information that could be submitted to address any identified issues. We may also discuss whether the submission of such information would be expected to trigger an extension of the PDUFA goal date if the review committee should decide, upon receipt of the information, to review it during the current review cycle.

Please note: if you submit any new information in response to the issues identified in this background package prior to this LCM, we may not be prepared to discuss that information at this meeting.

## **1. Discipline Review Letters**

No Discipline Review letters have been issued to date.

## **2. Substantive Review Issues to be discussed during the LCM**

### **Chemistry, Manufacturing and Controls**

#### **a. Discrepancies in (b) (4) testing results between data in the BLA and in-support testing performed at FDA.**

During in-support testing of lots (b) (4) (both 250 IU dosage strength) by (b) (4) both samples exhibited (b) (4) recombinant factor VIII (rFVIII) which was not observed in samples of higher dosage strengths. (b) (4) failing the acceptance criteria for (b) (4) Release limit and (b) (4) Shelf-life limit). This information was communicated in an information request (IR) on 20 January 2016. CSL submitted the response on 3 February 2016, which is currently under review.

#### **b. Deficiencies in method validation and specifications.**

Review of method validation and specifications identified multiple deficiencies which were communicated to CSL in IRs on 17 and 18 December 2015. CSL submitted partial responses to the IRs in amendments dated 30 December 2015, 8 January and 29 January 2016, which are currently under review. CSL proposed to submit the rest of the responses by 29 February 2016. The adequacy of the information to fully resolve these deficiencies will be determined upon review of CSL's responses, and additional information may be requested during the review.

### **Inspections**

During the inspection of the (b) (4) contract manufacturing facilities in (b) (4), FDA reviewers did not identify any deficiencies in the manufacture of AFSTYLA bulk drug intermediate. Final recommendation is pending at this time. However, if we learn of any issues the agenda will be modified accordingly.

### **Clinical**

An IR is currently being drafted to be sent next week concerning the discrepancy between the FVIII activity measurements provided by the one-stage (OS) and chromogenic substrate (ChS) assays. We have reviewed all of the submitted data, including the field study data, and would like to discuss your proposed conversion factor of (b) (4); specifically, whether a factor of 2.0 may be more appropriate.

One element of the forthcoming IR will ask you to plot the individual laboratory results for your product from the field study in a scatter plot of OS vs. ChS as you have done in 2.7.1 Summary of Biopharmaceutical Studies on pages 30 – 33.

We would also like to discuss your proposal for a communication strategy as part of your pharmacovigilance plan, in addition to the labeling strategy you have already proposed, to help to ensure the least amount of confusion on the part of providers when dosing and assessing the effectiveness of your product based on the OS assay. A request for you to propose additional communication strategies will be part of the forthcoming IR as well.

#### **Non-clinical pharmacology / toxicology**

There are no substantive review issues at this time.

#### **Clinical pharmacology**

There are no substantive review issues at this time.

#### **Biostatistics**

There are no substantive review issues at this time.

#### **Bioresearch Monitoring**

There are no substantive review issues at this time.

#### **Pharmacovigilance**

Please see 'Clinical' section above with reference to need for a communication plan to clinicians regarding dosing using the chromogenic vs. OS assay. This communication strategy will need to be incorporated into the pharmacovigilance plan.

#### **Labeling**

Please see the indications stated in the header. We plan to discuss the changes we have made to your proposed indications. These changes are based on our recent attempts to standardize the indications for all antihemophilic factor products.

#### **Amendments**

We acknowledge the receipt of your amendments listed below:

- a. 30 December 2015 amendment #14 (**partial** response to FDA IR dated 17 December 2015 regarding validation of bioburden and endotoxin methods).
- b. 8 January 2016 amendment #15 (**partial** response to FDA IR dated 18 December 2015 regarding specifications and method validations).
- c. 29 January 2016 amendment #18 (**partial** response to FDA IR dated 18 December 2015 regarding specifications and method validations).
- d. 29 January 2016 amendment #20 (response to FDA IR dated 17 December 2015 regarding validation of methods to measure bioburden and endotoxin).
- e. 3 February 2015 amendment #21 (response to FDA IR dated 20 January 2016 regarding discrepancies in between (b) (4) results presented in the BLA and those from in-support testing).

A review of this amendment is ongoing and a final decision of this issue is pending.

We also acknowledge the receipt of amendments #16, 17 and 19, which had been reviewed.

### **Outstanding Information Requests**

Pending IRs and their status are listed below.

- a. An IR for the controls of critical steps and intermediates, quality control assays for the drug substance and drug product, their validation reports and release specifications was sent on 18 December 2015. CSL submitted partial responses on 8 January and 29 January 2016; complete responses are still pending.

### **3. Advisory Committee Meeting**

An Advisory Committee meeting is not planned.

### **4. Risk Management Actions (e.g., REMS)**

While we do not believe that a risk management action (e.g., REMS) is needed at this time, a strategy to address potential risks associated with potency assay discrepancies will need to be developed.

## **LCM AGENDA**

1. Introductory Comments – 10 minutes (RPM/Chair)

Welcome, Introductions, Ground rules, Objectives of the meeting

2. Discussion of Substantive Review Issues – 30 minutes (*INCLUDE IF APPLICABLE*):

Each issue will be introduced by FDA and followed by a discussion.

- a. *Measures to mitigate the issues caused by discrepancies between one-stage clotting and chromogenic assays.*
- b. *Discrepancies in (b) (4) testing results*
- c. *Methods validation and specifications*

3. Information Requests – 10 minutes
4. Postmarketing Requirements/Postmarketing Commitments – 10 minutes
5. Major labeling issues – 10 minutes
6. Review Plans – 5 minutes
7. Applicant Questions – 10 minutes
8. Wrap-up and Action Items – 5 minutes

**Concurrence Page**

Application Number(s): BL 125591/0

Letter Type: Late-Cycle Briefing Document

cc: EDR

**History:**

Drafted: Thomas J. Maruna/ January 20, 2016  
Reviewed: Alexey Khrenov/ February 4 & 5, 2016  
Reviewed: Mitchell Frost/ February 5, 2016  
Reviewed: Howard Chazin/February 5, 2016  
Reviewed: Jennifer Reed/ February 5, 2016  
Reviewed: Adamma Mba-Jonas/February 5, 2016  
Reviewed: Mahmood Farshid/ February 5, 2016  
Reviewed: Trevor Pendley/ February 5, 2016

**Concurrence:**

<b>Office/Division</b>	<b>Name</b>
<b>OBRR/IO</b>	<b>Thomas J. Maruna</b>
<b>OBRR/DHRR</b>	<b>Trevor Pendley</b>
<b>OBRR/DHRR</b>	<b>Basil Golding</b>