DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

May 25, 2016

Our STN: BL 125591/0

BLA APPROVAL LETTER

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

Dear Mr. White:

Please refer to your Biologics License Application (BLA) for Antihemophilic Factor (Recombinant), Single Chain dated May 29, 2015, submitted under section 351(a) of the Public Health Service Act (PHS Act).

We have approved your BLA for Antihemophilic Factor (Recombinant), Single Chain effective this date. CSL Behring Recombinant Facility AG is hereby authorized to introduce or deliver for introduction into interstate commerce, Antihemophilic Factor (Recombinant), Single Chain under their existing Department of Health and Human Services U.S. License No. 2009. Antihemophilic Factor (Recombinant), Single Chain is indicated in children and adults with hemophilia A (congenital Factor VIII deficiency) for: (1) on-demand treatment and control of bleeding episodes, (2) routine prophylaxis to reduce the frequency of bleeding episodes, and (3) perioperative management of bleeding.

The review of this product was associated with the following National Clinical Trial (NCT) numbers: NCT01486927, NCT02172950, and NCT02093897.

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture Antihemophilic Factor (Recombinant), Single Chain bulk [redacted] The drug substance, the final formulated product including filling, labeling, packaging and the diluent, Sterile Water for Injection, will be manufactured at CSL Behring GmbH, located at Emil-von-Behring-Strasse 76, 35041 Marburg, Germany.

You may label your product with the proprietary name AFSTYLA and market it in dosage strengths of 250, 500, 1000, 2000 and 3000 international units (IU) per vial. The dosage sizes will be presented in either 6-mL (250, 500 and 1000 IU) or 10-mL (2000 and 3000 IU) single-use glass vials.

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

DATING PERIOD

The dating period for Antihemophilic Factor (Recombinant), Single Chain shall be 36 months from the date of manufacture when stored at +5°C (± 3°C). It can be stored for a single period of up to 3 months at +25°C within the expiration date. If stored at +25°C the product should not be refrigerated again and shall expire after 3 months, or after the expiration date on the product vial, whichever is earlier.

The date of manufacture shall be defined as the date of final sterile filtration of the formulated drug product. The final sterile filtration of formulated drug product according to the validated procedure . 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 when stored at

FDA LOT RELEASE

You are not currently required to submit samples or protocols of future lots of Antihemophilic Factor (Recombinant), Single Chain to the Center for Biologics Evaluation and Research (CBER) for release by the Director, CBER, under 21 CFR 610.2(a). 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, packaging, 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 BLA 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), Single Chain, or in the manufacturing facilities.

LABELING

Under 21 CFR 201.57(c)(18), patient labeling must be referenced in section 17 PATIENT COUNSELING INFORMATION. Patient labeling must be available and may either be reprinted immediately following the full prescribing information of the package insert or accompany the prescription product labeling.

We hereby approve the draft package insert labeling submitted under amendment 45, dated May 20, 2016, and the draft carton and container labeling submitted under amendment 38, dated May 6, 2016.

We acknowledge your statement of commitment, in your May 6, 2016, submission, to issue a Dear Health Care Provider - Important Prescribing Information letter within 60 days of this approval letter to alert healthcare providers about important information regarding monitoring laboratory tests.

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 125591, at the time of use (prior to marketing) and include implementation information on Form FDA 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 *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 Form FDA 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 advertising 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 ages 0 to 17 years for this application.

POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIRMENTS UNDER SECTION 506B

We acknowledge your written commitments as described in your letters of March 8, 2016, and April 15, 2016, as outlined below:

1. CSL Behring Recombinant Facility AG (CSL Behring) commits to assess data after producing [redacted] commercial scale GMP batches to revise the acceptance criteria of the [redacted] CSL Behring commits to perform an interim statistical re-assessment of the alert limits after evaluating commercial scale GMP batches manufactured by May 31, 2017, and submit the interim report as a Changes Being Effected Supplement by July 31, 2017. CSL Behring commits to submit the final acceptance criteria as a Prior Approval Supplement by September 30, 2018.

Final Study Report Submission: September 30, 2018

2. CSL Behring commits to investigate the [redacted].

   Final Report Submission: May 31, 2017

3. CSL Behring commits to develop and validate an [redacted] method in which the [redacted].

   Final Report Submission: May 31, 2017

We request that you submit information concerning nonclinical and chemistry, manufacturing, and control postmarketing commitments and final reports to your BLA, STN BL 125591. Please refer to the sequential number for each commitment.

Please use the following designators to prominently label 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**.

POST APPROVAL FEEDBACK MEETING

New biological products qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, please contact the Regulatory Project Manager for this application.

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 committee. 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 committee will be interviewed by ERG separately. While your participation in the interview is voluntary, your feedback will be helpful to these assessments.

Sincerely,

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