



Our STN: BL 125591/0

CSL Behring Recombinant Facility AG
Attention: Kevin Darryl White, MBA, RAC
1020 First Avenue
PO Box 61501
King of Prussia, PA 19406

Dear Mr. White:

Attached is a copy of the memorandum summarizing your February 18, 2016, Late-Cycle Meeting with CBER. This memorandum constitutes the official record of the meeting. If your understanding of the meeting outcomes differs from those expressed in this summary, it is your responsibility to communicate with CBER in writing as soon as possible.

Please include a reference to BL 125591/0 in future submissions related to the subject product.

If you have any questions, please contact LT Thomas J. Maruna, USPHS, MSc, MLS(ASCP), CPH at (240) 402-8454 or thomas.maruna@fda.hhs.gov.

Sincerely,

Iliana Valencia, MS, MCPM
Chief
Regulatory Project Management Staff
Office of Blood Research and Review
Center for Biologics Evaluation and Research

Late-Cycle Meeting Summary

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
Proposed Indications: (1) Control and prevention of bleeding episodes, (2) Routine prophylaxis to prevent or reduce the frequency of bleeding episodes, and (3) Perioperative management (surgical prophylaxis), in adults and children with hemophilia A (congenital Factor VIII deficiency)
Applicant Name: CSL Behring Recombinant Facility AG
Meeting Chair: Alexey Khrenov, PhD
Meeting Recorder: Thomas J. Maruna, MSc, MLS(ASCP), CPH

FDA ATTENDEES

Meghna Alimchandani, MD, CBER/OBE/DE
Natalya Ananyeva, PhD, CBER/OBRR/DHRR/LH
Victor Baum, MD, CBER/OBRR/DHCR/HPRB
Yolanda Branch, PhD, CBER/OBRR/DHCR/TRS
Karen Campbell, CBER/OCBQ/DBSQC/QAB
Howard Chazin, MD, MBA, CBER/OBRR/DHCR
Haecin Chun, CBER/OCBQ/DIS/BMB
Christine Drabick, CBER/OCBQ/DIS/BMB
LCDR Donald Ertel, MT(ASCP), CBER/OCBQ/DMPQ/BI
Mahmood Farshid, PhD, CBER/OBRR/DHRR
Mitchell Frost, MD, CBER/OBRR/DHCR/HPRB
Basil Golding, MD, CBER/OBRR/DHRR
Patricia Holobaugh, CBER/OCBQ/DIS/BMB
Jessica Hu, PhD, CBER/OBE/DB/TEB
Alexey Khrenov, PhD, CBER/OBRR/DHRR/LH
Tim Lee, PhD, CBER/OBRR/DHRR/LH
LT Thomas J. Maruna, MSc, MLS(ASCP), CBER/OBRR/IO
Adamma Mba-Jones, MD, CBER/OBE/DE/PB
Ginette Y. Michaud, MD, CBER/OBRR
Ze Peng, PhD, CBER/OBRR/DHRR/LH
Anne Pilaro, PhD, CBER/OBRR/DHCR/TRS
Lisa Stockbridge, PhD, CBER/OCBQ/DCM/APLB
Mark Weinstein, MD, CBER/OBRR
Claire Wernly, CBER/OCBQ/DBSQC/LMIVTS

EASTERN RESEARCH GROUP (ERG) ATTENDEES

Christopher Sese, CDER/OSP

APPLICANT ATTENDEES

Angela Azzara

Debra Bensen-Kennedy, MD

Dirk Bruns-Nagel

Catarina Edfjaell, PhD

Elisa Foltz

Hubert Metzner

Inna Pendrak

Martina Schneider

Norbert Schulze

Katie St. Ledger

Anthony Stowers, PhD

Alex Veldman, MD

Kevin Darryl White, MBA, RAC

Baldev Rana

BACKGROUND

BLA 125591/0 was submitted on May 29, 2016, for Antihemophilic Factor (Recombinant), Single Chain

Proposed indication(s): Control and prevention of bleeding episodes, Routine prophylaxis to prevent or reduce the frequency of bleeding episodes, Perioperative management (surgical prophylaxis) in adults and children with hemophilia A (congenital Factor VIII deficiency)

PDUFA goal date: May 28, 2016

In preparation for this meeting, FDA issued the Late-cycle Meeting Materials on February 5, 2016.

DISCUSSION:

1. Substantive Review Issues

Clinical:

Measures to mitigate the issues caused by discrepancies between one-stage clotting and chromogenic assays in patients' monitoring.

FDA confirmed that use of the chromogenic substrate (ChS) assay for potency assignment is acceptable.

FDA has reviewed the February 17, 2016, amendment to the BLA and concludes the data provided support the use of a conversion factor of ^{(b) (4)} for dose adjustment. The value of

2.0 might be better for ease of use but FDA understands that conversion factor of (b) (4) has been submitted to other health authorities, and use of different factors in different regions may cause confusion. Therefore, FDA indicated that it is open to the use of either conversion factor (b) (4) 2.0). CSLB requested and FDA agreed to continued negotiation concerning the conversion factor.

With respect to the communication plan proposed in the February 17, 2016, BLA amendment, FDA agreed to CSLB's proposals, requested clarification concerning the degree of coverage CSLB hopes to achieve, the duration and if surveillance activities designed to monitor efficacy of the program have been planned. CSLB stated that the preponderance of communication is expected to take place immediately following licensure at professional society meetings in seminar booths and through medical science liaisons; they have requested additional time to develop a surveillance plan. FDA asked that CSLB consider including patients, patient groups, and hospital based pharmacists in the communication plan.

FDA will provide separate written feedback on the proposed communication plan by next week.

Chemistry, Manufacturing and Controls:

FDA characterized the remaining CMC issues as minor and stated that they are likely to be resolved within the first review cycle. The following issues were discussed:

a. Discrepancies in (b) (4) test results

FDA stated that the information provided in the response to the related information request (IR) is reviewed, and in general considered acceptable. The data supported CSL's position that the (b) (4)

However, additional information is needed to fully resolve this issue and an IR was recently sent to CSLB. FDA noted that CSLB had previously been aware of this (b) (4) but did not inform FDA and did not mention it in the specification. Such situations should be avoided in the future.

b. Method validation and specifications

Most of the issues have been resolved. However, there are still outstanding issues on the verification of the performance of the (b) (4) at commercial scale, and the quality of the (b) (4) to evaluate of the (b) (4) of these (b) (4) CSLB is to submit the responses on February 29, 2016.

In the IR, FDA requested CSLB to revise Section 3.2.S.4.1 *Specification for the Drug Substance* to include updated acceptance criteria for (b) (4). CSLB explained that because there is insufficient data to establish statistically sound limits, the specification for (b) (4) is currently for reporting only and the quantitative limits are established as alert limits. FDA agreed that the specifications for (b) (4) do not

need to be updated at this time. Instead, CSLB will develop a post-marketing commitment to update these specifications on specified fulfillment dates.

c. Cell bank post-approval stability protocol

With reference to an FDA request to include genetic stability testing for the master and working cell banks, CSLB responded that the stability protocol included (b) (4), which should be sufficient to monitor stability. FDA stated that it may not be sufficient since some parameters (e.g., (b) (4)) cannot be monitored in the absence of genetic stability tests. Also, FDA noted that it is common practice to perform genetic stability testing for cell banks, which should not be a significant burden because genetic stability needs only to be verified infrequently, e.g., once every 10 years. CSLB should provide justifications if they do not include genetic stability testing in the post-approval stability protocol for the cell banks.

Inspections

No Form FDA 483 was issued at the (b) (4) inspection. The *Establishment Inspection Report* is being prepared and the inspection will be closed in a few weeks.

2. Postmarketing Requirements/Postmarketing Commitments

As requested in the IR dated February 17, 2016, CSLB will draft a postmarketing commitment with fulfillment dates to establish (b) (4) specifications when the data from (b) (4) batches are available.

3. Major labeling issues

FDA communicated that the requested change in the indication language from “control and prevention” to “on-demand treatment and control” is to resolve confusion about language related to prevention translating to prophylaxis. FDA also stated that these changes will be requested of sponsors of already licensed products when/if they submit supplements to their approved applications.

FDA introduced the idea of including language about overdosing, particularly in elderly individuals with mild hemophilia A. CSLB provided justification for why this was not necessary. Additional labeling comments will be sent to CSLB in the near future.

END

Concurrence Page

Application Type and Number: BLA 125591/0

Communication Type:

History:

Drafted: Thomas J. Maruna/ February 19, 2016

Revised: Alexey Khrenov/March 7 & 10, 2016

Revised: Victor Baum/March 9, 2016

Revised: Mitchel Frost/ March 1, 2016

Revised: Tim Lee/ March 9, 2016

Reviewed: Howard Chazin/ March 10, 2016

QC: Sonday Kelly/ March 10, 2016

QC: Trevor Pendley/ March 10, 2016

Concurrence:

Office/Division	Name
OBRR/IO	Thomas J. Maruna
OBRR/DHRR	Trevor Pendley
OBRR/DHRR	Alexey Khrenov
OBRR/DHCR	Victor Baum
OBRR/DHRR	Timothy Lee
OBRR/DHCR	Mitchell Frost
OBRR/DHRR	Basil Golding
OBRR/DHCR	Howard Chazin
OBRR/IO	Iliana Valencia