



Our STN: BL 125582/0

Late Cycle Meeting Summary

CSL Behring Recombinant Facility AG
Attention: Mr. Kevin D. White
CSL Behring
1020 First Avenue
PO Box 61501
King of Prussia, PA 19406-0901

Dear Mr. White:

Attached is a copy of the memorandum summarizing your August 25, 2015 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 as soon as possible.

If you have any questions, please contact Edward Thompson at (240) 402-8443.

Sincerely yours,

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

Late-Cycle Meeting Summary

Meeting Date and Time: August 25, 2015, 1:30 to 3:30 p.m., EDT

Meeting Location: Building 2, Room 2047
Federal Research Center
10903 New Hampshire Avenue
Silver Spring, MD 20993

Application Number: BL STN 125582/0

Product Name: Coagulation Factor IX (Recombinant), Albumin Fusion Protein [IDELVION]

Proposed Indications: In children and adults with hemophilia B (congenital Factor IX 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.

Applicant Name: CSL Behring Recombinant Facility AG (CSLB)

Meeting Chair: Ginette Michaud, MD

Meeting Recorder: Edward Thompson

FDA ATTENDEES

Bethany Baer, MD, Medical Officer, Division of Epidemiology, OBE
Karen Campbell, Biologist, Division of Biological Standards and Quality Control, OCBQ
Howard Chazin, MD, MBA, Deputy Director, Division of Hematology Clinical Review, OBRR
Chunrong Cheng, PhD, Mathematical Statistician, Division of Biostatistics, OBE
Christine Drabick, Consumer Safety Officer, Division of Inspections and Surveillance, OCBQ
John Eltermann, RPh, MS, Director, Division of Manufacturing and Product Quality, OCBQ
Donald Ertel, LCDR, Regulatory Review Officer, Division of Manufacturing and Product Quality, OCBQ
Mahmood Farshid, PhD, Deputy Director, Division of Hematology Research and Review, OBRR
Lisa Faulcon, MD, Medical Officer, Division of Hematology Clinical Review, OBRR
Basil Golding, MD, Director, Division of Hematology Research and Review, OBRR
Wayne Hicks, PhD, Chemist, Division of Hematology Research and Review, OBRR
Patricia Holobaugh, Chief, Bioresearch Monitoring Branch, Division of Inspections and Surveillance, OCBQ
Alexey Khrenov, PhD, Senior Staff Fellow, Division of Hematology Research and Review, OBRR
Chava Kimchi-Sarfaty, PhD, Research Chemist, Division of Hematology Research and Review, OBRR

Tim Lee, PhD, Acting Chief, Laboratory of Hemostasis, Division of Hematology Research and Review, OBRR

Yideng Liang, MD, PhD, Visiting Scientist, Division of Hematology Research and Review, OBRR

Ginette Y. Michaud, MD, Deputy Director, OBRR

Paul D. Mintz, MD, Director, Division of Hematology Clinical Review, OBRR

Loan Nguyen, PharmD, Consumer Safety Officer, Division of Case Management, OCBQ

Mikhail V. Ovanesov, PhD, Senior Staff Fellow, Division of Hematology Research and Review, OBRR

Ze Peng, PhD, Staff Fellow, Division of Hematology Research and Review, OBRR

L. Ross Pierce, MD, Medical Officer, Division of Hematology Clinical Review, OBRR

Renee Rees, PhD, Mathematical Statistician, Division of Biostatistics, OBE

Carolyn Renshaw, Chief, Review Branch I, Division of Manufacturing and Product Quality, OCBQ

Andrey Sarafanov, PhD, Chemist, Division of Hematology Research and Review, OBRR

Zuben Sauna, PhD, Senior Staff Fellow, Division of Hematology Research and Review, OBRR

Lisa Stockbridge, PhD, Chief, Advertising and Promotional Labeling Branch, Division of Case Management, OCBQ

Edward Thompson, RPM, OBRR

Mark J. Weinstein, PhD, Associate Deputy Director, OBRR

EASTERN RESEARCH GROUP (ERG) ATTENDEES

Christopher Sese, Independent Assessor, Eastern Research Group, Inc.

Peggha Khorrami, Independent Assessor, Eastern Research Group, Inc.

APPLICANT ATTENDEES

CSL Behring Recombinant Facility AG

Kevin Darryl White, MBA, RAC, Director, Regulatory Affairs & Site Head of KOP

Debra Bensen-Kennedy, MD, Therapeutic Area Head, Clinical Research and Development

Iris Jacobs, MD, Senior Global Clinical Program Director, Clinical R&D

Jay Newman, Senior Director, CMC Lead, R&D

Reiner Laske, PhD, Vice President Quality Management

Karl Fickenscher, PhD, Director Analytical Services Quality

Hartmut Landgrebe, PhD, Associate Director, Global Regulatory Affairs, Global Regulatory Lead

Monica Richardson, Manager, Global Regulatory Affairs, Regional Lead

Anthony Stowers, PhD, Senior Vice President, Recombinant Product Development

BACKGROUND

BL STN 125582/0 was submitted on December 5, 2014, for Coagulation Factor IX (Recombinant), Albumin Fusion Protein.

CSLB's proposed wording for the indications:

For patients with hemophilia B (congenital Factor IX deficiency) for:

- Routine prophylaxis to prevent or reduce the frequency of bleeding episodes,
- Control and prevention of bleeding episodes,
- Control and prevention of bleeding in the perioperative setting.

PDUFA goal date: December 4, 2015

In preparation for this meeting, FDA issued the Late-cycle Meeting Materials on August 12, 2015.

DISCUSSION

Introductory Comments:

FDA welcomed CSL Behring (CSLB) and the agenda items were introduced.

FDA explained that the meeting is not intended to discuss the pending regulatory decision on the application.

- 1. FDA presented the substantive issues, pending amendments for review, pending information requests (IR) for response from CSLB and advisory committee information.**

Chemistry, Manufacturing and Controls (CMC)

a. Deficiencies in method validation

Review of method validation identified multiple deficiencies that could be traced back to deficiencies in the standard operating procedures (SOPs) identified during the facility inspection. CSLB proposed to submit four amendments to address these deficiencies in method validation – on 15 July, 15 August, 15 September, and 30 September. These deficiencies are critical in that they have negative impact on several CMC aspects, including process validation, manufacturing controls, process development, and comparability studies.

b. Insufficient control of the albumin moiety

The proposed release assays are inadequate to control the quality of the albumin moiety. Specifically, analysis of albumin by (b) (4) is not validated as a quantitative assay. FDA acknowledges CSLB's 23 June 2015 proposal to re-validate the analysis of albumin by (b) (4) and to evaluate other approaches to develop release assays for the albumin moiety. The data analysis of albumin (b) (4) is not valid and needs to be redone. This information was communicated in an IR on 23 July 2015.

c. Deficiencies in justifications of specifications

The release specifications were not adequately justified. For example, the acceptance criteria for albumin by (b) (4) are not adequate to control product quality. The validations of many analytical methods are also deficient. These issues were communicated to CSLB in IRs on June 12 and July 20, 2015, and CSLB has committed to submitting the responses by September 30, 2015. The adequacy of the information to fully resolve these deficiencies will be determined upon review of CSLB's responses, and additional information may be required during the review.

d. Deficiencies in comparability studies

Inconsistencies in results from comparability studies of product lots manufactured at pilot vs. commercial scale, in (b) (4) Marburg, Germany, were identified. Of particular concern were the results from (b) (4) which indicated qualitative differences between the lots produced at the (b) (4) and those produced at the (b) (4). Deficiencies were communicated to CSLB in an IR on 23 July 2015.

e. FDA noted that CSLB's responses to deficiencies in extractable and leachable studies were received and reviewed by the FDA and are considered acceptable.

Facility inspection

During the pre-license inspection of the CSLB facilities in Marburg, Germany on 28 May – 5 June 2015, FDA reviewers documented on Form FDA 483 (issued to CSLB on 5 June 2015) 19 observations citing deficiencies in the manufacture of IDELVION. CSLB provided responses to these inspectional observations on 26 June 2015. Final recommendation is pending a complete review of these responses.

Clinical

Postmarketing Studies subject to reporting requirements of 21 CFR 601.70

During the review, four subjects were noted to have proteinuria. FDA requested further discussion of CSLB's plans, if any, to further evaluate the association between the proteinuria and rFIX.

Labeling

In a request dated 16 July 2015, FDA requested that CSLB conform to the Agency's efforts to harmonize labeling for blood coagulation factors, which removed the word "prevent" to avoid confusion between the "on-demand treatment and control" indication and the "routine prophylaxis" indication. CSLB responded with a proposal to retain the word "prevent" in the on-demand and prophylaxis indications. FDA continues to recommend that CSLB change the label as requested on 16 July 2015.

There are no substantive review issues at this time for the following disciplines:

- Non-clinical Pharmacology/Toxicology
- Clinical Pharmacology
- Biostatistics
- Bioresearch Monitoring
- Pharmacovigilance

Amendments

FDA acknowledged the receipt of CSLB amendments listed below:

- a. 29 July 2015 amendment #25 (response to FDA IR dated 15 July 2015 regarding residual moisture (b) (4))
- b. 30 July 2015 amendment #26 (response to FDA IR dated 16 July 2015 regarding the language for indication and usage claims)
- c. 31 July 2015 amendment #27 (partial response to FDA IR dated 17 July 2015 regarding method revalidation studies)
- d. 31 July 2015 amendment #28 (response to FDA IR dated 17 July 2015 regarding leachables)
- e. 7 August 2015 amendment #29 (response to FDA IR dated 23 July 2015 regarding characterization of post-translational modifications)
- f. 10 August 2015 amendment #30 (response to FDA IR dated 20 July 2015 regarding method validation and specifications and post-approval stability protocol and commitment)
- g. 10 August 2015 amendment #31 (response to FDA IR dated 13 July 2015 regarding proteinuria)

These amendments are under active review, and additional information may be requested should the need arise.

Outstanding Information Requests

The pending IRs with their status are listed below:

- a. An IR for: (1) the control of critical steps and intermediates and (2) quality control assays for the drug substance and drug product, their validation reports, and release specifications was sent on 12 June 2015 with responses due by 23 July 2015. Partial responses were received on 23 June and 15 July 2015; complete responses are pending.

- b. An additional IR regarding quality control assays for the drug substance and drug product and their validation reports was sent on 17 July 2015. Partial responses were received on 31 July 2015; complete responses are pending.

Advisory Committee Meeting

Presentation of the BLA at the *Blood Products Advisory Committee* is not planned.

2. Questions from CSL Behring

CSLB presented their pending actions for the application:

- a. August 31, 2015: CSLB plans to submit method validation reports.
- b. September 15, 2015: CSLB plans to submit the last portion of specification updates with justification.
- c. September 30, 2015: CSLB plans to submit data on the host cell protein antibody coverage.
- d. October 16, 2015: CSLB plans to update the eCTD sections in quality modules with respect to method validation, setting specifications and comparability studies.

FDA requested an update on validation of the release assay to control the albumin moiety. CSLB stated that the method revalidation data will be submitted in the 15 September 2015 amendment.

With regard to observed inconsistencies in results from comparative (b) (4) [REDACTED] FDA asked CSLB to comment on two possible explanations for the discrepant results: (a) poor comparability caused by poor robustness of (b) (4) methods or (b) real differences in product characteristics at small and commercial scales. CSLB stated that the investigation was performed, and that robustness of the method was improved. CSLB also stated that the study is ongoing but preliminary data point to the sensitivity of the (b) (4) method to the presence of (b) (4) in the product. The (b) (4) [REDACTED] polysorbate-80 and the difference in (b) (4) data between pilot and commercial scale lots may have been caused by the change of supplier of this material. FDA requested that CSLB provide data from studies assessing the impact of the observed differences on product quality, including stability-indicating parameters. CSLB confirmed that relevant product quality characteristics are studied in stability investigations.

CSLB sought FDA comments on the appropriateness of the approaches to method revalidation and justification of release specifications. FDA agreed with the overall approach to justification of specifications based on the statistical analysis of the manufacturing data. FDA also noted that while the data used in setting of the specifications included early production lots, the lots manufactured by the final commercial process demonstrated more consistency. To better control manufacturing process consistency, action and alert limits may need to be introduced for some of

the specification parameters. The details will be communicated in a separate IR after the Late Cycle Meeting. FDA also stated that the CMC information provided by CSLB, to-date, is insufficient to provide a meaningful assessment of the appropriateness of the validation approach because data on the most important analytical methods have not yet been submitted.

CSLB requested FDA's insight on the proteinuria issue. FDA stated that the urinalysis data for the four subjects with proteinuria are not sufficient to evaluate any possible association of proteinuria with the product. FDA stated that although no subjects had any systemic evidence of renal dysfunction, at least one subject did not have an alternative reason for proteinuria, and this subject is no longer available for review. FDA asked CSLB to obtain a spot urine protein/creatinine ratio, urinalysis, serum chemistry, and hematology testing for each subject at the next study visit, and to submit these data as an amendment to the BLA. A final decision on the need for a postmarketing commitment study will be made after review of the follow-up data from the three subjects who are currently enrolled in extension study 3003. FDA advised CSLB that the findings of proteinuria would be included in the package insert. CSLB stated that they did not find any other reports of proteinuria with their other albumin fusion products; the collection of these data is on-going.

CSLB requested clarification on FDA's position regarding removal of the word "prevention" in the indication and usage section of the package insert. FDA stated that this decision was made with consideration for the industry and the medical community, and reaffirmed that the revision is being requested of all sponsors of coagulation factor products moving forward. FDA clarified that the word "prevent" was removed to avoid confusion between the "on-demand treatment and control" indication and the "routine prophylaxis" indication. CSLB acknowledged FDA's position and commented that removal of the word "prevent" excludes situations when the product is used to prevent a potential bleed from occurring. FDA maintained that the revised language, "treatment and control," covered all indications for which the product would be approved. FDA also clarified that the revised language allowed the Agency to maintain boundaries that have been set for the use of "prophylaxis" by exclusivity.

CSLB requested an update on the review and potential issues that would prevent approval. FDA stated that this meeting does not allow the members to present the final action and can only state that the review is ongoing. FDA reiterated that CMC deficiencies are critical in that they have negative impact on several CMC aspects, including process validation, manufacturing controls, process development, and comparability studies. FDA noted that the most critical issues have not yet been addressed; CSLB plans to address these issues in future amendments. The extent and quality of the new data in the planned CMC amendments will be essential for further review by the review team.

3. Noted action items

CSLB will submit amendments stated in items 2a to 2d. FDA will issue a late-cycle meeting summary to CSLB within 30 days.

This application has not yet been fully reviewed by the signatory authorities, division directors, and review committee chair; therefore, this meeting did not address the final regulatory decision for the application.

End

Concurrence Page

Application Number: STN 125582/0

Letter Type: Late Cycle Meeting Summary (LCMS)

Cc: EDR

History: Drafted/Revised Edward Thompson / August 27, 2015
Reviewed John Eltermann/ August 28, 2015
Revised Mikhail Ovanesov / September 8, 2015
Revised Alexey Khrenov / September 8, 2015
Revised Nancy Kirschbaum/ September 9, 2015
Revised Lisa Faulcon/ September 2, 2015
Reviewed Bindu George/ September 9, 2015
Reviewed Ginette Michaud/ September 14, 2015
Revised Paul D. Mintz/ September 10, 2015
QC Sonday L. Kelly/ September 14, 2015
Revised Trevor Pendley/ September 15, 2015

Minutes verified:

(for attendees)

Mikhail Ovanesov, PhD

Tim Lee, PhD

Lisa Faulcon, MD

Bindu George, MD

Paul D. Mintz, MD

Summary Received:

Basil Golding, MD

Concurrence box

Office	Name/Signature
OBRR	Edward Thompson
OBRR	Sonday L. Kelly
OBRR	Trevor Pendley
OBRR	Iliana Valencia

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Template effective date:

Template POC: Linda Dixon