

PDUFA V, The Program, Internal Late Cycle Meeting
STN 125582/0
Coagulation Factor IX (Recombinant), Albumin Fusion Protein
CSL Behring Recombinant Facility AG

July 15, 2015
10 a.m. to 12 p.m.
White Oak Building 71
Room 1208/1210

Internal Late Cycle Meeting Agenda:

1. Review Team Introductions:

Chair: Mikhail Ovanesov, PhD, LH/DHRR
CMC Product Review: Alexey Khrenov, PhD, LH/DHRR
CMC Product Review: Ze Peng, PhD, LH/DHRR
CMC Product Review: Wayne Hicks, PhD, LBVB/DHRR
CMC Product Review: Yideng Liang, PhD, LH/DHRR
CMC Product Review: Andrey Sarafanov, PhD, LH/DHRR
Clinical Review: Lisa Faulcon, MD, CRB/DHCR
Clinical Pharmacology: Iftekhar Mahmood, PhD, CRB/DHCR
Toxicology Review: Yolanda Branch, PhD, DHCR
Postmarketing Safety: Laura Polakowski, MD, OBE/DE/AEB
Statistical Review: Chunrong Cheng, PhD, OBE/DB/TEB
Labeling Review: Loan Nguyen, OCBQ/DCM/APLB
CMC Facility Review: Donald Ertel, OCBQ/DMPQ/BI
BIMO: Christine Drabick, OCBQ/DIS/BMB
Josephine Resnick, OCBQ/DBSQC
Karen Campbell, OCBQ/DBSQC
Lokesh Bhattacharyya, PhD, OCBQ/DBSQC
Simleen Kaur, OCBQ/DBSQC/LMIVTS
Regulatory Project Manager: Edward Thompson

Other meeting participants:

Jay Epstein, MD, Director, Office of Blood Research and Review
Ginette Michaud, MD, Deputy Director, Office of Blood Research and Review
Paul Mintz, MD, Director, Division of Hematology Clinical Review/OBRR
Howard Chazin, MD, Deputy Director, Division of Hematology Clinical Review/OBRR

Mahmood Farshid, PhD, Deputy Director, Division of Hematology Research and Review/OBRR

John Eltermann, Director, Division of Manufacturing and Product Quality/OCBQ

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

Timothy K. Lee, PhD, Acting Chief, Laboratory of Hemostasis/DHRR/OBRR

2. Introduction of application

Summary Description of Product: Coagulation Factor IX (Recombinant), Albumin Fusion Protein with an approved proprietary name of IDELVION. This product is indicated to treat 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.

Ground Rules: The discussion with the applicant will not address the final regulatory decision. If the applicant requests a review status update, the Agency may inform the applicant that the review is ongoing.

Objective of the Meeting: The late cycle meeting with the applicant is to fulfill the PDUFA V objective regarding transparency of the review process. The Agency can provide clarity regarding topics requested by the applicant and can discuss substantive issues, which may impact approval by the action due date.

3. Substantive review issues/major deficiencies raised during review:

- a. Product/CMC: Dr. Ovanesov presented the following issues with inspections, method validation, release specifications, and comparability of product lots manufactured at pilot scale and commercial scale:
 - i. Inspection of the bulk drug substance (BDS) and final drug product (FDP) manufacturing facility in Marburg, Germany (May 28-June 5, 2015) resulted in 19 objectionable observations covering all aspects of operations, including process and method validation, setting specifications, documentation of deviations and facility issues. CSL provided preliminary responses outlining a plan to address all issues. The review of these responses is ongoing. Preliminary assessment indicates that the firm is capable of correcting the deficiencies before the action due date (ADD), with the exception of issues related to deficient method validation and inadequate justification of specifications. These remaining issues will be considered as part of the discipline review, see next point.

- ii. Review of method validation by Dr. Khrenov identified multiple deficiencies that could be traced back to SOP deficiencies uncovered during the facility inspection. CSL proposed to provide four method revalidation amendments on: July 15th, August 15th, September 15th and September 30th. The deficiencies are critical in that they have a negative impact on several CMC aspects, including process validation, manufacturing controls, process development, and comparability studies.
- iii. Dr. Hicks, Dr. Sarafanov, and Dr. Ovanesov identified inconsistencies in comparability studies of product lots manufactured at pilot scale in (b) (4) vs commercial scale in Marburg, Germany. Noted deficiencies can be related to inadequate design of comparability studies and to analytical method deficiencies. However, an inconsistency in manufacturing process or inadequacy of controls cannot be excluded at this time. Information Requests have been submitted and the review is ongoing.
- iv. The release assays are inadequate for assurance of albumin moiety quality. rIX-FP is the first albumin-fusion product regulated by CBER. The Agency has theoretical concerns regarding potential for immunogenicity; therefore, heightened control of albumin structure and function is warranted. Such concerns are supported by consultations with expert CDER reviewers. Note that our concerns are presently not supported by clinical safety signals. CSL will be required to develop better release assays, possibly as a post-marketing commitment (PMC).

CSL's plan to submit method validation late in the review cycle (September 30th) may not permit a complete review within this review cycle. A CR letter or extension of the review clock through a Major Amendment are possible outcomes. Additional review of CMC deficiencies can be found in the CMC reviewer reports below.

Dr. Khrenov presented issues with analytical methods and specifications. In general, the specifications were not adequately justified and acceptance criteria for tests for Albumin by (b) (4) were not adequate to control product quality. The validations of many methods were deficient. The issues were communicated to CSL (the applicant) in an information request and CSL committed to resolving the issues and submitting complete data by September 30, 2015. However, it is unknown at this time if the issues will be resolved and if additional information requests will be sent. Also, several inspectional observations, raised by the product office have not yet been resolved. Review of modified procedures will be necessary to close the observations.

Dr. Hicks presented issues with acceptance criteria for qualitative assessment of the albumin moiety and lack of assay for manufacturing consistency.

The (b) (4) data for the rIX-FP (b) (4) was generated using database searching of (b) (4) data. The database used to conduct the search was inadequate to support the applicant's conclusion. The database search needs to be done again with an appropriate database inclusive of all possible proteins.

There are also concerns regarding the (b) (4) assay for albumin. This would be the first recombinant albumin fusion protein approved by CBER. The (b) (4) assay may not be adequate to consistently control albumin folded into its native conformation, particularly in light of the results from the (b) (4) data, which seemed to indicate qualitative differences between the lots produced at the (b) (4) and those produced at the (b) (4). When attempting to analyze the data and conclusions generated from the (b) (4) data, it was difficult to draw definitive conclusions due to the lack of validation and statistical analysis associated with this method. If the (b) (4) method is to be used, it should be properly validated.

A (b) (4) method should be developed and validated for use as an (b) (4) test with reference to an appropriately qualified reference material.

Neither Dr. Peng, nor Dr. Liang had substantive issues for the late cycle meeting.

Dr. Sarafanov presented issues with impurities and leachables.

Additional information requests will be sent to address outstanding issues.

- b. Facility/CMC - LCDR Ertel indicated that CSLB responses to Form FDA 483 observations are under review. The preliminary assessment is that responses appear to be acceptable.
- c. Pharmacology/Toxicology – Dr. Branch had no substantive issues for the late cycle meeting.
- d. Clinical Pharmacology – Dr. Mahmood had no substantive issues for the late cycle meeting.
- e. Clinical – Dr. Faulcon discussed the post-marketing proposal for assessment of proteinuria in extension study 3003. This finding among four study subjects will be included in the label. CSLB will be asked to revise the language for indication and usage labeling claims to conform with FDA's efforts to harmonize labeling for blood coagulation factors.

- f. Epidemiology – Dr. Polakowski concurred with Dr. Faulcon’s proposal for post-marketing follow-up and labeling to address observations of proteinuria in four study subjects.
- g. Statistical Review – Dr. Cheng had no substantive issues related to statistical analysis and non-inferiority claim in labeling.
- h. Validation of Lot-release Assays for Drug Product, Lot-release Protocol and In-support Testing - Dr. Bhattacharyya had no substantive issues for the late cycle meeting.

LCDR Kaur provided email confirmation of no substantive issues associated with her review.

Ms. Campbell had no substantive issues for the late cycle meeting.

Ms. Resnick had no substantive issues for the late cycle meeting.

- i. BIMO Clinical Site Inspections: Ms. Drabick had no substantive issues for the late cycle meeting.

4. Review of upcoming timeline/deadlines:

Late Cycle Meeting briefing document due to applicant: 12-Aug -15

Face to Face Late Cycle Meeting 25-Aug-15

Inform OCOD (*RPM*) 25-Sep-15

SBRA & Draft PI to DHRR/DHCR (*Chair*) 6-Oct-15

Draft Approval Letter (*RPM*) 13-Oct-15

Draft PI and IR to Jennifer (*Chair*) 13-Oct-15

SBRA+ PI + Approval Letter - OBRR Management 20-Oct-15

Comments from OBRR Management 23-Oct-15

Press Release/Information Sheet N/A

Meeting with OBRR Management 5-Nov-15

Send complete package to RPM (*Chair*) 5-Nov-15

Send Final PI to applicant (RPM) 10-Nov-15

Route relevant documents

(i.e., xxxx) to OBE, OCBQ, and/or ADRM (*RPM*) 10-Nov-15

Review Completed -- T-x Date 20-Nov-15

Finalize package (*RPM*) 18-Nov-15

Inform Jennifer - ADD (*RPM*) 19-Nov-15

Route for signatures (<i>RPM</i>)	23-Nov-15
OBRR Management Signature	2-Dec-15
Target ADD	3-Dec-15

5. Assess status of the review including plans for completing outstanding discipline reviews and any remaining outstanding issues

Given the issues presented in the meeting, the participants discussed the remaining milestones and the proposed actions by the review team for the final action letter.

6. Reach agreement on meeting materials.

The meeting package will be uploaded to the sharepoint site for this submission and reviewers will include the issues for presentation to the applicant.

7. Come to agreement on the issues to be included on the agenda for the Late Cycle Meeting. Agreement regarding timeframes for resolving each agenda item should also be achieved and documented during the meeting.

Discuss the available resources to resolve the issues presented in the meeting and associated time lines with these actions by CBER.

End

Drafted: Edward Thompson
Revised: Mikhail Ovanesov
Revised: Laura Polakowski