Our STN: BL 125641/0

Laboratoire Francais du Fractionnement
et des Biotechnologies S.A. (LFB)
Attention: Mr. Richard A. Scotland
LFB USA
175 Crossing Blvd.
Framingham, MA 01702

Dear Mr. Scotland:

Attached is a copy of the memorandum summarizing your August 16, 2017 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 the appropriate Submission Tracking Number (STN) in future submissions related to the subject product.

If you have any questions, please contact Dr. Mark Levi at (240) 402-9662.

Sincerely,

Basil Golding, MD
Division Director
Division of Plasma Protein Therapeutics
Office of Tissues and Advanced Therapies
Center for Biologics Evaluation and Research

Late-Cycle Meeting Summary

Meeting Date and Time:	Wednesday, August 16 2017, 2:00 PM - 3:00 PM
Meeting Location:	Wo32 Rm. 1333
Application Number:	BL 125641/0
Product Name:	Coagulation Factor VIIa (Recombinant)
Proposed Indications:	Control of bleeding in patients with inhibitors to Factor VIII and Factor IX
Applicant Name:	Laboratoire Francais du Fractionnement et des Biotechnologies S.A.
Meeting Chair:	Mikhail Ovanesov, PhD
Meeting Recorder:	Mark Levi, PhD

FDA ATTENDEES

Bethany Baer, DE/OBE/CBER
Sarah Bembe, DBISM/ONADE/CVM
Kimberly Benton, PhD, OTAT/CBER
Lokesh Bhattacharyya, PhD, DBSQC/OCBQ/CBER
Jacob Bitterman, DHFS/ONADE/CVM
Wilson Bryan, MD, OTAT/CBER
John Dennis, DVM, DVP/OM/CBER
John Eltermann, MS, DMPQ/OCBQ/CBER
Mahmood Farshid, PhD, DPPT/OTAT/CBER
Bindu George, MD, DCEPT/OTAT/CBER
Harlan Howard, PhD, ONADE/CVM
Alexey Khrenov, PhD, DPPT/OTAT/CBER
Kristine Khuc, DCM/OCBQ/CBER
Colonius King, DIS/OCBQ/CBER
Stella Lee, ONADE/CVM
Tim Lee, PhD, DPPT/OTAT/CBER
Mark Levi, PhD, DRPM/OTAT/CBER
Nicole Li, DMPQ/OCBQ/CBER
Heather Lombardi, ONADE/CVM
Yideng Liang, PhD, DPPT/OTAT/CBER
Laura Moussa, ONADE/CVM
Mikhail Ovanesov, PhD, DPPT/OTAT/CBER
Renée Rees, PhD, DB/OBE/CBER
Andrey Sarafanov, PhD, DPPT/OTAT/CBER
Poornima Sharma, MD, DCEPT/OTAT/CBER
Edward Thompson, DRPM/OTAT/CBER
Grainne Tobin, PhD, DBSQC/OCBQ/CBER
Deborah Trout, DMPQ/OCBQ/CBER
Anne Van Auken, DTDNFA/ONADE/CVM
Linda Walter-Grimm, DVM, VPS/OSC/CVM
Hsiaoling Wang, PhD, DBSQC/OCBQ/CBER

Xiaofei Wang, PhD, DCEPT/OTAT/CBER
Boris Zaslavsky, PhD, DB/OBE/CBER

APPLICANT ATTENDEES

Allan Alexander, MD	Senior Medical Director, Medical Affairs, HEMA Biologics
Ludovic Burlot	Director, Biopharmaceutical Dvlpt., LFB Biotechnologies
Vincent Cazenave	Industrial Project Director, LFB Biotechnologies
(b) (4)	
Sean Evans	Senior Vice President, Development, LFB USA
Cédric Fournier	Director, Quality, LFB Biotechnologies
William Gavin	President, LFB USA
Supicha Kridaratikorn	Associate Director, Regulatory, LFB USA
Jeffry Lawrence	Senior Vice President, Chief Medical Officer, LFB
Mary Matthew	Senior Director, Regulatory, LFB USA
Mary Ann Murphy	Vice President, Regulatory, LFB USA
Marlène Nogier	Regulatory Affairs, LFB Biotechnologies
Fritz Reinhart	Senior Director, Project Management, LFB USA
Richard Scotland	Senior Vice President, Regulatory, LFB USA
Laurent Siret	CMC Strategist, LFB Biotechnologies

BACKGROUND

BLA 125641/0 was submitted on October 13, 2016, for Coagulation Factor VIIa (Recombinant) [rFVIIa].

Proposed indication(s):	Control of bleeding in patients with inhibitors to Factor VIII and Factor IX
PDUFA goal date:	October 13, 2017

In preparation for this meeting, FDA issued the Late-cycle Meeting Materials on August 4, 2017.

DISCUSSION

FDA explained that the purpose of the meeting is to discuss the substantive review issues and major deficiencies that FDA has identified to date. FDA can provide information about the identified issues and discuss additional information needed to address the identified issues.

FDA stated that the *Late-Cycle Meeting* (LCM) *Materials* dated August 4, 2017, were reflective of the status of the review at the Internal LCM on July 25, 2017. FDA noted that the primary reviews would usually be completed by the LCM, but had been delayed

for this BLA because many of the responses to our *Information Requests* (IRs) were received late, which included those to the deficiencies listed in the *Filing Letter*. The review is ongoing and additional deficiencies may be identified.

LFB asked whether FDA had any feedback on Amendment #s 56 and 57 dated August 8, 2017 and August 11, 2017, respectively. FDA explained that amendments received after July 25, 2017 had not been reviewed, and therefore, no comments would be provided on these amendments at this time.

1. **Discussion of Substantive Review Issues**

   a. Chemistry, Manufacturing and Controls (CMC)

      i. Visible particulates in reconstituted Final Drug Product

      Discussion summary:
      LFB informed FDA that LFB had made good progress in root cause analyses and the report will be available by the end of September.

      LFB stated that confirmation of the root cause is expected by the end of August 2017 with assistance from an external firm. Development and validation of a simplified method for drug product (DP) reconstitution were conducted using a risk analysis approach, and the reports will be available by mid-September 2017.

      FDA requested clarification on whether the dates are for when the report is completed or the final translated report is submitted to the FDA. LFB clarified that all communicated dates are estimates on when the final study reports are completed. Additional time may be needed to translate these reports and prepare them for submission to the FDA.

      LFB proposed to email FDA a list of all outstanding documents with their submission dates. FDA advised LFB to submit the list as an amendment to the BLA. LFB agreed.

      ii. Validation of the manufacturing process for Bulk Drug Substance (BDS)

      Discussion summary:
      LFB informed FDA that (b) (4) BDS lots had been produced so far. LFB explained that the root causes for the (b) (4) excursions and the (b) (4) deviation were identified and successfully resolved. The final investigation report for the (b) (4) deviation and the validation report for the BDS manufacturing process will be available by the end of September 2017. FDA inquired about the (b) (4) deviation. LFB explained that the level of (b) (4) in a BDS batch was out of specification due to a problem with the assay.

iii. Potency assay

Discussion summary:
LFB noted that additional data were submitted in Amendment #56 dated August 8, 2017.

iv. Release specifications for *Potency* and *Specific Activity*

Discussion summary:
LFB informed FDA that additional data on the qualification of the Potency Working Standard was submitted in recent amendments. FDA acknowledged receipt of the July 24, 2017 submission that included results from re-testing of some stability samples using the re-validated potency assay, which are under review.

v. Product stability

Discussion summary:
LFB informed FDA that they had submitted all the requested information and prepared slides with additional data on the (b) (4) batch (b) (4) (slide #9 of the attached presentation entitled "Sevenfact® BLA STN BL 125641 Late-Cycle Meeting" dated August 16, 2017). FDA explained that the slides were received on the day before the meeting and were not reviewed. However, FDA noted that the new data are in contradiction with the stability data obtained with the re-validated potency method as reported in Amendment #53 dated July 24, 2017. LFB responded that they will review the data in Amendment #53.

vi. Assessment of extractables and leachables

Discussion summary:
LFB stated that the data on the (b) (4) container closure system will be submitted to the FDA by the end of December 2017. Of the (b) (4) compounds (leachables) detected (b) (4) have been assessed. In the FDP, (b) (4) were detected and (b) (4) have been assessed. LFB will submit these reports as they become available. In response to an FDA question, LFB stated that no safety concern on any of the compounds was identified so far.

vii. Analytical methods for release testing of diluent

Discussion summary:
LFB explained that the validation of the non-USP analytical methods will be conducted in accordance with the protocol submitted in Amendment #57 dated August 11, 2017, and the method validation report is expected by the end of September 2017.

b. DMPQ Facilities

i. Regarding Diluent

Discussion summary:
LFB stated that there was a delay in receiving information from (b) (4) because the key personnel were on vacation. LFB is working actively with (b) (4) on obtaining the requested information and will update the FDA as the information becomes available. Regarding the diluent, the information will likely be provided by (b) (4) in October 2017. LFB will submit the information to the FDA by mid-October 2017.

ii. Regarding the drug product – depyrogenation, stopper washing, and (b) (4) of stopper-(b) (4)

Discussion summary:
For the information on the (b) (4) Water for Injection (WFI), the date of submission to the FDA is not yet known. LFB will provide an update on the timeline by early September 2017.

LFB noted that some of the requested qualification reports were delayed because of the limited availability of rFVIIa BDS needed for these studies. FDA responded that some of the qualification studies can use a mix of product and surrogate vials, and LFB should discuss these plans with the FDA.

2. Discussion of Minor Review Issues

a. Clinical-Discrepancies between FDA analysis and LFB analysis.

Discussion summary:
LFB informed the FDA that their team is working on the responses to this matter. FDA noted that they have no further questions.

b. Clinical Pharmacology- Difference in PK results between Processes A & B

Discussion summary:
LFB informed the FDA that they had submitted the data.

c. In-support Testing - Availability of Potency Reference Standard

Discussion summary:
FDA confirmed the receipt of the product-specific reference standard.

d. Chemistry, Manufacturing and Controls (CMC) - (b) (4) method for *Identity* testing

Discussion summary:
LFB noted that they have no further questions and are currently working on this issue.

e. Additional issues

Discussion summary:
LFB requested a meeting for further discussion on the particles and the syringe.

3. Additional Applicant Data

Discussion summary:

- LFB informed FDA that they were working with the Center for Veterinary Medicine (CVM) on the inspection of the rabbit facility in Charlton, Massachusetts. FDA noted that CBER does not plan to participate in this inspection.

- LFB believed that they are able to address all the FDA requests regarding the qualification of the source material (milk) collected at the Charlton rabbit facility.

- LFB informed FDA that the validation report for a revised method for the assessment of neutralizing antibodies will be provided in September 2017. LFB recently found that the original method was validated for (b) (4) samples but results of tests performed on patient (b) (4) samples were presented in the BLA. LFB acknowledged that it is critical to assess the immunogenicity of their rFVIIa product using a method that is validated for its intended use. In response to FDA question, LFB noted that no changes to the description of product immunogenicity in the labeling are expected.

- The shipping validation study data will not be available until June 2018.

4. Information Requests

Outstanding IRs by date:

- IR regarding possible refuse-to-file issues dated November 29, 2016

  - Request 2f (also repeated as Request #36 in the *BLA Filing Letter with Deficiencies* dated 12 December 2016, see below) regarding the design control overview and data to support design verification requirements per CFR 820.30(f): shipment validation studies of commercial product.

- *BLA Filing Letter with Deficiencies* dated December 12, 2016

    - Response to Request #6 regarding the validation of the non-USP and verification of the (b) (4) analytical methods used for the Final Drug Product (FDP) and diluent, Water for Injection (WFI).
    - Request #13 regarding equipment qualification performance qualification data for labeling and packaging equipment used in the manufacture of LR769 FDP.
    - Request #16 regarding test method validation protocol and results for the (b) (4) container closure integrity test method for the diluent pre-filled syringe and the lyophilized powder vial.
    - Request #19 regarding shipping validation for the (b) (4) diluent pre-filled syringe from (b) (4)

- IR dated April 05, 2017 regarding (b) (4) method validation deficiencies

- IR dated April 24, 2017 regarding Extractables and Leachables (E&L) studies:

    - Response to a request to revise the analytical methodology to consider the degree of extraction of organic E&L into the organic phase, and re-evaluate the final results and risk assessment for the leachables in the FDP.
    - The results of FDP Container Closure System Leachables studies.

- IR dated May 04, 2017 regarding release specifications:

    - Request to implement alert and action limits for bacterial endotoxin levels.
    - Evaluation of (b) (4) assay accuracy using (b) (4) standard.
    - Revision of the acceptance criteria for *Specific Activity* in (b) (4) FDP, (b) (4) Assay in FDP.

- IR dated May 31, 2017

    - Request regarding the deficiencies in the potency assay (also noted in Observation #1 in Form FDA 483 for the (b) (4) inspection).

- IR dated July 25, 2017 regarding the potency assay.

- IR dated July 28, 2017 regarding re-analysis of the primary efficacy endpoint as described in Item 2f.

Discussion summary:
LFB noted that they are working on the responses. LFB will summarize the status of all delayed responses to IRs in their upcoming amendment with revised timelines for the submission of additional data.

5. Discussion of Advisory Committee (AC) Meeting, Risk Management Actions (e.g., REMS), and Postmarketing Requirements/Postmarketing Commitment (PMC)

   Discussion summary:
   LFB stated that they have no additional questions regarding the AC, REMS and PMC, and they will respond to the FDA requests when they receive them.

6. Major Labeling Issues

   Discussion summary:
   FDA confirmed that labeling issues have not been communicated to LFB.

7. Review Plans

   Discussion summary:
   FDA is reviewing LFB's responses to IRs and inspectional observations. The PDUFA goal date of the BLA is October 13, 2017. FDA noted that the review schedule is not certain at this time because multiple amendments were received since late June. The review committee has not come to a conclusion on whether the submitted data address the identified deficiencies.

Action Items:

1. LFB will provide FDA a list of the dates on or about which the additional data will be submitted.

2. FDA will review the data and consider if a meeting is warranted to discuss the issue on particles.

FDA reiterated that this application has not yet been fully reviewed by the signatory authorities, Division Directors and Review Committee Chair, and therefore this meeting did not address the final regulatory decision for the application.