Mid-Cycle Meeting Agenda/Summary

Application type and number: Original BLA under STN 125641/0
Product name: Coagulation Factor VIIa (Recombinant)
Proposed Indication: Control of bleeding in patients with inhibitors to FVIII and FIX
Applicant: Laboratoire Francais du Fractionnement et des Biotechnologies S.A. (LFB S.A.)
Meeting date & time: March 29, 2017, 12:00 p.m. to 1:00 p.m.
Committee Chair: Dr. Mikhail Ovanesov
RPM: Dr. Mark Levi

Attendees:

Discipline	Name [with credentials (not title)]	Attended meeting?
Regulatory Project Manager (RPM)	Mark Levi, PhD	Y
Chair	Mikhail Ovanesov, PhD	Y
Clinical Reviewer	Poornima Sharma, MD	Y
CMC Reviewer, CMC Inspector	Mikhail Ovanesov PhD, Alexey Khrenov PhD, Wojciech Jankowski,	Y
CMC Reviewer	Andrey Sarafanov PhD, Yideng Liang	Y
Animal Pharmacology Reviewer Toxicology Reviewer Developmental Toxicology Reviewer	Wei Liang	
Clinical Pharmacology Reviewer	Xiaofei Wang, PhD	Y
OCBQ/DMPQ RPM	Amanda Trayer	N
OCBQ/DMPQ/Lead Inspector OCBQ/DMPQ Reviewer	Nicole Li, Nicole Trudel	Y
OCBQ/DMPQ/PRB Reviewer		
Statistical Reviewer of clinical data	Boris Zaslavsky, PhD	
Statistical Reviewer of non-clinical data		
Postmarketing Safety Epidemiological Reviewer	Firoozeh Alvandi, MD	Y
OCBQ/APLB Reviewer	Kristine Khuc	
OCBQ/BIMO Reviewer	Colonious King	Y
OCBQ/DBSQC	Grainne Tobin, Marie Anderson, Hsiaoling Wang, Claire Wernly	Y
Consult Reviewer(s): Veterinary Medicine CMC Consult	John Dennis, DVM	Y
Other Attendee(s)	CVM: Sarah Bembe, Heather Lombardi, Harlan Howard, Brinda Dass, Jacob Bitterman, Lynn Friedlander, Anne VanAuken, Aila Albrecht, Evgenij Evdokimov OTAT: Wilson Bryan, Tim Lee, Iwen	

Discipline	Name [with credentials (not title)]	Attended meeting?
	Wu, Kim Benton, Bindu George, Mercedes Serabian, Mahmood Farshid, Basil Golding, Ed Thompson DMPQ: Carolyn Renshaw, John Eltermann, BIMO: Pat Holobaugh OBE: Bo Zhen, Renee Rees, DSBQC: William McCormick CBER/IOD: Carol Rehkopf, Troy Reisch	

Discussion Summary:

The mid-cycle meeting addressed the status of the BLA review. Each discipline reviewer briefly presented his or her review focus and findings. There were CMC issues identified that would prevent approval; however, the review is ongoing. There were a number of additional issues, most of them pertaining to CMC and clinical, which need to be addressed by the applicant. A mid-cycle list of issues will be conveyed to the applicant during the Mid-Cycle Communication (MCC). Presentation of the BLA at an advisory committee (AC) meeting is not planned, and a waiver memo will be prepared to justify that referral to an AC is not needed.

Report and Discuss:

The following items were discussed at the mid-cycle meeting in accordance with the guidelines of the PDUFA V program:

1. Reviewer Reports.

Chemistry, Manufacturing and Controls (CMC)

CMC Reviewer & Chair: Mikhail Ovanesov

Several critical CMC deficiencies were identified:

1. Deficient validation of the BDS manufacturing process is evidenced from repeated process failures. The validated ranges of *Critical Process Parameters* (CPPs) were modified without new process development and validation studies. For example, problems with the performance of the (b) (4) steps resulted in rejected BDS batches and failed (b) (4), respectively.

2. The design of the combination product and validation of its use are deficient as evident from repeated instances of visible particulates found in the reconstituted

product during release testing and stability studies. The particulates do not appear to come from the biological product, and are most likely derived from the device components of the combination product, i.e., the rubber stopper, vial adapter and syringe with diluent. The investigations were not successful in identifying the true root cause(s) because the proposed CAPAs have so far failed to prevent recurrence of visible particulates in the FDP. LFB has no clear plan to address the particulate issue at this time. Regarding *Section 2.4 Administration* in the *Prescribing Information* which instructs users to "*Visually inspect the reconstituted solution for particulate matter and discoloration prior to administration. Do not use if particulate matter or discoloration is observed*", LFB noted that the user will not notice these particles: "*…visible particles of the aforementioned investigation cannot easily be detected by untrained human eye in a labelled vial and without appropriate light. So there is low probability that the user could detect visible particles of "Environment cause" and discard the vial*".

3. Deficient validation of analytical assays used for the control of the (b) (4) manufacturing process, FDP (b) (4) release, stability studies, and process validation studies. For example, the potency assay is not suitable for its intended use because the assay does not use a qualified reference standard of product potency. As a result, numerous unqualified reference preparations were used to determine product potency at the various stages of process development, product characterization, and in stability studies.

4. Adverse trends in product *Potency* were observed in stability studies. These trends were not properly investigated. For example, the data indicate poor stability of a batch of the (b) (4) FDP presentation, which is extrapolated to lose (b) (4) of its activity by the end of the proposed shelf-life.

5. The acceptance ranges for FDP release specifications are much wider than those of the licensed recombinant activated factor VII product, NovoSeven. The proposed specifications are not supported by manufacturing process capability, and are not suitable for the control of product quality and stability. Additional analytical methods are needed to control protein purity (e.g., (b) (4) , which LFB proposed to remove from the specifications.

6. The severity and scope of GMP issues described above suggest a systemic problem with LFB's quality systems. For example, the development of the combination product, and validation of the BDS manufacturing process were not properly designed and carried out, from a quality perspective.

Potential impact the substantive issues have on the review:

Failure to adequately address review findings #1 through #4 will most likely prevent the approval of the BLA. These issues reveal systemic problems within LFB that cannot be resolved within a few months.

Finding #5 may potentially be resolved within this review cycle, however, tightening the specification limits for *Potency* and *Specific Activity* can result in failures of FDP batches already in stability studies to meet the specifications.

CMC – Product office team defers to DMPQ to assess the criticality of finding #6.

CMC Reviewer - Validation of Analytical Procedures and Release Specifications: Alexey Khrenov

A. Inspectional status and findings

Participated in inspections of the testing facility in (b) (4) (issued a 6-item Form FDA 483), and Drug Substance Manufacturing facility in (b) (4) (issued a 16-item Form FDA 483). Inspection of the testing facility demonstrated significant issues with the potency assay (described under paragraph E below). Also, repeated out-of-specification (OOS) results for *Visible Particulates* were observed. The root cause(s) for the OOS results has not been identified, and the implemented CAPAs have found to be ineffective to date. Inspection of the (b) (4) facility revealed significant deficiencies in process validation, which led to multiple process failures in several DS batches, which were manufactured after the PPQ batches. A number of other issues were also observed during the inspection, which the DMPQ reviewers will comment on in details.

B. Key findings and substantive issues with the information and data in the application.

1. The Potency assay is not suitable for its intended purpose due to a lack of product-specific standard or other appropriate reference material. As such, the assay could not be properly validated, and its performance has not been verified and monitored over time.
2. The suitability of the (b) (4) used to measure Rabbit Milk Proteins (RMP) is not established. The coverage of the (b) (4) used in the assay was not assessed using (b) (4) . Also, the ability of the assay to quantify rabbit (b) (4) (a major component of RMP in (b) (4) Drug Product (DP)) was not established.
3. Most of the specifications are not properly justified. Appropriate statistical analyses of data were not performed.
4. Multiple minor method validation issues were identified.
5. The applicant did not provide data to validate the non-USP methods used for the control of DS and DP.

C. Potential impact the substantive issues have on the review especially those which could prevent approval and impact the review timeline

Review findings #1, #2 and #3 in section E and those identified during the two inspections can prevent BLA approval.

D. Plan for addressing issues and the reason for the suggested approach

We communicated our recommendations to LFB as to how they should address the following issues during the inspections:

1. For finding #1, LFB will need to characterize and establish a product-specific reference material, modify the potency assay to include this material and control samples and re-validate the modified assay method. Also, LFB needs to demonstrate the comparability of the results obtained by the modified and current methods by testing retain samples. These studies will probably take a significant amount of time, and may not be completed before the action due date of 13 October 2017. If the correlation between the modified and current assay methods is poor, it will require more extensive testing of retained samples and time.

2. To verify the performance of the (b) (4) for RMP, LFB will need to perform a number of experiments. Similar exercises performed by (b) (4) for (b) (4) took over 3 months. If the coverage of the current (b) (4) is found to be poor, LFB will have to develop an appropriate (b) (4) for the assay, which will mean the addition of a significant amount of time.

3. Although we discussed the *Particulate Matter* issue with LFB extensively during the inspections, LFB has not developed a clear pathway to address it at this time because they have not identified the root cause(s). Moreover, the effectiveness of the latest CAPA has yet to be demonstrated.

CMC Reviewer - Stability: Yideng Ling

1. Stability studies are ongoing and additional data will be requested. No significant changes in quality attributes over time were observed in stability studies except for (1) loss of potency in several FDP batches, and (2) visible particulates were detected in several FDP batches at several time-points and at different temperatures of storage.

Potency

2. Although the FDP Potency and Specific Activity are within the current release specification limits, the acceptance ranges are much wider than those of the licensed recombinant activated factor VII product, (b) (4) (see Fig. 1 below). LFB should review their data and establish more appropriate limits. However, tightening specification limits may result in some FDP batches to fall out of specification in the stability studies.

3. It is notable that the observed loss of potency over time was not associated with adverse stability trends in other quality attributes assessed in the stability studies. This, together with observed wide variability in Potency results, suggests poor robustness of the potency assay.

A notable loss in potency was observed in the ongoing real-time stability study for the (b) (4) conformance batch (b) (4). Note that (b) (4) is the only commercial Process B (b) (4) batch in the stability studies.

Visible particulates

4. LFB claims that the presence of visible particulates during stability studies is not related to changes in the FDP during storage. LFB concluded that the origin of the particles was environmental and not related to the manufacturing process or stoppers, and therefore it was not related to drug stability.

5. However, the investigations are deficient, i.e., the root causes for the visible particulates have yet to be found, and the effectiveness of the CAPA has yet to be demonstrated.

Potential impact the substantive issues have on the review:

1. The recurrence of visible particulates during stability studies may indicate quality issues with the combination product which can affect BLA approval.

2. Specification limits for Potency and Specific Activity are too wide, and tightening these limits can result in the failure of FDP batches already in stability studies to meet the specifications.

The presented stability data do not support the proposed shelf-life of 36 months stored at room temperature for the (b) (4) dosage strength.

CMC Reviewer - Structural Integrity: Wojciech Jankowski

Within the areas of review assigned to me, there are no substantive issues that could prevent approval or impact the review timeline. However, I have concerns about the release specifications that seem to be too wide, or have been removed but are crucial for product quality assessment. Specifically:

(i) (b) (4) (Section 3.2.P.5.1) that has been set to (b) (4)
(ii) (b) (4) analysis that was used to assess purity regarding the (b) (4) of rhFVIIa (Section 3.2.S.4.5.3.13) has been removed as a release specification without proper justification.

CMC Reviewer - Extractable & Leachable in the Drug Product; the Drug Product Diluent (Water for Injections in prefilled syringe) – Andrey Sarafanov

A. Key findings and substantive issues with the information and data in the application.

1. The analytical methodology used for the assessment of Extractable & Leachable in the Drug Product (DP) is deficient. This may have resulted in

the underestimation of the leachables level in the DP, which is a concern for product safety.

2. The assessment of extractables in the most critical materials used in the manufacturing process, e.g., i) (b) (4) devices (which (b) (4) step), was not performed. The concern for product safety is the same as above.
3. The Applicant has not provided data to validate the non-USP methods nor to verify the (b) (4) methods used for the control of the DP diluent, Water for Injection.

B. Potential impact the substantive issues have on the review especially those which could prevent approval and impact the review timeline

Review findings #1 and #2 can affect BLA approval.

C. Plan for addressing issues and the reason for the suggested approach

The analytical approach for the determination of Extractable & Leachable in the DP should be revised to validate the recovery of the organic compounds upon their extraction into organic phase used for sample preparation. Accordingly, the analytical data and risk for the patients should be re-evaluated by the Applicant. I will recommend sending a respective recommendation to the company.

In regard to the absence of data to support the validation of the analytical methods for the diluent, in a recent amendment to the BLA, the company committed to submit these data by the end of the second quarter of 2017. This is expected to resolve the issue.

CMC Reviewer – DMPQ/Facilities: Nicole Trudel and Nicole Li

There are no substantive review issues at this time. The DMPQ equipment and facility review is just beginning because the required data were only submitted months after the BLA was filed. The observations on the (b) (4) BDS 483 and the (b) (4) test facility 483 will need to be addressed before approval.

<u>Clinical Reviewer:</u> Poornima Sharma

Proposed indication: On-demand treatment of bleeding episodes in adults and adolescent hemophilia A or B patients with inhibitors to Factor VIII or IX. Recommended for both at home administration and in hospital setting under supervision of health care provider experienced in treatment of bleeding disorders.

BLA STN 125641/0 is original BLA submitted by LFB for recombinant Factor VIIa referred to as LR769 and under the proprietary name SEVENFACT. SEVENFACT is a lyophilized complex glycoprotein produced in and purified from milk of transgenic rabbits. It is produced by site directed expression of human factor VII gene in mammary

gland of genetically engineered rabbits and is under control of (b) (4) specific promoter. Factor VII protein is activated during the purification process.

To support licensure for the proposed indications, the clinical development program for SEVENFACT included data from 2 studies.

1. GTC-FVIIa-005-11-Phase1b, Dose Escalation study to Assess Safety, Pharmacokinetics and Pharmacodynamics of Coagulation Factor VIIa (Recombinant)in Congenital Hemophilia A or B patients.
2. RB-FVIIa-006-13- A Phase 3 Study on the Safety, Pharmacokinetics, and Efficacy of Coagulation Factor VIIa (Recombinant) in Congenital Hemophilia A or B Patients with Inhibitors to Factor VIII or IX. In Study RB-FVIIa-006-13, two doses (75mcg/kg and 225mcg/kg) are being evaluated for marketing approval.

A. Reviewer's assigned areas *not* completely reviewed to-date

Efficacy Review: To be completed pending receipt and review of the response to IR request.

Confirming hemostatic control has been problematic since objective criteria for hemostasis is based on the visual analog score (VAS) for pain .Other clinical components of hemostatic response assessment (mobility, swelling etc.) are missing from eCRFs. For subjects with missing or low baseline pain scores and lack of pain at baseline, it may be problematic to confirm the outcome of success in the absence of other supportive findings of hemostasis.

Protocol deviations in the high dose arm 225mcg/kg have resulted in challenges to interpreting the efficacy data in this arm.

Safety Review:

Safety- 42 subjects enrolled on Phase 1 and 2 trials are evaluated for safety analysis.

- No neutralizing inhibitors to Factor VIIa were identified.
- No thromboembolic events were identified.
- No deaths were reported on the studies.

B. Outstanding Information Requests

1. Discrepancies in efficacy outcome and CRF recording of efficacy assessment outcomes (VAS score) were noted . Sponsor has been asked to provide a listing of discrepancies between efficacy outcome that are considered successful for hemostasis and VAS score and provide justification for the deviation from protocol specified criteria. The response to IR request was received and is currently under review.

2. Protocol deviations were noted in a sample of subjects in the high dose 225 mcg/kg arms. IR requests for actual doses administered in subjects at 3, 6 and 12 hours with hemostatic assessments at these time points have been requested.

C. Date reviewer will complete the primary discipline review, if not complete.

Mid-June 2017 (assuming IR requests are complete)

D. Key findings and substantive issues with the information and data in the application.

Study RB-FVIIa-006-13 is the primary study for efficacy.

Primary objective: To evaluate the efficacy of two separate doses (75mcg/kg vs 225mcg/kg) of LR769 for the treatment of bleeding

Eligible population: Subjects ≥12 years and up to 75 years of age with congenital hemophilia A or B with positive inhibitors (both high or low titers) experiencing bleeding. Subjects had at least 3 bleeding episodes of any severity in past 6 months. Any type of bleeding (Mild-moderate-severe) was permitted. After 20 mild/moderate bleeds were evaluated and treated, severe bleeds were included on the study.

Randomization: Subjects were randomized to the low (75mcg/kg) or high (225 mcg/kg) dose arm with cross over to alternate regimen every 3 months until the end of the study.

Treatment: For both the high and low dose treatment, repeat dosing for severe bleeding differed from dosing for mild to moderate bleeding with regard to the frequency of administration.

Hemostatic efficacy: Assessment was based on 4 point scale, with rating of none, moderate, good or excellent. Good and moderate response is based on subjective improvement in symptoms making distinction between the 2 difficult.

Statistical considerations for Efficacy

- The pre-specified primary efficacy endpoint was proportion of successfully treated mild and moderate bleeding episodes at 12 hours after study drug administration.
- Hemostatic efficacy was assessed using a 4 point scale.
- Hemostasis was successful if all of the following were met:
    - Excellent to good control of bleeding with the 4 point scale at 12 hours following the drug administration .
    - did not require other hemostatic agents or blood products

- no increase in pain beyond the 12 hour time point.

- Protocol specified success was defined as statistically significant higher success compared to objective performance criterion (OPC) of 55%. Study was powered to detect 15% point difference from the OPC for each of the 2 treatment arms with 80% power and alpha of .0125.

Results

- 465 mild/moderate bleeding episodes were evaluated in 27 subjects. Overall 84.5% of the bleeds were treatment successes, 10.8% were failures.
- 84.9% of the bleeds treated in 75mcg/kg arm and 93.2% of the bleeds treated in 225mcg/kg arm were successful. Thus, the study met the criteria for success for both doses however treatment failures were higher in the low dose arm.
- 78% of the bleeds were moderate. Success rate was higher in the mild compared to moderate bleeds.
- Treatment failures at 12 hours were 2 times higher for 75mcg/kg compared to 225mcg/kg arm.
  Overall number of missing bleeds were 22 (4.7%) with 14 bleeds in 75mcg/kg arm and 8 bleeds in 225mcg/kg arm. Upon review of all missing data, most common etiology for missing data was lack of subject recorded efficacy data.

Review Issues

1. The lack of protocol defined objective criteria to distinguish between good (success) and moderate (failure) assessment of hemostatic efficacy poses a review issue in confirming the study outcome. Sensitivity analysis after excluding these "indeterminate outcomes" is planned

2. Missing data (symptoms of improvement of bleeds) or discrepancies with regard to VAS pain score and successful outcomes may impact the efficacy outcomes. 4 bleeds were identified during random audits with successful outcome and worsening pain scores at 12 hours compared to baseline. Individual pain scores of bleeds regarded as successful will require further review and applicant will be requested to provide this data as information request.
   Overall preliminary impression is that despite the missing data and sensitivity analyses for the "indeterminate outcomes" the study may likely be considered successful given the observed magnitude of benefit over OPC.

3. In addition to the above, dosing errors are noted with repeat dosing in the high dose (225mcg/kg) arm that may impact the interpretability of the maximum dose administered and efficacy outcomes. Additional sensitivity analysis for the primary efficacy variable will need to be performed.

4. Since subjects self-administered the product, the dosing errors in the high dose arm seem to have resulted from the complex dosing plan. Additionally, due to lack of clarity in protocol, patients recorded additional efficacy assessments at

earlier time points which could have prompted additional dose administration .Thus dosing errors may be observed in post-marketing setting in the high dose arm. An assessment of percentage of subjects who experienced dosing errors is planned.

5. Due to low incidence of severe bleeds during the study, only 3 severe bleeds were enrolled and treated. All 3 of these bleeds were randomized to high dose arm and were successfully treated. Thus, there is no data to support treatment of severe bleeds with low dose treatment. There is a paucity of data to support a known therapeutic level of FVII for hemostasis in severe bleeding. Therefore extrapolation of efficacy data from mild to moderate bleeding to severe bleeding may be challenging thereby we may limit the indication to mild/moderate bleeding.

6. Decision is made not to bring this BLA to advisory committee as similar biologic product NovoSeven has already been approved since 1999 with significant clinical experience. LR 769 has similar mechanism of action to NovoSeven as both are recombinant Factor VIIa product. Its safety profile is similar to NovoSeven and currently no significant safety issues are identified. The clinical study design is acceptable.

D. Potential impact of the substantive issues have on the review especially those which could prevent approval and impact the review timeline

None anticipated at the moment.

E. Plan for addressing issues and the reason for the suggested approach

Please refer to review issues under Item d. **Meeting Update-** Recent IR received from sponsor

Pharmacology / Toxicology Reviewer

No significant issues have been identified at this time.

Clinical Pharmacology Reviewer

No significant issues have been identified at this time.

Statistics Reviewer

No significant issues have been identified at this time.

Postmarketing Safety Epidemiological Reviewer

No significant issues have been identified at this time.

Labeling Reviewer

No significant issues have been identified at this time.

BIMO Reviewer

No significant issues have been identified at this time.

Veterinary Medicine CMC Consult

No significant issues have been identified at this time.

2. For PDUFA V Program submissions, indicate whether discipline review letters will be issued.

The review team and chair confirmed that Discipline Review Letters will not be issued.

3. If the application will be discussed at an Advisory Committee (AC), review potential issues for presentation.

This application will not be discussed at an Advisory Committee.

4. Determine whether Postmarketing Requirements (PMRs), Postmarketing Commitments (PMCs), or a Risk Evaluation Mitigation Strategy (REMS) are needed.

The review committee did not identify a need for PMCs, PMRs or REMS at this time.

5. National Drug Code (NDC) assignments to product/packaging (excludes devices).

This action is being performed by the RPM.

6. Proper naming convention.

The committee chair accepts the current naming convention for this product as follows: **Coagulation Factor VIIa (Recombinant)**

7. Status of inspections (GMP, BiMo, GLP) including issues identified that could prevent approval and the establishment inspection report (EIR).

a. Bioresearch Monitoring issued four clinical investigator inspection assignments, one foreign, and three domestic for protocol RB-FVIIa-006-13, *A Phase III Study on the Safety, Pharmacokinetics and Efficacy of Coagulation factor VIIa*

(Recombinant) in Congenital Hemophilia A or B Patients with Inhibitors to Factor VIII or IX. The inspections are still pending in the ORA district office.

b. Two GMP Pre-License Inspections (PLIs) are completed: downstream BDS manufacturing facility in (b) (4), and BDS & FDP release testing facility in (b) (4). The major findings:
    i. Process validation is deficient as evident from repeated manufacturing failures. Changes to acceptance criteria are implemented without prospective validation studies. Shipping and cleaning validation studies are incomplete.
    ii. Validation of analytical assays is deficient. Release assays *Potency: Activated FVII Assay* and *Visual Appearance of Reconstituted Solution: Visible Particulates* and In-Process Control assay (b) (4) *by* (b) (4) are not properly validated or suitable for their intended use.
    iii. Lack of established Reference Standard for product potency.
    iv. Investigations of unexpected results are not always opened. Deviation investigations are deficient in failing to identify the root cause(s) and in implementing an effective corrective action(s). Deviation investigations are not closed in a timely manner.
    v. Specifications for critical incoming materials and components are not established.
    vi. Gaps were identified in the coordination between the quality departments of the BDS manufacturer, FDP manufacturer, raw materials suppliers, and numerous off-site quality control laboratories.
c. A GMP PLI is scheduled on 7-12 May 2017 that will cover the rabbit farm, milk collection and Drug Substance Intermediate (DSI) manufacturing facilities at LFB USA located in Charlton, MA.
d. Six GMP PLIs are waived:
    i. The FDP manufacturer in (b) (4)
    ii. The diluent manufacturer (pre-filled syringe with water for injection) in (b) (4)
    iii. The labeling, packaging, and kitting facility in (b) (4)
    iv. Three quality control laboratories in (b) (4)
e. The rabbit farm facility in (b) (4) will not be inspected

Review

8. Major target and milestone dates from RMS/BLA. Discuss pending dates of targets and milestones (e.g. Late-Cycle meeting, Advisory Committee, labeling discussion).

Internal Late-Cycle Meeting	June 29, 2017
External Late-Cycle Meeting	tentative July 13, 2017
Circulate draft press release	Sept. 14, 2017
Complete PMC Study, Labeling Review,	Sept. 14, 2017
Review Addenda	Sept. 1, 2017
Complete Supervisory Review	Sept. 14, 2017

Request Compliance Check, Lot Release Clearance	Sept. 29, 2017
Send Press Release to OCTMA	Sept. 29, 2017
T-minus date	Sept. 29, 2017
Send FDA Action Letter	Oct. 13, 2017

9. Establish a labeling review plan and agree on future labeling meeting activities.

This task will be completed by the RPM.

Confirm, as applicable

10. Components Information Table was obtained and notification was sent to the Data Abstraction Team (DAT) if discrepancies were found per *SOPP 8401.5: Processing Animal, Biological, Chemical Component Information Submitted in Marketing Applications and Supplements*. If not complete, indicate date it will be completed.

The task will be completed by September 15, 2017 by the CMC reviewer and Chairperson.

11. New facility information is included in the application, requiring implementation of regulatory job aid *JA 910.01: Facility Data Entry.* If not complete, indicate date it will be completed.

This task was completed by the DMPQ RIS for those facilities that have an FEI number. Facility data cannot be entered into RMS-BLA for facilities without an FEI number.

12. Status of decisions regarding lot release requirements, such as submitting samples and test protocols and the lot release testing plan.

Exemption from CBER Lot Release: Under the provision described in Federal Register (FR) 58:38771-38773 and the 60 FR 63048-63049 publication (December 8, 1995), routine lot-by-lot CBER release is not required for Coagulation Factor VIIa (Recombinant) because it is a well-characterized recombinant product. Thus, exemption of Coagulation Factor VIIa (Recombinant) from CBER Lot Release is justified.

CBER will perform in-support testing of commercial scale Coagulation Factor VIIa (Recombinant) product lots of all nominal potencies. This task will be completed by DBSQC.

13. Unique ingredient identifier (UNII) code process has been initiated. See regulatory job aid *JA 900.01*: *Unique Ingredient Identifier (UNII) Code* for additional information.

This task will be completed by the RPM. Submitted on 29 March 2017.

14. PeRC presentation date is set, and the clinical reviewer has addressed waiver/deferral/assessment of the PREA decision.

This task will be completed by the Clinical Reviewer. Scheduled for 12 July 17.

15. Action Items:
Each of the reviewers was tasked with discussing issues to be included in the Mid-Cycle Meeting Agenda/Summary

16. For applications subject to the PDUFA V Program:

- **a.** Reach agreement on information to be included in the Mid-Cycle Communication telecon with the applicant (see section below).
- **b.** Reach agreement on dates for upcoming meetings such as the AC or Late-Cycle Meeting. **Note:** the RPM may choose to pre-populate these dates prior to the meeting.

AC meeting is not recommended.

Internal Late-Cycle Meeting	June 29, 2017
External Late-Cycle Meeting	tentative July 13, 2017

Mid-Cycle Communication Agenda/Summary

Application type and number:	Original BLA under STN BL 125641/0
Product name:	Coagulation Factor VIIa (Recombinant)
Proposed Indication:	Control of bleeding in patients with inhibitors to Factor VIII and Factor IX
Applicant:	Laboratoire Francais du Fractionnement et des Biotechnologies S.A. (LFB)
Meeting date & time:	Friday, April 7, 2017, 11:00 AM - 12:00 PM
Committee Chair:	Mikhail Ovanesov, PhD
RPM:	Mark Levi, PhD

1. **Introductions**

2. **Status of Review**

Our review is ongoing at this time. We continue to review recently received LFB responses to our Information Requests (IRs) and *Filing Letter with Deficiencies*.

Our review is significantly delayed because LFB had not provided critical process validation data in the original BLA. The deficiencies were communicated to LFB in a *Filing Letter with Deficiencies* on 12 December 2016. Moreover, LFB failed to meet its

commitment to respond by the agreed-upon date of 12 January 2017. The requested documents were not submitted in full until 17 March 2017.

3. Any significant issues/major deficiencies identified by the review committee to date:

a. Chemistry, Manufacturing and Controls (CMC)

Several significant CMC deficiencies have been identified:

1. FDA found the design of the combination product and validation of its use to be deficient as evident from repeated instances of visible particulates found in the reconstituted Final Drug Product (FDP) during release testing and stability studies. The investigations were not successful in identifying the true root cause(s) because the proposed *Corrective and Preventive Actions* (CAPAs) have so far failed to prevent the recurrence of visible particulates in the FDP.

   In addition to safety concerns, the presence of visible particulates could result in a high rate of rejections of FDP vials by the end-users because it is stated in *Section 2.4 Administration* of the *Prescribing Information* "*Visually inspect the reconstituted solution for particulate matter and discoloration prior to administration. Do not use if particulate matter or discoloration is observed*". LFB's response to our concern in Amendment 12, which we find unacceptable, is that "*there is low probability that the user could detect visible particles of "Environment cause" and discard the vial*". LFB should propose a clear plan to address the particulate issue.

2. FDA noted deficiencies in the validation of the manufacturing process for the Bulk Drug Substance (BDS). During the pre-license inspection in (b) (4), we noted repeated process failures after the completion of Process Performance Qualification (PPQ), some of these failures were related to the (b) (4) steps. As a result, the validated ranges of *Critical Process Parameters* (CPPs) were modified, but these changes were implemented without the support of new process development and validation studies.

3. FDA also found that assays were not suitable for the control of the (b) (4) manufacturing process, FDP (b) (4) release, stability studies, and process validation studies. The most significant deficiency is related to the potency assay, which is not suitable for its intended use because LFB has not been using a qualified reference standard for the determination of product potency. As a result, numerous unqualified reference preparations were used to determine product potency at the various stages of process development, product characterization, and in stability studies. Additionally, the suitability of the (b) (4) assay used for the control of

rabbit milk protein (RMP) impurities was not established because the ability of the (b) (4) used in the assay to detect the full range of RMPs was not properly evaluated.

4. FDA noted that your proposed acceptance ranges for the release specifications of FDP and BDS are not supported by manufacturing process capability, and are not suitable for the control of product quality and stability. In addition, we found that the (b) (4) analysis that was used to assess product purity regarding the (b) (4) of Coagulation Factor VIIa (Recombinant) has been removed from the FDP release specification without proper justifications.

5. FDA observed adverse trends in product *Potency* in the stability studies. These trends were not properly investigated. For example, the data indicate poor stability of batch (b) (4) of the (b) (4) FDP presentation, which is extrapolated to lose (b) (4) of its activity by the end of the proposed shelf-life when stored at (b) (4).

6. FDA found that the qualification of the analytical methods used for the assessment of extractables and leachables (E&L) is deficient in that it does not include an assessment of the recovery of organic compounds during sample preparation. In addition, the assessment of extractables in the critical materials used in the manufacturing process, such as the container closure system and (b) (4) system for the lyophilized FDP, was not performed. Taken together, these oversights may result in an underestimation of the amount of leachables in the FDP, which could pose a safety concern.

b. Clinical

No significant issues have been identified at this time.

c. Pharmacology / Toxicology

No significant issues have been identified at this time.

d. Clinical Pharmacology Reviewer

No significant issues have been identified at this time.

e. DMPQ Facilities

No significant issues have been identified at this time.

f. Statistics

No significant issues have been identified at this time.

g. Postmarketing Safety Epidemiological Reviewer

No significant issues have been identified at this time.

h. Labeling Reviewer

No significant issues have been identified at this time.

i. BIMO Reviewer

No significant issues have been identified at this time.

j. Veterinary Medicine CMC Consult

No significant issues have been identified at this time.

4. Information regarding major safety concerns

The review of the clinical data to date has not identified any major safety concerns.

5. Preliminary review committee thinking regarding risk management**

The current thinking of the review committee is that a *Risk Evaluation and Mitigation Strategy* (REMS) is not required.

6. Any information requests sent and not received

- FDA sent an IR on lot release assays on 5 April 17, and is expecting LFB's response by 19 April 2017.
- FDA sent an IR on activity and concentration assays on 3 April 17, and is expecting LFB's response by 17 April 2017.
- FDA sent an IR on clinical issues on 3 April 17, and is expecting LFB's response by 10 April 17.

7. Any new information requests to be communicated

FDA has also identified several less significant deficiencies regarding the validation of manufacturing process and analytical methods, which we will convey to LFB via IRs.

An IR will be submitted by the Clinical Pharmacology reviewer regarding the PK study used to support the comparability between the two manufacturing processes.

8. Proposed dates for the Late-Cycle Meeting and the Late-Cycle Meeting Materials

The *Late-Cycle Meeting* (LCM) is proposed for July 13, 2017. The LCM *Materials* will be submitted 2 business days prior to the LCM.

9. Updates regarding plans for the AC meeting

The current thinking of the review committee is that this BLA will not be presented at the *Blood Products Advisory Committee* meeting.

10. Other projected milestone dates for the remainder of the review cycle, including changes to previously communicated dates

- There are no changes to the previously communicated dates.

- A *Pre-license Inspection* is scheduled on 7-12 May 2017. It will cover the rabbit farm, milk collection and Drug Substance Intermediate (b) (4) manufacturing facilities at LFB USA located in Charlton, MA.

The PDUFA goal date for the BLA is 13 October 2017.