M E M O R A N D U M

Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
Office of Tissues and Advanced Therapies

To:	BLA STN 125641/0
From:	Andrey Sarafanov, PhD, DPPT/HB
Applicant:	Laboratoire Francais du Fractionnement et des Biotechnologies S.A.
Product:	Coagulation Factor VIIa (Recombinant) [Sevenfact]
Indication	Control of bleeding in patients with inhibitors to factors VIII and IX
Subject:	Review of CMC information (Extractables & Leachables, and Diluent)
Through:	Tim Lee, PhD, DPPT/HB
	Basil Golding, MD, DPPT
CC:	Mark Levi, DRPM/RPMB

EXECUTIVE SUMMARY

This memorandum summarizes the review of product-related information in the original biologics license application (BLA) for Coagulation Factor VIIa (Recombinant) [Sevenfact] submitted by Laboratoire Francais du Fractionnement et des Biotechnologies S.A. (LFB). I reviewed the information in Module 3 (Quality) on Extractables & Leachables (E&L) in the Drug Product (DP) and information on the Diluent, sterile Water for Injection (SWFI). During the review cycle, I requested additional information, which was provided by the company. Upon review of all the submitted data, I found them to be still insufficient to support the approval of the application, and thus, I recommend issuance of a Complete Response Letter for this BLA. The deficiencies are summarized under Review Conclusions.

BACKGROUND

The DP (Sevenfact also referred to as LR769) is produced from the milk of transgenic rabbits carrying a recombinant cDNA gene of human Factor VII (rhFVII). This gene was (b) (4) and modified to target the expression of rhFVII to the mammary gland. The rhFVII is activated during the purification process to rhFVIIa, the active pharmaceutical ingredient. The DP is intended to treat patients with hemophilia A or B with inhibitors. The rhFVIIa is formulated as sterile lyophilized powder in glass vial and reconstituted with SWFI prior to administration into patients. During manufacture, at LFB USA Inc. (b) (4) The lyophilized product is released in (b) (4) dosage forms containing 1 mg, (b) (4) 5 mg of rhFVIIa along with the diluent in a pre-filled syringe (PFS) containing 1.1 mL, (b) (4) 5.2 mL of SWFI, respectively.

REVIEW SUMMARY

LEACHABLES AND EXTRACTABLES

Drug Substance

(b) (4)

(b) (4)

(b) (4)

(b) (4) .

Drug Product

Leachables and Extractables Assessment (section 3.2.P.5.5).
Based on the preliminary risk assessment (section 3.2.S.4.5.2.9.2), the following high risk factors of the DP manufacturing process were identified.

- (b) (4) .
- (b) (4) .
- Container closure system.

Elemental Leachable (section 3.2.P.5.5.4)
The study was based on ICH Q3D guideline "*Guideline for Elemental Impurities*". (b) (4) DP lots representing each product dosage strength (1 mg, (b) (4) 5 mg) were tested. This study evaluated the content of elemental impurities and its risk with respect to the permitted daily exposure (PDE) as described in EMA SWP/4446/2000 and ICH Q3D guidelines. In particular, elements mandatory by the guidelines (risk classes (b) (4) and non-mandatory elements (class (b) (4)) were evaluated. The analytical methodology was based on (b) (4) and resulted in the detection of (b) (4) as the most abundant elemental leachables; no risk for the patients was determined. In addition, elemental leachables were assessed in each material considered to be at high risk in the production. The respective study reports were provided in Amendment 40 as reviewed under Communication for Additional Information (Question II. 2. b).

(b) (4) LEACHABLES ASSESMENT
(b) (4)

Reviewer's Comment
No study reports for the assessment of E&L were provided. These data were requested and received in Amendment 40 as reviewed under Communication for Additional Information (Question II.2 c).

(b) (4) EXTRACTABLE AND LEACHABLE ASSESMENT
Extractable Study
In this study, (b) (4)

Reviewer's Comment
In the original submission, no data were provided. Upon request, the company provided the study reports (R-15-2574-EXTC1 and R-15-3392-LEA1-MPGL, revision 2) for extractables. This information is reviewed under Communication for Additional Information (Question II. 2.c (i) b)).

Leachable Study
The study was performed (b) (4)

Reviewer's Comment
No study report was provided for leachables assessment for the (b) (4). Upon request, these data were received as reviewed under Communication for Additional Information (Question II.2.c (i) b)).

CONTAINER CLOSURE SYSTEM LEACHABLE ASSESMENT
The DP CCS consists of Type (b) (4) borosilicate glass containers and bromobutyl rubber closures (siliconized). Respective to the product dosage strengths (1 mg, (b) (4) 5 mg), (b) (4) vial sizes, 3 mL, (b) (4) and 10 mL, are used. The 3-mL vial (1 mg dosage strength) was defined as the worst-case packing format based on the highest surface contact ratio between the stopper and the cake volume, and thus used for the leachables study.

Reviewer's Comment
The E&L study results were not presented, and received upon request. The data are reviewed under Communication for Additional Information (Questions I. 4b (i), II. 2. b and II. 2. c. (i)).

WATER FOR INJECTION, PREFILLED SYRINGE (section 3.2.P)

The SWFI is manufactured by (b) (4). It is packaged in 1.25 mL, (b) (4) or 10 mL glass syringes (i.e., PFS) and sealed with a bromobutyl stopper. The respective filling volumes are 1.1 mL, (b) (4) 5.2 mL, supplied according to the lyophilized product dosage strength (1 mg, (b) (4) 5 mg, respectively).

Pharmaceutical Development (section 3.2.P.2)

There was no formulation development. The syringe construction was selected to deliver the respective volume of the diluent to achieve the concentration of 1 mg/mL of rhFVIIa upon reconstitution.

Extractables Study (section 3.2.P.2.4.2)
This study was performed for the syringe tip cap and plunger using extraction with either (b) (4) in the samples. The analytical study was performed by the syringe's supplier (b) (4) performed toxicological risk assessment of the results and concluded that these results were satisfactory for product safety.

Reviewer's Comment
In the initial submission, extractables were evaluated without using conditions of high temperature applied for (b) (4) the PFSs (b) (4) of the manufacturing process) and no data for organic compounds were provided. I requested LFB to perform the study under relevant temperature conditions to assess all respective compounds. This information was provided as reviewed under Communication for Additional Information ((Questions I. 4b (i) and II. 2. c. (ii)).

Leachables Study (section 3.2.P.2.4.3)
The study description and results were not presented in the original BLA and were submitted upon my request (section 3.2.P.2.4). However, the study was also not performed under conditions representative of actual manufacturing (b) (4). The data were received upon another request as reviewed under Communication for Additional Information (Question II. 2c. (ii)).

Microbiological assessment was performed per (b) (4) testing) and (b) (4) testing) (section 3.2.P.5.4). The (b) (4) testing was performed by (b) (4). Based on these results and stability testing (section 3.2.P.8), the company concluded that the CCS is compatible with the product and suitable for the intended use.

Manufacture (section 3.2.P.3)

The manufacture of SWFI PFS is performed by (b) (4). Labeling and packaging are performed by (b) (4) The SWFI nominal batch sizes are (b) (4) (1.1 mL, (b) (4) 5.2 mL, respectively).

The manufacturing process involves the following steps.
(b) (4)

Reviewer's Comment
The information related to the whole aseptic process (filling equipment qualification, cleaning and sterilization of product contact equipment and environmental monitoring) was reviewed by Ms. Nicole Trudel from the Division of Manufacturing and Product Quality.

(b) (4).

(b) (4).

Manufacturing process validation.

(b) (4)

Specifications and Analytical Methods (section 3.2.P.5)

The specifications and respective analytical testing (Table 1) are justified by relevance to the requirements of the (b) (4) for Sterilized Water for Injections (b) (4)

Table 1. Specifications (sterile Water for Injection, Prefilled Syringe) *

Test	Method	Acceptance Criteria
Characteristics	In-house	Colorless, clear and free of visible particles
Extractable volume	(b) (4)	(b) (4)
Particle contamination		
(b) (4)		
Sterility		
Bacterial endotoxins		

* No reference standards are used in the testing of SWFI (section 3.2.P.6).

Validation of Analytical Procedures (section 3.2.P.5.3)
Besides the methods reviewed below, the initial submission did not have information supporting the verification of the (b) (4) methods and validation of the non-USP methods for their intended use. It is only stated that as the analytical methods used are described in (b) (4), thus, no validation of the procedures is required. No data were provided except for the following methods:

(b) (4)

Reviewer's Comment.
This test corresponds to (b) (4).

Verification of Sterility test (report IV-067/16).
This assay was performed per (b) (4) and similarly to the test above, with the difference is that upon filtration (b) (4) of the samples with the (b) (4). For each strain, the acceptance criteria that the growth must occur within specific time period (b) (4) were met.

Verification of Bacterial Endotoxins test (IV-078/16).
This assay was performed using a (b) (4) method per (b) (4) The sWFI test samples with (b) (4) were tested and the acceptance criteria for endotoxin recovery of (b) (4) were met. The actual samples of SWFI taken from stability study met the specification limit of endotoxin (b) (4)

Reviewer's Comment.

1. The data for verification of the Sterility and Bacterial Endotoxin methods were missing in the original submission, and received upon request (Communication for Additional Information, Question I. 6a).
2. The studies for each test, Bioburden, Sterility and Bacterial Endotoxins, were entitled as "Validation" (of the method). However, the actual designs corresponded to verification of each procedure. This is acceptable, as the methods are described in the (b) (4).
3. Regarding other methods, the company was requested to provide data to verify the (b) (4) methods and validate the non-USP methods. This was followed up as described under Communication for Additional Information (Questions I. 6a and II. 1).

Batch Analysis (section 3.2.P.5.4)

The results of analysis of (b) (4) clinical (b) (4) and (b) (4) process-validation commercial lots of the SWFI PFS (b) (4) per the release specifications were within the respective limits.

Container Closure System (section 3.2.P.7)

SWFI is packaged in 1.25 mL, (b) (4) or 10 mL Type (b) (4) glass syringes, which are sealed with a bromobutyl stopper (plunger). The inner wall of the glass barrel is (b) (4)

complying with (b) (4), and the plunger stopper is made of elastomer composed of bromobutyl (free from latex). The syringe and all its parts are manufactured by (b) (4) The syringes are received from the supplier (b) (4) as ready to use (i.e., pre-filled with SWFI). The plunger rod and the backstop are provided as accessories, and not an integral part of the prefilled syringe. The review of LFB's evaluation of E&L from the CCS is provided above and under Communication for Additional Information (Questions I. 4b (i) and II. 2. c. (ii)).

Stability (section 3.2.P.8.1)

The risk assessment included assessment of leachables coming from the glass barrel and stopper, (b) (4) This assessment identified the 1.1 mL and 5.2 mL formats to be the extreme configurations that justified using those in the (b) (4). Thus, (b) (4) clinical lots (1.1 mL and 5.2 mL syringe size) and (b) (4) process-validation commercial lots (b) (4) per each syringe size, 1.1 mL, (b) (4), and 5.2 mL) of SWFI PFS were placed on long-term stability at 5ºC (except clinical lots), 25ºC and 30ºC (0, 3, 6, 9, 12, 18, 24, 36 (b) (4) months' time points) and accelerated stability at (b) (4) months' time points). The analysis is being performed per the specification parameters; also, three additional parameters are tested (b) (4) At present, the available data support a shelf-life of 24 months when the SWFI syringes are stored at 5°C, 25°C and 30°C. The study is ongoing and the firm committed to proceed post-approval. The accelerated study has been completed and supported stability at (b) (4) months.

COMMUNICATION FOR ADDITIONAL INFORMATION

I. On December 12, 2016, a Filing Letter with Deficiencies was sent to the company. The following questions, relevant to my review, were communicated.

4b. Please provide, for both the Factor VIIa and diluent, in Section 3.2.P.7, data on extractables from the Container Closure System.

Response (February 27, 2017, Amendment 17)
i) Lyophilized product leachable studies. The company provided data of the ongoing study to evaluate leachables in the lyophilized DP monitored for (b) (4) months at 30°C during stability study. The results were available for 3 months of storage (section 3.2.P.2.4, reports TE 152111, TE 160247 and TE 161277 A by a contractor laboratory, (b) (4). LFB performed a toxicological risk assessment for the found leachables (in particular, (b) (4) and concluded that their presence should not be harmful to patients (report 000146586). Elemental analysis for (b) (4) metals by (b) (4) resulted in conclusion of safety for patients.

Reviewer's Comment
For organic leachables, the analytical procedure involved extraction of the reconstituted DP or SWFI samples by (b) (4)) either (b) (4) (lyophilized samples) or (b) (4) times (b) (4) solution samples). Then, (b) (4) different compounds were added into the (b) (4) samples to serve as (b) (4) and to use one of them for quantitation. However, the recovery of leachables from (b) (4) into the (b) (4) phase was not assessed that could have resulted in underestimation of those. In further communication, I requested the company to evaluate the recoveries (Question II. 2. a, b).

ii) Water for injection leachable studies. The company provided data evaluating leachables in the SWFI PFS (process validation lots), which is being monitored in the ongoing stability study. At present, the data are available for 12-month storage (section 3.2.P.2.4, reports TE 141055, TE

141664AR, TE 150105AR, TE 151275, TE 141045AR and TE 141046AR by (b) (4) . Using the same methodology as described above, it was found that leachables, presented at the highest concentrations, were (b) (4) .
The toxicological risk assessment concluded that their presence in SWFI is acceptable (report 000119576).

Reviewer's Comment
a) The analytical methodology used for sample preparation for (b) (4) analysis is similar to that used for the lyophilized DP. The difference is that the (b) (4) solutions were (b) (4) which can significantly improve the (b) (4) Still, the recovery of those should be evaluated for proper risk assessment as further communicated with the company (Question II. 2. a, b).

b) The company did provide data on extractables for both types of CCS (lyophilized product and SWFI). This information was further requested (Questions II. 2. *c(i-ii)*). Also, I requested the review of the toxicological assessment by a toxicologist.

6a. Regarding the diluent, Water for Injection (SWFI), your specifications for SWFI, Prefilled Syringe (Section 3.2.P.5.1) are based on analytical methods which comply with the (b) (4) , but not the (b) (4) These methods are (b) (4) .
Section 3.2.P.5.3, Validation of analytical procedures, states that no validation of analytical procedures was required and did not contain data. According to FDA's 2015 Guidance on Analytical Procedures and Methods Validation for Drugs and Biologics, all non-USP methods should be validated, and the (b) (4) methods should be verified under actual conditions of use. Therefore, please provide the data for the validation of the non-USP methods, and the verification of the (b) (4) methods.

Response (February 17, 2017, Amendment 16)
The company submitted data for the validation of the Sterility and Bacterial Endotoxins assays as required by (b) (4) for sterilized water for injection. The studies were performed by the SWFI manufacturer, (b) (4). The data were provided in reports IV-067/16 and IV-078/16 as reviewed above (Specifications and Analytical Methods for SWFI) and found to be acceptable. The company stated that the data for the other methods can be available by the end of June 2017.

Reviewer's Comment.
The response is acceptable.

II. On April 24, 2017, the following IR was sent to the company.
1. In your February 17, 2017 response to the review issue #6a from the December 12, 2016 Filing Letter with Deficiencies, you stated that data for the validation of the non-USP and verification of the (b) (4) analytical methods used for the Final Drug Product (FDP) diluent (except for methods for Bioburden, Sterility and Bacterial Endotoxin), if required by the FDA, can be available by the end of 2Q 2017. Please submit reports for the validation of non-USP and verification of (b) (4) analytical methods used for the FDP diluent, except for the methods for Bioburden, Sterility and Bacterial Endotoxin, by 30 June 2017. If you are unable to provide these reports by June 30, 2017, please provide a timeline for the submission of the delayed reports.

Response (May 31, 2017, Amendment 40)
The company informed FDA that they work with the SWFI manufacturer (b) (4) to obtain reports for the validation of non-USP analytical methods and verification of (b) (4) analytical methods (except for Bioburden, Sterility and Bacterial Endotoxins) and will provide the data by the end of June 2017.

On August 11, 2017 (Amendment 57), the company informed FDA that the verification/validation reports will be available by the end of September 2017. The respective protocols for all these methods were provided. The response was acceptable.

During the Late-Cycle Meeting on August 16, 2017, the company stated that they would provide these data in mid-October 2017.

On August 31, 2017 (Amendment 60), the company informed FDA that they would provide these data by October 06, 2017.

Reviewer's Comment.
The absence of data by the timeline of the review memo completion (September 28, 2017) is not acceptable.

2. We found the following deficiencies related to the Extractables and Leachables (E&L) studies:

- In your February 27, 2017 response to the review issue #4b from the December 12, 2016 Filing Letter with Deficiencies, you provided supporting information on the ongoing Leachables study evaluating the compatibility of LR769 with the FDP Container Closure System (CCS). The description of analytical methodology to analyze organic compounds (provided in the (b) (4) reports TE 152111, TE 160247 and TE 161277A) lacks an assessment of the efficiency of extraction of organic compounds into (b) (4) from the (b) (4) phase. Phase distribution of organic compounds can depend on their polarity indices, e.g., polar compounds migrate into the organic phase at lower degree than less polar compounds. We acknowledge that this concern was partially addressed in the report TE 141055 by performing such extraction at different (b) (4) to assess Leachables in the Water for Injection (SWFI) CCS.

- The methodology to assess E&L described for the testing of (b) (4) (section 3.2.P.5.5) was deficient. Only (b) (4) were used as the extraction solutions for the testing. These conditions do not cover such extremes as (b) (4) conditions (b) (4) and presence of organic component(s), such as (b) (4) which was used to assess Extractables in the SWFI CCS (section 3.2.P.5.3).

- Assessment of Extractables for the CCS for the FDP was not provided (section 3.2.P.7).

- Extractables study on the SWFI prefilled syringe did not consider conditions of high temperature (b) (4)
  Also, data on organic Extractables were not provided to support your statement that "*extractables detected in* (b) (4) *were lower than the ones detected in* (b) (4) *extract*" (section 3.2.P.2.4.2).

- Data and description of the analytical methodology were not provided for the E&L studies for the (b) (4) In addition, assessment of elemental impurities was not provided.

Taken together, these oversights may result in an underestimation of the amounts of E&L in the FDP, which poses a safety concern. To address this issue, please perform a reassessment of the E&L and the respective toxicology risks as follows:

a. In general, the studies should be performed under conditions representative of the use of the devices or equipment, and cover a comprehensive set of conditions, such as different (b) (4) and appropriate

organic solvents. The reports should also include justifications on how the studies are performed, such as the extraction conditions and solvents used.

b. Please revise your analytical methodology for organic E&L to consider the degree of their extraction into the organic phase (b) (4) to ensure correct quantitation of the levels of determined compounds. You may consider (b) (4) representative of the major classes of the expected E&L, into the (b) (4) phase and use its extraction by (b) (4) under different (b) (4) (as was done for the SWFI prefilled syringe).

c. Please provide study reports for the assessment of the following.

   i. Extractables for the LR769 FDP CCS.

   ii. E&L for the SWFI prefilled syringe under conditions representative of its manufacture, i.e., at (b) (4)

   iii. E&L for the (b) (4)-related materials: (i) the (b) (4) used to store LR769 (b) (4), and (iii) (b) (4) CCS (b) (4) Please include the assessment of elemental impurities in these studies.

Please submit your responses by May 31, 2017.

Response (May 31, 2017, Amendment 40)
The company summarized the results and provided additional data. They listed the high-risk materials for leachables as follows.

(b) (4)

Extractables study reports were obtained from each supplier of the materials. The leachables studies were designed based on this information. The company provided study reports (DEV/MBh/16.011/03R and DEV/EGa/16.016/01R) for the evaluation of elemental leachables in DP. These studies were performed by a contractor, (b) (4). As reviewed above, the major leachables were (b) (4) assessed as not having a risk for patients.

Reviewer's Comment
a) The information for assessment of elemental impurities in the DP is acceptable.
b) In the reports, the source of SWFI used for the reconstitution of lyophilized product is described as that supplied in PFS. This covers the cumulative leachables originated from both the manufacturing process and CCSs.

Response to Questions 2.a and 2.b.
The company stated that the assessment of the efficiency of extraction of organic compounds from the (b) (4) solutions into (b) (4) is on-going. The approach used is based on the (b) (4) by (b) (4) followed by (b) (4) and analyzing

them. The results will be used in the ongoing study for leachables in the final DP upon storage. The recoveries study results were expected to be available in July 2017.

Reviewer's Comment
The technique of sample preparation follows the (b) (4) and thus, is acceptable. The response was acceptable.

During the Late-Cycle Meeting on August 16, 2017, the company confirmed that the studies to assess the recovery of the potential leachables are ongoing and will be submitted later.

Response to Question 2.c (i).
a) The company provided study reports for the assessment of extractables in the DP CCS: for bromobutyl rubber stoppers (Report IP-GEP (b) (4) and for glass vials (E&L Analysis of Glass Containers for Pharmaceutical Packaging). These studies identified a number of organic and non-organic compounds typically found in the tested materials. No concerns were raised.

The assessment of leachables was based on the assessment of extractables. For the reconstitution of the lyophilized product, they used the supplied SWFI PFS. The analytical methodology used (b) (4) . The recoveries assessed for (b) (4) organic compounds were in the (b) (4) the respective results were used for analytical quantitation of these compounds. For the other (b) (4) compounds, the recoveries were not determined and the company committed to conduct additional studies.

Reviewer's Comment
The response was acceptable.

During the Late-Cycle Meeting on August 16, 2017, the company confirmed that the studies to assess the recovery of potential leachables are ongoing and would be submitted later.

b) For the assessment of extractables in (b) (4) (the results are reviewed above), the company provided study reports R-15-2574-EXTC1 and R-15-3392-LEA1-MPGL (revision 2), obtained from (b) (4) , were identified. The respective leachables study results are reviewed above under (b) (4) Extractable and Leachable Assessment.

Reviewer's Comment
The response is acceptable.

Response to Question 2.c.(ii)
To assess extractables from the SWFI CCS, the company provided a study report for the rubber stopper (Extractable Report Rubber Formulation FM457, *Edition 3*, by (b) (4) . This study used an extraction process performed under conditions more stringent than those used for the (b) (4) . The extraction solutions were (b) (4)

The study for leachables in SWFI CCS is ongoing. The PFS (lot (b) (4) are to be stored for up to (b) (4) months at 25°C, and 30°C. The data are available for 24 months of storage. The analytical methodology involved (b) (4) . The results indicated the presence of low amounts of (b) (4) (below the quantification limits) and (b) (4) (report TE 161470 by (b) (4) . The toxicological analysis indicated no risk for patients (report 000119576).

Reviewer's Comment
The response is acceptable.

Response to Question 2.c.(iii) i, ii
The company confirmed that the (b) (4) (items 1 and 2 from the above list) are used for the storage of (b) (4)

The extractables study data were provided by the (b) (4) (report CX5-14). The study was conducted under (b) (4)

In the ongoing leachables study (report TE160672, (b) (4) Leachables Assessment, reviewed above) to assess the analytical recoveries of organic compounds, standard solutions of (b) (4)

Reviewer's Comment
The response is acceptable.

Response to Question 2.c.(iii) iii
(b) (4)

Reviewer's Comment.
The response is acceptable.

Additional Information (July 24, 2017, Amendment 53)

The company provided updated assessment of E&L for all materials listed under questions 2.c.i-iii (IR on 04/24/2017). Based on the assessment of extractables by the respective manufacturers, the company assessed analytical recoveries for (b) (4) out of (b) (4) compounds, found as leachables from the respective materials and in the DP. These experiments were performed by (b) (4) the company reassessed the respective toxicological risk. For (b) (4) remaining compounds the respective assessment was committed to be submitted by the end of September, 2017.

Reviewer's Comment

Notably, the least recoveries (b) (4), etc) were observed for the most (b) (4) . Most likely, this was caused by (b) (4) .

Anyway, this could have resulted in an overestimation of the compounds in DP, which would not be a concern for safety. The response is acceptable.

Additional Information (08/31/2017, Amendment 60)

The company provided timeline for resolving the remaining issues upon discussion with FDA at the Late-Cycle Meeting on 08/16/2017. In particular, they stated the following (the paragraphs' numeration corresponds to that used in the meeting agenda).

2.a.vi. Analytical methods for extractables and leachables (E&L).

Recovery and safety assessment of (b) (4) out of the (b) (4) remaining compounds would be completed by 09/05/2017. Recovery and safety assessment for the (b) (4) remaining compounds would be completed by the end of December, 2017 (post-approval commitment).

2.a.vii. Validation of non-USP methods and verification of (b) (4) used to test SWFI PFS. These data were committed to be submitted to FDA by 09/05/2017.

Reviewer's Comment

The response indicated that the company is not able to provide the information for our review by the action due date. Since there are other deficiencies in the application, the decision is made to include these items in the CR Letter.

Additional Information (09/15/207, Amendment 62)

The company provided results of assessment of analytical recoveries of (b) (4) of the (b) (4) remaining compounds (reports TE 171028 and TE 171423 by (b) (4) . The recoveries were in the range of (b) (4) compounds were not recovered and the company stated that they would develop specific methods for them. The determined recoveries factors were applied to calculate the concentrations of the leachables in the DP for toxicological analysis, which indicated no safety risk raised for the DP.

The company summarized results of all studies as follows. A total of (b) (4) potential E&L coming from materials in contact with LR769 have been identified and investigated. For (b) (4) of them, safety assessment has been completed and no concerns have been raised (Amendment 53 and the current one). The remaining compounds are the following:

(b) (4)

The company stated that regarding these compounds, development of specific extraction protocols or the use of additional analytical techniques are required. The development of these analytical techniques has been started by (b) (4). The safety assessment of these compounds will be available by the end of December 2017 and will be communicated as a post-approval commitment to the FDA.

Reviewer's Comment

The response is partially acceptable. The company should comment on very low recoveries of some organic compounds and possible effect of that on the analytical quantitation and risk assessment. Again, the company is not able to provide the information for our review by the action due date. Since there are other deficiencies in the application, the decision is made to review them as part of the re-submission to the CR Letter.

REVIEW CONCLUSION

The analytical methodology to test the diluent (SWFI) of the lyophilized product per its release specifications is not supported by studies. The company failed to demonstrate validation of the respective non-USP methods and verification of (b) (4) methods.

Evaluation of leachables in the DP has not been completed. Though the company provided evaluation of analytical recoveries for most of the identified compounds, the data are still questionable due to very low recoveries of many compounds; the recoveries of (b) (4) compounds were not assessed. Dr. Evi Struble provided review of toxicological assessment of the data; her review (in the form of our email communication) is attached. She will provide the final review of the analytical data when they are available and the company addresses all concerns of FDA related to the analytical methodology.

Based on these deficiencies, approval is not recommended. The letter-ready comments for the company are provided below.

Comments for the company

1. Please provide results on the validation of the non-USP analytical methods, and verification of the (b) (4) analytical methods used for the release of the Diluent (except for *Bioburden*, *Sterility* and *Bacterial Endotoxin*).

2. In studies to evaluate leachables in the FDP, the recovery values were in the range of (b) (4) of the amounts of reference compounds spiked (b) (4) samples (Amendment 53 dated July 24, 2017). We noticed that the lowest values were mostly associated with the most (b) (4) compounds. Please explain the low recoveries for such compounds, and their impacts on analytical quantitation and safety assessment of the respective leachables in the DP.