



DEPARTMENT OF HEALTH & HUMAN SERVICES

U.S. Food and Drug Administration
Center for Biologics Evaluation and Research
Office of Compliance and Biologics Quality
Division of Manufacturing and Product Quality

To: Administrative File: STN 125506/0 for Coagulation Factor X (Human)

From: Randa Melhem, PhD, MRBII/DMPQ/OCBQ/CBER

Through: Marion Michaelis, Chief, MRBII/DMPQ/OCBQ/CBER
John Eltermann, Jr., R.Ph., M.S., Director, DMPQ/OCBQ/CBER

Cc: Mikhail Ovanesov, PhD, LH/DH/OBRR/CBER
Pratibha Rana, RPMB/DBA/OBRR/CBER

Subject: **Review Memo BLA:** [Bio Products Laboratory, Ltd., License # 1811].
Approval for human coagulation Factor X supplied as single-dose
lyophilized product in vials and sterile WFI diluent in vials manufactured
at BPL facilities in Elstree, Hertfordshire, UK.

Action Due: March 11, 2014

Action Recommended:

A Complete Response (CR) Letter should be sent to Bio Products Laboratory, Ltd.

CR Letter Ready Comments:

1. Outstanding issues from the Pre-License Inspection performed on 12 October through 25 October 2013 at BPL facilities in Elstree, UK and detailed in FDA form 483 issued on 25 October 2013 have yet to be resolved. Please submit documentation that demonstrates that all outstanding inspectional issues identified during the PLI have been corrected.
2. You listed the minimum required time of the primary and secondary drying phases and the minimum duration of the heat treatment. Please provide the maximum allowed times for the drying phases and terminal heat treatment, and the studies performed to support these limits.

SUMMARY

Bio Products Laboratory, Limited (BPL) submitted this paper BLA submission (with electronic content) on 11 July 2013 to provide information to support US market authorization of lyophilized human coagulation Factor X (FX) supplied with Sterile Water for Injection (SWFI) as diluent. FX is presented in single-dose vials containing two strengths of 250 and 500 International Units (IU) of lyophilized product per vial, and the SWFI diluent is supplied in vials filled to 2.5mL and 5mL nominal volume, respectively. The drug product (FX) and diluent (SWFI) are manufactured by BPL at their facility in Elstree, Hertfordshire, UK.

This BLA submission was given a priority review status as FX is an orphan drug.

The reconstituted FX drug product solution is for intravenous injection and is indicated for treatment and prophylaxis of bleeding in patients (at least 12 years old) with hereditary Factor X deficiency, covering on-demand treatment, pre-operative management in connection with surgery.

BPL briefly described the manufacturing of FX from receipt of plasma, to fractionation, viral inactivation, FX purification, concentration and sterile filtration, filling, lyophilization, heat treatment and final primary packaging and labeling of FX drug product as well as visual inspection.

They also briefly described the process validation for filling and terminal sterilization of WFI diluent and described visual inspection of diluent.

BPL provided information about the facility (layout, flow diagrams, room classifications, environmental monitoring) and equipment (shared and dedicated), and the controls in place to prevent contamination/cross contamination in the multi-product facility. They briefly described the container closure, and discussed the container closure integrity testing. They briefly discussed the cleaning and sterilization processes.

However the initial submission lacked details about the qualification of the facility, equipment and processes. Four information requests were submitted to address missing/insufficient information: 08 August 2013, 13 September 2013, 07 October 2013, and 16 January 2014, and BPL provided additional information in amendments 125506/0/3, 125506/0/10, 125506/0/13 and 125506/0/29.

CBER performed a Pre License Inspection (PLI) for BPL facility and the manufacturing operations of FX drug product and SWFI diluent from 21-25 October 2013, to support the review of the original BLA 125506/0. Seven deficiencies were identified during the inspection, and cited as 483 observations. The findings of the inspection are documented in the Establishment Inspection Report (EIR).

On 15 November 2013, BPL submitted their responses to the 483 observations which provided a plan of action for addressing the deficiencies and the time line when the corrective actions will be implemented. BPL's proposed completion of the corrective actions is 30 June 2014 which is after the Action Due Date (11 March 2014) of this Priority BLA submission. Review of the preliminary responses is documented in the 483 Response Review Memo.

BPL does not have to submit an Environmental Assessment in support of STN 125506/0, per 21 CFR Part 25.31(c) as documented in a separate Categorical Exclusion Memo.

Review of the original submission and amendments 125506/0/3, 125506/0/10, and 125506/0/13 is documented in the Primary Memo (09 January 2014). In this memo, I review the information provided in the last amendment 125506/0/28 received 02 February 2014.

CBER comments are in *italics* followed by BPL responses in plain lettering.

INFORMATION REQUEST SUBMITTED 16 January 2014

Lyophilization

You provided the following parameters/specifications for the manufacturing of Factor X.

<i>Process</i>	<i>Parameters</i>
<i>Formulation</i>	(b) (4) (b) (4) citrate (b) (4) (b) (4) phosphate (b) (4) sodium chloride (b) (4) sucrose (b) (4)
<i>Freeze-drying conditions during the primary drying phase</i>	Shelf temperature = (b) (4) Chamber pressure = (b) (4) Duration = (b) (4)
<i>Freeze-drying conditions during the secondary drying phase</i>	Shelf temperature = (b) (4) Chamber pressure = (b) (4) Duration = (b) (4)
<i>Conditions during terminal heat-treatment</i>	Temperature = (b) (4) Duration = (b) (4)

You listed the minimum required time of the primary and secondary drying phases and the minimum duration of the heat treatment. Please provide the maximum allowed times for the drying phases and terminal heat treatment, and the studies performed to support these limits.

BPL stated that the maximum duration for primary drying is (b) (4) and the maximum duration for secondary drying is (b) (4) based on results of statistical analysis of all the data from lyophilization development studies. They included report FXR467, *Multivariate data analysis of freeze-drying and heat-treatment data from development – version 2* (approved 29 January 2014) and concluded that the following parameters (listed in the Table below) appear to be robust for the lyophilization of FX. The statistical analysis report will be reviewed by the statistician on the review team and the findings will be documented in a separate memo.

(b) (4)

For the terminal heat treatment duration, BPL stated that the maximum limit is (b) (4) as described in report FXR465, *Determination of heat treatment duration for FACTOR X* (approved 29 January 2014). However BPL attached the wrong report: *Reprocessing of Factor X report 25D17*.

Reviewer's comment: The response is not adequate. Information to support the maximum duration will be requested as part of the CR letter.

Container Closure Integrity Testing

You stated in your response to a previous information request, and you confirmed during the Pre-License Inspection that you are conducting new validation studies (b) (4) to demonstrate container closure integrity. Please provide the protocol(s) and final report(s) for the new CCIT validation results for both the Factor X and SWFI diluent presentations.

- **FX CCIT**

As documented in the Primary review memo, BPL submitted CCIT results for (b) (4) studies on (b) (4) vials having the same neck size as that of 10mL vial used for FX manufacture and having identical stopper and overseal to those used for FX. They stated in response to previous information request that they are performing (b) (4) testing using the 10mL vials. Both the initial study (b) (4) and the new study (10mL) used positive controls created by inserting (b) (4) in the stopper. BPL added that they are testing

(b) (4) to see if the positive control can be reduced further in size to be a closer match to the theoretical limit (b) (4). We discussed container closure during the PLI, and BPL stated that they have been able to get positive controls using (b) (4).

BPL provided the protocol and Validation Report CCIR/532/0/01/01, *Container Closure Integrity Testing Report for* (b) (4)

(b) (4) (approved 18 October 2013). I reviewed the protocol and the results documented in the final report. Data showed that all positive controls were positive for (b) (4) and all test items did not show (b) (4).

BPL added that they do not plan to do additional (b) (4) testing on the lyophilized product container closure after their discussion with FDA during the PLI. FDA indicated that the 100% final product (b) (4) testing is more sensitive in detecting leaks than the (b) (4) test, and thus there is no need to perform both tests. (b) (4) testing for the FX vials has a theoretical hole size limit of detection of (b) (4) after the minimum (b) (4) post sealing hold period.

- SWFI diluent CCIT

BPL stated that they have performed (b) (4) testing for the SWFI 5mL vials using positive controls created by inserting the (b) (4). They provided the report which was reviewed in the Primary review memo and deemed acceptable.

They added that they have completed developmental studies which demonstrated that (b) (4) can reliably be used for the positive controls, and this size will be used for all future (b) (4) CCI testing. In addition, BPL is developing a (b) (4) method for measurement of (b) (4), to determine if it is a more sensitive method than (b) (4) method. BPL then intends to repeat the test work using (b) (4) for the positive control. The theoretical value will be determined after qualification of the (b) (4) method.

Reviewer's comment: It is acceptable that BPL eliminates using (b) (4) for FX container closure as they perform a (b) (4) test that is more sensitive. In addition it is acceptable that BPL will defer performing a CCIT on the SWFI container closure (using the (b) (4) for positive control) until they complete the (b) (4) method.
(b) (5), (b) (7)(E)
