



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, OCBQ/DMPQ/MRBII

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

Cc: Mikhail Ovanesov, PhD, OBRR/DHRR/LH
Pratibha Rana, OBRR/DBA/RPMS

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: October 23, 2015

ACTION RECOMMENDED

I reviewed Bio Products Laboratory, Limited (BPL) responses to the CR letter items applicable to DMPQ: Outstanding inspectional issues from the Pre-License Inspection (PLI) performed 21-25 October, 2013, and found them to be acceptable.

- I recommend approval of this BLA submission with the following PMC received 14 August 2015 (amendment 125506/0/47):
 - BPL commits to implement (b) (4)
[REDACTED]
[REDACTED] Results of the
validation studies of the (b) (4) will be submitted to CBER
as a CBE supplement in Q3 of 2016.

REVIEW OF THE COMPLETE RESPONSE

On 10 March 2014, a Complete Response letter (CR) was sent to Bio Products Laboratory, Ltd., for the production of Coagulation Factor X. DMPQ items included in the CR letter were outstanding inspectional issues which were listed as the first item of the CR letter. The inspectional observations included deficiencies in the following areas: process validation, analytical method validation, reprocessing conditions and documentation, validation of the lyophilization process, validation of cleaning and sterilization ^{(b) (4)} of lyophilizers, visual inspection of the final product, and ^{(b) (4)}

BPL described additional studies and provided the results and additional information to address the outstanding inspectional issues in the following telecons and amendments:

- Amendment 125506/0/37 received 27 April 2015 – Complete Response
- Amendment 125506/0/38 received 15 June 2015 – Response to 08 May telecon and information request (OCBQ/DMPQ)
- Amendment 125506/0/43 received on 20 July 2015 – Response to 06 July information request (OBRR/DH)
- Amendment 125506/0/47 received 14 August 2015 – Response to 15 July telecon and information request (OCBQ/DMPQ)

I reviewed the DMPQ relevant issues, documented in the **483-response review memo**, and concluded that the studies performed and the data collected, as well as the analysis of the results and historical data, demonstrate that the corrective actions implemented addressed the deficiencies for the most part. All inspectional issues are considered to be satisfactorily resolved with the following PMC:

- BPL agreed to a post marketing commitment to ^{(b) (4)}
^{(b) (4)} Description of the modifications, and the results of the validation studies will be provided to CBER in a CBE supplement; and this is documented above under the “Action Recommended” section.

In addition to the inspectional issues, BPL did not fully respond in amendment 125506/0/28 (in response to IR 16 Jan 2014) to justify the maximum validated times for the primary and secondary drying phases of the lyophilization cycle and the terminal heat treatment.

BPL explained in response to 483-observation #4 (amendments 125506/0/38 and 125506/0/47) that the lyophilization cycle parameters were investigated and set during the developmental studies. They validated the minimum times to ensure completion of each phase prior to moving to the new phase of the cycle. Thus they did not perform studies to validate the maximum process times as the use of set times obviates the need to validate the upper limit of a proven acceptable range.

However, in response to our questions, BPL provided supportive data to show that ^{(b) (4)} the primary drying phase by ^{(b) (4)} did not impact the quality of the product,

and all product release criteria were met. For secondary drying, the duration range is (b) (4) based on multivariate analysis of data collected during developmental studies.

BPL also provided the data collected during the lyophilization of the (b) (4) PQ and PPQ batches which shows very little variability in the times for the freezing, primary drying and secondary drying, and all the product test results met the accepted release criteria.

In addition, BPL submitted in amendment 125506/0/49 report *FXR465, Determination of heat treatment duration for FACTOR X* (approved 29 January 2014), which was erroneously missing from their response (in amendment 125506/0/28) to our 16 Jan 2014 information request.

In this study, Factor X (batch (b) (4)) which had already received the full heat treatment cycle at 80°C for 72 hours, was (b) (4)

The appearance of the vials before reconstitution and the time for reconstitution were recorded. In addition, vials were assayed for Factor X activity by clotting assay (CFP0058-00) and by (b) (4) to determine antigenicity against an antibody raised to heat inactivated Factor X.

BPL presented the results of the study in Table 1 and Figure 1 of the report which showed that the appearance and reconstitution time are not affected by the (b) (4) of heat treatment. The data also indicated that while Factor X potency remains within specification (80- (b) (4) IU/mL) up to the (b) (4) time point, the Factor X as a percentage of the assigned vial potency remains at (b) (4). As the acceptance criteria for recovery is (b) (4), BPL concluded that Factor X is stable for a heat treatment period of 72- (b) (4) hours at 80°C.
