



FOOD AND DRUG ADMINISTRATION
CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

MEMORANDUM

To: File (STN BL: 125506/0) and Pratibha Rana

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Subject: *Final Review Addendum for Stability Studies of Coagulation Factor X (Human)*

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1. Executive Summary

On 10 July 2013, Bio Products Laboratory Limited (BPL) submitted an original biologics license application (BLA) for Coagulation Factor X (Human) with the proprietary name COAGADEX. COAGADEX was developed as a replacement therapy to treat hereditary Factor [F] X deficiency, a rare bleeding disorder, for which no specific coagulation factor replacement therapy is currently available. The product contains a human plasma derived FX concentrate indicated for the control and prevention of bleeding episodes as well as for perioperative management in adults and children (aged 12 years and over) with a hereditary FX deficiency.

The FDA granted this product Orphan Drug status (No. 07-2469) on 8 November 2007, Fast Track designation on 12 April 2012, and Priority Review for this BLA on 6 September 2013. On 10 March 2014, FDA issued a complete response (CR) letter delineating multiple Chemistry, Manufacturing and Controls (CMC) deficiencies and the information required to address them. On 27 April 2015, BPL submitted a complete response to deficiencies.

As part of the complete response, BPL designated as Bulk Drug Substance (BDS), (b) (4) previously considered as part of the Final Drug Product (FDP) process.

In this memorandum, I summarized my review of new batch analyses and stability data for the BDS, FDP and sterile Water for Injection (sWFI) provided in the amendment 37 dated 23 April 2015, as part of BPL's complete response and amendment 53 dated 9 September 2015, which was a response to an information request dated 9 September 2015.

The proposed storage periods for Factor X BDS, FDP and sWFI are as follows:

- For BDS: (b) (4)
- For FDP: 36 months at +5°C to +30°C, protected from light
- For sWFI: 48 months at +5°C to +25°C
- For stability upon reconstitution: Factor X is stable for 1 hour after reconstitution.

(b) (4) were included in the BDS stability study. The monitored stability indicating parameters were: (b) (4). All provided stability data demonstrate that BDS is stable for (b) (4) when stored at temperatures (b) (4).

For batch analysis, data from (b) (4) new Process Performance Qualification (PPQ) batches and (b) (4) previous batches were provided. The results from test parameters measured in batch analysis are consistent and comply with the BDS specification.

For sWFI (2.5 mL and 5 mL), a total of (b) (4) batches were included in the study. All the available data support the conclusion that sWFI is stable for up to 48 months at +5 to +25 °C.

For the FDP stability study, a total of (b) (4) batches were included. Results from all stability batches met the FDP specifications at +5°C, +25°C and +30°C for the duration of the proposed shelf-life of 36 months.

Two stability after reconstitution studies were performed on (b) (4) FDP batches. The data support the recommendation to use COAGADEX within 1 hour after reconstitution.

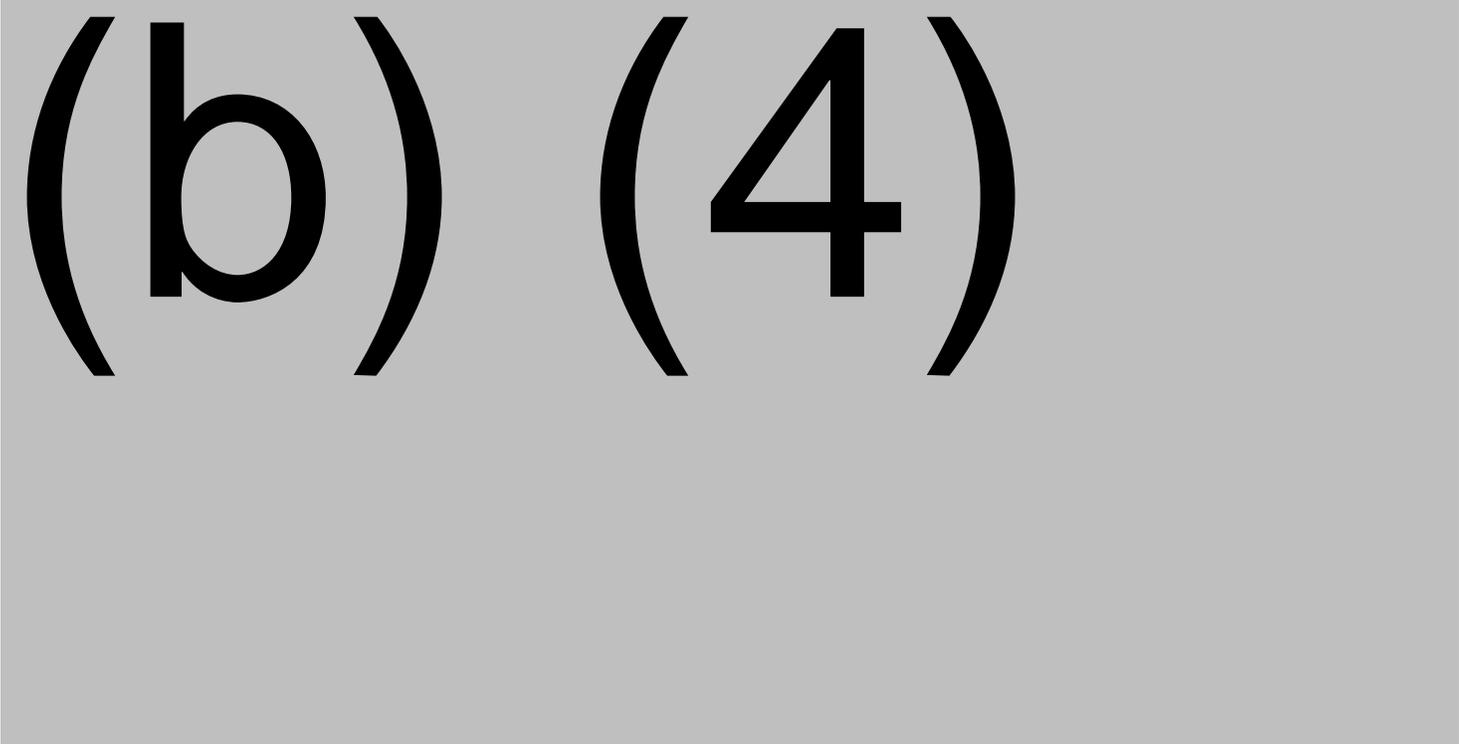
One out of specification (OOS) incident reported that two BDS batches' (b) (4) were below the acceptance limit at (b) (4) when stored at (b) (4) respectively. The reported OOS was found to have no significant negative impact on stability study conclusions that the BDS could be stored for up to (b) (4) (see explanation below).

Conclusion: The proposed shelf-life for final drug product and sWFI and dating period for BDS are supported by the results of stability studies.

2. BDS Stability Study
- Specification

The specification for Factor X BDS is shown in Table 1.

Table 1: COAGADEX BDS Specification



Abbreviations: NGT, Not Greater Than; NLT, Not Less Than; LT, Less Than
^a Action level

The specifications set by BPL were reviewed by primary CMC reviewer, Dr. Mikhail Ovanesov. The BDS specification compliance was designed to ensure BDS is suitable for subsequent manufacture into FDP.



(b) (4)

(b) (4)

[Redacted]

[Redacted]

[Redacted]

4. FDP Stability Study

A total of (b) (4) batches were included in the FDP stability study. Stability trial design was not changed from the study I reviewed in my memo for the original STN BL 125506. The following temperatures were studied: +5°C, +25°C, +30°C and (b) (4). All stability results met the requirements of the FDP specifications at +5°C, +25°C and +30°C for the time points inclusive of the proposed shelf-life of 36 months.

Reviewer's comments:

I have reviewed FDP stability in a previous submission. In the complete response, BPL provided an up to date addition to the stability study as follows: (b) (4) batches reached the 36 month time point and one batch reached 24 months. All data indicate that COAGADEX is stable for 36 months at +5°C to +30°C if stored protected from light.

5. Post-approval Stability Protocol and Stability Commitment for FDP

The unfinished FDP stability studies will continue for up to 36 months. Post-approval studies will be initiated on a minimum of (b) (4) per year where manufactured. In addition to batch release testing (time 0), sampling points will be at 6, 12, 18, 24 and 36 months. The post-approval stability protocol is listed in Table 2.

Table 2. COAGADEX Stability Protocol

Test	Time points tested
Description of freeze-dried plug	Tested at all time points for (b) (4) +5°C, +25°C and +30°C storage conditions .
Solubility a (b) (4)	
Appearance of solution	
Stability at (b) (4)	
Factor X activity, IU/mL	
Specific Activity, IU/mg protein	
NAPTT (b) (4)	
NAPTT (b) (4)	
FCT (b) (4)	
(b) (4)	
Total Protein , g/L	Tested at the 36 month time point for +5°C, +25°C and +30°C storage conditions
Chloride ion, (b) (4)	
Sodium ion (b) (4)	
Phosphate (b) (4)	
Citrate, (b) (4)	
Sucrose (b) (4)	
Factor II, IU/mL	
Factor IX (b) (4) IU/mL	
(b) (4)	
(b) (4)	
Bacterial Endotoxin, EU/mL	Tested at the 36 month time point for the +30°C storage condition
Sterility	

BPL will inform the regulatory authorities if the stability studies show any deviation from specification.

Reviewer's comments: The post-approval stability protocol and commitment are acceptable.

6. FDP Reconstitution Stability Study

(b) (4) batches from two reconstitution studies were reported in this submission. Study 1 was performed on Factor X 500 IU reconstituted product for up to 1 hour after reconstitution, i.e. same as in a previous submission. Study 2 included the Factor X 250 IU FDP for up to (b) (4) after reconstitution (see Table 3 for study details).

Reviewer's comments: The data indicated that Factor X is stable for up to 1 hour after reconstitution.

7. Study of the compatibility of Factor X with the reconstitution device

The Mix2Vial™ is a dual-sided device that allows rapid transfer of the diluent into the product vial, and an easy transfer of reconstituted product into a syringe. (b) (4) batches of 250 IU FDP and (b) (4) batches of 500 IU FDP were included in this study. The result is shown in Table 5.

Table 5 Compatibility Summary of Mix2Vial and Needle & Syringe system

(b) (4)

Reviewer's comments:

The study results indicate that use of the Mix2Vial™ transfer device does not change the Factor X potency or other stability-indicating parameters. This transfer device is suitable for reconstituting COAGADEX product and for transferring it to the administration syringe.

8. sWFI Stability Study

a. Materials and Methods

(b) (4) batches of 2.5 mL and (b) (4) batches of 5 mL sWFI were included in the study. Initially, the stability study samples had been inverted and stored at +5°C, +25°C, and (b) (4). An additional (b) (4) storage condition was studied for (b) (4) 5 mL batch. Stability test specifications are listed in Table 6.

Table 6. Stability Test Specification for sWFI.

(b) (4)

Reviewer's comments:

All sWFI results were in compliance with the stability test specifications, and no adverse trends were observed at recommended storage conditions. The data support the conclusion that sWFI is stable for up to 48 months at +5 to +25 °C.

c. Post-approval stability protocol and stability commitment

The stability studies will be continued for up to (b) (4) months. BPL committed to inform the regulatory authorities if the stability studies show any out of trend (OOT).

Reviewer's comments: This post-approval stability protocol and stability commitment are acceptable.

9. BPL's Response to the Complete Response Letter

Below, please find a summary of BPL's complete response to deficiencies cited regarding product specification.

FDA question Q7a.

Please address the following deficiencies regarding specifications:

- a. (b) (4) Factor X (b) (4) intermediate prepared at the conclusion of Step (b) (4) (as indicated in the Manufacturing Process Chart) qualifies as the Bulk Drug Substance (BDS). Therefore,
 - i. Please list all manufacturing steps leading to this intermediate in Section 3.2.S Drug Substance.
 - ii. Please develop BDS specifications, which can be comprised of existing parameters and acceptance limits for the intermediates (b) (4).
 - iii. Please provide Batch Analyses for the BDS.

BPL's Response Summary:

A new BDS section has been formed and was included in the BLA 3.2.S Drug Substance module. All sections relating to manufacturing steps up to step (b) (4) Factor X, have been moved to section 3.2.S Drug Substance, with appropriate adjustment in terminology. A Bulk Drug Substance specification has been developed and is described in section 3.2.S.4.1. Batch Analysis for the BDS is provided in section 3.2.S.4.4.

Reviewer's comments:

BDS stability data and all the related documents were submitted to the appropriate stability sections in module 3.2.S. Stability data met specification. Therefore this response is satisfactory.

10. Out of Specification (OOS) events

Below is the summary of BPL's responses received on 9 September 2015 to the 3 September 2015 information request regarding OOS events.

FDA question:

Regarding the Bulk Drug Substance (BDS) and FDP stability studies,

Please explain the OOS result for the parameter (b) (4) for BDS batches (b) (4)

BPL's Response Summary:

(b) (4)

Reviewer's comments: BPL's explanation for OOS of specific activity is acceptable. In addition, the data indicating (b) (4)

11. Conclusion and Recommendation

- a. Stability studies support the BDS storage period of up to (b) (4)
- b. BDS batch analyses demonstrate that new PPQ batches and historical batches are consistently in compliance with the BDS specifications.
- c. FDP stability data support the FDP claimed shelf-life of 36 months when stored at +5°C to +30°C protected from light.
- d. Reconstitution studies indicated that FDP is stable for 1 hour after reconstitution.
- e. The sWFI data support the sWFI claimed shelf-life of up to 48 months at +5 to + 25 °C.