



**FOOD AND DRUG ADMINISTRATION**  
CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

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MEMORANDUM

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

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**Subject:** *Final Review of Stability Studies in BPL's BLA for 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) [FACTOR X]. 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.

The product 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 FX concentrate indicated for the control and prevention of bleeding episodes as well as for peri-operative management in adults and children (aged 12 years and over) with a hereditary FX deficiency.

For the final drug product (FDP) stability study, a total of <sup>(b)(4)</sup> batches were included. All stability batches presented met the requirements of the FDP Specification at both +5°C, +25°C and +30°C for the time points inclusive of the proposed shelf-life of 36 months.

For stability after reconstitution study, 3 batches were included; all data supported the recommendation to use FACTOR X within 1 hour after reconstitution.

**Conclusion:** I recommend approval of this BLA with regard to the proposed shelf-life as supported by the results of stability studies.

## 2. Summary of Drug Product Stability Study:

FACTOR X is a sterile, (b) (4) freeze-dried concentrate of human FX, presented as two nominal dose sizes of 250 International Units (IU) and 500 IU of FX. After reconstitution with sterile Water for Injection (sWFI), FACTOR X forms a clear, colorless solution.

The two dose sizes contain the same concentration of FX active ingredient (about 100 IU/mL) and formulation chemicals upon reconstitution. FX concentration is approximately 100-fold greater than that in normal plasma. Dose sizes differ only in the corresponding volumes at the point of fill and the point of use, e.g., 2.5 mL sWFI is supplied with the 250 IU dose, and 5 mL sWFI is supplied with the 500 IU dose.

A Mix2Vial device (510(k) number: K031861) is also supplied. The device is a sterile, non-pyrogenic, single-use fluid transfer device that allows quick transfer of sWFI to the FACTOR X freeze-dried product and of the reconstituted FACTOR X product into a syringe for administration.

FACTOR X FDP batches will comply with the specification presented in Table 1 at release and throughout the shelf-life of the product.

Table 1. FACTOR X FDP Specification

Test	Compliance	Test Limits
<b>Characteristics</b>		
Description of freeze-dried plug	BPL	Smooth white plug
Moisture, (b) (4)	BPL	(b) (4)
Solubility at (b) (4)	BPL	
Appearance of solution	BPL	Colourless, clear or slightly opalescent solution.
(b) (4)		
Stability at (b) (4)	BPL	(b) (4)
Identity	BPL	Product complies with limits of factor X assay
<b>Biological Safety Tests</b>		
Sterility test	BPL	Pass
Bacterial Endotoxin Test, (b) (4)	BPL	(b) (4)
General Safety Test	BPL	Pass
<b>Purity/Specific Function</b>		
Factor X activity, IU/mL	BPL	80 (b) (4)
Factor X per vial, IU/vial	BPL	200 (b) (4) (250 IU dose) 400 (500 IU dose)
(b) (4)		
Total Protein, g/L	BPL	(b) (4)
Specific activity, IU/mg protein	BPL	
NAPTT (b) (4)	BPL	
NAPTT (b) (4)	BPL	
FCT (b) (4)	BPL	
<b>Excipients</b>		
Chloride, (b) (4)	BPL	
Phosphate, (b) (4)	BPL	
Citrate, (b) (4)	BPL	
Sucrose (b) (4)	BPL	
Sodium, (b) (4)	BPL	
<b>Impurities</b>		
Factor II, IU/ml	BPL	NGT 1
Factor IX, IU/ml	BPL	NGT 1
(b) (4)		

NGT, Not Greater Than  
 NLT, Not Less Than  
 LT, Less Than

A total of (b) (4) batches were included for the FDP stability study, (b) (4) batches of 250 IU and (b) (4) batches of 500 IU.

### Stability trial design

Vials from each of the batches under assessment are stored at a range of temperatures, in the dark. Humidity is monitored.

The temperatures tested during stability study were:

- (b) (4)
- +5°C (recommended / real-time storage)
- +25°C (recommended / real-time storage)
- +30°C (recommended / real-time storage)
- (b) (4)

Table2. Storage temperatures and sampling points for stability trial

Storage temperature	Sampling Point (months)						
	3	6	9	12	18	24	36
(b) (4)							
+5°C ±3°C	*	*	*	**	*	**	**
+25°C ±2°C	*	*	*	**	*	**	**
+30°C ±2°C			*	**	*	**	**

(b) (4)

+ tests employing a (b) (4) reference only

\* key stability indicating tests

\*\* additional biochemical, chemical and microbiological test methods dependant on time point.

## Results

The results of FX activities, NaPTT clotting test, Activities of impurity Factors IX and II, in all FDP batches stored at 5°C, are presented in Figures 1 to 4. For all the FDP batches stored at 25°C, the test results of the same parameters are presented in Figures 5 to 8. The testing result of Factor X activities, NaPTT clotting time, Factor IX and II impurities are within specification limits. Results of all parameters tested for samples stored at 30°C also meet specification. No undesirable trends were observed for these stability-indicating parameters.

Figure 1. Factor X activity in batches stored at 5°C

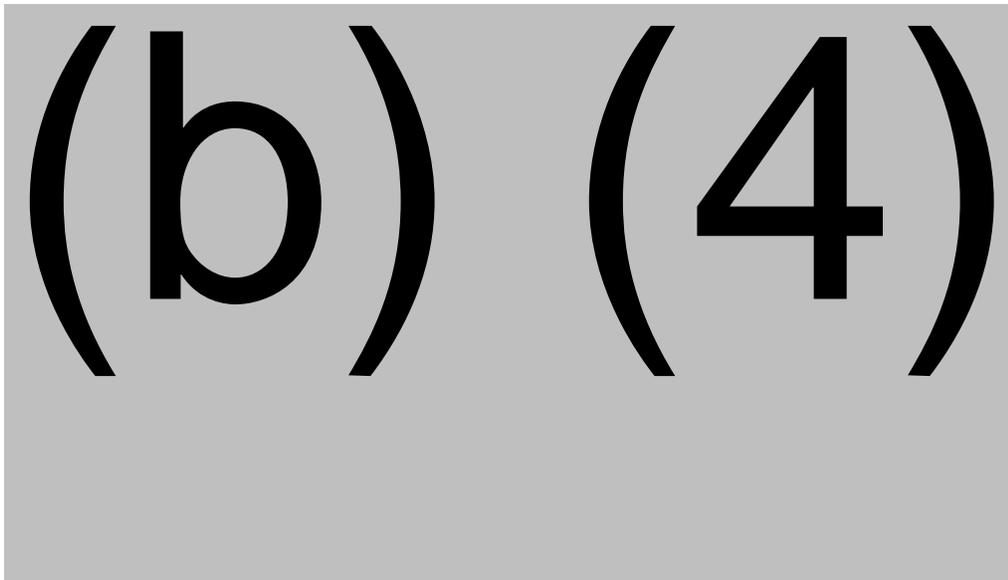


Figure 2. NaPTT clotting test results in all batches stored at 5°C



Figure 3. Factor IX impurity in batches stored at 5°C

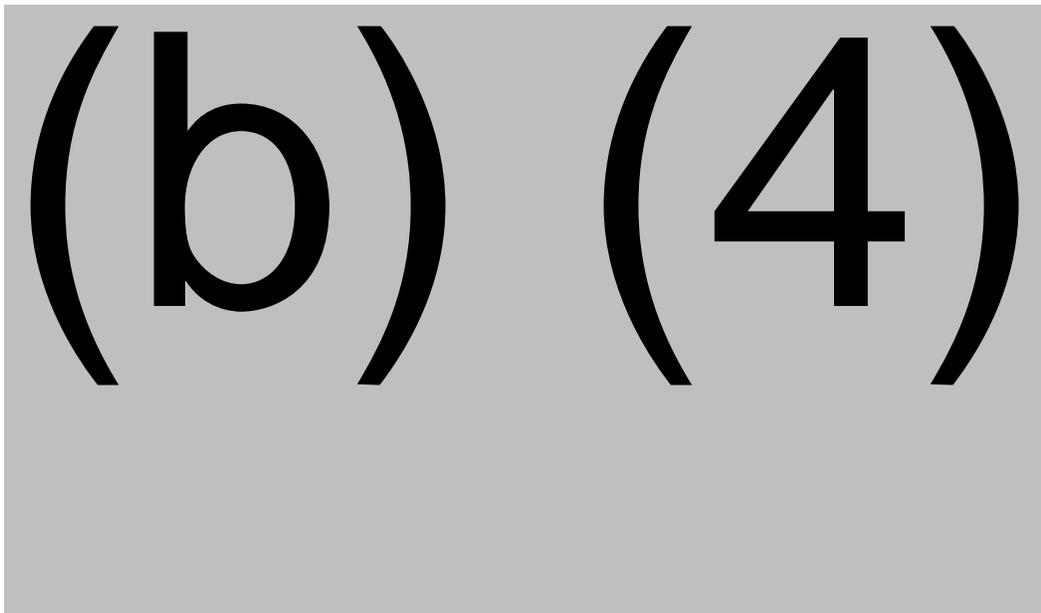


Figure 4. Factor II impurity in batches stored at 5°C

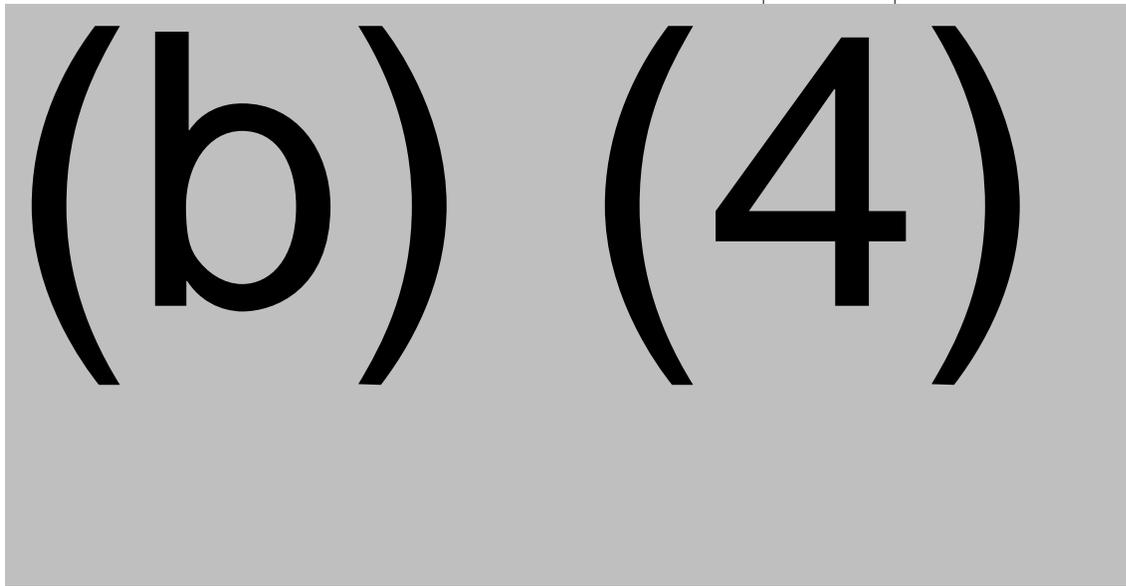


Figure 5. Factor X activity in batches stored at 25°C

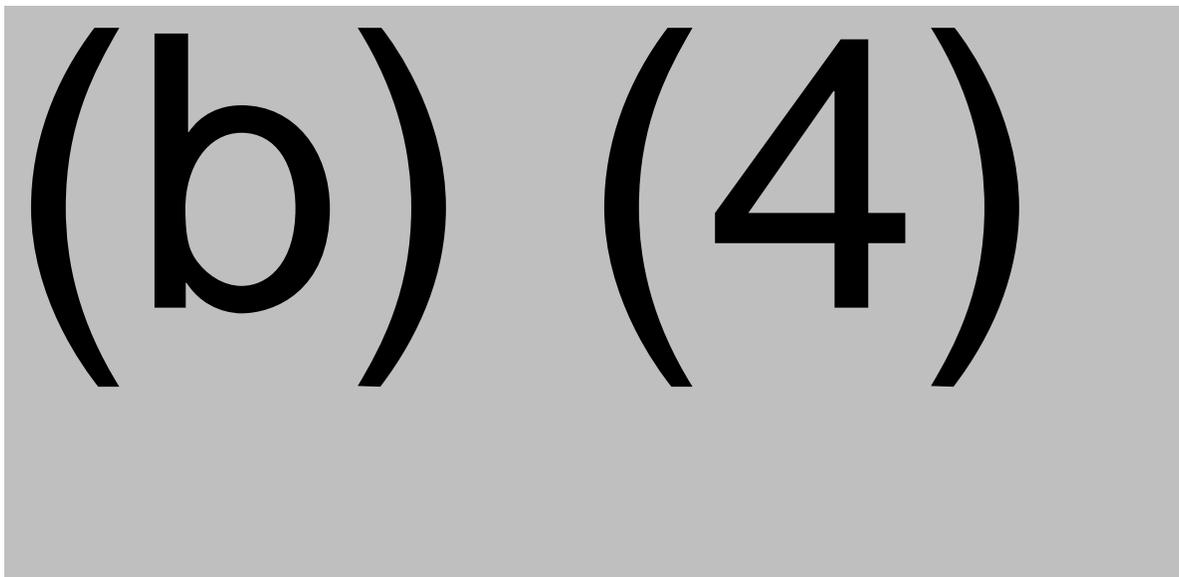


Figure 6. NaPTT clotting test results in all batches stored at 25°C

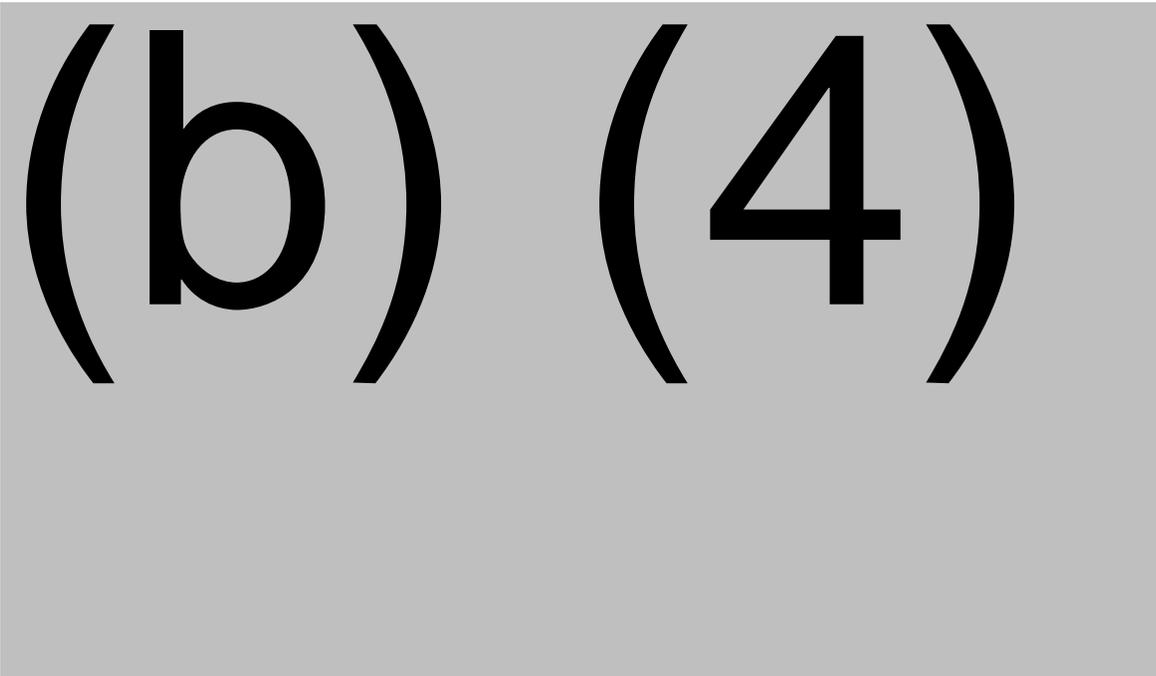


Figure 7. Factor IX impurity in batches stored at 25°C

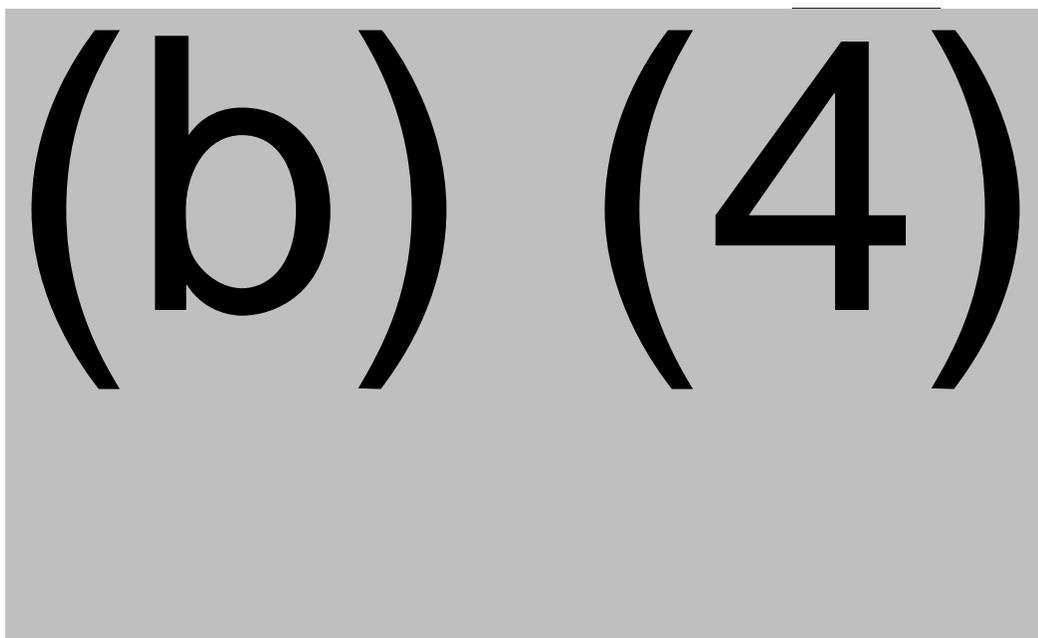
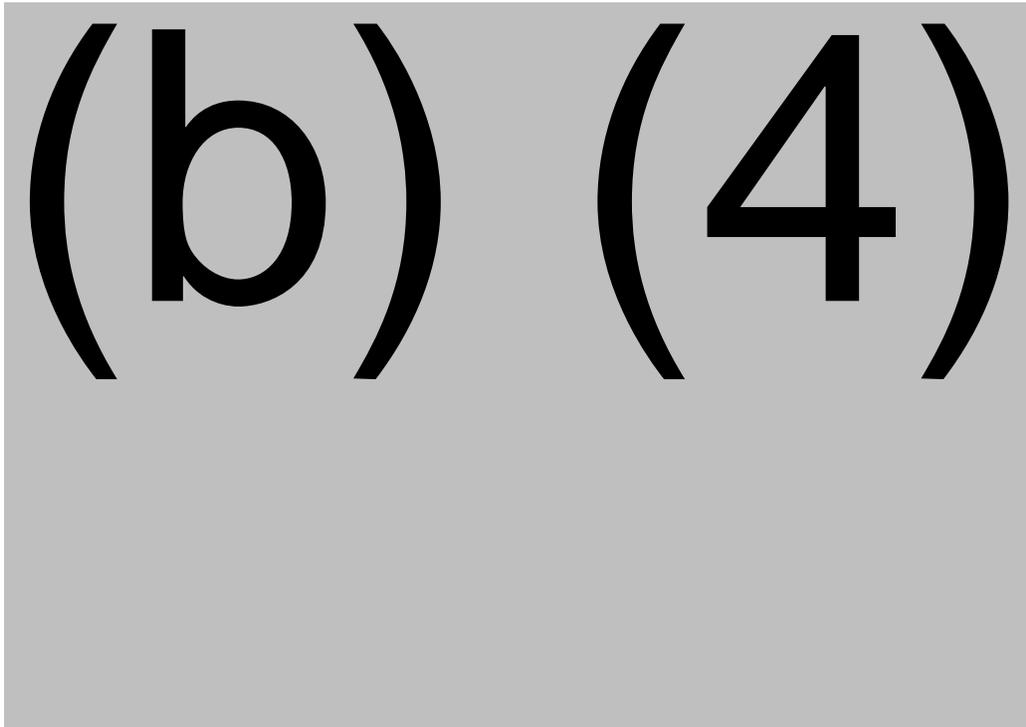


Figure 8. Factor II impurity in batches stored at 25°C



Stability data amounting of up to 36 months real time have been provided on <sup>(b) (4)</sup> pilot scale and <sup>(b) (4)</sup> manufacturing scale batches of FACTOR X. Data are also presented from <sup>(b) (4)</sup> batches still in trial.

At the routine storage temperatures of +5°C, +25°C and +30°C, appearance and stability after reconstitution remained in compliance throughout the course of the trial. Sterility has been maintained for those batches which have reached 36 months storage.

The test parameters measured during the trial have produced results that are broadly consistent, in compliance with the FDP specification, and provide no evidence of significant change during storage.

**Reviewer's comments:**

All batches presented met the stability Specification at +5°C, +25°C and +30°C for the time points inclusive of the proposed shelf-life of 36 months.

The stability studies for the batches still in trial will be continued for up to 36 months. Impurity of clotting factors II and IX are within specification limits.

### **3. Summary of Reconstitution Study**

Vials from 3 FACTOR X batches were assessed in the reconstitution study. These batches were within the proposed shelf-life period of 3 years and had been stored under controlled conditions at 2°C - 8°C. Table 3 indicates reconstitution stability study design.

Table3. FACTOR X reconstitution stability study design

	Time 0	1 hour	(b) (4)
<b>Control</b>			
<b>Control: Upright</b>	Description; solubility; appearance; clarity; factor X; FCT; (b) (4)	N/A	NAPTT; Stability of solution.
<b>Test: Upright</b>	N/A (equivalent to Time 0)	Appearance; clarity; factor X; FCT; clarity; (b) (4)	NAPTT; Stability of solution.
<b>Test: Inverted</b>	N/A (equivalent to Time 0)	Appearance; clarity; factor X; FCT; clarity; (b) (4)	NAPTT; Stability of Solution.

Table4. Result of Comparison of Upright, Inverted and Control Conditions

Test	Specification	(b) (4)	(4)
Description	Complies		
Solubility (b) (4)	(b) (4)		
Appearance of Solution	Complies		
Clarity	n/a		
Stability (b) (4)	(b) (4)		
(b) (4)			
NAPTT (b) (4)			
NAPTT (b) (4)	n/a		
FCT at (b) (4)	(b) (4)		
Factor X potency, IU/mL	80 (b) (4)		

<sup>[a]</sup> the period for which reconstituted product was monitored at ambient temperature to confirm appearance remained satisfactory

<sup>[b]</sup> performed at (b) (4) after reconstitution in accordance with routine specification test procedure

**Reviewer's comments:**

The study supports the in-use stability claimed that the FACTOR X product may be held for up to 1 hour after reconstitution before use.

**4. Conclusion & Recommendation**

- For the FDP stability study, all batches met the specifications at +5°C, +25°C and +30°C, supporting the proposed shelf life of 36 months at +2°C to +30°C for 250 IU

and 500 IU presentations of FACTOR X, within its original packaging, stored in the dark.

- For stability of reconstitution study, all data support the recommendation to use FACTOR X within 1 hour after reconstitution.

**I recommend approval of this BLA based on the review of stability data that support the proposed shelf-life of 36 months at +2°C to +30°C.**