

2 pages redacted (b)(4)

- -----(b)(4)-----
- -----(b)(4)-----
- -----(b)(4)-----
- Sterilizing filtration

6) Conditions of use and reuse of material

- -----(b)(4)-----

-----**(b)(4)**-----

(b)(4)	(b)(4)	----- (b)(4) - ---	(b)(4)
(b)(4)	----- (b)(4) -- -----	(b)(4)	(b)(4)
(b)(4)	----- (b)(4) -- -----	(b)(4)	(b)(4)
(b)(4)	(b)(4)	(b)(4)	(b)(4)

- ---**(b)(4)**-----

-----**(b)(4)**-----

7) Transfer and storage conditions

-----**(b)(4)**-----

-----**(b)(4)**-----.

8) Control of Materials

- Starting material - Human plasma

FXIII Concentrate is exclusively produced from human plasma obtained from FDA approved US plasmapheresis centers.

The plasma is tested according to the following principles:

The plasma donations used for FXIII Concentrate (Human) have been tested negative for serological markers (mandatory testing for HBsAg, antibodies against HIV-1/2 and HCV).

---b(4)-----

----- (b)(4) -----

----- and do not show high titers of B19V
DNA above the threshold are released.

Comment: CSLB has changed the limit for B19 virus DNA (tested by NAT) in the plasma pools for fractionation from (b)(4) IU/mL to 10⁴ IU/mL. This change is acceptable.

- ----- (b)(4) -----

----- (b)(4) -----

----- (b)(4) -----	----- (b)(4) -----
----- (b)(4) -----	----- (b)(4) -----
----- (b)(4) -----	----- (b)(4) -----
----- (b)(4) -----	----- (b)(4) -----
----- (b)(4) -----	----- (b)(4) -----
----- (b)(4) -----	----- (b)(4) -----
----- (b)(4) -----	----- (b)(4) -----
----- (b)(4) -----	----- (b)(4) -----
----- (b)(4) -----	----- (b)(4) -----
----- (b)(4) -----	----- (b)(4) -----
----- (b)(4) -----	----- (b)(4) -----
----- (b)(4) -----	----- (b)(4) -----
----- (b)(4) -----	----- (b)(4) -----
----- (b)(4) -----	----- (b)(4) -----
----- (b)(4) -----	----- (b)(4) -----
----- (b)(4) -----	----- (b)(4) -----

----- (b)(4) -----

- ----- (b)(4) -----

----- (b)(4) -----

- ----- (b)(4) -----

----- (b)(4) -----

----- (b)(4) -----	----- (b)(4) -----
----- (b)(4) -----	----- (b)(4) -----
----- (b)(4) -----	----- (b)(4) -----

• -----(b)(4)-----

----- (b)(4) -----

----- (b)(4) -----	----- (b)(4) -----
----- (b)(4) -----	----- (b)(4) -----
----- (b)(4) -----	----- (b)(4) -----
----- (b)(4) -----	----- (b)(4) -----
----- (b)(4) -----	----- (b)(4) -----

----- (b)(4) -----

9) Controls of critical steps and intermediates

The critical process control parameters (PCPs) were evaluated and summarized in risk assessment reports for the manufacture of FXIII Concentrate (Human). Further information on the critical PCPs is presented in Table 7 in Module 2.3.S.

----- (b)(4) -----

-----:

----- (b)(4) -----

----- (b)(4) -----	----- (b)(4) -----	----- (b)(4) -----	----- (b)(4) -----
----- (b)(4) -----			
----- (b)(4) -----	----- (b)(4) -----	----- (b)(4) -----	----- (b)(4) -----
	----- (b)(4) -----	----- (b)(4) -----	----- (b)(4) -----
	----- (b)(4) -----	----- (b)(4) -----	----- (b)(4) -----
----- (b)(4) -----			
----- (b)(4) -----	----- (b)(4) -----	----- (b)(4) -----	----- (b)(4) -----
	----- (b)(4) -----	----- (b)(4) -----	----- (b)(4) -----
----- (b)(4) -----	----- (b)(4) -----	----- (b)(4) -----	----- (b)(4) -----
----- (b)(4) -----	----- (b)(4) -----	----- (b)(4) -----	----- (b)(4) -----
----- (b)(4) -----	----- (b)(4) -----	----- (b)(4) -----	----- (b)(4) -----

3 pages redacted (b)(4)

----- (b)(4) -----

----- (b)(4) -----

----- (b)(4) -----

----- (b)(4) -----

In addition, product sterility and -----
----- (b)(4) -----

----- (b)(4) -----

11) Manufacturing process development

The development and major changes in the manufacture of FXIII Concentrate (Human) are as follows:

- Introduction of Pasteurization/Heat treatment step for virus inactivation (1981)
- ---b(4)-----
- ----- (b)(4) -----

- ----- (b)(4) -----
- ----- (b)(4) -----

- ----- (b)(4) -----

2. Characterization

1) Elucidation of structure and other characteristics

- Structure

Factor XIII is the zymogenic form of the glutaminyl-peptide γ -glutamyl transferase factor XIIIa. Plasma-derived FXIII is a 320 kDa hetero-tetramer (A2B2), which is the product of two separate genes coding for the A and B chains. The A chain is composed of 730 amino acids (83 kDa) and dimerizes to form a non-glycosylated globular molecule. It is also found intracellularly in monocytes, macrophages, platelets, megakaryocytes. All FXIII-A2 molecules found in plasma exist in the hetero-tetrameric form in complex with FXIII-B2. The FXIII-A chain has nine free sulfhydryl groups, including the active site with Cys 314. The A chain also contains an activation peptide, the catalytic triad, a calcium binding site, fibrin-binding, and substrate-recognition domains. The B chains are secreted by hepatocytes, and complex rapidly with the A2 subunits but also circulate in the homo-dimeric form in plasma. The plasma FXIII-A2B2 complex is present at a concentration of 14 ~ 28 mg/L plasma according to ELISA data (Murdock *et al.*, 1992).

Factor XIII is one of the zymogens to become activated in the coagulation cascade and is the only enzyme in this system that is not a serine protease. The conversion of plasma FXIII to FXIIIa (A2') results from the hydrolysis of the Arg36-Gly37 at the NH₂-terminus of the A subunit by thrombin. Full expression of activity is achieved only after the Ca²⁺ and fibrin(ogen) dependent dissociation of the B subunit dimer from the A2' dimer.

- Function

In the coagulation cascade, FXIIIa functions to stabilize the fibrin clot by crosslinking the α - and γ -chains of fibrin. Other proteins known to be substrates for FXIIIa which may be hemostatically important include fibronectin, α 2-antiplasmin, collagen, Coagulation Factor V, von Willebrand Factor, and thrombospondin. Cross-linked fibrin is the end result of the coagulation cascade, and provides tensile strength to a primary hemostatic platelet plug.

2) Impurities

------(b)(4)-----
-----.

------(b)(4)-----

2 pages redacted (b)(4)

 -----(b)(4)-----

The physico-chemical and biological properties of the final product FXIII Concentrate are summarized as follows:

Physico-chemical properties

Parameter	Specification
Albumin	6 - 10 mg/mL
Appearance	Colorless to slightly yellowish, slightly opalescent
Dissolution time	----- (b)(4) -----
Glucose	4 - 6 mg/mL
----- (b)(4) ----- protein	----- (b)(4) -----
----- (b)(4) ----- protein	----- (b)(4) -----
pH value	----- (b)(4) -----
Protein	6 - 16 mg/mL
Purity	----- (b)(4) -----
Residual moisture	(b)(4)
Sodium chloride	7 - 11 mg/mL

Biological properties

Parameter	Specification
Abnormal toxicity	Specifications CFR/(b)(4)
Potency	50 – 80 IU/mL
Pyrogens	Specification CFR/(b)(4)
----- (b)(4) -----	----- (b)(4) -----
Sterility	Specification CFR/(b)(4)

- 2) CSLB and its predecessors have been producing FXIII Concentrate since 1976, ---b(4)----- first licensed, pasteurized FXIII product derived from human plasma was introduced in 1993 under the trade name Fibrogammin HS. The product was renamed from Fibrogammin HS to Fibrogammin P in 2007.

 -----(b)(4)-----

In 2009, an ----- (b)(4) ----- was implemented that comprised the following improvements:

- ----- (b)(4) -----
- ----- (b)(4) -----

1) Please also refer to the respective section of FXIII DS with regard to the other manufacturing process development.

3. *Manufacture*

1) Manufacturer

The manufacture of FXIII Concentrate (Human) starting from the FXIII final bulk solution (drug substance, DS) to the FDP is performed at CSL Behring GmbH, Emil-von-Behring-Str.76, 35041 Marburg, Germany.

2) A brief description of manufacturing process and process controls

- Filling into the final containers and lyophilization

----- (b)(4) -----

-----.

- Packaging

----- (b)(4) -----
-----.

3) Flow chart of the production process

----- (b)(4) -----
----- (b)(4) -----

----- (b)(4) -----

4) Control of critical steps and intermediates

The lyophilization process is assessed as critical for the manufacture of the DP.

Critical PCPs for the production process of FXIII Concentrate (Human)

Production procedure	Critical process step	Process control parameter	Target value of the PCP
---(b)(4)--	----- ----- ----- -----	----- ----- ----- -----	----- ----- ----- -----

List of In-Process Control

Production step	Parameter	Testing method	Requirement	Analytical procedure
---(b)(4)--	---(b)(4)--	----- -----	----- -----	---(b)(4)--

5) Process validation and/or evaluation

The entire DP production process was validated at full-scale with manufacturing batches that were produced with PCPs set to the target values. All critical PCPs and IPTs were evaluated.

Overview of the documentation resulting from the process validation methodology for the manufacture of Fibrogammin P drug product

Production procedure number and title	Process steps described in the respective production procedure	Report number and title related to the respective production procedure
		<u>Risk analysis report:</u> ----- -----

albumin -----(b)(4)----- . The product is licensed in the US under the trade name of --(b)(4)--.

 -----(b)(4)-----
 -----.

Overview of addition of excipients during the process

Excipients	Production step
Human Albumin ((b)(4))	----- (b)(4) -----
Glucose -----(b)(4)--- (---- (b)(4))	----- (b)(4) -----
Sodium chloride (---- (b)(4))	----- (b)(4) -----
	----- (b)(4) -----
Sodium hydroxide (---b(4)-----)	----- (b)(4) -----
	----- (b)(4) -----

1) Validation of Analytical procedures

Apart from the tests performed by the manufacturer of the respective excipients, the analytical procedures/testing instructions performed by CSLB for each excipient are listed in the table below.

Analytical procedures for testing of excipients

Excipient	Parameter	Testing instruction
Sodium chloride	----- (b)(4) -----	----- (b)(4) -----
	----- (b)(4) -----	----- (b)(4) -----
	----- (b)(4) -----	----- (b)(4) -----
	----- (b)(4) -----	----- (b)(4) -----
	----- (b)(4) -----	----- (b)(4) -----
Sodium hydroxide	----- (b)(4) -----	----- (b)(4) -----
Glucose -----(b)(4)-----	----- (b)(4) -----	----- (b)(4) -----
	----- (b)(4) -----	----- (b)(4) -----
	----- (b)(4) -----	----- (b)(4) -----
	----- (b)(4) -----	----- (b)(4) -----
	----- (b)(4) -----	----- (b)(4) -----
	----- (b)(4) -----	----- (b)(4) -----

Excipient	Parameter	Testing instruction
	------(b)(4)-----	------(b)(4)-----
Human albumin (b)(4)	------(b)(4)-----	------(b)(4)-----

These analytical methods have been validated, and the pre-defined criteria of all parameters are met. Therefore, the validation data support these analytical methods used for testing of the respective excipients.

2) Excipients of human or animal origin

FXIII Concentrate is manufactured with the US licensed human albumin ------(b)(4)-
----- which complies with 21 CFR 640 and the (b)(4).

Excipient of biological origin with compendial requirement

Material	Compendial requirement	Process step	Function
Human albumin ----- ------(b)(4)-----	(b)(4); complies with requirements in 21 CFR 640.80 to 640.86	----- -----(b)(4)-----	--(b)(4)---

No excipients of animal origin are used in FXIII Concentrate (Human).

3) Novel excipients

None of the excipients in the FXIII DP is a novel excipient.

5. *Control of drug product*

1) Specification and justification for final product testing

Product quality attribute		Specification	Testing method	Justification
Practicability and organoleptic properties	Dissolution time	---(b)(4)---	Dissolution of the solid and visual control	Manufacturing experience
	Appearance	Colorless to slightly yellowish, slightly opalescent solution		
------(b)(4)--- protein		------(b)(4)---	----- ----- (b)(4)----- ----- --	Manufacturing experience. Part of identity testing according to 21 CFR 610.14
------(b)(4)--- protein		------(b)(4)---	----- ----- (b)(4)----- -----	Ph. Eur. and Part of identity testing according to 21 CFR 610.14
Purity		----- -----	------(b)(4)-----	Manufacturing experience

Product quality attribute	Specification	Testing method	Justification
	----- ----- ----- ---(b)(4)----- ----- -----		
Protein	6 – 16 mg/mL	----- (b)(4)----- -----	Total protein content according to Ph. Eur. includes all protein ingredients. The range reflects process and assay variability and was based on historical data.
----- (b)(4) -----	----- (b)(4) ----- -----	----- (b)(4)----- -----	--(b)(4)--
Albumin	6 – 10 mg/mL	----- (b)(4) -----	Range reflects process and assay variability and was based on historical data.
Glucose	4 – 6 mg/mL	----- (b)(4)-----	Manufacturing experience
Sodium chloride	7 – 11 mg/mL	----- (b)(4)----- -----	Range reflects process and assay variability and was based on historical data
pH	--(b)(4)--	----- (b)(4)-----	--(b)(4)--
Residual moisture	--(b)(4)--	----- (b)(4) -----	Specification set according to manufacturing experience. Range reflects process variability and was based on historical data. Assay method according to --- (b)(4)-----
Potency	50 – 80 IU/mL	---b(4)----- ----- -----	Specification set according to manufacturing experience. Range reflects process variability and was based on historical data.

Product quality attribute	Specification	Testing method	Justification
------(b)(4)-----	------(b)(4)-- -----	(b)(4)-----	----- ----- ------(b)(4)----- -----
Sterility	As specified in CFR/(b)(4)	Inoculation method in accordance with 21 CFR 610.12 and (b)(4)	CFR/(b)(4)
Pyrogens	As specified in CFR/(b)(4)	Test in rabbits in accordance to 21 CFR 610.13(b) and (b)(4) Dose/kg body weight: 3.0 mL	CFR/(b)(4)
Abnormal toxicity/General safety test	Specification CFR/(b)(4)	Test in accordance with 21 CFR 610.11 and (b)(4)	21 CFR 610.11/(b)(4)
Identity: (b)(4) ----- ----- ----- -----	------(b)(4)-- -----	----- ---(b)(4)----- -----, -----	CFR

Comment: With regard to the amount of protein used in the calculation of the -----(b)(4)-----, CSLB made clarification that it includes ---b(4)----- in Amendment 2 under IND -b(4)-. Therefore, it is acceptable. Also, FDA informed CSLB in the pre-BLA meeting -----
------(b)(4)-----
-----.

We consulted with Dr. Alfred V. Del Grosso from OCBQ with regard to the lot release protocol. We agreed with him to request CSLB to keep one decimal place to the specification of residual moisture (--(b)(4)--), and the analytical results be reported down to the defined limit of quantitation of the method, rather than zero.

2) Analytical procedures for FXIII FDP testing

- Determination of dissolution time and appearance: Practicability and Organoleptic test
- Visual inspection of preparations to assess the color of the solution
- --b(4)-----
- Determination of protein -b(4)-----
- Determination of -b(4)-----
- Quantitative determination of human albumin on the -----b(4)-----

- --b(4)----- determination of glucose
- Chloride determination
- pH [------(b)(4)-----]

Validation parameter	Acceptance criteria	Results
	-----(b)(4)-----	
----- (b)(4) -----	-----(b)(4)----- -----(b)(4)----- -----(b)(4)----- -----(b)(4)-----	----- --(b)(4)-----

- Quantitative determination of human albumin on the -----
----- (b)(4) -----

5 pages redacted (b)(4)

----- (b)(4) -----	----- (b)(4) -----	----- (b)(4) -----
----- (b)(4) -----	----- (b)(4) -----	----- (b)(4) -----
----- (b)(4) ----- -----	----- (b)(4) -----	----- (b)(4) ----- --
----- (b)(4) -----	----- (b)(4) -----	----- (b)(4) -----
----- (b)(4) ----- -----	----- (b)(4) -----	----- (b)(4) -----

----- (b)(4) -----

Comment: The validation report showed that the method Q-10-093 met all validation criteria. Therefore, it can be used for release testing of FXIII Concentrate (Human) FDP, -----
----- (b)(4) ----- . In addition, the data indicate that the method Q-10-093 is comparable to the previous method Q-10-009 in terms of the determination of FXIII activity.

4) Batch analysis

(b)(4) lots manufactured according the production procedure P-642 were used in the clinical trials including pharmacokinetic study BI71023_2002, Phase 3b study BI71023_3001, and a long-term open enrollment study BI712023_3002. In addition, ----(b)(4)--- validation lots produced according production procedure P-642 and released according quality control procedure Q-642U are provided including the results of the --- (b)(4) -- test and the ----- (b)(4) -----.

Certificates of analysis for (b)(4) lots manufactured at full-scale and stabilized with US licensed albumin (b)(4) are included in the BLA. The release testing results from all (b)(4) lots met the specifications of FXIII FDP.

	----- (b)(4) -----	----- (b)(4) -----	----- (b)(4) -----
-----	----- (b)(4) -----	----- (b)(4) -----	

------(b)(4)----- ----- -----	------(b)(4)----- ------(b)(4)-----	------(b)(4)----- ------(b)(4)-----	------(b)(4)----- -----
------(b)(4)----- ----- -----	------(b)(4)----- ------(b)(4)----- ------(b)(4)-----	------(b)(4)----- ------(b)(4)----- ------(b)(4)-----	------(b)(4)----- -----

5) Characterization of impurities

Relevant information concerning the impurity profile of the product is included in Report IR-642-015. CSLB identified the major protein impurities in the FDP as

------(b)(4)-----

6. Container closure system

The FXIII Concentrate (Human) container closure system consists of an injection vial and a rubber stopper sealed with a combination crimp cap. The vial containing the lyophilized DP is packaged in carton boxes. Each carton box contains one vial and one diluent vial.

List of container/closures used for FXIII Concentrate

Presentation	Container	Stopper	Crimp caps
1250 U	Injection vial 30 mL ------(b)(4)-----glass	------(b)(4)----- rubber	---(b)(4)--- cap, luminum/polypropylene dead gold/red

Details on the containers and closures of the diluent are included in CSL’s Drug Master File “sWFI” (---b(4)-----), referring to the vial data of the (b)(4) filling size.

Container closure integrity has been validated through ------(b)(4)-----
---(b)(4)----- test.

1) Vial

The single-dose injection glass vial with a nominal size of 30 mL for FXIII Concentrate (Human) meets the requirements for -(b)(4)-glass that is suitable for most

----- (b)(4) -----	----- (b)(4) -----	----- (b)(4) -----	----- (b)(4) -----
----- (b)(4) -----	----- (b)(4) -----	----- (b)(4) -----	----- (b)(4) -----
----- (b)(4) -----		----- (b)(4) -----	----- (b)(4) -----
----- (b)(4) -----		----- (b)(4) -----	----- (b)(4) -----

2) Tested parameters

Parameter	Testing instruction No.	Specification
Organoleptic properties (visual inspection after reconstitution)	----- (b)(4) -----	Colorless, slightly opalescent solution
Dissolution time	----- (b)(4) -----	----- (b)(4) -----
----- (b)(4) -----	----- (b)(4) -----	----- (b)(4) -----
pH	----- (b)(4) -----	----- (b)(4) -----
FXIII potency	----- (b)(4) -----	50 – 80 IU/mL
Protein	----- (b)(4) -----	6 – 16 mg/mL
Residual moisture	----- (b)(4) -----	----- (b)(4) -----
----- (b)(4) -----	----- (b)(4) -----	----- (b)(4) -----
Abnormal toxicity	----- (b)(4) -----	Negative
Sterility	----- (b)(4) -----	Sterile
Pyrogen	----- (b)(4) -----	Pyrogen free

3) Stability protocol

Storage at 5°C, 25°C/60%RH, or 6 months at 25°C/60%RH and -----
 (b)(4)-----

Parameter	Specification	Storage time (months)							
		0	3	6	(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)
Organoleptic properties	Colorless to slightly yellowish, slightly opalescent solution	X	X	X	(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)
Dissolution time	----- (b)(4) -----	X	X	X	(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)
----- (b)(4) -----	----- (b)(4) -----	X	X	X	(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)
pH	----- (b)(4) -----	X	X	X	(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)
Potency	50 – 80 IU/mL	X	X	X	(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)
Protein	6 – 16 mg/mL	X	X	X	(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)
Residual moisture	--(b)(4)--	X	X	X	(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)
----- (b)(4) -----	----- (b)(4) -----	X	X	X	(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)
Abnormal toxicity	Negative	X	NT	NT	(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)
Sterility	Sterile	X	NT	NT	(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)
Pyrogen	Pyrogen free	X	NT	NT	(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)

X: Tested; NT: Not tested; ----- (b)(4) -----

----- (b)(4) -----

(b)(4)	(b)(4)	(b)(4)			
(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)

(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)
(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)
(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)
(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)
(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)
(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)
(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)
(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)
(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)
(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)

------(b)(4)-----

------(b)(4)-----

(b)(4)	------(b)(4)-----											
	(b)(4)			(b)(4)			(b)(4)			(b)(4)		
	(b)(4)											
(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)
(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)
(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)
(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)
(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)
(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)

------(b)(4)-----

4) Current available results from the stability study of FXIII DP

------(b)(4)-----

------(b)(4)-----

------(b)(4)-----

5) ------(b)(4)-----

Based on the available data for Fibrogammin P -----(b)(4)-----
----- rubber stopper, CSLB is proposing that the shelf-life of Fibrogammin P is 24 months when stored at 2 - 8°C. Within this period, this product may be stored at 25°C, not to exceed a cumulative storage period of 6 months.

-----~~(b)(4)~~-----
 -----.

Comment: The available stability data indicate that no critical trends are detected during the observed long-term storage period. It supports the proposed shelf-life of FXIII Concentrate (Human). Regarding the reconstitution, please refer the comments on labeling.

In Container Closure System section, CSLB stated the vials used for FXIII Concentrate (Human) are 30-mL injection vials, glass ~~(b)(4)~~. However, the vials described in the stability report STR-642-013-02-US are 30-mL injection vial, glass ~~(b)(4)~~. Please confirm the type of vials used for FXIII Concentrate (Human) in US market. Please clarify if it is compatible with regard to ~~(b)(4)~~ 30-mL injection vials.

FACILITIES AND EQUIPMENT

Production and quality control of FXIII Concentrate (Human) is performed by CSLB in Marburg, Germany. The facilities used for the manufacture of FXIII Concentrate (Human) are listed in the following table.

FXIII Concentrate (Human) manufacturing facilities

(b)(4)	(b)(4)	(b)(4)
(b)(4)	(b)(4)	
	(b)(4)	
	(b)(4)	(b)(4)
	(b)(4)	
(b)(4)	(b)(4)	(b)(4)
	(b)(4)	
	(b)(4)	
(b)(4)	(b)(4)	
(b)(4)	(b)(4)	(b)(4)

The facilities are designed and constructed to provide appropriate material-, product- and personnel flows for the various products produced in the facilities. Manufacturing areas and procedures utilized in the manufacturing of FXIII Concentrate (Human) are designed to maintain segregation and to prevent cross-contamination of product by appropriate clean room design.

Comment: I defer to the comments on this section to our colleagues from DMPQ.

TRANSPORT VALIDATION FINISHED PRODUCT TO U.S.

----- (b)(4) -----

Comment: All (b)(4) transportation validation runs support the current procedure for loading, transport, and unloading operations maintaining the product temperature of -- (b)(4)-.

ADVENTITIOUS AGENTS SAFETY EVALUATION

1. *Virus safety*

The starting material human plasma is controlled at the single donation level by a rigorous process of selecting plasma centers, plasma donors and donations. In addition, the plasma pool for fractionation is tested for the ---b(4)-----

-----and high titers of human parvovirus B19 (B19V). Other ingredients or auxiliary substances added during the manufacturing process are also controlled and specified.

Production processes are performed according to GMP regulations and include process steps to reduce or remove microbes, prions, and viruses. The production processes are controlled by specified process control parameters and monitored by in-process control concerning microbes. Production processes have been investigated and validated concerning their effect to reduce microbes, prions, and viruses.

Removal of prions potentially present in the plasma pool by selected steps of the manufacturing process has been shown based on -----(b)(4)----- studies -----
----- (b)(4) -----
----- The results are summarized as follows:

Mean prion reduction factors of FXIII Concentrate (Human)

----- (b)(4) -----	(b)(4)	----- (b)(4) -----
--------------------	--------	--------------------

		(b)(4)	(b)(4)
------(b)(4)----- ----- -----	(b)(4)	(b)(4)	(b)(4)
------(b)(4)----- -----	(b)(4)	(b)(4)	(b)(4)
(b)(4)	(b)(4)	(b)(4)	(b)(4)
------(b)(4)----- -----	(b)(4)	(b)(4)	(b)(4)

------(b)(4)-----

Concerning the viruses reduction capacity of the manufacturing procedure --(b)(4)-- were tested in validated, -----(b)(4)----- for their capacity to inactivate and/or remove the test viruses. Virus inactivation and/or removal by the individual stages of the manufacturing process were tested at -----(b)(4)----- using HIV-1, bovine viral diarrhea virus (BVDV – a model virus for HCV), herpes simplex virus type 1 (HSV-1 – an unspecific model virus), HAV, and canine parvovirus (CPV – a model virus for resistant non-enveloped viruses). Also, the virus inactivation capacity of the pasteurization/Heat treatment (Heating in solution at 60°C for 10 hours) step was studied for West Nile virus (WNV) and B19V. The resulting virus reduction factors are summarized in the following table.

Cumulative rates (log₁₀) for inactivation/elimination of various viruses achieved by the manufacturing procedure of FXIII Concentrate (Human)

Manufacturing step	Virus reduction factor (log ₁₀)					
	Enveloped viruses				Non-enveloped viruses	
	HIV	BVDV	WNV	HSV-1	HAV	CPV
Al(OH) ₃ Adsorption/Vitacel and defibrination	≥ 5.8	2.8	Not done	≥ 7.6	1.3	(0.4) ^a
Ion exchange chromatography	5.0	3.4	Not done	Not done	3.4	3.7
Pasteurization/Heat treatment	≥ 5.8	≥ 8.1	≥ 7.4	≥ 7.6	4.3	1.0 ^b
Cumulative virus reduction (log ₁₀)	≥ 16.6	≥ 14.3	≥ 7.4	≥ 15.2	9.0	4.7

BVDV: bovine viral diarrhea virus; WNV: West Nile virus; HSV-1: herpes simplex virus type 1; CPV: canine parvovirus; a: not included in the calculation of the cumulative virus reduction factor; b: Studies using human parvovirus B19, which are considered experimental in nature, have demonstrated a virus reduction factor of ≥4.0 log₁₀ by Pasteurization/Heat treatment.

The only biological material added to Fibrogammin P is human albumin, which is added -----(b)(4)----- . This human albumin (b)(4) is manufactured by ----(b)(4)-- and is licensed in US under the trade name -----(b)(4)----- for further safety information).

2. Virus inactivation/elimination on equipment

Besides the assurance provided with the virus inactivation/elimination in the manufacturing processes, further assurance that any virus potentially retained in the production system would be adequately destroyed prior to re-use of the system is provided by sanitization of equipment. -----
----- (b)(4) -----

Comment: Although CSLB performed an assessment of prion removal by several steps of the manufacturing process of FXIII Concentrate (Human), they cannot make any claims on prion clearance in the package insert because they did not assess the clearance of prion proteins using animal infectivity assays.

The sponsor provided validation results on the capacity of several steps in the manufacturing process to inactivate or remove viruses. For this review, we consulted with Dr. Mahmood Farshid who confirmed that the data are sufficient to support the capability of the manufacturing process for virus clearance. Dr. Farshid also confirmed that the adsorption/precipitation and the chromatographic steps can be considered as orthogonal, thus, the log reduction factors can be added together.

----- (b)(4) -----

----- (b)(4) -----

-----:

----- (b)(4) -----

----- (b)(4) -----

----- (b)(4) -----

----- (b)(4) -----

----- (b)(4) -----

the period for room temperature storage, whichever comes first. Store vial in the original carton in order to protect **it** from light. Do not freeze.

This product does not contain a preservative and should be administered promptly after reconstitution. The product must be used within 4 hours after reconstitution.

Accordingly, please revise the carton and vial label to include the relevant changes recommended by the FDA. Please provide a space on the carton for marking the date when the product is stored at room temperature.

CONFORMANCE LOTS TESTED BY CBER

The conformance lot testing has been performed at CBER for the following parameters: Dissolution time, pH and residual moisture. The testing results from CBER met the specification and are consistent with those from the CSL Behring. Lot release of the FXIII Concentrate (Human) final product will be conducted through protocol review at CBER only.

Review of CSL Behring’s response to the CBER’s information request

At mid-cycle, I had five IR items, in *italics*, which were sent to CSLB on 2 December 2010. The sponsor responded in an amendment on 13 December 2010.

1. -----(b)(4)-----
-----.

CSLB’s response: -----

-----~~(b)(4)~~-----
-----~~(b)(4)~~-----

Comment: -----~~(b)(4)~~-----

2. *Regarding the specification for residual moisture, please provide the results to one decimal place (e.g., (b)(4)) or the validated limit of quantitation of the analytical method (e.g., (≤ 0.1 %)).*

CSLB's response: The results of residual moisture are provided to one decimal place in the table below.

Table 1: Results to one decimal place of FXIII's residual moisture

----- (b)(4) ----- ----- (b)(4) ----- ----- (b)(4) -----	----- (b)(4) -----
(b)(4)	(b)(4)

These results for residual moisture according QC procedure Q-642U-2.0 obtained of the lyophilized finished product of FXIII Concentrate (Human) have been clearly below (b)(4).

Comment: Regarding this response from CSL Behring, I discussed with Dr. Alfred V. Del Grosso. We all agreed that this response is acceptable.

3. *Please provide the report for the validation of the Factor XIII (FXIII) -----~~(b)(4)~~-----.*

-----~~b(4)~~-----

---~~b(4)~~--- -----

Comment: Pursuant to Guidance for Industry, Bioanalytical Method Validation, FDA, May 2001, the validation report on the FXIII -----(b)(4)----- is acceptable.

4. *Please provide the reports for the validation of methods to assess container closure integrity------(b)(4)-----.*

CSLB's response: The sensitivity of the -----(b)(4)----- for FXIII's container closure system is shown in the report "Sensitivity of the container closure integrity------(b)(4)" PM/2010/01/II in section 3.2.P.7.3-1.1. It confirms that this method is sensitive and can be used for closure integrity testing of all vial stopper combinations filled with aqueous or media fill medium.

The "—b(4)----- method for container and closure integrity testing" (Q-24-133) has been successfully used for the container closure system of FXIII Concentrate (Human). The results of the —b(4)-----, MI-642-001-0 demonstrate that the container closure systems are capable of protecting the sterile product from microbial contamination since none of the containers placed in the bacterial culture showed turbidity or formation of sediment due to microbial growth.

Comment: Please refer to the final review memo from CAPT Martha O'Lone from DMPQ on this issue.

5. *In the Container Closure System section, you stated that the vials used for FXIII Concentrate (Human) are 30-mL injection vials, glass-(b)(4)-----.* However, the vials described in the stability report STR-642-013-02-US are 30-mL injection vial--(b)(4)-----.

- A. *Please clarify the type of glass vials used for FXIII Concentrate (Human) in the US market.*
- B. *If different types of glass vials are used, please describe the differences between the ---(b)(4)-- injection vials, and demonstrate their compatibility with the product.*

CSLB's response: CSL Behring confirms that for the lyophilized product FXIII Concentrate (Human) only 30-mL injection vials------(b)(4)----- are used as specified in section 3.2.P.7.1-1. No glass --(b)(4)-- was used to fill in the lyophilized product since today.

However, the mentioned glass----(b)(4)---- in stability study report STR-642-013 is unfortunately a typo as stated in the confirmation by the stability expert in section 3.2.P.8.1-2.

Comment: This response is adequate.

I also had three IR items with regard to package insert, in *italics*, which were sent to CSLB on 23 December 2010, 11 January 2011 and 26 January 2011. The sponsor

responded in amendments on 6 January 2011, 17 January 2011 and 28 January 2011, respectively.

1. *Please revise the description in Section 16.2 Storage and Handling in the package insert as follows:*

When storage in the refrigerator at 2 – 8 °C (36 – 46 °F), [Trade Name] is stable for the period indicated by the expiration date on the carton and vial labels. Within the expiration date, [Trade Name] may be stored at room temperature not to exceed 25 °C (77 °F) for up to 6 months. Do not return the product to the refrigerator after it is stored at room temperature. Clearly mark the date of room temperature storage on the carton label. Do not use beyond the expiration date on the carton and vial labels, or end of the period for room temperature storage, whichever comes first. Store vial in the original carton in order to protect it from light. Do not freeze.

This product does not contain a preservative and should be administered promptly after reconstitution. The product must be used within 4 hours after reconstitution.

Please revise the carton and vial labels accordingly to include the changes recommended by the FDA. Please provide a space on the carton label for marking the date when the product is stored at room temperature.

CSLB’s response: CSLB accepted all the comments for Storage and Handling section except for the following discrepancy (refer to the amendment with STN 125385/0/0006):

CSLB requests to keep “within -(b)(4)- after reconstitution” as opposed to “within 4 hours after reconstitution” as stability data supports this time period.

Comment: Because of this disagreement, we had a teleconference with CSLB on 11 January 2011. After the discussion, in CSLB’s reply, they accepted our suggestion and updated the package insert as shown in the amendment under STN 125385/0/0009. Thus, the PI now states that the product must be used within 4 hours after reconstitution.

2. *Please define the unit used for potency of FXIII in this package insert as follows:*

“The potency expressed in units is determined using the Berichrom activity assay, referenced to the current International Standard for Blood Coagulation Factor XIII, Plasma. Therefore, a unit herein is equivalent to an International Unit.”

CSLB’s response: CSLB add this information under the Table 1: “Dose Adjustment Using the Berichrom Activity Assay” (refer to the amendment with STN 125385/0/0009).

Comment: This response is adequate.
