M E M O R A N D U M

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

To: File (STN 125385/0) & Nannette Cagungun, RPMB/DBA/OBRR

From: Ze Peng, LH/DH/OBRR

Through: Timothy Lee, Acting Chief, LH/DH/OBRR

Subject: Mid-cycle Review of CMC information in CSL Behring's original BLA for Factor XIII Concentrate (Human)

This memorandum summarizes the review of CMC information in an original biologics license application (BLA) with STN 125385 submitted by CSL Behring (CSLB) for plasma-derived Coagulation Factor XIII (FXIII) Concentrate (Human). The proposed indication for this product is for routine prophylactic treatment of congenital Factor XIII deficiency.

Upon review, I identified a few deficiencies in this submission, and will need to request from CSLB additional information as summarized at the end of this memo.

Background

FXIII is a plasma proenzyme composed of four polypeptides: two A subunits and two B subunits. FXIII is activated in the presence of calcium ions by thrombin cleavage of the A-subunit to become active enzyme FXIIIa, which covalently cross-links fibrin molecules to each other. FXIII is essential for normal coagulation, wound healing, and the physiological protection of the clot against fibrinolysis.

FXIII Concentrate (Human) is a sterile, preservative-free, heat-treated, lyophilized plasma protein product made from pooled US-sourced human plasma. It is manufactured in the CSLB facility in Marburg, Germany. This product has been marketed in the UK since 1976 and subsequently licensed in other 12 countries worldwide. ---b(4)----------
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Pasteurization was introduced as a virus inactivation step in 1981. More recently, a process upgrade for the production of FXIII Concentrate was introduced to improve the process and safety profile of the product, such as the use of ----------
---(b)(4)----------.

CSLB submitted the BLA for FXIII Concentrate (Human) under the accelerated approval program using FXIII activity trough levels as the surrogate endpoint, and is indicated for

routine prophylactic treatment of congenital FXIII deficiency. Of note, CSLB outlined a manufacturing plan that included an ----------(b)(4)---------- based on the teleconference between the FDA and CSLB dated 4 May 2010. This manufacturing change is proposed to be submitted as a prior approval supplement once the data is available.

Summary of Review

DRUG SUBSTANCE

1. Manufacture

1) Manufacturer

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

2) A brief description of manufacturing process and process controls

- ------(b)(4)------ plasma to cryodeleted plasma (-(b)(4)-)

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

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- (b)(4)-ethanol precipitation ----------(b)(4)----------

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- Sterilizing filtration

6) Conditions of use and reuse of material

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7) Transfer and storage conditions

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8) Control of Materials

- Starting material - Human plasma

  FXIII Concentrate is exclusively produced from human plasma obtained from the 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).

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

Comment: CSLB has been changed the limit for B19 virus DNA (tested by NAT) in the plasma pools for fractionation from (b)(4) IU/mL to 10^4 IU/mL. This change is acceptable.

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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). The further information on the critical PCPs is presented in Table 7 in Module 2.3.S.

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In addition, product sterility and ----------(b)(4)---------- ----------
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Comment: ----------
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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)
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2. Characterization

1) Elucidation of structure and other characteristics

- Structure

  FXIII 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 A and B chains. The A chain is composed of 730 amino acids (83 kDa) and dimerizes forming a non-glycosylated globular molecule. It is also found intracellularly in monocytes, macrophages, platelets, megacaryocytes. 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 Cys314. 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).

  FXIII is one of the zymogens to become activated in the coagulation cascade and it is the only enzyme in this system that is not a serine protease. The conversion of plasma FXIII to FXIIIa (A2') results from hydrolysis of the Arg36-Gly37 at the NH_2-terminus of the A subunit by thrombin. Full expression of activity is achieved only after the Ca^{2+} 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, α2-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

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DRUG PRODUCT

1. *Description and Composition of the drug product*

FXIII Concentrate (Human) is a highly purified, pasteurized, lyophilized substance containing the active ingredient, human coagulation FXIII 1000 - 1600 IU per vial for the US market. Human albumin, glucose, sodium chloride, and sodium hydroxide serve as excipients.

The presentation consists of one vial with the lyophilized FXIII DP, and one vial with a diluent (Sterile WFI, sWFI). Furthermore, a transfer device is supplied to allow for the transfer of the diluent into the product vial.

Composition

Ingredient	Amount	Function
Total protein	120 – 320 mg	------(b)(4)------
FXIII	1000 – 1600 IU	Active ingredient
Human albumin (b(4))	120 – 200 mg	------(b)(4)------
Glucose ----(b)(4)----- (b(4)/-----.)	80 – 120 mg	------(b)(4)------
Sodium chloride (b(4)/----	140 – 220 mg	------(b)(4)------
Sodium hydroxide (-b(4)-/------.)	Small amounts	pH adjustment
sWFI	20 mL	Diluent for reconstitution

The reconstitution diluent for FXIII Concentrate (Human) is sWFI, complying with the USP monograph "sWFI".

2. *Pharmaceutical development*

1) ----------

---------- (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)----------. The 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.

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

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

3) 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

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

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

List of In-Process Control

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

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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
--(b)(4)---	---------- ---------- -------(b)(4)---------- ----------	Risk analysis report: ---------- ---------- ----------(b)(4)---------- ---------- **-----(b)(4)----**: ---------- ----------**(b)(4)**---------- ---------- ---------- ---------- ------**(b)(4)**---------- ---------- ------**(b)(4)**---------- ---------- ------**(b)(4)**---------- ---------- ----------**(b)(4)**---------- ---------- ---------- ----------**(b)(4)**---------- ---------- **--------(b)(4)---------**: ---------- ----------**(b)(4)**---------- ---------- ----------

CSLB did revalidation of lyophilizer -(b)(4)--, which is designated for manufacture of Fibrogammin P for the US-market. During the revalidation, the sponsor had performed extensive sampling and analytical testing of final product vials in the production of Fibrogammin P -----b(4)----------No deviations occurred.

Comment: The validation results met the pre-defined criteria, which support the manufacturing process of FXIII FDP.

4. Control of excipients

Human albumin (b)(4), Glucose and Sodium chloride serve as excipients in FXIII Concentrate. They all comply with the requirements of --------(b)(4)----------.

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

Excipient	Parameter	Testing instruction
	------(b)(4)-----	------(b)(4)-----
	------(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 fully 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)---------- ----------	Ph. Eur.
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	FXIII activity by chromogenic substrate assay, Berichrom FXIII	Specification set according to manufacturing experience. Range reflects process variability and was based on historical data.
------(b)(4)-----	-------(b)(4)-- -------	---------- -----(b)(4)-----	---------- ---------- ------(b)(4)---------- ---------- ----------

Product quality attribute	Specification	Testing method	Justification
			---------- ---------- ----------
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) vial of the finally labeled drug product is subjected to the test "Potency"	-------(b)(4)-- -------	-----b(4)---------- ---------- ---------- ----------	CFR

Comment: With regard to the amount of –b(4)--- 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)----------
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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 (% 0).

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)----------
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- --b(4)------ determination of glucose
- Chloride determination
- pH [--b(4)-----
- Determination of residual water in dry substance ----b(4)----------
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- Sterility (--b(4)-------) [CFR 21, --b(4)----------]

- Testing for pyrogens [21 CFR 610.13 (b) and b(4)]
- General safety test [CFR/b(4)]

3) Validation of analytical procedures

- Testing proteins for identity and purity

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

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Comment: The acceptance criteria of all parameters investigated were fully met. Therefore, this method is suitable for the specific detection of human plasma proteins and FXIII-A/-S in Fibrogammin HS.

- Analysis of protein composition by ------(b)(4)-----

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Validation parameter	Acceptance criteria	Results
------(b)(4)-----	----------(b)(4)----------	----------(b)(4)-----
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------(b)(4)-----	----------(b)(4)------	----------(b)(4)-----
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- Quantitative determination of human albumin on the ----------(b)(4)-----

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----------(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 ---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)-----
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	------(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 has identified the protein impurities in the FDP, ----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 packed 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, aluminum/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.

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

acidic and neutral, aqueous preparations including products for parenteral administration in accordance with Section ----*b(4)*----------

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

2) Stopper

The vial is closed with ----------(b)(4)---------- rubber stopper (----------
----------(b)(4)----) that comply with ---(b)(4) ----------
and is free of latex.

3) Crimp cap

The stopper is secured by combination cap consisting of an aluminum crimp cap with a concentric hole and an integrated polypropylene plastic disc (flip-off). The crimp cap meets international standards for dimensional criteria.

Comment: Please provide the method validation reports on container closure ----------(b)(4)---------- ---------.

7. Stability

1) Lots tested

There are 3 conformance lots in the stability study, which are listed as follows:

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

Parameter	**Testing instruction No.**	**Specification**
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 proterties	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)**	**(b)(4)**	**(b)(4)**
(b)(4)	**(b)(4)**	**(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)---------------------------- and ----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 --(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)----------	----------(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.

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

----------(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)----------

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 step was studied for West Nile virus (WNV) and B19V. The resulting virus reduction factors are summarized in the following table.

Cumulative rates (log_{10}) 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	≥ 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 log_{10} by Pasteurization.

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)---------- as shown in the following table.

Removal/inactivation of pathogens by ----(b)(4)----

Pathogen	**Reduction factor [log_{10}] // time [h]**
Viruses	
HIV	**(b)(4)**
BVDV	**(b)(4)**
HHV-1 (HSV-1)	**(b)(4)**
PRV	**(b)(4)**
HPV-1 (poliovirus type 1)	**(b)(4)**
HAV	**(b)(4)**
BPV	**(b)(4)**
CPV	**(b)(4)**
Prions (----(b)(4)----------)	
(b)(4)	**(b)(4)**
(b)(4)	**(b)(4)**
(b)(4)	**(b)(4)**

Comment: The manufacturing processes for production of FXIII Concentrate (Human) are validated for the capability in virus inactivation and/or removal. The data support current manufacturing process which is used for virus clearance.

LABELING

Please revise the description on "16.2 Storage and Handling" in the package insert, which areas are highlighted as below:

> When storage in a 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.

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.

Recommendation

Please convey the following information request to CSL Behring and request their responses to be submitted to the FDA by 13 December 2010:

1. Please include data on -----(b)(4)-- in microbiological testing of -------(b)(4)-------, which we had requested during the review of the IND.

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 %).

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

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

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, glass --(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.

6. 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.