

DEPARTMENT OF HEALTH & HUMAN SERVICES



Food and Drug Administration
Center for Biologics Evaluation and Research
Office of Compliance and Biologics Quality
Division of Manufacturing and Product Quality

Memorandum

To: Administrative File for CSLB Factor XIII Concentrate (Human) STN 125385/0

CC: Xe Peng, OBRR/DH/LH, HFM-392

From: CAPT Martha O’Lone, Committee Chair, MRBI/DMPQ/OCBQ/CBER

Through: Carolyn Renshaw, Branch Chief, MRBI /DMPQ/OCBQ/CBER
Deborah Trout, Team Lead, MRBI/DMPQ/OCBQ/CBER

Subject: DMPQ review of manufacturing and facility data in BLA.

Applicant: CSLB Behring GmbH, Marburg, Germany, U.S. License # 1756

Action Due Date: February 17, 2011

Recommendation: Approval with the following post marketing commitment to be included in the approval letter;

- 1. -----

Indication for Use

The proposed indication for Corifact™ is “routine prophylactic treatment of congenital FXIII deficiency.” (This product is labeled for use with adult and adolescent patients.)

Dosage/ Administration

The recommended initial dose is 40 International Units (IU)/kg body weight. Dosing will be guided by the most recent trough FXIII activity level, with dosing every 28 days (4 weeks) to maintain a trough FXIII activity level of approximately 5% to 20%. Recommended dosing adjustments of ±5 IU/kg will be based on trough FXIII activity levels as determined by the Berichrom® chromogenic activity assay and the patient’s clinical condition. It is to be administered at room temperature by slow intravenous injection at a rate not exceeding 4 mL per minute.

Summary

CSLB Behring (CSLB) is requesting approval to manufacture lyophilized Factor XIII Concentrate (Human) for prophylactic treatment of congenital Factor XIII deficiency. On January 16, 1985, FDA granted orphan designation to FXIII Concentrate (Human) for the treatment of FXIII deficiency under application No. 84-0044. This FXIII Concentrate (Human) BLA was submitted as an electronic document under the accelerated approval program and was granted priority review. CSLB plans to market this product which is a longer acting version than currently marketed FXIII products, using the trade name of "Corifact™." CSLB has been approved by the EU for more than 12 years to market this product in Europe and other regions of the world outside of the United States as Fibrogammin P®. The primary difference between the manufacture of Fibrogammin P® for the EU and "Corifact™" is that "Corifact™" will be only be sourced from US licensed plasma centers.

There were two DMPQ review issues for this submission. The first issue was that the sensitivity of CSLB's -----(b)(4)----- . CSLB was contacted during this review and provided -----(b)(4)----- . The second issue for this review was that the -----(b)(4)----- did not reflect CSLB's in process capabilities which documented results of ---(b)(4)----. After discussion with FDA, CSLB provided in Amendment #8 a revision of their protocol in the submission which states that they have now revised their in process parameters for this -----(b)(4)----- is exceeded, CSLB will investigate the lots.)

The CSLB facility has been inspected several times in the last two years with a routine GMP inspection completed in April 2010, a routine biennial GMP inspection in 2008, and a May/June 2008 (PAI for C1 Esterase Inhibitor). These biennial and PAI inspections were classified as VAI. With this inspection history, an inspection waiver was requested and the approved memorandum has been placed in the EDR.

Items Reviewed

- BLA 125385/0; an ectd submission dated August 18, 2010,
- BLA Amendments #1, #4, #8, and #9;
- Teleconference memorandums dated August 20, 2010 and January 18, 2011
- Vial stopper information in -----(b)(4)-----.

The final review of the product and stability data has been deferred to the product office.

Summary Conclusion: CSLB will need to provide the data that they have agreed upon -----(b)(4)----- . CSLB has amended their requirements for their -----(b)(4)-----

----- There are no other issues identified during this review that would prevent approval.

Review Narrative

Description of Product

Factor XIII Concentrate (Human) or “Corifact™” is a sterile, preservative free, heat-treated, lyophilized FXIII (coagulation factor XIII) concentrate. It is derived from human plasma that is sourced from U.S. licensed centers as per 21§CFR 640.60. Each vial contains 1000-1600 IU Factor XIII, 120 to 200 mg human albumin, 120 to 320 mg total protein, 80 to 120 mg glucose and 140 to 220 mg sodium chloride. The final packaging of this product is a kit containing one single-use 30 mL vial of the lyophilized Factor XIII Concentrate (Human), a 20 mL vial of Sterile Water for Injection (USP) to be used for reconstitution, a Mix2Vial filter transfer set, and one alcohol swab. The final FXIII Concentrate product has the following specifications:

Factor XIII Concentrate (Human) or “Corifact™”	
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
Abnormal toxicity	Specifications CFR/--(b)(4)--
Potency	50 – 80 IU/mL
Pyrogens	Specification 21 CFR 610.13/--(b)(4)--
------(b)(4)-----	------(b)(4)-----
Sterility	Specification CFR/--(b)(4)-- (no growth)

Further review of the product specifications and stability data are deferred to the product office.

CSL states that the shelf life of Corifact™ is 6 months when stored at 2-8°C. Within the expiration date this product may be stored at room temperature (max. 25°C), not to exceed a cumulative storage period of 6 months.

CSLB provides Factor XIII Concentrate (Human) as a packaged kit. The kit includes a 30 ml (b)(4) clear glass vial of lyophilized Factor XIII Concentrate (Human) that is packaged in opaque packaging material to protect the lyophilized product from light. The Factor XIII vial is manufactured by ------(b)(4)-----
 ---. After filling and lyophilization, the vial is stoppered with a ------(b)(4)----- grey colored -----(b)(4)---- stopper (------(b)(4)-----). The stoppered vial is sealed with a combination aluminum crimp cap. CSLB states in the submission that “all these components contain no latex” and provided a product insert label that states “no latex.” Although the ------(b)(4)----- for this vial stopper that was reviewed in the -----

----(b)(4)----- does not contain natural rubber latex, -----
------(b)(5)-----

----- After reconstitution with a 20 mL vial of Sterile Water for Injection, USP, the solution contains 50-80 IU/mL of Factor XIII. (In the final packaging CSLB provides a sterile filter transfer device; manufactured by -----(b)(4)-----). The Mix2 Vial filter transfer set is provided to allow for needless transfer of diluent and filtering of the reconstituted product before it is withdrawn into a syringe. The Mix2 Vial filter transfer set is a 510(k) cleared device K031861 that is currently approved for other CSLB products such as Beriate P. (In Section 3.2.R.3-2 of the submission, CSLB stated that in addition to the testing performed by the supplier that is reviewed on the Certificate of analysis, they test the following parameters for each delivery of the Mix2Vial; identity; (------(b)(4)-----), general design, and performs a practice test with the filter. In addition to their supplier auditing, CSLB performs (b)(4) testing to evaluate this device for -----(b)(4)-----). (CSLB provided data for Mix 2 vials that demonstrated passing results for -----(b)(4)-----.)

Conclusion: CSLB has provided an adequate description of the final Factor XIII product and evidence of appropriate incoming specifications, auditing, and verification testing for the Mix2 vial.

MANUFACTURERS

The manufacture of Factor XIII Concentrate (Human) starting from plasma to the Factor XIII final product is performed at:

CSL Behring GmbH (US License Number: 1765)
Emil-von-Behring-Str. 76
35041 Marburg, Germany

The manufacture of the Human Albumin (b)(4) Excipient used for Factor XIII Concentrate (Human) was approved in -----(b)(4)-----). The manufacturing site for the Human Albumin (b)(4) is:

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

TESTING LABORATORIES

In-process testing during drug substance production as well as testing of the final product are carried out at:

CSL Behring GmbH
Emil-von-Behring-Strasse 76
35041 Marburg, Germany

Contract Testing Laboratory

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

Building / Site	Floor	Manufacturing Activity
----- (b)(4) -- -----	(b)(4)	----- ----- ----- (b)(4) ----- -----
	(b)(4)	----- ----- ----- (b)(4) ----- -----
	(b)(4)	----- (b)(4) -----
----- (b)(4) -- -----	(b)(4)	----- (b)(4) -----
	(b)(4)	----- (b)(4) -----
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	(b)(4)	----- ----- ----- (b)(4) ----- -----
	(b)(4)	----- ----- (b)(4) ----- -----
----- (b)(4) -- -----	(b)(4)	----- ----- ----- (b)(4) ----- ----- -----
Building / Site	Floor	Testing
----- (b)(4) -- -----	(b)(4)	----- (b)(4) ----- -----
----- (b)(4) -- -----	(b)(4)	----- (b)(4) -----
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----- (b)(4) -- -----	(b)(4)	-- (b)(4) --
----- (b)(4) -- -----	(b)(4)	-- (b)(4) --

These (b)(4) buildings at the Marburg -----(b)(4)----- sites are currently approved for manufacture of other US licensed products, such as: Fibrinogen Active Substance (STN 125356), Thrombin Active Substance (STN 125357), Vivaglobin® (Immune Globulin, STN 125115), Humate-P® (AHF/von Willebrand, STN 103960), RiaSTAP® (Fibrinogen Concentrate, STN 125317), and BERINERT® (C1 Esterase Inhibitor, STN 125287).

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

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CSLB based their process validation on formal studies of their European product, a risk analysis of the critical process steps, an evaluation of the parameters for the critical process control steps, multiple full scale investigation reports and the process simulations performed for Factor XIII. Process validation studies were conducted at full-scale specifically assessing the ability of -----(b)(4)-----

----- Separate validation reports were provided for the lyophilization process, -----(b)(4)-----

----- Full-scale studies were conducted to evaluate the -----(b)(4)----- levels throughout the production process of Factor XIII up to the lyophilized final product and to identify the major potential protein impurities (residual plasma proteins and non-protein impurities such as auxiliary substances) up to the drug product. In addition, product sterility was verified by process simulation using sterile nutrient medium (media fill studies).

Based on CSLB’s risk assessment described below, the entire drug product production process for Factor XIII was validated at full scale with manufacturing batches that were produced with Process Control Parameters (PCPs) set to the target values. All critical PCPs and in-process tests were evaluated.

Critical Process Steps from Risk Analysis

CSLB validated their production process for Factor XIII based on the following critical process steps. These critical process steps were identified by a risk analysis approach:

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

Section 2.3.S. Control of Critical Steps and Intermediates

CSLB evaluated the critical process control parameters (PCPs) and provided risk assessment reports in the submission for the manufacture of Factor XIII. In Table 7 of this section CSLB 3 pages redacted (b)(4)

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

In Section 3.2.P.5.1 CSLB listed the following final product release testing:

Specifications 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) -----	-(b)(4)-. and Part of identity testing according to 21 CFR 610.14
Purity		----- (b)(4) -----	----- (b)(4) -----	Manufacturing experience
Specifications for Final Product Testing (continued)		Specifications for Final Product Testing (continued)	Specifications for Final Product Testing (continued)	Specifications for Final Product Testing (continued)
Protein		6 – 16 mg/mL	----- (b)(4) -----	Total protein

Specifications for Final Product Testing			
Product quality attribute	Specification	Testing method	Justification
		----- (b)(4) -----	content according to -(b)(4)- . 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) -----, Berichrom -----	Specification set according to manufacturing experience. Range reflects process variability and was based on historical data.
----- (b)(4) -----	----- (b)(4) ----- -----	----- (b)(4) -----	----- ----- ----- ----- -----

Specifications for Final Product Testing			
Product quality attribute	Specification	Testing method	Justification
			(b)(4)----- -----
Sterility	As specified in CFR/(b)(4)	Inoculation method in accordance with 21 CFR 610.12 and -(b)(4)-	CFR/(b)(4) No growth
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 USP	21 CFR 610.11 and (b)(4)
Identity: ----- ---(b)(4)----- -----	------(b)(4)-----	----- ------(b)(4)----- -----	CFR

Conclusion: The release criteria for Factor III include appropriate tests for evaluation of potential contamination; appearance, pyrogenicity, and sterility testing. The review of the appropriateness of the release testing for product performance is deferred to the product office for final review.

Full Scale Process Validation Study PV-642-004-03

This full-scale process validation study completed in November 2009 was conducted by manufacturing three consecutive lots of Fibrogammin P 1250 U (Factor XIII) under routine conditions at full-scale to validate the effect of individual processing steps and holding times on particular process quality attributes. These steps included the -----
------(b)(4)-----

----- were validated at full-scale under the following “worst case” conditions;

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

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

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

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

In the review of the information for these three validation lots; ------(b)(4)-----
-----, it was noted that the study passes all pre-defined acceptance criteria which confirmed the maximum hold times evaluated throughout the production process. The filling investigative study verified that the filling process, including holding times and storage conditions, can reproducibly deliver a homogeneous lyophilized

6 pages redacted (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)

The results for this study demonstrate that the -----(b)(4)-----, sterility and pyrogen levels all met the acceptance criteria. -----
------(b)(4)-----

----- gray ----(b)(4)---- rubber stopper in accordance with -----
 ----(b)(4)----- and a product color coding of both the aluminum crimp
 cap with a punched hole and integrated polypropylene disc. The suppliers were listed and
 letters of authorization for their Drug Master Files were provided in the submission. The 30 ml
 glass -(b)(4)- vial is supplied by the company -----
 -----(b)(4)----- vials
 and CSLB products manufactured in the -----(b)(4)-----
 -----.

The 32 mm -----(b)(4)--- lyophilization stopper is identified by the supplier (----- (b)(4)-----)
 as model -----(b)(4)----- . In the review of ----(b)(4)----- dated July 10, 2007, the
 formulation was noted to contain only -----(b)(4)----- which is a -----(b)(4)-----
 formulation. The stopper formulation reviewed in this DMF does not contain natural rubber
 latex. This lyophilization stopper is currently approved for RiaStap (BLA 125317) since
 February 2010 and Fibrinogen 2G (December 2010) and will use the -----
 -----(b)(4)-----
 ----- . Quality control measures are routinely used to ensure the consistent quality of
 the packaging components and include supplier audits, inspection program for incoming
 packaging components and materials and receipt of certificates of analysis from the vendor and
 appropriate identification testing by CSLB. The stopper has been tested according to-----
 -----(b)(4)----- , although the firm did not include any -----(b)(4)-----
 test data to support the use of the -----(b)(4)----- stopper material with Factor XIII, this
 information has been reviewed and approved during the review of RiaSTAP in BLA 125317.
 Since the RiaSTAP document is not electronic, the memorandum reviewing this information in
 the EDR was referenced. The review of the -----(b)(4)----- data for this stopper was
 found acceptable for the RiaSTAP BLA submission.

After lyophilization in (b)(4), the stoppered Factor XIII vial is sealed with a combination
 aluminum crimp cap, -----(b)(4)----- for labeling and
 packaging. Final packaging is in opaque outer packaging for light protection since the vial is
 clear glass. In the submission CSLB provided evidence of quality control measures in place
 for ongoing evaluation of the quality of the container closure from receipt through manufacture
 of the final product. In addition to Factor XIII, the final kit packaging also contains a 20 ml
 vial of Sterile Water for Injection, USP, alcohol swabs, and a Mix2 Vial filter transfer set
 which allows for needless transfer of diluent and filtering of the reconstituted product before it
 is withdrawn into a syringe at the point of care. The Mix2 Vial filter transfer set is a 510(k)
 cleared device K031861 that is currently approved for other CSLB products that are
 reconstituted prior to use with Sterile Water for Injection, USP such as Humate P.)

CSLB states in the submission that “all these components contain no latex” and provided a
 product insert label that states “no latex.” Although the -----(b)(4)----- for
 this vial stopper that was reviewed in the -----(b)(4)----- does not
 contain natural rubber latex, -----

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

Conclusion: CSLB has provided an adequate description of the container closure systems and final packaging of the Factor XIII product.

“Compatibility of Mix2 Vial Device with Fibrogammin P”

CSLB performed this compatibility study for the use of the Mix2Vial transfer device with Fibrogammin P1250 U/ Factor XIII during August- September 2008. This report describes testing to evaluate the ability of this needless device to transfer 20 ml of the Sterile water for Injection, USP provided as diluent for the product in the final packaging and filter the reconstituted product prior to removal from the vial by syringe. Testing by their QC labs included -----

----- (b)(4) -----
----- Testing was also performed -----
----- (b)(4) ----- (only for test purposes since the product is used immediately after reconstitution.) The results provided in the report showed that all vials were reconstituted within --(b)(4)-- which met the ---(b)(4)-- criteria and appearance requirements for the reconstituted product in solution; colorless, clear to slightly opalescent. Although the results indicate that the -----(b)(4)----- met the required criteria in (b)(4) for Factor XIII, the review of the product parameters is deferred to the product office for final determination of the compatibility of this transfer device with Factor XIII.

Conclusion: CSLB has demonstrated the ability to use the Mix2Vial needless transfer device to reconstitute Factor XIII within the recommended dissolution time.

CONTAINER CLOSURE VALIDATION

Container Closure Integrity---(b)(4)---

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

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

Conclusion: These monitoring results show that the bioburden, airborne particulates and airborne viable particulates were within specifications during operation and that excursions are investigated for potential product impact

CONTAMINATION/CROSS-CONTAMINATION

Contamination and cross-contamination of Factor XIII is controlled by manufacturing practices and procedures, which include environmental, personnel, processing, and cleaning type of equipment cleaned varies by building.

A general description of CSLB procedures used in cleaning to control contamination/cross contamination by building follows;

Note: CSLB has provided evidence of continuing to perform their scheduled revalidation of cleaning for these production areas. The practices and procedures described below for Factor XIII are identical to the information approved for Fibrinogen Active Substance 2G in April 2010.

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

----- (b)(4) -----	----- (b)(4) -----
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7 pages redacted (b)(4)

Facility Cleaning of Buildings -----(b)(4)-----

Facility cleaning of rooms is carried out according to detailed schedules and procedures, using validated disinfectant agents (-----(b)(4)-----) and defined cleaning intervals. Cleaning is monitoring by an environmental monitoring program.

Conclusion: CSLB continues to follow their facility cleaning processes which have been approved for the multiple licensed US products manufactured in these areas.

References:

SOPP 8401.4 Review Responsibilities for the CMC Section of Biologic License Applications and Supplements

FDA Guidance for Industry, Container Closure Systems for Packaging Human Drugs and Biologics (1999).