

Summary Basis for Regulatory Action

Date	
From	Ze Peng, Committee Chair
Subject	Summary Basis for Regulatory Action
BLA #	STN 125385/0
Applicant	CSL Behring GmbH
Date of Submission	18 August 2010
PDUFA Goal Date	17 February 2011
Proprietary Name / Established names	Corifact™ Factor XIII Concentrate (Human)
Dosage forms	Lyophilized powder: each vial contains 1000 – 1600 IU of Factor XIII to be reconstituted with 20 mL of Sterile Water for Injection, USP, for intravenous administration
Proposed Indication(s)	Routine prophylactic treatment of congenital Factor XIII deficiency
Orphan Designation	Yes
Recommended Action:	Approval
Signatory Authorities Action	<p>Jay S. Epstein_____</p> <p><i>Offices Signatory Authority:</i></p> <p><input type="checkbox"/> <i>I concur with the summary review</i></p> <p><input type="checkbox"/> <i>I concur with the summary review and include a separate review or addendum to add further analysis</i></p> <p><input type="checkbox"/> <i>I do not concur with the summary review and include a separate review or addendum</i></p>

Other Signatory Authority: **John Eltermann**_____

Material Reviewed/ Consulted SBRA	List of specific documentation used in compiling
Clinical	Daniela J. Vanco & Nisha Jain
Bio-Statistics	Renee Rees
Pharmacology/Toxicology	La’Nissa A. Brown-Baker
CMC – Product / Facilities	Ze Peng & Tim Lee / Martha O’Lone
Bioresearch Monitoring	Dennis Cato
Advisory Committee	Not presented
Labeling	Michael Brony
Clinical Pharmacology	Iftekhar Mahmood
Epidemiology	Alan C. Ou

1. Introduction

CSL Behring GmbH (CSLB) submitted the BLA for Factor XIII Concentrate (Human) under the Accelerated Approval regulation [21 CFR 314.510] using plasma Factor (F) XIII activity trough levels as the surrogate endpoint. As mandated by the Accelerated Approval regulation, a postmarketing study to correlate the achieved plasma FXIII trough levels to clinical benefit is currently ongoing. The product, with the proprietary name of Corifact™, is indicated for routine prophylactic treatment of congenital FXIII deficiency. This product is presented as a lyophilized powder to be reconstituted in Sterile Water for Injection for intravenous administration.

Factor XIII circulates in plasma as a glycoprotein consisting of two A-subunits and two B-subunits (A₂B₂) with a molecular weight (MW) of ~ 320 kDa. When the A-subunit is cleaved by thrombin in the presence of calcium ions, FXIII is activated to FXIIIa. FXIII is also present in platelets, monocytes, and macrophages as a homodimer of A-subunits (A₂) with a MW ~ 166 kDa. The B-subunit (~ 77 kDa) in plasma has no enzymatic activity and functions as carrier molecules for the A-subunits. The B subunits stabilize the A-subunits and protect them from proteolysis.

Activated FXIII is a transglutaminase that catalyzes the cross-linking of the α- and γ-chains of fibrin, thus stabilizing fibrin clots by rendering them more elastic and resistant to fibrinolysis.^{1,2} FXIIIa also cross-links α₂-plasmin inhibitor to the α-chain of fibrin, further protecting the clot from degradation by plasmin. Cross-linked fibrin is the end product of the coagulation cascade, and provides tensile strength to the primary hemostatic platelet plug.²

2. Background

Corifact™ [Factor XIII Concentrate (Human)] is a sterile, preservative-free, heat-treated, lyophilized protein product made from pooled US-sourced human plasma. It is manufactured in the CSL Behring facility in Marburg, Germany. CSLB's Factor XIII Concentrate (Human) has been marketed in the EU since 1993. In recent years, various improvements have been made to the manufacturing process, such as -----(b)(4)-----
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3. Chemistry, Manufacturing and Controls (CMC): Product, Facilities and Equipment

Manufacture

Corifact™ starting from frozen human plasma to the Factor XIII final drug product, is manufactured at CSL Behring GmbH, Emil-von-Behring-Str.76, 35041 Marburg, Germany.

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cryo-depleted plasma. -----

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

----- treated at 60 °C for 10 hours. After heat-treatment, -----

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

----- After formulation and sterile filtration,
the FXIII Concentrate (Human) is filled into vials, lyophilized, and capped. -----

----- (b)(4) ----- subjected to visual inspection prior to
labeling and packaging.

Control of Starting Materials

Corifact™ is produced from human plasma obtained from FDA approved U.S. plasmapheresis centers. The plasma donations used for Corifact™ are tested and found to be negative using serological assays for hepatitis B surface antigen (HBsAg), and antibodies to HIV-1/2 and HCV. The plasma donations are tested ----- (b)(4) ----- with Nucleic Acid Testings (NAT) for HBV, HCV, HAV and HIV-1 and found to be negative. The plasma donations are also tested by NAT for human parvovirus B19 DNA to exclude high titers B19 donations, to ensure that the limit of B19 DNA in the manufacturing pool does not exceed 10⁴ IU per mL.

In addition, in-process controls are performed on the manufacturing pool. -----

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----- The limit for B19V DNA in these pools is set not to exceed 10⁴ IU per mL.

Reference Standards or Materials

In April 2009, CSL Behring introduced the 1st International Standard for Blood Coagulation Factor XIII, Plasma, as the reference standard for their Berichrom® FXIII potency assay. The new method is coded Q-10-093. The original Berichrom® FXIII assay method Q-10-009 was calibrated against a commercially available FXIII plasma standard ----- (b)(4) ----- . FXIII activity of the latter plasma standard is determined by the manufacturer by comparison to the FXIII activity in a pool of fresh plasma samples from healthy donors.

Both methods are based on the same biochemical principle using identical reagents and equivalent reaction schemes. A comparison of the old versus the new Berichrom® FXIII assay methods indicated that the results are equivalent. This assures consistency of unitage in the clinical studies and provides validation for the replacement of Q-10-009 with Q-10-093 as the assay for in-process testing as well as final product release.

Analytical Methods for Product Quality

Analytical methods have been validated, or covered by European or US Pharmacopoeias.

Container Closure System

The container closure system for Corifact™ consists of a 30-mL ---(b)(4)-- glass vial and a ---(b)(4)--- rubber stopper sealed with a combination crimp cap. Container closure integrity was validated through -----(b)(4)----- . In addition, a reconstitution device, Mix2Vial™, supported by compatibility study, is used for the reconstitution and filtration of the final product before intravenous administration

Specification for Final Product Testing

Product quality attribute		Specification	Testing method
Practicability and organoleptic properties	Dissolution time	--(b)(4)--	Dissolution of the solid and visual control
	Appearance	Colorless to slightly yellowish, slightly opalescent solution	
----(b)(4)---- protein		----(b)(4)---	----- ----- ----- ----- -----
----(b)(4)---- protein		----(b)(4)---	----- ----- ----- ----- -----
Purity		----- ----- ----- ----- ----- ----- -----	----(b)(4)---
Protein		6 – 16 mg/mL	----- ----- ----- ----- -----
----(b)(4)---		----(b)(4)---	----- ----- ----- ----- -----
Albumin		6 – 10 mg/mL	----(b)(4)---
Glucose		4 – 6 mg/mL	----- ----- ----- ----- -----
Sodium chloride		7 – 11 mg/mL	----- ----- ----- ----- -----
pH		----(b)(4)---	----- ----- ----- ----- -----
Residual moisture		(b)(4)	----- ----- ----- ----- -----
Potency		50 – 80 IU/mL	----- ----- ----- ----- ----- ----- -----
----- ----- ----- ----- ----- ----- -----		----- ----- ----- ----- ----- ----- -----	----- ----- ----- ----- ----- ----- -----
Sterility		As specified in CFR/(b)(4)	Inoculation method in accordance with 21

		CFR 610.12 and (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
General safety test	As specified in CFR/(b)(4)	Test in accordance with 21 CFR 610.11 and (b)(4)
* Identity: ----- ------(b)(4)----- -----	-----(b)(4)----	------(b)(4)----- -----

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

Stability Studies

The available real-time stability data indicate that no critical trends are detected during the observed long-term storage period. The data support the proposed shelf-life of Corifact of 24 months at 2 – 8 °C. Within this period, this product may be stored at room temperature not to exceed 25 °C for up to 6 months. The product must be used within 4 hours after reconstitution.

Evaluation of Safety Regarding Adventitious Agents

The production process is performed according to cGMP regulations, and is controlled and monitored by specified process control parameters. The production process was assessed and validated for its capability to remove or inactivate adventitious agents.

Microbes

The level of microbial contamination is reduced by ------(b)(4)-----
----- sterile filtration step of the final bulk solution. Aseptic filling is performed before the product is freeze-dried. Final release testing includes assessment of sterility and pyrogens.

Viruses

The current manufacturing process for FXIII Concentrate (Human) includes one dedicated viral clearance step, i.e., heat treatment at 60 °C for 10 hours. However, three independent manufacturing steps, including, Al(OH)₃ Adsorption, Ion exchange chromatography and Heat treatment (60 °C, 10 h), were validated for their capacity to clear viruses ------(b)(4)----- experiments. Virus clearance by the individual steps were tested at least ------(b)(4)----- using HIV-1, bovine viral diarrhea virus (BVDV – a model virus for HCV), herpes simplex virus type 1 (HSV-1 – a model virus for large enveloped DNA viruses), HAV, and canine parvovirus (CPV – a model virus for non-enveloped viruses). The heat-treatment step was also studied for its capacity to clear West Nile virus (WNV) and B19V. The results of virus reduction studies are summarized in the following table below.

Cumulative rates (log₁₀) for inactivation/removal 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
Heat treatment (60 °C, 10 h)	≥ 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 heat treatment.

The only biological material added to FXIII Concentrate (Human) is human albumin as a -----(b)(4)----- . This human albumin is licensed in the U.S. under the trade name -----(b)(4)-----, and is manufactured by -----(b)(4)-----.

The product has been marketed outside the U.S. since 1993 without any reports of viral transmission.

Conformance Lots Tested by CBER

Conformance lots were tested by CBER for dissolution time, pH and residual moisture. The results meet the release specifications, and are consistent with those from CSL Behring.

Conclusion:

The product reviewers find that CSL Behring GmbH has provided sufficient data and information on chemistry, manufacturing and controls to support the licensure of Corifact™.

Facilities and Equipment

Site Description

The manufacture of Corifact™ starting from plasma to the FXIII final drug product is performed at CSL Behring GmbH in Marburg, Germany (License #1765), FEI# -----(b)(4)----- of equipment is conducted at the Main Work site in Marburg. Manufacture of the -----(b)(4)-----, final product, storage of intermediates, filling, and lyophilization are conducted at the ----(b)(4)---- complex in Marburg. Human albumin excipients -----(b)(4)-----.

Process Validation

Full-scale process validation studies were conducted by manufacturing 3 full-scale consecutive Factor XIII lots. These lots were manufactured under routine conditions at full-scale to validate

Office team for C1-Esterase Inhibitor (STN 125287) and classified as Voluntary Action Indicated (VAI).

Inspection of the Manufacturing Facility

An inspection of the CSL Behring GmbH facility located in Marburg, Germany was conducted on May 26, 2010 and classified as VAI. Based on recent inspection of the facility, an inspection waiver was recommended and approved on January 13, 2011.

Per the January 28, 2011 memo to the file from the CBER Office of Compliance and Biologics Quality, Division of Case Management, the compliance status of this manufacturing site is acceptable for product approval.

Environmental Assessment

The BLA included a request from the applicant for a categorical exclusion for an Environmental Assessment under 21 CFR § 25.31(c). The FDA concluded that this request is justified, as the active ingredients of the proposed product are naturally occurring substances and no extraordinary circumstances, which would require an environmental assessment, exist.

Conclusion:

The DMPQ reviewer recommends approval of this submission. -----

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4. Non-clinical Pharmacology/Toxicology

Corifact™ was determined to be safe as a FXIII replacement therapy based on its pre-clinical program (GLP and non-GLP studies). The non-clinical program for Corifact™ consisted of studies to demonstrate the safety and effectiveness of the product. Pre-clinical studies were conducted for local tolerance (rabbit), acute dose toxicity (rat and mice), repeat dose toxicity (rat), safety pharmacology and efficacy (rat, FXIII knock-out mice, and Hemophilia A dogs), and pharmacokinetics (rat) at doses ranging from clinical dose up to five-fold maximal clinical dose (repeat dose regimen) and 200 times clinical dose (acutely). Animal models for FXIII deficiency and wound treatment demonstrate a reduction in blood loss; and improved time to hemostasis and clot strength following Corifact™ administration. *In vitro* or *in vivo* mutagenic, carcinogenic studies were not conducted as they are not required for plasma derived products like Corifact™; studies to address the potential of long-term effects from Corifact™ were also not performed but adequate clinical data are available to allay any concerns for long-term toxicity. Antigenicity (rabbit and guinea pig) and thrombogenicity studies (rabbit) were

performed using Corifact™. Corifact™ was administered up to fifteen times the acute clinical dose. The results did not raise concerns regarding immunogenicity and thrombogenicity. Taken

together, these data support a determination that Corifact™ is safe and effective for its intended use.

Conclusion:

The Pharmacology/Toxicology Reviewer recommends Biologics License Application approval for Corifact™.

5. Clinical Pharmacology

As Pivotal Study BI71023 2002, CSL Behring conducted an open-label, single-arm, multicenter, pharmacokinetic study of Corifact™ in patients with congenital factor XIII deficiency. The dose of Corifact™ was 40 U/kg and it was administered every 4 weeks as a bolus intravenous (IV) injection at 250 U/minute for a total of 3 doses over 12 weeks. There were 13 subjects in the study (6 males and 7 females). There were 4 Caucasians, 5 African Americans, 2 Asians and 2 Hispanics. The mean weight and age of the patients were 65 kg (19 to 102 kg) and 23 years (5 to 42 years), respectively. There were 5 patients <16 years of age and 8 patients >16 years of age. Blood samples for determination of Factor XIII level were obtained pre-infusion, and at the end of the infusion at 30 minutes, 60 minutes, 4 hours, 8 hours, 24 hours, 72 hours, and on days 7, 10, 14, 21, and 28. The primary analysis of the PK of Factor XIII was baseline adjusted and assessed on the basis of measurements of Factor XIII activity using the standard Berichrom® assay. As supplementary analyses, the PK of Factor XIII was assessed on the basis of measurements of Factor XIII activity using the -----(b)(4)----- test and the amended Berichrom® assay (see below). Pharmacokinetic parameters were assessed for Factor XIII activity using a non-compartmental model. The results of the pharmacokinetic study are summarized in the Table below.

Pharmacokinetic parameters of Factor XIII after dose 3

Parameters	Baseline non-adjusted			Baseline adjusted		
	Standard	Amended*	Antigen	Standard	Amended*	Antigen
C _{max}	0.99 ± 0.22	0.93 ± 0.22	0.85 ± 0.19	0.88 ± 0.20	0.88 ± 0.22	0.83 ± 0.18
C _{min}	0.15 ± 0.03	0.08 ± 0.04	0.06 ± 0.02	0.05 ± 0.05	0.05 ± 0.06	0.04 ± 0.02
AUC _(0-inf)	312 ± 66	222 ± 52	186 ± 47	184 ± 66	189 ± 67	158 ± 39
Clearance	0.13 ± 0.03	0.19 ± 0.05	0.23 ± 0.06	0.25 ± 0.09	0.25 ± 0.11	0.27 ± 0.07
Half-life	310 ± 112	200 ± 52	208 ± 57	158 ± 55	158 ± 60	159 ± 41
V _{ss}	58 ± 15	53 ± 12	67 ± 20	51 ± 13	50 ± 13	61 ± 19

Units of AUC_(0-inf) = IU.hr/mL; C_{max} and C_{min} = IU/mL; Clearance = mL/hr/kg; Volume of distribution at steady state (V_{ss}) = mL/kg, half-life = hrs

*The amended potency assay (Berichrom®) is calibrated against the current 1st International Standard for Blood Coagulation Factor XIII, Plasma. The standard potency (Berichrom®) assay was calibrated against a commercially available FXIII plasma standard (---(b)(4)----). FXIII activity of this plasma standard is determined

by the manufacturer by comparison to the FXIII activity in a pool of fresh plasma samples from healthy donors. A comparison of the standard versus the amended potency assay shows the result to be equivalent.

Due to the small sample size, the impact of age, gender, and race on the pharmacokinetics of Corifact™ cannot be evaluated with definitive conclusions.

Conclusion:

From a clinical pharmacology perspective pharmacokinetic study results are acceptable.

6. Clinical/Statistical

Overall Clinical:

The licensure of Corifact™ is granted under the provisions of Accelerated Approval [21 CFR 314.510] using Factor (F) XIII activity trough levels as the surrogate endpoint. The clinical development program to support licensure of Corifact™ consisted of a PK study that evaluated plasma trough levels as a surrogate marker likely to predict clinical benefit. A postmarketing study to validate the clinical benefit of hemostasis by achieving prespecified plasma trough levels is currently ongoing.

Data obtained under US IND (b)(4) that appeared to show effectiveness of Corifact™ in congenital FXIII deficient patients could not be accepted to support licensure because -----
------(b)(4)-----.

The safety program consisted of 12 clinical studies conducted in various populations. These included Pivotal Study BI71023 2002, and eleven supportive studies (one in healthy volunteers, eight in congenital Factor XIII deficiency, and two in -----(b)(4)-----). Clinical experience in the EU since 1993 further supports the determination of safety.

Efficacy:

The effectiveness of Corifact was evaluated based on a surrogate marker of maintaining a trough FXIII activity level of approximately ≥5% to 20%. Based on historic evidence, maintaining a trough Factor XIII level of ≥5% was selected as the surrogate endpoint for hemostatic efficacy for Factor XIII replacement therapy. Maintaining the trough FXIII activity level at Day 28 between 5% -20% is expected to prevent breakthrough bleeding in congenital FXIII deficient patients, and was therefore used as a surrogate marker in the pivotal study BI71023_2002. The outcomes of the pivotal PK efficacy Study BI71023-2002 that evaluated trough FXIII levels as a surrogate endpoint can be found under Section 5: Clinical Pharmacology. These data are interpreted to demonstrate a presumption of hemostatic efficacy of Corifact for routine prophylactic treatment of congenital FXIII deficiency.

A postmarketing study to validated the surrogate endpoint by showing a correlation between trough levels of FXIII (5% to 20%) and clinical efficacy, is currently ongoing. The study with a size of 41 subjects will have the ability to detect, with a one-sided level of significance less than 0.025 and power greater than 90%, a reduction of 50% incidence of breakthrough bleeding with

treatment compared to the historical rate without treatment. The subjects in this study will be followed for one year to determine the annual bleed rate. This study is expected to be completed by April 2011.

7. Safety

The safety program of Factor XIII Concentrate (Human) consisted of a total of 12 clinical studies and included 187 subjects, 90 of whom were subjects < 16 years old. CSL Behring's Summary of Clinical Safety focused on data from pivotal Study 2002, which was an uncontrolled, single-arm study. This study was conducted between March 2009 and February 2010 in subjects with congenital Factor XIII deficiency. The other 11 supportive studies include one study in healthy volunteers (Study 1003), 8 studies in patients with congenital Factor XIII deficiency (Studies 3001, 3002, 7D-101PK, 7MN-101PK, 8J/201, 7MN-101PK [extension], 5001, 5986), and 2 studies in patients with -----(b)(4)----- (Studies 301CL and 302CL).

A total of 3,930 doses of Corifact™ have been administered to 187 subjects in the 12 clinical studies. Of the 3930 doses of Corifact™, 3,590 doses were administered to subjects with congenital Factor XIII deficiency.

Pivotal Study BI71023_2002:

In the pivotal study to support this BLA application there were no deaths, life-threatening events or adverse events that led to subject study discontinuation. Eight subjects in this study experienced treatment-emergent adverse events (TEAE) of mild to moderate severity (5 subjects experienced infections, injury, bruising and contusion, ecchymosis, borderline diabetes). No episodes of thromboembolism or viral transmission were reported during the study. In two subjects increase in laboratory values of thrombin-antithrombin III complex, prothrombin and fibrin D-dimer were reported, but were not associated with any clinical signs and symptoms of thromboembolism. The cause of these deviations was considered to be possibly related to the product by both the investigator and sponsor. FDA agreed with this causality assessment. Another subject experienced a mild rash that was considered unrelated to study product.

Ongoing Study 3002:

The safety data from the ongoing postmarketing study had a collection cut-off date on February 15, 2010. These data were submitted to the BLA in November 2010. An SAE consistent with neutralizing inhibitor to Factor XIII was reported in a 26-year old subject with congenital FXIII deficiency. The patient's FXIII levels returned to baseline after plasmapheresis. The patient was re-exposed to Corifact™ and has not reported any breakthrough bleeding or reappearance of FXIII inhibitory antibodies as of the patient's last reported assessment.

Other clinical studies including Study 302 CL:

In a study of -----(b)(4)----- consisting of 33 subjects, a 74-year old male with a history of coronary heart disease experienced a myocardial infarction (MI) one day after the last study drug infusion. Baseline plasma Factor XIII levels were normal in this patient who received five times the dose normally given for congenital deficiency patients.

Postmarketing safety reports:

Three cases of thrombo-embolic complications were reported. All three cases were assessed as serious, one as unlikely and two as possibly related to the FXIII concentrate administration. Two of the thrombo-embolic events occurred in patients with no known FXIII deficiency.

Bioresearch Monitoring (BIMO)

-----Removed per the Privacy
Act-----

8. Pediatric Research Equity Act (PREA)

This submission did not trigger PREA because of Orphan Drug status.

9. Advisory Committee Meeting

OBRR reviewed information from this application and determined that referral to the Blood Products Advisory Committee (BPAC) prior to licensure is not needed for the following reasons (FDAAA [HR 3580-138 SEC. 918: REFERRAL TO ADVISORY COMMITTEE]):

- The mechanisms of action of Factor XIII Concentrate (Human) and its role in blood coagulation are well understood.
- The safety profile of the product is well understood, as it has been used widely outside the U.S. since 1993. In particular, safety reporting in the EU would have identified any serious toxicities of the product.
- The review of the clinical data identified infrequent events of thrombogenicity and immunogenicity consistent with a favorable risk/benefit ratio for the intended use.
- BPAC discussion of this application is unlikely to change the outcome of the review of this file from a regulatory standpoint.

10. Pharmacovigilance

In addition to routine pharmacovigilance activities, CSL Behring proposes to collect detailed information about certain spontaneously reported cases (such as thromboembolic events, viral transmission, and AEs in pregnant patients) with identified risks and follow them up with a targeted questionnaire. To characterize AEs, CSL Behring proposes to collect general information about the patient and risk factors. Given that the identified risks for Corifact are as expected from foreign post-marketing experience, CSL Behring's plan for routine pharmacovigilance combined with additional activities, as outlined in their BLA application for Corifact, are sufficient. Therefore, a Title IX invoked Postmarketing Requirement is not needed.

FDA agreed with CSL Behring's plan to further characterize the identified risks through additional pharmacovigilance activities.

Conclusion:

The CSL Behring's proposed pharmacovigilance activities submitted on June 30, 2010 are acceptable to OBE. As noted in the pharmacovigilance plan, CSL Behring will conduct routine monitoring and reporting of adverse events, including submitting 15-day expedited reports for serious, unlabeled adverse events and Periodic Safety Update Reports (PSURs), quarterly for the first three years after licensure and yearly thereafter, as required under 21 CFR 600.80. In addition, FDA agrees with CSL Behring's plan to further characterize the identified risks through additional pharmacovigilance activities, such as collecting more detailed information about certain spontaneously reported cases with identified risks, following them up with a targeted questionnaire, and collecting general information about the patient and risk factors.

11. Labeling

Proprietary Name

The Advertising and Promotional Labeling Branch (APLB) performed an evaluation of the proposed proprietary name, Corifact, Factor XIII Concentrate (Human), to determine if any new products had been approved since the primary review dated 18 August 2010. APLB found the proposed proprietary name acceptable.

Conclusions:

The proposed prescribing information and the PPI submitted on February 2, 2011 is acceptable. Carton and immediate container labels submitted in the original application were reviewed by APLB and found them to be acceptable.

12. Recommendation/Risk Benefit Assessment

The CBER review committee unanimously recommends approval of this BLA. There are currently no concerns regarding the risk/benefit ratio.

13. Post Marketing Requirement:

Under the Accelerated Approval regulations, the sponsor is currently conducting a Phase 4 study (Study No BI71023_3001) to verify the clinical benefit by showing a correlation between trough levels of FXIII (5% to 20%) and clinical efficacy and also by comparing the incidence of bleeding with treatment to a modeled historical control without treatment. This is a multicenter prospective, open-label, study that will include 41 subjects followed for one year. The efficacy endpoint is reduction in incidence of bleeding episodes (i.e. decreased number per person-year) following prophylactic treatment. The study with a size of 41 subjects will have the ability to detect, with a one-sided level of significance less than 0.025 and power greater than 90%, a reduction of 50% incidence of breakthrough bleeding with treatment compared to the historical rate without treatment. This study is ongoing (since August 2009) and the projected completion date is April 17, 2011. The final study report will be submitted by December 31, 2011.

14. Post Marketing Commitments

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

15. References

1. Lauer P, Metzner HJ, Zettlmeißl G, Li M, *et al.*, Targeted Inactivation of the Mouse Locus Encoding Coagulation Factor XIII-A: Hemostatic Abnormalities in Mutant Mice and Characterization of the Coagulation Deficit. *Thromb Haemost.* 2002;88:967-74.
2. Dardik R, Loscalzo J, and Inbal A., Factor XIII (FXIII) and Angiogenesis. *J Thromb Haemost.* 2006;4:19-25.