Summary Basis for Regulatory Action

Date	October 19, 2015
From	Mikhail V. Ovanesov, PhD, Committee Chair
BLA STN	125506/0
Applicant	Bio Products Laboratory, Limited
Date of Submission	September 9, 2013
PDUFA Goal Date	October 27, 2015
Proprietary Name / Established Name	COAGADEX / Coagulation Factor X (Human)
Dosage Form	Lyophilized powder with nominal potencies of 250 IU and 500 IU per vial
Indication	To treat adults and adolescents (aged 12 years and above) with hereditary Factor X deficiency for (1) on-demand treatment and control of bleeding episodes and (2) perioperative management of bleeding in patients with mild hereditary Factor X deficiency.
Recommended Action	Approval
Signatory Authority Action	Jay Epstein, MD_____ *Offices Signatory Authority* ☐ *I concur with the summary review* ☐ *I concur with the summary review and include a separate review or addendum to add further analysis* ☐ *I do not concur with the summary review and include a separate review or addendum* Mary Anne Malarkey_____ *Offices Signatory Authority* ☐ *I concur with the summary review* ☐ *I concur with the summary review and include a separate review or addendum to add further analysis* ☐ *I do not concur with the summary review and include a separate review or addendum*

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1. Introduction

Bio Products Laboratory, Limited (BPL) submitted an original biologics license application (BLA) for Coagulation Factor X (Human) with the proprietary name COAGADEX. COAGADEX is a human plasma-derived Factor X concentrate purified from Source Plasma of U.S. origin at an FDA-licensed multi-product manufacturing facility. COAGADEX is supplied as a sterile, freeze-dried concentrate in single-use vials containing nominal potencies of 250 International Units (IU) and 500 IU of Factor X per vial. Both the nominal and actual Factor X potencies are provided on the vial and carton labels.

COAGADEX is indicated to treat adults and adolescents (aged 12 years and above) with hereditary Factor X deficiency for (1) on-demand treatment and control of bleeding episodes and (2) perioperative management of bleeding in patients with mild hereditary Factor X deficiency. Hereditary Factor X deficiency is a rare bleeding disorder for which no specific coagulation factor replacement therapy is currently available in the US. FDA granted this product Orphan Drug Status (No. 07-2469) on November 8, 2007, Fast Track Designation on April 12, 2012, and Priority Review for this BLA on September 6, 2013.

2. Background

Factor X deficiency is an extremely rare bleeding disorder (prevalence ~ 1:1,000,000). Factor X deficiency can result in bleeding patterns similar to, but less frequent than, those in males with hemophilia A or B, severe bleeding disorders caused by deficiency of Factors VIII and IX, respectively. Unlike hemophilia, Factor X deficiency is not restricted to males, and patients with Factor X deficiency also experience significant bleeding from mucous membranes. Factor X deficiency produces a variable bleeding tendency, although more severe bleeding is typically observed in individuals with lower Factor X activity, e.g., below 5 % of the normal level.

Factor X is synthesized in the liver as a single chain precursor which is processed and secreted and circulates as a two-chain glycoprotein with a molecular weight of approximately 59,000 Daltons. The published estimates of the half-life of Factor X after intravenous injection of a prothrombin complex concentrate (PCC) or Fresh Frozen Plasma (FFP) range from 20 hours to up to 40-60 hours. In the blood coagulation cascade, Factor X is the precursor to the enzyme, activated Factor X (Factor Xa), which activates prothrombin (Factor II) to thrombin. Factor X can be activated by either the intrinsic Factor Xase complex of Factor IXa and Factor VIIIa, or by the extrinsic Factor Xase complex of Tissue Factor and Factor VIIa. Factor X is activated by the cleavage of a 52-residue peptide from the heavy chain. Factor Xa can play a pro-inflammatory role by activating leukocytes and vascular cells through protease-activatable receptors (PARs) and Effector Cell Protease Receptor-1 (EPR-1). Inhibition of Factor Xa in plasma is relatively rapid (circulatory half-life < 1 minute) and is mediated by antithrombin III, tissue factor pathway inhibitor and protein Z-dependent inhibitor.

COAGADEX is the first purified Factor X concentrate licensed in the U.S. and the rest of the world, but the use of plasma-derived Factor X is not an entirely new clinical practice. Factor X in pharmacologically significant amounts is found in FFP, various U.S. marketed PCCs and a Factor X/Factor IX concentrate (manufactured by CSL Behring) licensed in Europe under the trade name *Factor X P Behring*. Existing treatments have the disadvantages associated with the infusion of additional plasma proteins besides Factor X, and they often contain unknown amounts of Factor X, making precise and repeat dosing difficult.

BPL is a well-established plasma fractionator and manufacturer of many plasma-derived products including concentrates of coagulation Factors VIII, IX and XI, human albumin and various immune globulin products. Of these products, only Gammaplex 5 % is currently licensed in the U.S.

The manufacturing process for COAGADEX is based on the modification of the process used for another BPL product, a purified plasma-derived Factor IX concentrate, which is currently licensed in the United Kingdom (UK) but not in the U.S. In addition, several manufacturing steps, such as prothrombin complex purification and viral inactivation (solvent/detergent treatment and terminal heat inactivation), are used in the manufacture of other BPL products.

Documents pertinent to the review of COAGADEX were also provided in IND 14235. The BLA under STN 125506 was received on July 10, 2013. During the review process, the Chemistry, Manufacturing, and Controls (CMC) data were found to be insufficient to support the approval of the application. As a result, on March 10, 2014, a Complete Response (CR) letter was issued to the company summarizing the deficiencies. On April 27, 2015, the company responded to the CR letter with additional CMC information. The review team determined that BPL has satisfactorily addressed all major issues, and recommends approval of the original BLA for COAGADEX.

3. Chemistry, Manufacturing and Controls

a) Product Quality

Manufacturing Process

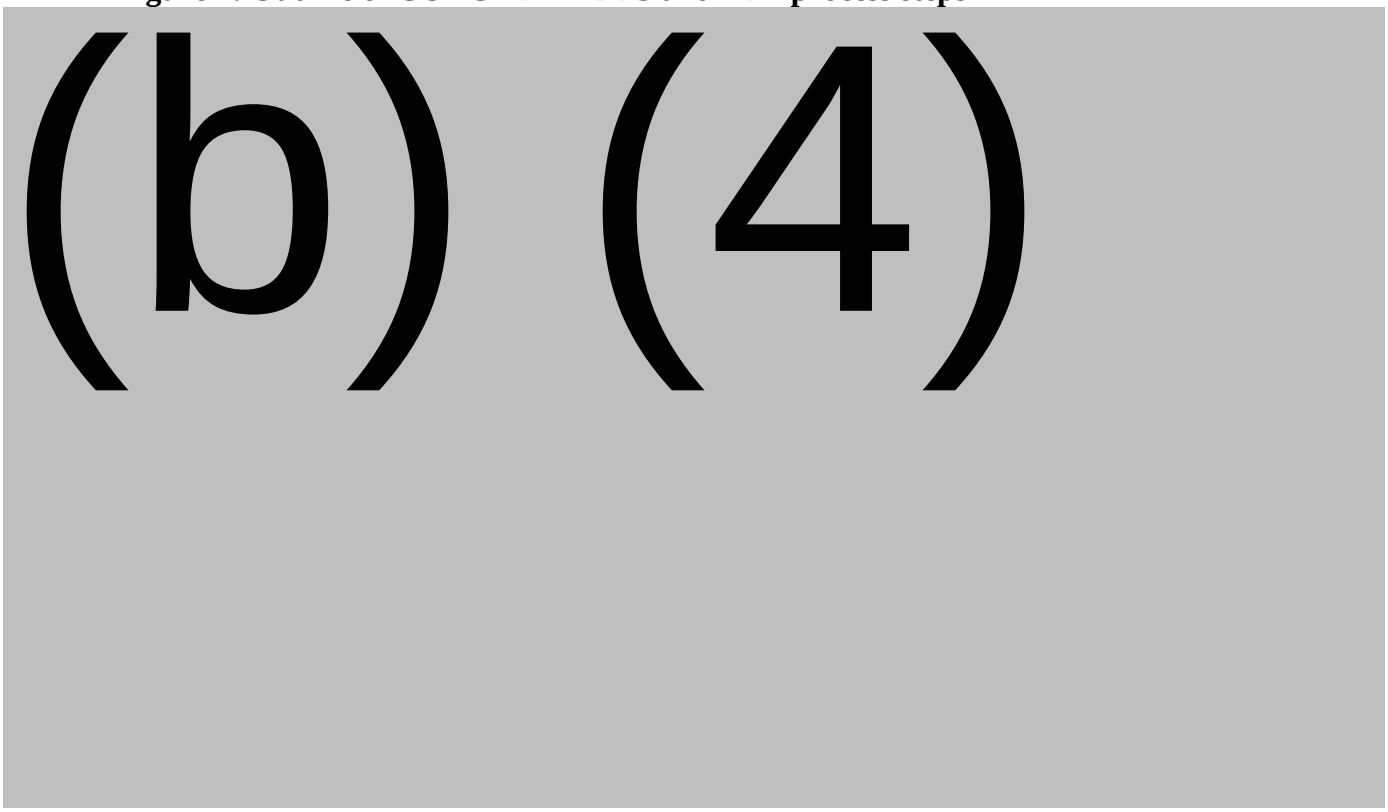
COAGADEX is manufactured from Source Plasma of U.S. origin at the FDA-licensed multi-product manufacturing facility in Elstree, United Kingdom. Source Plasma is collected by FDA-licensed suppliers in accordance with 21 CFR 640.60. The manufacturing process includes three steps specific for viral clearance: solvent/detergent treatment, nanofiltration through a (b) (4) filter, and terminal dry heat treatment.

The COAGADEX Bulk Drug Substance (BDS) manufacturing process includes (b) (4)

(b) (4)

The remaining Factor X-dedicated steps and all Final Drug Product (FDP) process steps have been operated at full scale at BPL's facility since 2007. These steps include (b) (4) a 15-nm virus-retentive filter ((b) (4) , formulation, sterilizing filtration, and heat-treatment of freeze-dried COAGADEX in the final closed container to inactivate viruses.

Figure 1: Outline of COAGADEX BDS and FDP process steps



In-Process Controls

Process risk management by risk assessment, validation and risk review was established for COAGADEX production according to the principles of ICH Q9 Quality Risk Management.

Process Validation and Qualification

Manufacturing consistency of the previously established steps was demonstrated with a retrospective statistical process qualification analysis of data on over (b) (4) batches of intermediates produced over 15 years. Demonstration of the state of control for the Factor X-dedicated process steps was achieved through the prospective validation studies conducted in 2009 prior to the initiation of the clinical trials, and again in 2014-2015 in response to the CR letter. In addition, continued process validation studies demonstrated acceptable manufacturing consistency and the ability of the existing in-process control and release specifications to

control product quality through the rejection of intermediates that do not meet the acceptance criteria for product quality attributes.

Final Drug Product

COAGADEX is a sterile, (b) (4) freeze-dried concentrate of human Factor X, presented as two nominal dose sizes of 250 IU and 500 IU of Factor X activity. After reconstitution with sterile Water for Injection (sWFI), COAGADEX forms a clear, colorless solution. The two dose sizes have the same composition upon reconstitution: 100 IU/mL Factor X (Active Ingredient); (b) (4) citric acid (b) (4) phosphate ((b) (4) sodium chloride ((b) (4) and (b) (4) sucrose (Stabilizer). Dose sizes differ only in the corresponding volumes at the point of fill and the point of use, e.g., 2.5 mL sWFI is supplied with the 250 IU dose, and 5 mL sWFI is supplied with the 500 IU dose.

Mix2Vial, a sterile, non-pyrogenic, single use fluid transfer device (510(k) number: K031861) is also supplied which allows for the quick transfer of sWFI to COAGADEX lyophilized product, and of the reconstituted COAGADEX product into a syringe for administration.

Container Closure

COAGADEX freeze-dried product is supplied in 10 mL (b) (4) glass vials (b) (4) closed with (b) (4) Grey (b) (4) rubber stoppers (b) (4)) and over-sealed with aluminum caps, lacquered silver outside surface, with a flip-off (b) (4) button so that the assembly provides a tamper evident seal ((b) (4) The container closure integrity testing (CCIT) was initially validated by (b) (4) testing. In addition vials containing the lyophilized product are subjected to 100% (b) (4) testing using (b) (4) . Results of CCIT are acceptable.

The sWFI diluent is supplied in 5 mL (b) (4) glass vials (b) (4)) filled to 2.5 mL and 5 mL nominal volume respectively. After filling, the vials are closed with grey, (b) (4) rubber with (b) (4) stoppers (b) (4)), and capped with aluminum overseals with (b) (4) flip off tamper evident caps ((b) (4) The container closure integrity testing for the sWFI diluent was validated by (b) (4) testing, and the results are acceptable.

COAGADEX Potency

The chromogenic substrate-based Factor X activity assay is used to determine the potency of COAGADEX. The method follows (b) (4) . method for the assay of human coagulation Factor X. The potency standard is calibrated in Factor X International Units using the current WHO 3rd International Standard for Factors II and X Concentrate. The actual Factor X potency determined by this assay is printed on the vial and carton labels.

Characterization of Impurities

The levels of impurities presented in the table below were found to be acceptable and not likely to adversely affect COAGADEX safety and efficacy as demonstrated in analytical, preclinical and clinical studies (Table 1). For example, in comparison with plasma-derived Factor IX containing products, COAGADEX was demonstrated to contain low procoagulant

activity, which is also controlled at release with two traditional assays, Non-Activated Partial Thromboplastin Time (NaPTT) and Fibrinogen Clotting Time (FCT). (b) (4)

Table 1: Product- and Process-Related Impurities

Impurities	Upper limit	Source of impurity
Factor II	NGT 1 IU/mL [a]	Residual protein components from plasma
Factor IX	NGT 1 IU/mL [a]	
Factor Xa and (b) (4)	NaPTT (b)	
(b) (4)	(b)	
(b) (4)		
	(b)	In-process impurity introduced during virus inactivation.
	(b)	
		Immobilized ligand for Factor X purification

Abbreviations: NGT, Not Greater Than; NLT, Not Less Than; (b) (4) **FCT, Fibrinogen Clotting Time; NaPTT, Non-activated Partial Thromboplastin Time.**

Notes:

[a] **Calculated from upper limits in the specification.**

[b] **Non-quantitative functional coagulation test.**

[c] (b) (4)

Release specifications

The relevant product quality attributes were included in the product release specifications. To control these parameters, suitable analytical methods were established. The specifications for COAGADEX are shown in Table 2 below:

Table 2: COAGADEX Final Drug Product Specifications

Release Test	Test Limits
General Characteristics	
Description of freeze-dried plug	Smooth white plug
Moisture, (b) (4)	(b) (4)
Solubility at (b) (4), min	(b) (4)
Appearance of solution	Colorless, clear or slightly opalescent solution.
(b) (4)	

Stability at (b) (4)	(b) (4)
Identity	Product complies with limits of Factor X assay
Biological Safety Tests	
Sterility test	Pass
Bacterial Endotoxin Test, (b) (4)	(b) (4)
General Safety Test	Pass
Purity/Specific Function	
Factor X activity, IU/mL	80 - (b) (4)
Factor X per vial, IU/vial	200 - (b) (4) (250 IU dose) 400 - (b) (4) (500 IU dose)
(b) (4)	
Total Protein, g/L	(b) (4)
Specific activity, IU/mg protein	NLT 80
NAPTT (b) (4)	
NAPTT (b) (4)	
FCT (b) (4)	
Excipients	
Chloride, (b) (4)	(b) (4)
Phosphate, (b) (4)	(b) (4)
Citrate (b) (4)	5 - 15
Sucrose, (b) (4)	(b) (4)
Sodium, (b) (4)	(b) (4)
Impurities	
Factor II, IU/mL	NGT 1
Factor IX, IU/mL	NGT 1
(b) (4)	

Abbreviations: NGT, Not Greater Than; NLT, Not Less Than; LT, Less Than

[a] **A visual inspection method to detect abnormalities in COAGADEX solution. The specification limit provides a (b) (4) margin of safety beyond the time which is specified for use in the COAGADEX prescribing information.**

[b] **The endotoxin test limit for COAGADEX is defined according to dose size and intended patient exposure.**

Analytical Methods

The release methods were validated for their suitability for the intended use. The respective reference standards and maintenance program were also established.

Evaluation of Safety Regarding Adventitious Agents

For the non-viral adventitious agents such as bacteria, fungi, and mycoplasma, the potential contamination of these agents is well controlled through the use of validated cleaning and sanitization procedures ((b) (4) and in-process filtration steps including (b) (4) sterile filtration. The final container of

COAGADEX is further guaranteed to be free of non-viral adventitious agents by the testing for Sterility and Endotoxins.

To minimize the risk of transmissible spongiform encephalopathy (TSE) agents, donors who are potentially at risk are excluded from plasma donation as specified in the current FDA guidance regarding donations collected in the U.S. The routine cleaning of equipment with (b) (4) can minimize the risk of TSE cross contamination of subsequent lots in the manufacturing process. Furthermore, the manufacturing steps including (b) (4) nanofiltration (pore size, 15 nm) may contribute to the removal of potential TSE agents.

The potential viral load in the starting material is well controlled in the manufacture of COAGADEX. This product is manufactured using only U.S. Source Plasma (21 CFR 640.60), which is obtained from FDA-licensed U.S. plasma collection centers. Plasma donations used for COAGADEX have to be tested negative for serological markers, including mandatory testing for Hepatitis B surface Antigen (HBsAg), antibodies against Human Immunodeficiency Virus (HIV)-1/2 and Hepatitis C Virus (HCV). Mini-pools of donations are tested by nucleic acid test (NAT)/(b) (4) for the presence of genomic material of Hepatitis A Virus (HAV), Hepatitis B Virus (HBV), HCV, HIV-1, and human parvovirus B19 (B19V). Donations reactive to HAV, HBV, HCV, HIV-1 or with a high titer (b) (4) for a single donation) of B19V are excluded from further manufacture. In-process controls are performed on the manufacturing pools. Each pool is tested to be negative for HBsAg and anti-HIV-1/2. Also, manufacturing pools are non-reactive for HAV, HBV, HCV, and HIV-1. The limit for B19V in the manufacturing pools ((b) (4) per pool) is set not to exceed 10^4 IU/mL.

Additionally, the potential of viral contamination of COAGADEX is mitigated by three dedicated viral clearance steps: solvent/detergent (S/D) treatment using (b) (4) terminal dry-heat treatment (80 ºC for 72 hours), and (b) (4) nanofiltration. BPL has evaluated these three steps in down-scale studies. The viruses selected in the studies include enveloped viruses, HIV-1, Infectious bovine rhinotracheitis (IBR, bovine herpesvirus model for enveloped DNA viruses including HBV), Herpes simplex virus type 1 (HSV-1, model virus for large enveloped DNA viruses), Sindbis virus (SBV, model virus for HCV), Bovine viral diarrhea virus (BVDV, model virus for enveloped RNA viruses), West Nile virus (WNV), and non-enveloped viruses, HAV, Canine parvovirus (CPV, model virus for B19V), and B19V. These viruses resemble viruses which may contaminate the COAGADEX FDP, and represent a wide range of physico-chemical properties in the testing of the ability of the manufacturing process to eliminate viruses. Small-scale studies on the relevant steps resulted in the following total cumulative log reduction factors, in parenthesis, for these viruses: HIV-1 (>16.9), IBR (> 5.3), HSV-1 (> 14.7), SBV (6.0), BVDV (> 14.8), WNV (4.9), HAV (> 11.1), CPV (8.5), and B19V (> 5.9). These results are sufficient to support the effectiveness of viral clearance in the commercial manufacturing process.

Stability
All FDP stability batches met the specifications at +5°C, +25°C and +30°C for up to 36 months. Therefore, the proposed shelf-life of 36 months at +2°C to +30°C is acceptable.

b) CBER Lot Release

The lot release protocol template was submitted to CBER for review and found to be acceptable after revisions. COAGADEX samples were submitted to CBER in support of the BLA, tested by CBER and found to be acceptable. For routine lot release, the applicant will submit final container samples together with the respective lot release protocols. A lot release testing plan was developed by CBER and will be used for routine lot release.

c) Facilities review/inspection

Facility information in the BLA was reviewed by CBER and found to be acceptable. The facilities involved in the manufacture of COAGADEX are listed in the table below.

Table 3. Manufacturing Facilities Table for Factor X

Name/address	FEI number	DUNS number	Inspection/ waiver	Results/ Justification
Drug Substance *Drug Product* *Release Testing* Bio Products Laboratory, Limited (BPL) Dagger Lane Elstree, Hertfordshire, United Kingdom WD6 3BX	1000184635	216845337	Pre-License Inspection	CBER, October 21-25, 2013 Voluntary Action Indicated (VAI)

CBER conducted a pre-license inspection (PLI) of BPL in Elstree, UK from October 21-25 2013 for the purification, filling and lyophilization of the COAGADEX drug product and the filling and terminal sterilization of the sWFI diluent.

At the end of the inspection, CBER issued a Form FDA 483 with seven observations. The inspectional observations included deficiencies in the following areas: process validation, analytical method validation, reprocessing conditions and documentation, validation of the lyophilization process, validation of cleaning and sterilization ((b) (4)) of lyophilizers, visual inspection of the final product, and (b) (4) . The firm responded to the observations on November 15, 2013 and provided a plan of action for addressing the deficiencies and the time line when the corrective actions would be implemented. BPL's proposed completion date of the corrective actions was June 30, 2014 which was after the Action Due Date of the original BLA submission (March 11, 2014). A CR was sent to BPL on March 10, 2014 with outstanding inspectional issues as the first item of the CR letter. The corrective actions were reviewed and found to be acceptable, including one post-marketing commitment to address

(b) (4) . All inspectional issues are considered to be satisfactorily resolved.

d) Environmental Assessment

The BLA included a request for categorical exclusion from an Environmental Assessment under 21 CFR 25.31(c). The FDA concluded that this request is justified as the manufacturing of this product will not alter significantly the concentration and distribution of naturally occurring substances and no extraordinary circumstances exist that would require an environmental assessment.

SIGNIFICANT ISSUES RESOLVED DURING THE BLA REVIEW

The CR letter, which was sent to BPL on March 10, 2014, listed a number of CMC issues that were not resolved at that time. These issues included the following:

- Issues found during the FDA PLI of the BPL Facility in Elstree, UK from October 21-25 2013 are discussed in the facilities inspection section above.

- Multiple deficiencies in the validation of analytical methods used for FDP and sWFI release testing, lack of established protocols and qualification reports for potency reference standards and lack of established specifications for BDS and two intermediates.

- Insufficient control of identity and purity

- Initial process validation of dedicated process steps conducted in 2009 was not successful as evidenced by the high number of deviations observed and the need to terminate or reject 5 of (b) (4) batches manufactured after process validation.

- Insufficient process validation data for manufacturing options, including (b) (4) COAGADEX(b) (4)

- Insufficient information on differences between the clotting and chromogenic Factor X activity assays

These issues were addressed in BPL's response to the CR letter on April 27, 2015 and through further communications with FDA. In particular, all issues related to deficiencies in the validation of the analytical methodology were resolved. In the additional process validation studies presented in BPL's response to the CR letter, all pre-defined process qualification criteria including lot release specification criteria were met for the 3 consecutive BDS and FDP batches demonstrating the state of control.

Regarding the identity and purity tests, BPL did not agree to the proposal to establish Factor X (b) (4) as an additional release assay. BPL stated that the existing specification limits for Factor X Potency and Specific Activity assays are sufficiently informative to demonstrate COAGADEX identity and purity. This approach is acceptable

because the existing assays were found to be sufficient to detect a process failure resulting in (b) (4) in the product. BPL's approach is generally consistent with the release assay strategies used for similar plasma-derived coagulation factor products. BPL agreed to retain (b) (4) as investigative tools for use in the event of a quality failure.

Regarding the Factor X activity assay, BPL demonstrated that the proposed chromogenic substrate-based assay generates results that are essentially identical to those produced by the clotting-based Factor X activity assay used in most clinical laboratories. In addition, good agreement between the results derived from the clotting and chromogenic Factor X activity assays was found in pharmacokinetic studies described below.

Chemistry, Manufacturing and Controls Conclusion
The CMC data support the quality and safety of COAGADEX for the treatment of Factor X deficient patients.

4. Nonclinical Pharmacology/Toxicology

Pharmacology Studies
The primary pharmacodynamic activity of COAGADEX was demonstrated using *in vitro* studies. Addition of COAGADEX to Factor X-depleted plasma corrected or restored the prolonged activated partial thromboplastin time, prothrombin time, and thrombin generating activity to levels within the range of normal plasma, in a dose-dependent manner. These results were similar to those obtained with a comparator, plasma-derived Factor X + Factor IX product that isapproved outside of the United States. When tested using an *in vivo* (b) (4) (b) (4) assay (i.e., the (b) (4) assay in Factor X replete rabbits), there was a dose-related response in both the incidence and severity of thrombus formation in rabbits injected intravenously with COAGADEX at doses 2- to 10-fold higher than the recommended clinical dose; however, thefindings for the COAGADEX-treated groups were not statistically significantly different from the control (0.9% saline) dosed group. Nonclinical studies to evaluate the in vivo primary pharmacodynamic effects of COAGADEX on hemostasis were not performed, due the lack of an available animal model for Factor X deficiency.

In summary, the nonclinical pharmacodynamic studies showed the pro-coagulant activity of COAGADEX in multiple in vitro studies with Factor X-depleted plasma, and in the (b) (4) assay in vivo in rabbits. The results with COAGADEX were similar to those obtained with a Factor X + Factor IX concentrate. These data were used as proof-of-concept to support the rationale for entering COAGADEX into clinical trials.

Pharmacokinetic Studies
The initial pharmacokinetic profile was obtained in COAGADEX-dosed, Factor X replete (b) (4) rats. Factor X activity was measured using a chromogenic substrate assay. The pharmacokinetic profile in (b) (4) rats showed a dose-dependent increase in all parameters measured, with linear, dose-proportional increases in both the maximum plasma concentration

(C_{max}) and exposure (area under the concentration-time curve, AUC) with increasing doses of COAGADEX.

Toxicology

Overall, toxicity studies with COAGADEX conducted in Factor X replete (b) (4) rats did not identify any unexpected findings or significant concerns. (b) (4) rats dosed with a single intravenous injection of COAGADEX at doses up to 24-fold greater than the maximum clinical dose demonstrated no systemic or tissue pathologies. In a 28-day, repeat dose toxicity study with COAGADEX in rats, animals were dosed every other day by bolus intravenous injection with COAGADEX doses equal to, and up to 6-fold greater than, the maximum recommended clinical dose. Although statistically significant differences in some measured parameters were reported, the findings were not consistent or dose-related between the COAGADEX dose groups, and no corresponding histopathological findings were detected. Animal findings for toxicity studies were expected and included microthrombus formation of minor severity in lung, pancreas and thymus, and elevations in liver transaminases with no apparent relationship to dose of COAGADEX. These findings are consistent with the exaggerated pharmacologic effects i.e., pro-coagulant activity reported with other recombinant and plasma-derived coagulation factors. Local tolerance study conducted in rabbits administered the clinical dose of COAGADEX revealed acceptable levels of inflammation and edema at the injection site.

There were no animal studies for carcinogenicity, *in vivo* mutagenicity, fertility, reproductive toxicity, or teratogenicity conducted with plasma-derived Factor X. As COAGADEX is a plasma-derived human protein, animals receiving repeated doses of the product developed antibodies against Factor X. Therefore, long-term, repeat-dose toxicity studies, as well as the standard carcinogenicity bioassay (i.e., 2 years of daily Factor X dosing in both rats and mice) were not feasible to conduct.

Because Factor X is a protein, the standard genotoxicity testing recommended in the ICH S2(R1) guidance document would not provide information to address potential mutagenicity of COAGADEX, and as per the ICH S6 guidance on biotechnology-derived protein therapeutics, these studies were not required. The lack of carcinogenicity, mutagenicity, and chronic toxicity data are addressed in the appropriate section of the package insert for COAGADEX.

No nonclinical reproductive or developmental toxicity studies were conducted. COAGADEX labeling includes a statement that nonclinical reproductive and developmental toxicity studies have not been conducted, and COAGADEX should be used during pregnancy or lactation only if clearly needed. This labeling is consistent with that included in prescribing information for other approved recombinant and plasma-derived human coagulation factors.

5. Clinical Pharmacology

The clinical pharmacokinetics of COAGADEX have been assessed in a clinical study entitled, *A Phase III open, multi-center study to investigate the pharmacokinetics, safety and efficacy of BPL's high purity Factor X in the treatment of severe and moderate Factor X deficiency*.

This was an open-label, multi-center, nonrandomized, prospective study in subjects with severe and moderate Factor X deficiency to assess the pharmacokinetics (PK), safety, and efficacy of COAGADEX. The primary objective was to assess the PK of Coagadex after a single dose of 25 IU/kg in subjects with severe or moderate Factor X deficiency. After an initial dose and PK assessment at the baseline visit, subjects received COAGADEX for spontaneous or traumatic bleeds or for specific short-term preventative use. A repeat PK assessment occurred at the six-month study visit. The duration of the study for each subject was at least 27 weeks.

There were 13 and 8 subjects in the single and repeat dose assessments, respectively. The mean age was 29.9 years with a range of 14 to 58 years (2 subjects aged 14 and 17 years). There were 4 males and 9 females in the study. Of the 13 subjects in the study, 12 had severe Factor X deficiency with Factor X:C level <1%, and 1 subject had moderate disease with Factor X:C level in the range of 1% to <5%. The subjects were diagnosed with Factor X deficiency for a mean duration of 22.8 years. Before entering this study, all 13 subjects had been treated with replacement Factor concentrates, and 11 had been treated with FFP. In addition, 12 subjects had experienced spontaneous bleeding in the past.

Subjects received 25 IU of Factor X per kg body weight (25 IU/kg) by intravenous infusion at a rate of approximately 10 mL/min, but no more than 20 mL/minute. For the pharmacokinetic study, blood samples were taken at 0.25, 0.5, 1, 3, 6, 24, 48, 72, 96, 120, 144, and 168 hours post-dose. Factor X concentrations were measured by both the one-stage clotting and chromogenic assays. The concentrations of Factor X at pre-dose were subtracted from all subsequent post-dose concentrations. Pharmacokinetic parameters were calculated by non-compartmental analysis and are shown in Table 4 below.

Table 4: Pharmacokinetic parameters (mean ± SD) of Factor X following 25 IU/kg intravenous dose to subjects with severe and moderate Factor X deficiency

Parameters	**Clotting Assay**		**Chromogenic Assay**	
	Single dose	Repeat dose	Single dose	Repeat dose
Sample size (n)	13	8	13	8
$AUC_{(0\text{-inf})}$	18.9 ± 4.1	17.3 ± 4.8	23.2 ± 5.8	20.2 ± 6.1
CL (mL/h/kg)	1.27 ± 0.31	1.47 ± 0.36	1.15 ± 0.39	1.29 ± 0.38
Half-life (hrs)	32 ± 9	30 ± 5	34 ± 7	30 ± 5
MRT (hrs)	44 ± 10	41 ± 8	48 ± 9	42 ± 10
V_{ss} (mL/kg)	56 ± 18	59 ± 8	54 ± 17	52 ± 9
IR (IU/dL)/(IU/kg)	2.23 ± 0.51	1.79 ± 0.34	2.34 ± 0.59	2.01 ± 0.40

Abbreviations: AUC = Area under the curve (Unit = IU x hr/mL); CL = Clearance; MRT = Mean residence time; V_{ss} = Volume of distribution at steady state; IR = Incremental recovery

Conclusions: COAGADEX is a low clearance drug with a half-life of 30 hours. Repeat dosing of COAGADEX did not accumulate in the systemic circulation as there was no difference in the PK parameters of COAGADEX between the first dose and the repeat dose. The PK

parameters were comparable between the clotting assay and chromogenic assay. The impact of gender and age were not evaluated in this study.

6. Clinical/ Statistical

a) Clinical Program

The clinical development program to support licensure of COAGADEX is summarized in the table below.

Table 5: Summary of Clinical Studies

Trial ID (Type of Study)	Objectives	Dosage Regimen	Subjects (n)	Diagnosis	Treatment duration	Study status
Ten01 (Efficacy, safety, PK)	PK profiles, safety and efficacy in on-demand treatment of bleeds including surgery	On demand: 25 IU/kg Surgery: calculated from a nominal recovery of 1.5 IU/dL per IU/kg to raise Factor X level to 70 to 90 IU/dL before surgery; maintain Factor X level at 50 IU/dL after surgery	16	Moderate to severe hereditary Factor X deficiency	6 months to 2 years for on-demand; up to 14 days for surgery	Completed
Ten03 (Efficacy, safety, PK)	Safety and efficacy in control of bleeding during surgery	Same surgery dose as in Ten01	2 (4 surgical procedures)	Mild to severe hereditary Factor X deficiency	21 days maximum	Completed

Abbreviations: PK = pharmacokinetics

In the phase 3 study Ten01, a total of 16 subjects with severe and moderate hereditary Factor X deficiency were enrolled and treated with at least one dose of COAGADEX for on-demand treatment and control of bleeding or for perioperative management of bleeding. This trial was designed as an open-label, multicenter, nonrandomized, prospective study in adults and adolescents (aged ≥12 years) with severe and/or moderate Factor X deficiency to assess the pharmacokinetics, safety, and efficacy of COAGADEX. The primary objective was to assess the PK after a single dose of COAGADEX. Secondary objectives included: to assess the safety and hemostatic efficacy of COAGADEX in the treatment of bleeding episodes and for perioperative management. Eligible subjects were aged ≥12 years of age, had a history of hereditary severe or moderate Factor X deficiency with <5% (<5 IU/dL) basal Factor X:C at

diagnosis; and had a history of a minimum of one spontaneous or menorrhagic bleed that required treatment with FFP, PCC, or a Factor IX/X concentrate.

Of the 16 subjects treated, 14 (87.5%) had severe Factor X deficiency (Factor X:C level <1 IU/dL) and two subjects had moderate disease (Factor X:C level in the range of 1 to <5 IU/dL). The majority of subjects were female (n=10; 62.5%) and Caucasian (n=12; 75%). A total of 15 (94%) subjects were previously treated with replacement factor, 14 (87.5%) with FFP and 12 (75%) with other blood products. Subjects were recruited at 11 sites in 5 countries.

Efficacy Analyses

The efficacy results presented below summarize the analyses and conclusions of the clinical and statistical reviewers.

On-demand Treatment and Control of Bleeding Episodes

The clinical efficacy of COAGADEX for on-demand treatment and control of bleeding was demonstrated in 15 subjects who had at least one overt (obvious), menorrhagic, or covert (hidden) bleed selected by the Data Review Committee (DRC) for review of efficacy. Efficacy was assessed by the subject and/or investigator for each new bleeding episode using bleed-type specific four-point rating scales (Appendix I). In addition, a separate four-point rating scale was used by the investigator to provide an overall assessment of the efficacy of COAGADEX for each subject.

A total of 208 bleeding episodes were treated with COAGADEX. The average number of bleeding episodes per subject was 13, and the mean number of bleeds per subject per month was fewer than one.

Narratives of Subjects with Greater than Fifteen bleeds on Study

- Subject (b) (6) was a 15 year old Caucasian female with a history of moderate Factor X deficiency (diagnosed 10 years prior to enrollment on study) who experienced 59 bleeds while on study (listing 12.5). Most (n=42; 71%) were considered major bleeds; 12 (20%) were menorrhagic, and 20 (34%) were due to injury. The subject had an extensive history of spontaneous and traumatic bleeds, including joint bleeds (resulting in synovitis and arthrosis in her left knee, as well as arthrosis in both ankles), for which she routinely received 600 units *Factor X P Behring*. She also suffered from menorrhagia, which was routinely treated with antifibrinolytics. The subject's bleeding history in the previous year included at least eight bleeds (listing 7.6) that were treated with PCCs; five of these were joint bleeds and one was a menorrhagic bleed. Three of these bleeds were due to injury. This subject was enrolled into study Ten01 on September 20, 2011 and completed the first PK assessment in the following week. She completed the study on January 17, 2013 (listing 3.1).
- Subject (b) (6) was a 20 year old Caucasian male with a history of severe Factor X deficiency who experienced 20 bleeds while on study. Most (70%) were minor bleeds and were either mucosal (45%), muscle (30%) or joint (25%) bleeds. The patient had an extensive history of spontaneous and traumatic bleeds, including muscle and nose bleeds, which were treated with on-demand therapy with low doses of PCC.

- Subject (b) (6) was a 12 year old Caucasian male with a history of moderate Factor X deficiency who experienced 19 bleeds while on study. Most (88%) were major bleeds; 7 (37%) were joint bleeds; 5 (26%) were muscle bleeds. The subject had a history of gastrointestinal and muscle bleeds and had received >150 exposure days (EDs) of replacement factor concentrates, >20 EDs to FFP and >10 EDs to other blood products.
- Subject (b) (6) was a 17 year old Caucasian female with a history of severe Factor X deficiency who experienced 18 bleeds while on study. The majority of bleeds were mucosal (72%); 44% were major bleeds. The subject's history was significant for numerous menorrhagic bleeds, requiring blood transfusions. She had >150 EDs to replacement factor concentrates, >100 EDs to FFP and >20 EDs to other blood products.

Of the 208 bleeds that were treated during the trial, 207 bleeds were reviewed by the DRC. One bleed was not reviewed before datalock. The DRC selected 187 bleeds for review of efficacy, and 186 of these bleeds in 15 subjects were considered assessable for efficacy analysis. Review of the case narratives for the 20 on-demand bleeds in eight subjects that were not reviewed by the DRC revealed that the bleeds were not selected because either there were insufficient data to determine the nature and/or extent of bleeding (n=4), there was concomitant use of other hemostatic agents (n=8) or inappropriate dosing with COAGADEX (n=4), there was simultaneous treatment of another bleed (n=3) or the subject completed the study before the treatment for the bleed had been completed (n=1).

As summarized in the following table below, the characteristics of the 187 bleeds that were reviewed by the DRC were major (52%), spontaneous (42%), covert (59%).

Table 6: Summary of Bleed Characteristics

Bleed Characteristics	**Bleeds Selected by DRC (N=187)**
Type	
Overt	16 (9%)
Covert	110 (59%)
Menorrhagic	61 (33%)
Location	
Joint	63 (34%)
Mucosal	73 (39%)
Cut/wound	4 (2%)
Muscle	26 (14%)
Other	21 (11%)
Cause of Bleed	
Spontaneous	79 (42%)
Injury	47 (25%)
Menorrhagia	61 (33%)
Severity	
Major	98 (52%)
Minor	88 (47%)
Not evaluated	1 (0.5%)

Of the 187 bleeds, 98% (184/187; 95% confidence interval: 95.4% to 99.7%) were considered a treatment success (i.e. excellent or good response). The mean dose per infusion of COAGADEX was 25.3 IU/kg, which confirms that the recommended dose of 25 IU/kg is appropriate. Refer to the table below for a summary of efficacy.

Table 7: Summary of Efficacy

Efficacy Endpoint	**Bleeds Selected by DRC (N=187)**
Assessment of Efficacy	
Excellent	170 (91%)
Good	14 (7.5%)
Poor	2 (1%)
Unassessable	1 (0.5%)
Number of Infusions to treat a bleed (IU/kg), mean (SD)	1.2 (0.47)
Dose per infusion (IU/kg), mean (SD)	25.3
Total dose (IU/kg), mean (SD)	30.4 (12.5)

SD: standard deviation

Although only two bleeds received a poor response, four bleeding episodes in two subjects were considered treatment failures. This was because treatment failure was defined as the need for more than two doses of Coagadex to treat an overt or menorrhagic bleed, or more than three doses to treat a covert bleed. These treatment failure bleeds in the two subjects are summarized below:

- *Subject* (b) (6) The subject received four doses of COAGADEX to treat a covert muscle bleed. The subject did not seek medical attention until three days after the bleed started, at which time it was considered severe. As a result of the delay in treatment, the initial dose of 25 IU/kg of COAGADEX was considered insufficient, and an additional dose of 8 IU/kg was given on the same day. The site considered these two infusions as a single treatment. As per the definition of treatment failure, because four infusions were administered, the assessments of efficacy by the investigator and subject were recorded as 'poor'.
- *Subject* (b) (6) On three separate occasions, the subject required more than two doses of COAGADEX to treat a menorrhagic bleed, which met the definition of treatment failure.

During the review, data from the following ten bleeds were excluded by FDA because these data were considered to potentially bias the efficacy assessments:

- The standard dose of COAGADEX was increased for two subjects in an attempt to resolve future bleeding episodes with a single infusion.
- Eight covert bleeds were reported to have lasted longer than 48 hours but did not receive a second or third infusion. These bleeds were considered potentially undertreated by the sponsor and the reviewer. Assessment of efficacy was based on the number and timing of infusions of COAGADEX required to achieve hemostasis, and

per protocol, all ongoing covert bleeds were to be assessed 48 hours after the first infusion of COAGADEX to determine whether further doses were required (no subjective criteria were considered in the assessment). For seven of the eight bleeds, the subject was treated with only one infusion, so a second infusion would have still qualified the bleed as a successful treatment. Of the eight bleeds that were potentially undertreated, the DRC excluded one of these bleeds from the efficacy analysis.

A sensitivity analysis with exclusion of these data by FDA did not alter the conclusions drawn about the efficacy of COAGADEX for treatment and control of bleeding episodes.

Perioperative Management of Bleeding

The data to support the use of COAGADEX for perioperative management of bleeding was obtained from trials Ten01 and Ten03. The primary efficacy endpoints, dosing regimens, and key inclusion/exclusion criteria were sufficiently similar between the two trials to allow for an integrated analysis of efficacy for this indication. The primary efficacy endpoint for surgery was blood loss during and after surgery. The following four parameters were assessed by the investigator at the subject's End of Treatment assessment, and contributed to an assessment of efficacy as 'excellent', 'good', 'poor' or 'unassessable':

1. Clinical estimation of volume of blood loss during surgery;
2. Requirement for blood transfusion (units of Red Blood Cells or units of Whole Blood) or infusion of autologous red cells during and after surgery;
3. Number and duration of post-operative bleeding episodes;
4. Measurements of hemoglobin pre-operatively, post-operatively, and at discharge.

Five subjects (three subjects in Ten01 and two subjects in Ten03) underwent seven surgical procedures. Subjects had severe (n=2), moderate (n=1) or mild disease (n=2) and ranged in age from 14 to 59 years (age ranges 14-36 years in Ten01 and 55-59 in Ten03).

A total of four major surgeries were performed in two subjects with mild disease (Ten03) and an additional three minor procedures of tooth extractions were performed in three subjects with moderate or severe disease (Ten01). One minor surgical procedure was excluded from the per-protocol analysis as this subject's plasma Factor X:C levels were ≥20 IU/dL at the pre-surgery visit, which reflected her use of COAGADEX the day prior to the procedure. This subject experienced a serious adverse event of persistent blood-stained saliva that required overnight hospitalization for observation. Surgical data is summarized in Table 8 below.

Table 8: Summary of Surgical Data

Trial ID	Severity of Factor X deficiency	Surgery Classification	Type of surgery	Investigator's assessment of Factor X efficacy
Ten01	Severe	Minor	Dental extraction	Excellent
Ten01	Severe	Minor	Dental extraction	Excellent
Ten01*	Moderate	Minor	Dental extraction	Excellent
Ten03	Mild	Major	Coronary artery bypass graft (CABG)	Excellent

			Multiple dental extractions (n=6)	Excellent
Ten03	Mild	Major	Knee replacement	Excellent
			Knee replacement	Excellent

Notes: *Excluded from per-protocol analysis

The estimated blood loss was 'as expected' for five of the seven surgeries, and 'less than expected' for two surgeries, including the CABG (Ten03) and tooth extraction (Ten01). In four surgeries (three major and one minor), hemoglobin and hematocrit levels decreased significantly after the surgery; however, no subjects received blood transfusions. The pre-surgery dose for all surgeries ranged from 30.6 – 51.4 IU/kg and resulted in increments of 70 – 120 IU/dL. In Ten03, the pre-surgery dose ranged from 30.6 to 54.4 IU/kg and resulted in increments of 70-120 IU/dL.

b) Pediatrics

This product received orphan designation for treatment of hereditary Factor X deficiency on November 8, 2007. Because of orphan designation, a waiver of pediatric study Ten02 was granted.

c) Other Special Populations

There is no information regarding the presence of COAGADEX in human milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for COAGADEX and any potential adverse effects on the breast-fed infant from COAGADEX or from the underlying maternal condition. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when COAGADEX is administered to a nursing woman.

d) Overall Comparability Assessment

Not applicable to this BLA.

e) Bioresearch Monitoring

Five clinical sites were selected for inspection. Subjects were enrolled at one site in the U.S., and seven sites outside of the U.S. Four of the five inspections were conducted outside of the U.S. The five sites selected represented 63% of the clinical study sites that enrolled subjects and 77% of the total subjects in the study. The inspections were conducted in accordance with FDA's Compliance Program Guidance Manual (CPGM) 7348.811, Inspection Program for Clinical Investigators. Bioresearch monitoring inspections did not reveal significant problems that impacted the data submitted in this BLA.

7. Safety

The safety of COAGADEX was assessed using the following endpoints: frequency of adverse events, vital signs, clinical laboratory tests, and immunogenicity testing. Adverse events (AEs)

were coded using Medical Dictionary for Regulatory Activities, Version 13 and were analyzed based on the principle of treatment emergence during study treatment. All safety analyses were based on the safety population, which included all subjects who received at least one dose of COAGADEX (n=18) to treat a bleeding event, for perioperative management, or for PK assessment:

- *Ten01*: 16 subjects with moderate or severe hereditary Factor X deficiency who received COAGADEX for PK assessment, on-demand treatment of bleeding episodes or for controlling bleeding in surgical procedures. Three subjects with severe (n=2) or moderate (n=1) Factor X deficiency underwent three minor surgical procedures.
- *Ten03*: 2 subjects with mild Factor X deficiency underwent four major surgical procedures and received COAGADEX for perioperative management.

The safety concerns for this product are hypersensitivity and allergic reactions, thromboembolic events, and inhibitor development. Neutralizing antibodies against human Factor X (anti-human Factor X inhibitors) were measured in a central lab using a Nijmegen-Bethesda assay at these pre-specified time points: Screening Visit, pre-dose at the Baseline Visit (Day 1), at the 1-Month Visit, the 3-Month Visit, pre-dose at the 6-Month Visit, at Study Extension Visits, the End-of-Study Visit and at any Unscheduled Visit for a bleed. The safety data showed that COAGADEX intravenous infusions were well tolerated with few adverse drug reactions. There were no reports of anaphylaxis, thromboembolic events, or Factor X inhibitor development in any subject. In addition PK parameters did not show change over time after repeated dosage. Three of the 18 subjects (17%) experienced significant elevations in at least one of the thrombogenic markers measured (thrombin-antithrombin complex, d-dimer, prothrombin fragments 1+2) following a dose of 25 IU/kg. These findings were not associated with clinical signs or symptoms of thrombosis.

There was one unrelated death of a 58 year old female with severe Factor X deficiency and hepatitis C, who died from bilateral pneumonia and multi-organ failure after presenting to the hospital with six days of nausea, diarrhea, shortness of breath, productive cough, fever, and chest pain.

Adverse Events

A total of 202 adverse events were reported in 18 subjects, including 176 in trial Ten01 and 26 in Ten03. Most were mild or moderate in severity. The most frequently reported AEs (≥25%) were: headache (reported by 8 subjects; 6.7% of all AEs), nasopharyngitis (reported by 7 subjects; 5.4% of all AEs), back pain (reported by 6 subjects; 5.0% of all AEs), and pain in an extremity (reported by 6 subjects; 4.0% of all AEs). Adverse reactions were reported in two subjects (11.1%). The most frequently reported adverse reactions were site erythema (2 reports in 1 subject [5.6%]), fatigue (2 reports in 1 subject [5.6%]), back pain (1 report [5.6%]) and infusion site pain (1 report [5.6%]).

A total of 11 nonfatal serious adverse events (SAEs), presented in the table below, were reported in 5 of the 18 subjects (28%) treated with at least one dose of COAGADEX, and all were reported in Ten01. None of the SAEs were considered related to study treatment by the investigator, applicant, or the clinical reviewer.

Table 9: Serious Adverse Events from Clinical Trials

Subject	Preferred Term	Severity	Outcome	Relationship to COAGADEX
(b) (6)	Muscle hemorrhage	Moderate	Recovered	Unrelated
	Dysmenorrhea	Moderate	Recovered	Unrelated
	Menorrhagia	Moderate	Recovered	Unrelated
(b) (6)	Tooth abscess	Moderate	Recovered	Unrelated
(b) (6)	Gastritis	Moderate	Recovered	Unrelated
	Anemia	Moderate	Recovered	Unrelated
	Anemia	Moderate	Not Recovered	Unrelated
(b) (6)	Anemia	Severe	Recovered	Unrelated
	Gastric ulcer Helicobacter	Severe	Recovered	Unrelated
(b) (6)	Syncope	Mild	Recovered with sequelae	Unrelated
	Post procedural hemorrhage	Mild	Recovered	Unrelated

Selected Narratives for SAEs:

- *Subject* (b) (6) a 32 year old female with severe Factor X deficiency was hospitalized for a right forearm hemorrhage after presenting with pain and swelling in the right forearm associated with tingling and numbness. She was treated with COAGADEX and tranexamic acid and discharged home without incident. She was hospitalized on a separate occasion for dysmenorrhea and menorrhagia after presenting with pain and was treated with COAGADEX and tranexamic acid. All three events were classified as serious due to hospitalization.
- *Subject* (b) (6) a 19 year old female with a history of anemia, gastrointestinal bleeding and gastroesophageal reflux was hospitalized after presenting with a hemoglobin of 5.3 g/dL at her Baseline PK visit. She was given a Red Blood Cell transfusion without incident. On a separate occasion the subject was hospitalized with acute gastritis and anemia after presenting with headache, nausea, reduced appetite, and abdominal pain. An abdominal ultrasound was unremarkable. She was treated with a proton pump inhibitor and ferritin.
- *Subject* (b) (6) a 14 year old male was hospitalized with gastric bleeding and a hemoglobin of 5.4 g/dL for which he received a Red Blood Cell transfusion and was treated with COAGADEX. Endoscopy confirmed *Helicobacter pylori* infection.
- *Subject* (b) (6) a 14 year old female was hospitalized for observation after fainting while showering. The unwitnessed fall and resultant head trauma and concussion warranted a CT scan, which did not show any evidence of an intracranial bleed. A clinical investigation showed a peri-occipital hematoma of the head. The fainting was not associated with anemia. The subject was not on any concomitant medications. The incident occurred three days after her last dose of COAGADEX. The subject continued

to experience intermittent headaches and dizziness. A MRI scan of the brain done to evaluate the recurring symptoms was unremarkable.

Overall Clinical Assessment/Conclusions
COAGADEX demonstrated adequate efficacy with an acceptable safety profile in adult and adolescent (≥ 12 years of age) subjects with Factor X deficiency, and the clinical reviewer recommends approval for the following indications:

- On-demand treatment and control of bleeding episodes
- Perioperative management of bleeding in patients with mild hereditary Factor X deficiency.

Perioperative management of bleeding in major surgery in patients with moderate and severe hereditary Factor X deficiency has not been studied.

8. Advisory Committee Meeting

The *Division of Hematology Research and Review* and the *Division of Hematology Clinical Review* in the *Office of Blood Research and Review* reviewed the information in this application and determined that referral to the *Blood Products Advisory Committee* prior to product approval was not needed for the following reasons (FDAAA [HR 3580-138 SEC. 918: REFERRAL TO ADVISORY COMMITTEE]):

- The new molecular entity provision (NME) does not apply to COAGADEX as it does not represent a novel product class. There are several licensed prothrombin complex concentrates and Factor IX complex products which consist of human Factor X and other coagulation factors.

- The mechanism of action and function of Factor X in the blood coagulation cascade are well studied and understood. It involves proteolytic activation of Factor X by Factors VIIa and IXa; the resultant activated Factor X in turn activates prothrombin by proteolysis. When infused into a Factor X deficient patient, COAGADEX temporarily replaces the missing endogenous Factor X.

- COAGADEX is manufactured using only U.S. Source Plasma collected in FDA approved plasma facilities. All donations comply with the requirements of 21 CFR 640.60.

- The measures taken by BPL to control adventitious agents in the manufacture of COAGADEX are acceptable. The manufacturing process includes three steps specific for viral clearance: solvent/detergent treatment, nanofiltration through a (b) (4) filter, and terminal dry heat treatment.

- The design of the phase 3 clinical trials to evaluate the safety and efficacy of COAGADEX were adequate and the results of the trials did not raise any concerns.

- Review of information submitted in the BLA for COAGADEX did not raise any controversial issues or pose unanswered scientific questions which would have benefited from Advisory Committee discussion and recommendations.

9. Other Relevant Regulatory Issues

There were no other regulatory issues raised during the review of BLA STN 125555/0.

10. Labeling

The proposed proprietary name for the product, COAGADEX, was reviewed by the Advertising and Promotional Labeling Branch (APLB) and was recommended to be acceptable on August 7, 2014. The product labeling (i.e., prescribing information, patient package insert, and instructions for use) and the product package and container labels were reviewed, commented, and/or revised by the appropriate discipline reviewers before APLB conducted its review from a promotional and comprehension perspective.

FDA comments and recommendations regarding the product labeling and labels were initially conveyed to BPL on July 21, 2015, and negotiated throughout September and October 2015.

COAGADEX was found acceptable as the proprietary name for the product by the agency on August 12, 2014. Final versions of the product labeling and labels submitted to the BLA on October 16, 2015 were considered acceptable.

11. Recommendations and Risk/ Benefit Assessment

a) Recommended Regulatory Action

The review committee recommends the approval of the BLA for Coagulation Factor X (human), under the proprietary name of COAGADEX, for the following indications to treat adults and adolescents (aged 12 years and above) with hereditary Factor X deficiency for:

- On-demand treatment and control of bleeding episodes
- Perioperative management of bleeding in patients with mild hereditary Factor X deficiency.

Perioperative management of bleeding in major surgery in patients with moderate and severe hereditary Factor X deficiency has not been studied.

b) Risk/ Benefit Assessment

Hereditary Factor X deficiency is a rare type of bleeding disorder with an estimated prevalence of approximately 1 in 1 million people. Currently there is no approved pure Factor X treatment; Factor X-deficient patients are generally treated with FFP or PCC products, which

contain numerous other plasma proteins and are not labeled with the specific Factor X content. PCCs are associated with a risk of thrombotic adverse events. FFP requires large volumes because of the low Factor X content, which increases the risk of adverse transfusion reactions including circulatory overload and transfusion related acute lung injury (TRALI). The availability of a purified Factor X concentrate would increase treatment options by providing a more accurate dosing regimen and lesser exposure to other plasma proteins.

Risks

The safety concerns for this product are hypersensitivity reactions, thromboembolic events, and the development of Factor X inhibitors. The ability to clearly define these risks in this patient population and for this product is limited by the study size. However, of the 18 subjects treated with COAGADEX, no subjects were positive for Factor X inhibitors or had a reported thromboembolic event. Minor elevation of thrombogenicity markers was observed in some subjects, but no clinical signs or symptoms of thrombosis were observed in any subject. There were no reports of anaphylaxis. The potential for these risks is discussed in the Warnings and Precautions section of the Package Insert. No serious AEs were found to be attributable to COAGADEX.

Benefits

The clinical response to COAGADEX for on-demand treatment and control of bleeding was good or excellent for 98% of 187 bleeds in 15 subjects that were assessed by the DRC. Amongst the small number of surgical procedures included in the per-protocol analysis, COAGADEX was considered effective in controlling bleeding in three subjects with severe or moderate Factor X deficiency undergoing minor surgery; and in two subjects wild mild Factor X deficiency undergoing major surgery. Data from Ten01 and Ten03 demonstrate that the proposed dosing for the treatment of acute bleeding episodes is appropriate, as is the dosing for perioperative management of major surgical procedures in subjects with mild disease.

Overall Benefit/Risk Profile

The safety of COAGADEX was demonstrated in the 18 subjects who were enrolled in phase 3 trials Ten01 and Ten03. No SAE was considered related to COAGADEX. There were no reports of Factor X inhibitor development or reports of thrombosis in the Ten01 and Ten03 studies. No safety signals were identified. If approved, COAGADEX would be the first purified plasma-derived Factor X product approved in the U.S. Approval of this product would fulfill an unmet medical need.

c) Recommendation for Postmarketing Risk Management Activities

The safety data reviewed do not substantiate a need for a post-marketing requirement (PMR) or Risk Evaluation and Mitigation Strategy.

d) Recommendation for Postmarketing Activities

BPL agreed to conduct a post-marketing commitment (PMC) registry study to collect additional data in severe and moderate Factor X deficient patients undergoing major surgery. BPL committed to submit the final study report to the FDA in September 2022.

BPL agreed to a post-marketing CMC commitment to address (b) (4)

To (b) (4)
BPL has agreed to a post-marketing development of methods to (b) (4) BPL committed to submit the final study report to the FDA in October 2016.

Appendix I. Assessment Criteria for Efficacy in Treating a Bleed

Criteria for Assessment of Coagadex in Treating an Overt bleed

Category	Criterion
Excellent	Bleeding stopped within 12 hours, with 1 dose of FACTOR X
Good	Bleeding stopped within 24 hours, with or without a second dose of FACTOR X
Poor	Bleeding stopped after 24 hours, or >2 doses of FACTOR X were needed to stop bleeding, or there was no response to therapy.
Unassessable	Other replacement therapy given before response to FACTOR X (if given) could be assessed.

Criteria for Assessment of Coagadex in Treating a Menorrhagic Bleed

Category	Criterion
Excellent	1 or 2 doses of FACTOR X required within 48 hours
Good	2 doses of FACTOR X required over >48 hours
Poor	>2 doses of FACTOR X required; or Bleeding could not be maintained at a manageable level.
Unassessable	Other replacement therapy given before response to FACTOR X (if given) could be assessed.

Criteria for Assessment of Coagadex in Treating a Covert Bleed

Category	Criterion
Excellent	1 or 2 doses of FACTOR X required within 48 hours.
Good	3 doses of FACTOR X required within 48 hours.
Poor	>3 doses of FACTOR X required within any timeframe; or No response to therapy.
Unassessable	Other replacement therapy was given before response to FACTOR X (if given) could be assessed.