



FOOD AND DRUG ADMINISTRATION
CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

MEMORANDUM

To: File (STN BL 125506/0) & Pratibha Rana

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Through: Tim Lee, PhD, Acting Chief, LH/DHRR/OBRR
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Subject: Final review addendum to CMC review of BPL’s resubmission to BLA for Coagulation Factor X (Human)

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1. Executive Summary

On 10 July 2013, Bio Products Laboratory, Limited (BPL) submitted an original biologics license application (BLA) for Coagulation Factor X (Human) with the proprietary name COAGADEX. 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 U.S. FDA granted this product Orphan Drug Status (No. 07-2469) on 8 November 2007, Fast Track Designation on 12 April 2012, and Priority Review for this BLA on 6 September 2013.

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 nominally 250 International Units

(IU) and 500 IU of Factor X per vial. Both the nominal potency range and actual Factor X potency are provided on the vial and carton labels. 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 incubation), are used in the manufacture of other BPL products.

During the first review cycle, the Chemistry, Manufacturing and Controls (CMC) team identified multiple deficiencies in the validation studies of the manufacturing process including those for cleaning and analytical methods. These deficiencies were also confirmed at the pre-license inspection (PLI) of the BPL facility conducted on 21-25 October of 2013, which were conveyed to BPL as observations in Form FDA 483. As a result, FDA also issued a complete response (CR) letter on 10 March 2014 delineating these deficiencies and the information required to address them.

On 27 April 2015, FDA received BPL's resubmission to BLA STN BL 125506/0. The resubmission contains additional CMC information as a response to the CR letter. In accordance with SOPP 8405.1 *Procedures for Resubmissions of an Application or Supplement*, BPL's resubmission was classified as a complete, class 2 response to the CR letter, with a PDUFA goal date of 27 October 2015.

Review of new CMC information in BPL's response to the CR letter and further communications with the FDA demonstrates that all CMC issues were successfully addressed. In particular, all deficiencies in the validation of analytical methods were resolved. In the additional process validation studies, all pre-defined process qualification criteria including lot release specification criteria were met for the 3 consecutive BDS and FDP batches demonstrating that the manufacturing process is in a state of control.

Conclusion and Recommendation

I conclude that BPL has satisfactorily addressed all the major issues raised in the 10 March 2014 CR letter, and recommend approval of the original BLA for COAGADEX.

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, e.g., of the two patients with identical Factor X level, one patient may experience severe bleeding tendency and the other moderate bleeding tendency. Nevertheless, similar to other factor deficiencies, more severe bleeding is typically observed in individuals with lower Factor X activity, e.g., below 5 % of the normal level.

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.

3. Review of updated Chemistry, Manufacturing and Controls information

a) Product Quality

Manufacturer:

COAGADEX is manufactured by BPL from Source Plasma of U.S. origin at the FDA-licensed multi-product manufacturing facility in Elstree, United Kingdom. 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.

Manufacturing Process

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 three previously established steps which yield a Factor X-enriched intermediate (see Figure 1). The previously established steps include (b) (4)

virus inactivation by incubation with solvent (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) storage of BDS, formulation, sterilizing filtration, and heat-treatment of freeze-dried COAGADEX in the final closed container to inactivate viruses.

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.

(b) (4)

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) (b) (4) (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 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))

COAGADEX Potency

The chromogenic substrate-based Factor X activity assay is used to determine the potency of COAGADEX. The method follows the (b) (4) method for the assay of human coagulation Factor X. The potency standard is calibrated in Factor X International Units against the 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) (4)	
Thrombin	(b) (4)	
(b) (4)	(b) (4)	

	(b) (4)	

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 BDS and FDP release specifications. To control these parameters, suitable analytical methods were established. The specifications for BDS and COAGADEX FDP are shown in Tables 2 and 3, respectively.

Table 2: COAGADEX Bulk Drug Substance Specifications

(b)	(4)
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Abbreviations: NGT, Not Greater Than; NLT, Not Less Than; LT, Less Than

^a Action level. The purpose of the (b) (4) test is to monitor and demonstrate control of (b) (4).

Table 3: 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)	(b) (4)
Appearance of solution	Colorless, clear or slightly opalescent solution.
(b) (4)	(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)	(b) (4)
Total Protein, g/L	(b) (4)
Specific activity, IU/mg protein	(b) (4)
NAPTT (b) (4)	(b) (4)
NAPTT (b) (4)	(b) (4)
FCT (b) (4)	(b) (4)
Excipients	
Chloride, (b) (4)	(b) (4)
Phosphate, (b) (4)	(b) (4)
Citrate (b) (4)	(b) (4)
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)	(b) (4)
(b) (4)	(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. Assay validation reports have been reviewed by CBER's Lot Release Branch and Dr. Andrey Sarafanov.

Batch analyses

Batch analyses were reviewed by Dr. Yideng Liang. I support her conclusion that the available batch data demonstrate that the BDS and FDP manufacturing process is robust.

Evaluation of Safety Regarding Adventitious Agents

Adventitious agents safety evaluation has been reviewed by Dr. Ze Peng. He found that the data provided by BPL are acceptable. 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 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. In-process controls are performed on the manufacturing pools and mini-pools. For example, each pool is non-reactive for HAV, HBV, HCV, and HIV-1. 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 °C for 72 hours), and (b) (4) nanofiltration. BPL has evaluated these three steps in down-scale studies using model viruses that 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.

Stability

Stability studies have been reviewed by Dr. Yideng Liang. 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, passing the BPL specifications. 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 Dr. Randa Melhem from CBER's Division of Manufacturing and Product Quality, and found to be acceptable. CBER conducted a pre-license inspection (PLI) of BPL in Elstree, UK on 21-25 October 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)

A CR letter was sent to BPL on 10 March 2014 with outstanding inspectional issues as the first item of the letter. Corrective actions were provided in the response to the CR letter and found to be acceptable, including one post-marketing commitment to address (b) (4). All inspectional issues are considered to be satisfactorily resolved.

4. Significant issues resolved during the BLA review

The CR letter, which was sent to BPL on 10 March 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 on 21-25 October 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

All these issues were addressed in BPL's response to the CR letter on 27 April 2015 and through further communications with the FDA.

Detailed review of BPL's responses is provided below.

4.1. Review of BPL's response to the CR letter

FDA Question 1: Outstanding issues identified at the Pre-License Inspection performed on 12-25 October 2013 at the BPL facilities in Elstree, UK, and described in Form FDA 483 issued on 25 October 2013 have yet to be resolved. Please submit documentation that demonstrates all outstanding inspectional issues identified during the Pre-License Inspection have been corrected.

Response summary:

BPL has provided responses to observations described in Form FDA 483 issued on 25 October 2013. Responses to CMC-related observations are listed below.

- **Form 483 Observation 1**

Written procedures for production and process controls did not assure that products have the strength, quality and purity they purport to possess. For example, 6 out of (b) (4) batches of Coagulation Factor X (Human) [FX] manufactured after the process validation batches either failed to meet the final drug product release specification or were aborted due to deviation.

Response summary:

BPL have manufactured (b) (4) new conformance batches, representing a 250 IU batch at the minimum intended batch size, (b) (4) complete 250 IU batch, and (b) (4) complete batch finished in the larger dose (500 IU). These conformance batches incorporated the revised BDS and FDP specifications and upstream process controls.

Additional information was provided on 20 July 2015 in BPL's response to the following Information Request (IR): *Please provide a summary of the results from in-process control and product release testing for the (b) (4) process performance qualification batches of Coagulation Factor X drug product, Batch #s (b) (4).*

The process validation protocols and reports were reviewed by me and Dr. Ze Peng. We conclude that the three conformance lots were manufactured without deviations and the acceptable state of process validation has been demonstrated.

- **Form 483 Observation 2**

Written procedures are not established for the reprocessing of batches of products, in that the conditions under which reprocessing, e.g. (b) (4), is allowed are not defined.

Response summary:

BPL has addressed this observation by establishing written procedures for the reprocessing of Factor X batches and providing additional validation data to support (b) (4) (b) (4)

- **Form 483 Observation 3**

The Non-Activated Partial Thromboplastin Time test (SOP No. QCA/00008) used for the release of FX final drug product has not been validated.

Response summary:

BPL has revalidated the NaPTT test.

FDA Question Q: The data you provided have not demonstrated that the following analytical methods used for the evaluation of potency and safety indicating parameters in the Final Drug Product (FOP) are adequately validated.

Response summary: Revised assay validation reports have been reviewed by Dr. Lokesh Bhattacharyya from CBER's Lot Release Branch at the Laboratory of Analytical Chemistry and Blood Related Products of the Division of Biological Standards and Quality Control. Dr. Bhattacharyya concluded that method validation deficiencies were successfully resolved.

FDA Question 3: Please establish specifications for all source materials per the (b) (4)

Response summary:

The release criteria were established as requested by the FDA. All source materials were specified to comply with (b) (4) where relevant (b) (4) are available.

FDA Question 4a: Please provide additional data to validate the following proposed manufacturing options:

a. With reference to FACTOR X Manufacturing Batch Formula (Table 3.2.P.3.2-TI), please provide data to validate the option of (b) (4) FACTOR X (b) (4)

Response summary:

BPL will not exercise the option to (b) (4) at this time. The relevant statements have been deleted from the BLA drug product sections for batch formula and manufacturing process.

FDA Question Q4b Please provide additional data to validate the following proposed manufacturing options:

b. Regarding the validation of the (b) (4) (3.2.P.3.5.13 Validation of (b) (4)), please provide data to demonstrate the (b) (4)

Response summary:

Additional data have been provided to demonstrate (b) (4)

. New

data demonstrated that process performance and product characteristics are comparable between (b) (4).

FDA Question 4c Please provide additional data to validate the following proposed manufacturing options:

c. With reference to Section 3.2.P.3.3.1.2.8. Step (b) (4) Aseptic filling and lyophilization, please provide justifications for the following statement "Excursions from these expected conditions would not result in batch failure, subject to compliance of the batch with final product specification after appropriate risk- and impact-assessment.

Response summary:

BPL explained that the batch would not be released if:

- (b) (4)

FDA Question 5: Please provide the protocol and qualification reports for the establishment of Factor X potency reference standards used for the release of FACTOR X.

Response summary:

Qualification report for the establishment of Factor X potency reference standard was provided. This standard is identified as the (b) (4).

FDA Question 6: Please address the following deficiencies regarding (b) (4) and plasma pools: a. During the Pre-Licensure Inspection, you indicated that (b) (4) will not be used for FACTOR X manufacture. Please remove references to the use of (b) (4) from the BLA. b. Please remove references to manufacturing steps and conditions that are not relevant to the manufacture of FACTOR X. (b) (4)

Please transfer the information currently presented in Section 3.2. Drug Substance to Section 3.2.S.2.3 Control of Materials. d. Regarding Plasma Container Closure System, you indicated that "Alternative containers when evaluated and approved will be accepted." Please change this statement to "Alternative containers when evaluated and approved will be accepted and reported to the FDA." e. Please list all the facilities where plasma donations and plasma pools are tested in Section 3.2.S.2.1 Manufacturers.

Response summary:

BPL have agreed with the FDA and made requested changes. The responses are acceptable.

FDA Question 7a: Please address the following deficiencies regarding specifications:

a. (b) (4) Factor X (b) (4) intermediate prepared at the conclusion of Step (b) (4) (as indicated in the Manufacturing Process Chart) qualifies as the Bulk Drug Substance (BDS). Therefore,

i. Please list all manufacturing steps leading to this intermediate in Section 3.2. Drug Substance.

ii. Please develop BDS specifications, which can be comprised of existing parameters and acceptance limits for the intermediates (b) (4)

iii. Please provide Batch Analyses for the BDS.

Response summary:

BPL has agreed with the FDA and made the requested changes. The responses are acceptable.

FDA Question 7b: Please label FDP vials with the actual (not nominal) Factor X potency, and make the following changes to the FDP specification for "Factor X activity per vial":

i. (b) (4) of nominal potency at release.

ii. (b) (4) of labeled potency during the shelf-life of the product.

Response summary:

BPL confirmed that FDP vials are labelled with the actual Factor X potency measured for each batch, expressed as IU per vial.

With regard to the FDP specification, BPL proposed to use the existing (b) (4) limits (80-(b) (4) of nominal potency at release).

With regard to the shelf-life specification, BPL explained that the stability study acceptance criteria of 80-(b) (4) IU/mL for the duration of shelf-life is no less restrictive than 80(b) (4) of the labelled potency because the nominal potency of the FDP is 100 IU/mL. In addition, BPL re-evaluated all stability data to demonstrate full compliance with the 80(b) (4) specification limit.

FDA Question 7c: With reference to the deviation report 62654 related to the rejection of batch (b) (4) due to low potency caused by (b) (4), the associated change in (b) (4) was clearly demonstrated by the Factor X (b) (4). Therefore, please establish Factor X (b) (4) as an additional identity and purity test for FDP. Please establish the specification as "comparable to a reference standard which is derived from FACTOR X".

Response summary:

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 an (b) (4)

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. This response is acceptable.

FDA Question Q7d: Regarding the studies of the clotting and chromogenic assays for Factor X potency,

- i. For all pharmacokinetics (PK) and in vitro spiking studies, please evaluate the ratios of chromogenic to clotting potencies using statistical methods described in Bland JM and Altman DG, Statistical methods for assessing agreement between two methods of clinical measurement. Lancet 1986; 1:307-310.**
- ii. For the in vitro spiking study presented in Table 3.2.P.2.2.3-T1 6, please explain the following: 1. The test values from the parallel line clotting assay are noticeably smaller than those from the calibration curve-based clotting assay. 2. Factor X potency values at release (labeled potency) derived from the clotting assays are noticeably less than those derived from the chromogenic assay.**
- iii. For the PK studies presented in Section 5.3.3 Reports of Human PK Studies, please explain why the chromogenic assay gives slightly higher Factor X potency values than the clotting assay, and comment on the potential implications for the safe and effective use of FACTOR X in clinical practice where the clotting assay is used predominantly in clinical laboratories.**

Response summary:

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. I conclude that BPL's response is acceptable.

4.2. Review of BPL's responses regarding potency labeling and purity assays

BPL's 14 September 2015 response to FDA Question 1: With reference to your statement in Section 11 Description of the Full Prescribing Information "Each vial of COAGADEX is labeled with the factor X potency in International Units (IU).", please

- 1. Revise the statement to read "Each vial of COAGADEX is labeled with the actual factor X potency in International Units (IU)."**
- 2. Add the word "Range" to the potency identifiers on the carton and container labels, e.g., 250 IU Range, etc., and**
- 3. Add the actual factor X potency on the COAGADEX carton label.**

Response summary:

BPL agreed with the FDA and made the requested changes. The responses are acceptable.

FDA Question 2: Regarding the Final Drug Product (FDP) release specifications,

- 1. Please provide the justification for the limit of "(b) (4) [redacted]" for the parameter "Stability at (b) (4) [redacted]" and submit the Standard Operating Procedure for this test.**

2. In section 3.2.P.5.2 Analytical Procedures, you indicated that batches must show no significant defects during the (b) (4) of stability observations. Please explain the (b) (4) requirement and the criteria for “significant defects”.

Response summary:

BPL provided the requested information. With regard to Stability assay, BPL explained that a visual inspection method is used to detect abnormalities in the 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.

FDA Question 2 (continued). 3. Please explain the out-of-specification (OOS) results in the test for Factor IX Impurity for batches (b) (4). Please confirm that these batches were rejected.

Response summary:

BPL explained that the data presented in the revised BLA response represents retrospective reporting of the batches against the new, more stringent specification that was generated in response to the FDA request for a separate BDS section with associated specification. All (b) (4) batches had been rejected at the Bulk Drug Substance stage.

FDA Question 3A: Regarding the identity and purity tests, Please demonstrate the ability of the existing and proposed Factor X (b) (4) assays to monitor the (b) (4) impurity in the COAGADEX product.

Response summary:

BPL provided the requested information using non-routine characterization of FACTOR X process performance qualification batches and comparison to other batches of FACTOR X final drug product. (b) (4) can be used to detect (b) (4) but these methods are not quantitative. The response is acceptable.

FDA Question 3B: Regarding the identity and purity tests, We agree with BPL’s proposal to continue to retain (b) (4) as investigative tools for use in the event of a quality failure. However, please establish an identity and purity reference standard, which is derived from COAGADEX, to be included in this analysis.

Response summary:

BPL committed to developing a reference material comprising appropriate FACTOR X final product, which will be included when these characterization tests are performed.

4.3. Review of BPL’s responses regarding immunogenicity program

One of the main safety concerns for COAGADEX is anti-drug antibody development. Neutralizing antibodies against human Factor X (anti-human Factor X inhibitors) were measured in a central laboratory using a screening assay and a quantitative 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 and not associated with FX inhibitor development in any subject. Lack of inhibitor development was also evident from the observation that pharmacokinetics (PK) parameters did not show change over time after repeated dosage. However, BPL has not provided inhibitor assay qualification data and have not evaluated binding antibodies. These deficiencies have been resolved as described below.

BPL's 27 September 2015 Response to FDA Question 6: Regarding the evaluation of COAGADEX immunogenicity, 1. Please submit results of method qualification for Factor X inhibitor screen and quantitative Nijmegen-Bethesda assays and describe the measures employed to maintain the acceptable performance of these assays in the COAGADEX clinical trials

Response summary:

All assays were performed in the central laboratory at the Haematology Department of (b) (4). The inhibitor screen and Nijmegen-Bethesda inhibitor assay methods were based on the existing method used for the detection of inhibitory antibodies in patients with Factor VIII and Factor IX deficiencies. Qualification of the screening test and Nijmegen-Bethesda assay was performed by the clinical trial central testing laboratory, to demonstrate the capability of each to detect Factor X inhibitors. Qualification was based on a commercially-available Factor X immuno-depleted plasma spiked with a polyclonal inhibitory antibody which had been deliberately raised against human Factor X.

Approach to qualification of the screening test

The screening test measures prolongation of the plasma clotting time beyond normal ranges, as an indicator that an inhibitor is present. The measurement of clotting time is based on the Prothrombin Time (PT) method or the Activated Partial Thromboplastin Time (APTT) method, which are routinely performed in clinical laboratories and are sensitive to Factor X deficiency. Both methods were qualified using commercial reagents supplied for use with an automated coagulometer. (b) (4)

Approach to qualification of the Bethesda assay

The Nijmegen modification of the Bethesda assay followed the standard procedure. This was adapted from the routine methods used for the quantitation of Factor VIII and Factor IX inhibitors in patient plasma. The test calculates the amount (titer) of inhibitor in the patient test plasma which reduces the Factor X activity in normal plasma by 50% (= one Bethesda Unit [BU]), using a clotting-based Factor X assay. The assay was qualified by measuring the inhibitor in the Factor X antibody-spiked Factor X immune-depleted plasma (which was also used for the screening qualification) (b) (4)

(b) (4) to demonstrate that the Bethesda assay was measuring the correct amount of inhibitor.

Qualification results

To select appropriate methods suitable for interpretation of the results of screening test, several methods were studied which are typical for assessing the formation of inhibitory antibodies in response to hemophilia treatments, the formation of other autoantibodies (e.g., lupus anticoagulant) or the elevation of other anticoagulant proteins in clinical laboratories. The “correction back to within 50% of the normal plasma value”, a method commonly used for the assessment of clotting factor inhibitors during hemophilia treatment, was found to be acceptable.

Both the PT- and APTT-based screening methods were able to detect (b) (4) plasma samples. The Bethesda assay (Nijmegen modification) returned a value of (b) (4) against a manufacturer’s label value of (b) (4), which is acceptable. The use of an (b) (4) Bethesda assay showed no benefit.

Reviewer conclusions: Note that qualification of inhibitor methods was difficult due to the rarity of Factor X deficiency and the absence of clinical Factor X inhibitors which would normally be used as controls and reference materials. A (b) (4) level is typically recognized as the lower detection limit of the Bethesda assay, therefore the results of qualification are acceptable.

Measures to maintain acceptable performance of the screening test and the Bethesda assay in the COAGADEX clinical trial

Ongoing assessment of the screening assays was limited by the absence of commercially available positive reference plasma. Factor X inhibitor screen and quantitative Nijmegen-Bethesda assays were performed by a central clinical laboratory that is registered for and participates in the National External Quality Assessment Service (NEQAS), a recognized external quality assurance program for the PT in the UK. PT performance was monitored (b) (4) by the laboratory using a (b) (4) (b) (4) internal quality control (IQC). This is similar to the monitoring of Factor VIII inhibitors (except that Factor VIII assays are performed by the APTT method) and is recognized as sufficient for monitoring purposes.

Reviewer conclusions: Assays were conducted by an expert central laboratory. Ongoing assessment of the assay was maintained through routine monitoring of the IQC sample for the PT assay platform. The quantitative Nijmegen-Bethesda assay (both immediate acting and time dependent) were qualified using inhibitory antibodies and same basic principles as used for Factor VIII and Factor IX inhibitor detection assays. The approach is acceptable for the intended purpose.

Evaluation of binding antibodies

Binding antibodies are rarely evaluated in clinical studies of plasma-derived products (unlike recombinant products). However, to address any potential risks associated with this orphan product, clinical reviewers suggested that further evaluation of binding antibodies may provide additional assurance of product safety. Therefore, (b) (4)

BPL's 15 September 2015 Response to FDA Question 6: Regarding the evaluation of COAGADEX immunogenicity, please comment on the potential of the development of (b) (4) [redacted]. Please assay the (b) (4) [redacted] using appropriate assays as a Post-Marketing Commitment..

Response summary:

(b) (4)

BPL's 6 October 2015 Response to FDA Question 1: Please provide a schedule of milestones for the post marketing commitment study to evaluate (b) (4) [redacted] and include target dates for (a) study completion and (b) submission of the final study report.

Response summary:

BPL has provided detailed schedule summarized in Table 5 below.

Table 5. Milestone schedule to evaluate (b) (4) [redacted]

Milestone	Milestone Date
Develop test methods and qualify the assay.	June 2016
Test (b) (4) [redacted].	August 2016
Study completion	September 2016
Submit final study report to FDA	October 2016

Reviewer conclusions: BPL's post-licensure commitment and timeline are acceptable.

5. Conclusions and Recommendation

All issues related to the deficiencies in the validation of the analytical methods 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 that the manufacturing process is in a state of control.

The CMC data support the quality and safety of COAGADEX for the treatment of Factor X deficient patients.

From a CMC perspective, this BLA can be approved.