DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

October 20, 2015

Our STN: BL 125506/0 **BLA APPROVAL**

Bio Products Laboratory
Attention: Mary Ann Lamb, PhD
Bio Products Laboratory USA, Inc.
302 East Pettigrew Street, Suite C-190
Durham, NC 27701

Dear Dr. Lamb:

We have approved your biologics license application for Coagulation Factor X (Human) effective this date. You are hereby authorized to introduce or deliver for introduction into interstate commerce Coagulation Factor X (Human) under your existing Department of Health and Human Services U.S. License No. 1811. Coagulation Factor X (Human) is indicated for the treatment of 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.

Under this license, you are approved to manufacture Coagulation Factor X (Human) at your facility in Elstree, Hertfordshire, United Kingdom. The final drug product will be manufactured, filled, and lyophilized at your facility in Elstree, Hertfordshire, United Kingdom. The Sterile Water for Injection will be manufactured at your facility in Elstree, Hertfordshire, United Kingdom. You may label your product with the proprietary name COAGADEX and will market it in single-use vials containing nominal potencies of 250 International Units (IU) and 500 IU of Factor X per vial.

We did not refer your application to the Blood Products Advisory Committee because our review of information submitted in your BLA, including the clinical study design and trial results, did not raise concerns or controversial issues which would have benefited from an advisory committee discussion.

The dating period for Coagulation Factor X (Human) shall be 36 months from the date of manufacture when stored at +2 °C to +30 °C. The date of manufacture shall be defined as the date of final sterile filtration of the formulated drug product. Following the final sterile filtration, no reprocessing/reworking is allowed without prior approval from the Agency. The dating period for your drug substance shall be [redacted] when stored at temperatures [redacted]

Please submit final container samples of the product in final containers together with protocols showing results of all applicable tests. You may not distribute any lots of product until you receive a notification of release from the Director, Center for Biologics Evaluation and Research (CBER).

You must submit information to your biologics license application for our review and written approval under 21 CFR 601.12 for any changes in, including but not limited to, the manufacturing, testing, packaging, or labeling of COAGADEX, or in the manufacturing facilities.

You must submit reports of biological product deviations under 21 CFR 600.14. You should identify and investigate all manufacturing deviations promptly, including those associated with processing, testing, packing, labeling, storage, holding, and distribution. If the deviation involves a distributed product, may affect the safety, purity, or potency of the product, and meets the other criteria in the regulation, you must submit a report on Form FDA-3486 to the Director, Office of Compliance and Biologics Quality, at the following address:

Food and Drug Administration
Center for Biologics Evaluation and Research
Document Control Center
10903 New Hampshire Ave
WO71-G112
Silver Spring, MD 20993-0002

Please provide your final content of labeling in Structured Product Labeling (SPL) format and include the carton and container labels. In addition, please submit three original paper copies for carton and container final printed labeling. All final labeling should be submitted as Product Correspondence to this BLA at the time of use (prior to marketing) and include implementation information on FDA Form 356h.

In addition, please submit the final content of labeling (21 CFR 601.14) in SPL format via the FDA automated drug registration and listing system, (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Information on submitting SPL files using eLIST may be found in the guidance for industry titled, "*SPL Standard for Content of Labeling Technical Qs and As* at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

You may submit two draft copies of the proposed introductory advertising and promotional labeling with an FDA Form 2253 to the Advertising and Promotional Labeling Branch at the following address:

Food and Drug Administration
Center for Biologics Evaluation and Research
Document Control Center
10903 New Hampshire Ave
WO71-G112
Silver Spring, MD 20993-0002

You must submit copies of your final advertisement and promotional labeling at the time of initial dissemination or publication, accompanied by Form FDA 2253 (21 CFR 601.12(f)(4)).

All promotional claims must be consistent with and not contrary to approved labeling. You should not make a comparative promotional claim or claim of superiority over other products unless you have substantial evidence or substantial clinical experience to support such claims (21 CFR 202.1(e)(6)).

ADVERSE EVENT REPORTING

You must submit adverse experience reports in accordance with the adverse experience reporting requirements for licensed biological products (21 CFR 600.80) and you must submit distribution reports as described in 21 CFR 600.81. You should submit postmarketing adverse experience reports and distribution reports to the Office of Biostatistics and Epidemiology, at the following address:

Food and Drug Administration
Center for Biologics Evaluation and Research
Document Control Center
10903 New Hampshire Ave
WO71-G112
Silver Spring, MD 20993-0002

Prominently identify all adverse experience reports as described in 21 CFR 600.80.

In addition, you must submit adverse event reports for any infectious disease transmission within 15 days after learning of the event. Infectious disease transmission refers to an adverse event that involves suspected or confirmed transmission of an infectious agent, whether the recipient develops the infectious disease or only has serologic or other evidence. If an infectious disease transmission event is serious and unexpected, you must submit a 15-day "alert report," as required under 21 CFR 600.80 (c)(1)(i). Infectious disease transmission events that do not meet criteria for expedited submission require periodic reports and must be submitted as individual case reports within 15 days, as authorized under 21 CFR 600.80(c)(2)(i). You should submit reports for all other non-expedited adverse events under the periodic reporting requirements specified in 21 CFR 600.80(c)(2).

PEDIATRIC REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because the biological product for this indication has an orphan drug designation, you are exempt from this requirement.

AGREED UPON POSTMARKETING COMMITMENTS

Postmarketing Studies subject to reporting requirements of 21 CFR 601.70.

We acknowledge your written commitments as described in your letter of October 15, 2015 as outlined below:

1. BPL commits to evaluate the safety and efficacy of COAGADEX for perioperative management in patients with moderate to severe hereditary Factor X deficiency undergoing major surgical procedures in Study TEN06, *A post-marketing registry study of perioperative management of moderate to severe hereditary factor X deficient patients receiving Coagadex (human factor X concentrate) for major surgical procedures*.

   Final protocol submission date: April 30, 2016
   Trial completion date: December 31, 2021
   Final Report Submission date: September 30, 2022

Please submit clinical protocols to your IND 14235, and a cross-reference letter to this BLA, STN BL 125506 explaining that this protocol was submitted to the IND. If the information in the final study report supports a change in the labeling, the final study report must be submitted as a supplement. Supplements in support of labeling changes based on a postmarketing study report may be subject to a user fee. Please use the following designators to prominently label all submissions, including supplements, relating to these postmarketing study commitments as appropriate:

- **Postmarketing Study Commitment – Protocol**
- **Postmarketing Study Commitment – Correspondence**
- **Postmarketing Study Commitment – Final Study Report**
- **Supplement contains Postmarketing Study Commitments – Final Study Report**

For each postmarketing study subject to the reporting requirements of 21 CFR 601.70, you must describe the status in an annual report on postmarketing studies for this product. Label your annual report as an **Annual Status Report of Postmarketing Study Requirements/ Commitments** and submit it to the FDA each year within 60 calendar days of the anniversary date of this letter until all Requirements and Commitments subject to the reporting requirements of section 506B of the FDCA are fulfilled or released. The status report for each study should include:

- the sequential number for each study as shown in this letter;
- information to identify and describe the postmarketing commitment;
- the original schedule for the commitment;
- the status of the commitment (i.e., pending, ongoing, delayed, terminated, or submitted); and
- an explanation of the status including, for clinical studies, the patient accrual rate (i.e., number enrolled to date and the total planned enrollment).

As described in 21 CFR 601.70(e), we may publicly disclose information regarding these postmarketing studies on our Web site (http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Post-marketingPhaseIVCommitments/default.htm).

Postmarketing Studies not subject to reporting requirements of 21 CFR 601.70.

We acknowledge your written commitments as described in your letters of August 11, September 9, October 1, and October 16, 2015 as outlined below:

2. BPL will develop and qualify test methods to (b) (4) BPL will submit the final study report to the FDA by October 31, 2016 under Postmarketing Study Commitment – Final Study Report.

   Final Report Submission: October 31, 2016

3. BPL commits to implement Results of the validation studies of the will be submitted to CBER as a Changes Being Effected (CBE) supplement in Q3 of 2016.

   Final Report Submission: September 30, 2016

We request that you submit information concerning nonclinical and chemistry, manufacturing, and control postmarketing commitments and final reports to your BLA, STN BL 125506. Please refer to the sequential number for each commitment and the submission number as shown in this letter.

Please use the following designators to label prominently all submissions, including supplements, relating to these postmarketing study commitments as appropriate:

- **Postmarketing Study Commitment – Correspondence**
- **Postmarketing Study Commitment – Final Study Report**
- **Supplement contains Postmarketing Study Commitment – Final Study Report**

For each postmarketing commitment not subject to the reporting requirements of 21 CFR 601.70, you may report the status to FDA as a **Postmarketing Study Commitment – Status Update**. The status report for each commitment should include:

- the sequential number for each study as shown in this letter;
- the submission number associated with this letter;
- describe what has been accomplished to fulfill the non-section 506B PMC; and,
- summarize any data collected or issues with fulfilling the non-section 506B PMC.

When you have fulfilled your commitment, submit your final report as **Postmarketing Study Commitments – Final Study Report** or **Supplement contains Postmarketing Study Commitment – Final Study Report**.

Sincerely yours,

Jay S. Epstein, MD
Director
Office of Blood Research and Review
Center for Biologics Evaluation and Research