DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

Our STN: BL 125426/0 **BLA APPROVAL**

Cangene Corporation
Attention: Mr. Steve McGregor
155 Innovation Drive
Winnipeg, Manitoba R3T 5Y3
Canada

Dear Mr. McGregor:

This letter supersedes the April 29, 2015 letter which incorrectly stated that labeling and packaging will be performed at the [redacted] facility.

We have approved your biologics license application for Coagulation Factor IX (Recombinant) effective this date. You are hereby authorized to introduce or deliver for introduction into interstate commerce, Coagulation Factor IX (Recombinant) under your existing Department of Health and Human Services U.S. License No. 1201. Coagulation Factor IX (Recombinant) is indicated for control and prevention of bleeding episodes, and for peri-operative management, in adults and children ≥ 12 years of age with hemophilia B.

The review of this product was associated with the following National Clinical Trial (NCT) numbers: NCT00768287, NCT01271868.

Under this license, you are approved to manufacture Coagulation Factor IX (Recombinant) drug substance at your contract manufacturer, [redacted]. The final formulated drug product will be manufactured, filled, and lyophilized at your contract manufacturer, (b)(4) [redacted]. The diluent will be manufactured at your contract manufacturer, [redacted]. Drug product labeling and packaging will be performed at Cangene BioPharma in Baltimore, Maryland, USA. Alternate drug product and diluent (Sterile Water for Injection) labeling, secondary packaging and storage will be performed at (b)(4) [redacted]. You may label your product with the proprietary name IXINITY and market it in nominal dosage strengths of 500, 1000 and 1500 IU per vial.

We did not refer your application to the Food and Drug Administration Blood Products Advisory Committee because our review of the information submitted in your biologics license application, 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 IX (Recombinant) shall be 24 months from the date of manufacture when stored at 25 °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 (b)(4). We have approved the (b)(4) in your license application fo (b)(4)

You are currently not required to submit samples of future lots of Coagulation Factor IX (Recombinant) to the Center for Biologics Evaluation and Research (CBER) for release by the Director, CBER, under 21 CFR 610.2. We will continue to monitor compliance with 21 CFR 610.1 requiring completion of tests for conformity with standards applicable to each product prior to release of each lot.

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 Coagulation Factor IX (Recombinant), 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, packaging, 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

Under 21 CFR 201.57(c)(18), patient labeling must be reprinted at the end of the package insert. We request that the text of information distributed to patients be printed in a minimum of 10-point font.

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.

We are deferring submission of your pediatric study for ages 0 to 12 years for this application because the product is ready for approval for use in adults and the pediatric study has not been completed.

Your deferred pediatric study required under 505B(a) of the Federal Food, Drug, and Cosmetic Act is a required postmarketing study. The status of this postmarketing study must be reported according to 21 CFR 601.70 and section 505B(a)(3)(B) of the Federal Food, Drug, and Cosmetic Act. This required study is listed below:

1. Deferred pediatric study IB1001-02 under PREA for the treatment of hemophilia B in pediatric patients ages 0 to 12. As appropriate, pediatric data from ongoing study IB1001-01 should be included in the submission.

   Final Protocol Submission: By July 31, 2015, you will submit a protocol revision that reopens pediatric study IB1001-02 to enrollment, in order to fulfill the commitment in your pediatric deferral request dated June 17, 2014.

   Study Completion Date: September 30, 2017

   Final Report Submission: December 31, 2017

Submit final study reports to this biologics license application. For administrative purposes, all submissions related to this required pediatric postmarketing study must be clearly designated **"Required Pediatric Assessment(s)."**

Sincerely,

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

Enclosure