DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

Our STN: BL 125426/0 **BLA COMPLETE RESPONSE**

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

Dear Mr. McGregor:

This letter is in regard to your biologics license application (BLA) for Coagulation Factor IX (Recombinant) manufactured at the (b) (4) location, submitted under section 351 of the Public Health Service Act (42 U.S.C. 262).

We have completed our review of all the submissions you have made relating to this BLA. After our complete review, we have concluded that we cannot grant final approval because of the deficiencies outlined below.

CMC:

1. With regard t (b) (4) from August 2013 to May 2014, in the manufacture of recombinant Coagulation Factor IX (rFIX or F90) FDA has following comments:

   (b) (4)

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

c. Please provide the reports on complete characterization of three consecutive lots of rFIX (b) (4) Drug Product (DP) manufactured since June 2014.

d. Please submit the data from the comparison of manufacturing-scale and bench-scale (b) (4) campaigns using the last three (b) (4) lots that were tested in your facility. The data should include, but not be limited to, (b) (4)

2. In your response to item #1d in the CR Letter, dated January 28, 2014 and Information Request (IR) dated June 6, 2014 (STN 125426/0031), you submitted results of (b) (4) on three former process lots (b) (4) and three modified process lots (b) (4) after the implementation of several improvements to the (b) (4) method, such as (b) (4)

(b) (4)

b. Additionally, please perform (b) (4) analysis on the same samples using a different laboratory. Please ensure that the samples are handled properly before testing.

3. In your response to CR item #4, you proposed new limits for (b) (4) However, you have not completed the validation of the (b) (4)
Please submit the validation data.

4. Regarding process-related impurities, please provide the following:

a. Results validating the removal of (b) (4), Chinese Hamster Ovary Host Cell Protein (CHO HCP), (b) (4).

b. Acceptance limits to the DP specifications for (b) (4) because you stated in your response to CR item # 12c, dated 28 January, 2014, that there (b) (4) is not tested for (b) (4) and there are no DP specifications in place for (b) (4) (section 3.2.P.5.1).

5. In your response to CR items #12 and #14, you described changes in data processing procedures, and reported that the potency test analyzer for (b) (4) was changed. Please clarify if the change also applies to DP. In addition, please provide data to compare the potency values determined using the (b) (4)

6. In Tables 67 and 78 in your response to CR items #12b and #14b, dated January 28, 2014, you provided the acceptance criteria and limits for the in-process control parameters for (b) (4) DP manufacture. However, the response is not complete and should be amended with the following information:

a. Per the Agency recommendation in the CR Letter and in the April 2014 IR, (b) (4) In addition, the Agency also recommended including the activity units by which the final product vials are filled in the manufacturing process narrative. Please include (b) (4) and revise the process narrative accordingly.

b. The proposed acceptance criteria for (b) (4) in the Release and Stability Specifications of the DP are too broad, and not representative of the test results derived from (b) (4) lots. Moreover, the acceptance limit for (b) (4) is not aligned with that for potency (the acceptance limit for potency is (b) (4) of the upper limit, while that for (b) (4) is (b) (4) of the upper limit). Please revise the acceptance limits based on your manufacturing experience.

c. In the Release and Stability Specifications of the DP, the proposed acceptance criteria for the (b) (4), are too broad, and not representative of the test results derived from (b) (4) lots. Please revise the acceptance limits based on your manufacturing experience.

d. In your response to the April 2014 IR concerning CR item #5a, the term "FIX (b) (4) is misleading since the (b) (4) method measures (b) (4) only, not (b) (4). Please revise accordingly.

7. In Figure 7 of your response to the April 2014 IR concerning CR item #5a, you provided the (b) (4) lots. However, the report includes the (b) (4) of only one of the (b) (4) lots. Please include results from all (b) (4) lots (b) (4) in this figure. In addition, please provide the (b) (4) (b) (4) and (b) (4) results of all (b) (4) lots.

8. (b) (4)

(b) (4)

9. In your April 2014 response to the IR concerning CR item # 5c, you provided the Validation Master Plan Summary Report (VAL-90019-01) which contains the generation numbers of three conformance lots. However, this report does not contain detailed information of the study, which should include, but not be limited to, testing for (b) (4) testing. Please provide the detailed results of the process validation study.

10. In your response to observation #2 in Form FDA 483, you described the changes you will implement in the governing procedures, *QC-1207, Invalid Assay Handling Procedure* and *GMP-0401, Quality Control Laboratory Investigation Procedure.* Your response is deficient in that you did not describe the implementation of the specific instructions regarding invalid assay handling in the specific QC laboratory SOPs, and you did not link the governing procedures to the specific SOPs. In addition, you did not describe the training that accompanies the changes in the governing documents. Please implement the referenced changes and provide the revised documents.

11. In your response to observation #5 in Form FDA 483, you described the changes you will implement to further evaluate the reagents and kits in the QC laboratory. Your response is partially adequate: Although an assessment of some reagents and kits used in the QC laboratory was performed, no stability tests were performed to establish the expiration dates after the reagent containers are opened or stability during testing. Please explain why the proposed stability testing will include only materials that are kept for longer than (b) (4) at the facility, and why the exact storage conditions are not stated. Moreover,

please specify the reagents listed as "critical reagent" that will be included in stability testing. Stability testing of a portion of the reagents or kits in the QC laboratory may result in potentially inconsistent laboratory results. Therefore, please improve the design of the stability testing of the QC laboratory reagents.

Clinical/Statistical:

12. In the prescribing information and other locations in the submission, the mean annualized bleeding rates are reported as square-root transformed numbers, rather than on the original scale. FDA information request of 2014-05-22 recommended updating the study report to use original scale to report the mean annualized bleeding rates. You declined to update to the data using original scale in Sequence e0029 dated 2014-05-29, stating that use of transformed numbers was previously agreed upon by the FDA. FDA acknowledges agreeing with the Statistical Analysis Plan using square-root transformed numbers for statistical calculations as data transformation is an acceptable approach to compare two treatment regimens/groups for non-normalized data. However, use of square-root transformed numbers as the primary or only presentation of mean efficacy rates in the package insert does not capture the information in a way that allows the treaters to easily comprehend the information.

    Please submit the data on mean annualized bleeding rates and any other efficacy measures using the original scale.

13. Section 11.4.1.2.1.1 in Amendment 125426/0.23 Sequence e0024 states that some data from bleeding diaries could not be obtained in time to be submitted in this amendment. Please submit the data from these diaries.

14. In the latest version of the prescribing information from Sequence 0027, on Page 16 in the section on *Treatment of Bleeding Episodes*, it says "Majority of the bleeds, 360 (70.9%) resolved after a single infusion of IXINITY and 65 (13.0%) after two infusions." However, the *Summary of Clinical Efficacy* states (1) for prophylaxis, "Majority of bleeds 189 (37.2%) resolved after a single infusion and 41 (8.1%) after two infusions," and (2) on-demand "Majority of bleeds 169 (33.3%) resolved after a single infusion and 25 (4.9%) after two infusions." Please check the numbers and percentages of infusions in all documents and ensure that these are accurately captured in the package insert.

15. Page 52 of the *Summary of Clinical Safety* states that nine events were probably related and seven events were possibly related to study drug, which should add up to 16 adverse reactions. However, only 15 reactions are reported. Please submit in tabular format the complete information on the nine events. This table should include the subject ID, events, causality, days when occurred and severity.

16. Under related adverse drug reactions (ADR), you include one case of non-inhibitory anti-FIX antibody. Please provide a narrative of this case (or provide its location in the

submission) and explain why this case was selected as an ADR while the other subjects who developed such non-inhibitory anti-FIX antibodies were not categorized as ADRs.

17. The number of subjects who developed non-neutralizing anti-FIX antibodies during the study, and were negative at baseline, is not clear. Page 50 in the *Summary of Clinical Safety says that* 21 subjects (27%) had non-inhibitory antibodies not present at baseline, but page 91 in the same document says that 5 of those 21 subjects were positive at baseline. Please clarify.

We stopped the review clock with the issuance of this letter. We will reset and start the review clock when we receive your complete response.

Within 10 days after the date of this letter, you should take one of the following actions: (1) amend the application; (2) notify us of your intent to file an amendment; or (3) withdraw the application.

You may request a meeting or teleconference with us to discuss the steps necessary for approval. For PDUFA products please submit your meeting request as described in our "Guidance for Industry: *Formal Meetings Between the FDA and Sponsors or Applicants*," dated May 2009. This document is available on the internet at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf or may be requested from the Office of Communication, Outreach, and Development, at (240) 402-8020. For non-PDUFA products, please contact the regulatory project manager. For details, please also follow the instructions described in CBER's *SOPP 8101.1: Scheduling and Conduct of Regulatory Review Meetings with Sponsors and Applicants*. This document also is available on the internet at http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ProceduresSOPPs/ucm079448.htm, or may be requested from the Office of Communication, Outreach, and Development.

Please be advised that, as stated in 21 CFR 601.3(c), if we do not receive your complete response within one year of the date of this letter, we may consider your failure to resubmit to be a request to withdraw the application. Reasonable requests for an extension of time in which to resubmit will be granted. However, failure to resubmit the application within the extended time period may also be considered a request for withdrawal of the application.

If you have any questions regarding the above, please contact the Regulatory Project Manager, Edward Thompson at (240) 402-8443.

Sincerely yours,

Basil Golding, MD
Director
Division of Hematology Research and Review
Office of Blood Research and Review
Center for Biologics
Evaluation and Research