DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
1401 Rockville Pike
Rockville, MD 20852-1448

Our STN: BL 125426/0

Inspiration Biopharmaceuticals, Inc.
Attention: Mark A. De Rosch, PhD
One Kendall Square, Building 1400 East
Cambridge, MA 01239

Dear Dr. De Rosch:

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 to the comparability plan, submitted on October 11, 2012, for drug substance (DS) lots manufactured using the current and modified purification processes, in order to remove the Chinese Hamster Ovary (CHO) cell-derived host cell proteins (HCP), please provide the following:

    a. (b) (4) .

    b. (b) (4)

    c. Data from the re-validation study of the viral filtration step using at least one model virus, such as (b) (4)

    d. (b) (4)

2. In your response to our Information Request dated July 25, 2012, you reported an approximate (b) (4) recognition of HCP by the (b) (4) as determined by comparison of the (b) (4) We consider this level of HCP coverage by the (b) (4) to be insufficient, and a potential cause for the under-estimation of HCP levels in the (b) (4) of IB1001. Therefore, please improve the (b) (4) for HCP by using (b) (4)

3. With regard to the testing of (b) (4) please provide the following data for the rFIX, (b) (4) transgenes:

   (b) (4)

4. You stated in Section *Overview of Process Validation Studies* (3.2.S.2.5.1):

   "*A Parameter Justification Report was generated for each unit operation. The report summarizes in a single document how the commercial manufacturing parameter ranges were defined and where process development and/or characterization reports primarily justify parameter set points and ranges. In general, process parameters ranges are deduced from scientific principles, defined equipment tolerances and/or sourced from historical clinical GMP runs and characterization studies. Likewise, performance parameter ranges (e.g. In-process Limits, In-process Controls, and In-Process Specifications) are deduced from scientific rationale, statistical analysis of historical batch performance, and/or known process outcomes required to achieve the defined Release Specifications for the* (b) (4)

   However, you have not provided scientific evidence to demonstrate that the manufacturing process is capable of consistently producing quality product and justify the proposed control strategy for each unit operation. Specifically, you have not demonstrated understanding of the causes of process variations, ability to detect the

variations, and assessment of the potential impacts of the variations on the process and product quality attributes.

Therefore, please provide summaries of relevant data gathered during the developmental and qualification stages of process validation that demonstrate your scientific understanding of each unit operation regarding its performance and control strategies. Justification of the proposed operating ranges should include, but not be limited to, a short description of the analytical methods used to monitor each unit operation, a summary of the results, and an assessment of the potential impact of a variation on process performance and quality attributes of your product.

5. With regard to the in-process controls for the (b) (4), please include Acceptance Limits for the following in-process control parameters:

   (b) (4)

   .

6. The criterion for the (b) (4) is based solely on the (b) (4). Please establish additional (b) (4) criteria that are based on the (b) (4)

7. With regard to the in-process controls for the (b) (4) process steps, please:

   a. Adjust the acceptance limits based on your manufacturing experience since the currently proposed acceptance limits for (b) (4) are too broad and not justified by historical data.

   b. Calculate (b) (4) based on the (b) (4).

8. With regard to the in-process controls for the (b) (4) step, please:

    a. Adjust the acceptance limits based on your manufacturing experience since the currently proposed acceptance limits for (b) (4) are too broad and not justified by historical data.

    b. Explain why the operating parameters relevant to (b) (4) were classified as non-critical.

9. With regard to the in-process controls for (b) (4) , please include the Acceptance Limits for the following in-process control parameters:

    (b) (4)

    .

10. With regard to process validation (PV) for the *Downstream Process Unit Operations*, please provide the following:

    (b) (4)

e. Summary of the results from the (b) (4) studies.

11. Please provide, in tabular form, results of the clearance studies for the following process-related impurities: (b) (4) *CHO HCP,* (b) (4) The tables should include but not be limited to: (b) (4) for each of the referenced impurities.

12. With regard to *Control of* (b) (4) - *Justification of Specifications:*

    a. Please provide more specific information (e.g., side-by-side comparison between the original and modified results) about the re-evaluation of the original raw specification data using "*the current data processing method*".

    b. Please note that the proposed acceptance criteria for (b) (4) are too broad and not fully representative of the release testing results of the (b) (4) batches. Specifically, please set the acceptance limits based on historical data for the following specification tests:

(b) (4)

    c. Please include acceptance limits for (b) (4).

    d. Please provide a detailed description of the standard (b) (4)

e. Please provide images and a detailed description of the (b) (4)

f. Please identify the (b) (4)

13. Please note that your risk assessment of Extractables and Leachables (E&L) for all direct product contact materials and equipment used in the production of IB1001 DS is not adequate because it was based solely on the information provided by the vendors. Therefore, please provide results of E&L studies that are specific to the DS manufacturing process and your product. In addition, based on the identified E&L profile, please evaluate the toxicity and potential impact on product quality, including its stability.

14. With regard to *Control of Drug Product - Justification of Specifications:*

a. Please provide more specific information (e.g., side-by-side comparison between the original and modified results) about the re-evaluation of the original raw specification data using "*the current data processing method*".

b. Please note that the proposed acceptance criteria for *Drug Product Release and Stability Specifications* are too broad and not fully representative of the release testing results derived from the (b) (4) released lots. Specifically, please set the acceptance limits based on historical data for the following specification tests:

- *Factor IX Potency* – the lower acceptance limit should not exceed (b) (4) and the upper acceptance limit should not exceed (b) (4) of the nominal lot potency

(b) (4)

c. (b) (4)

(b) (4)

15. Please note that the amount of factor IX activity on the product label of each lot should be the actual activity of factor IX measured at lot release.

16. With regard to the validation of analytical procedure for *Factor IX Potency*, please provide the validation study protocol and study report that contains the raw experimental data. In addition, please provide the technical transfer data from the (b) (4) and relevant Standard Operation Procedures for the methods performed at both facilities.

CLINICAL:

17. Please submit the data on recipient antibodies against factor IX in a SAS transport file (.xpt).

18. Please modify the ACHOBAT file including revision of the patient identification field and presentation of titer values in a proper numerical and tabular format.

PHARMACOLOGY/TOXICOLOGY:

19. You have not provided adequate nonclinical data to fully evaluate the safety of IB 1001, Coagulation Factor IX (Recombinant). Before the BLA for IB 1001 can be approved, please conduct and submit the results from the nonclinical *in vivo* immunogenicity studies detailed in the letter sent to you on November 29, 2012.

LABELING:

20. We reserve comment on the proposed labeling until the application is otherwise acceptable. We may have comments when we see the proposed final labeling.

STATISTICAL REVIEW:

We have reviewed your responses to the two statistical comments included in the October 11, 2012 IR letter.

21. We are not able to replicate your results for the annualized bleeding rate in Table 11.4-7. We recognize that you need more time to obtain necessary information to address the

issue. Please submit your clarification to the Agency as soon as you obtain relevant information to resolve it.

22. It is not appropriate to use the cutoff date to calculate the annualized bleed rates because the bleeding events that occurred between the last visit and the cutoff date cannot be captured in the calculation for some subjects. Therefore, the annualized bleed rate can be underestimated. FDA's original comment did not suggest using the last infusion date as it would also not work for study periods without infusions. We recommend that the annualized bleed rate should be calculated based on the longest study period with bleeding information available. For example, the last visit date of September 16, 2011 should be used instead for Subject (b) (6) Please submit the updated analysis.

FACILITY:

23. Regarding drug substance manufacturing at (b) (4) :

    a. An acceptable inspection of your drug substance contractor's facility in (b) (4) is required prior to licensure. This inspection could not be scheduled during your first cycle review due to proposed changes in your process.

    b. Manufacturing information was provided for (b) (4) but only (b) (4) testing results are provided for (b) (4) , and no information was provided for (b) (4) . Please provide a manufacturing summary for (b) (4) .

24. Regarding drug product manufacturing at (b) (4) :

    a. You state in Section 2.3.P.3 "Manufacture" of the original BLA submission (page 11) that (b) (4) testing is performed (b) (4) but it is unclear whether this method is validated. Please provide validation summary (e.g., including a description of test parameters, test conditions, testing procedures, and acceptance criteria for parameters evaluated) and results (a summary of validation data) for the (b) (4) testing method.

    b. The information provided in Section "Responses to Oct 11, 2012 Information Request" of Amendment 9 in response to 4.5 Question 4d (regarding the (b) (4)) does not fully address the issue indicated in our question (4.5 Question 4d in Amendment 9). Your response only describes the (b) (4)

(b) (4)

c. Your temperature mapping study at (b) (4) (included in Section 3.2.P.2 Pharmaceutical Development) that supports the development of the lyophilization cycle does not include clear information on where thermocouples are placed on shelves and the correlation between product and shelf temperatures. Please indicate locations of the thermocouples per shelf and shelves used for the temperature mapping study and collapse temperature of the product and discuss any warm and cold spots identified, consistency of temperature readings and the relation between the product and shelf temperatures.

25. Regarding diluent manufacturing at (b) (4) : You state in Amendment 9 that the (b) (4) diluent syringes will be tested for integrity at specified time points. You have also included a description of integrity testing (b) (4) you plan to perform, but it is unclear whether it is validated. Please provide validation summary and results for the integrity test method you described in Amendment 9.

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 (301) 827-1800. 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, Leigh Pracht, at (301) 827-6116.

Sincerely yours,

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