From: Pracht, Leigh
Sent: Thursday, October 11, 2012 10:01 AM
To: 'Tung Koh'
Subject: STN 125426/0 Information Request
Our Reference: BL 125426/0

Inspiration Biopharmaceuticals, Inc.
Attention: Ms. Tung Koh
Oct 11, 2012,
Sent by email

Dear Ms. Koh:

We are reviewing your April 5, 2012 biologics license application (BLA) for Coagulation Factor IX (Recombinant). We are providing the following comments and requests for additional information to continue our review:

Statistical:

1. We are not able to replicate your results for the annualized bleeding rate in Table 11.4-7 using the variables "PBLDR" and "OBLDRT" in dataset "bld2.xpt", though we understand that you modified your SAS program to recalculate time on prophylaxis and on-demand using the termination dates instead of the data cut-off date (December 21, 2011). Please clarify in details how you derived the annualized bleeding rate in Table 11.4-7 and provide all the necessary datasets for FDA to conduct analysis (e.g., datasets under your library name "clinical").
2. Related to above item, in dataset "bld2.xpt", it seems that the prophylaxis total time (variable "pttm") was calculated based on the difference of these two variables: "p1stdt" and "p1endt'. However, the last infusion date of treatment phase was much earlier than the "p1endt" in some cases. If subjects dropped out around the last infusion date, there should be more subjects with follow up time less than <6 months than you reported (5 subjects). For example, the following two subjects' last infusion date was around 3-4 months earlier than the end of prophylaxis date. Please clarify.

ID	P1STDT	P1ENDT	INFENDT
(b)(6)	11MAY2011	21DEC2011	02AUG2011
(b)(6)	11JUN2011	21DEC2011	15SEP2011

Manufacturing/Product Quality:

A. Regarding the drug product manufacturing at (b)(4) :

1. Insufficient information was provided on the validation of (b)(4) integrity testing method for the product container closure system. Please provide the following information:
   - description of test method

- description of positive/negative controls used in the method validation and their preparation
- description of test parameters, testing conditions and procedures
- number of the container closure system used in the validation (vials)
- acceptance criteria
- validation data and its analysis

2. Insufficient information was provided on the validation of sterile filtration of the drug product prior to filling step. Please provide the following information:
   - It is unclear from the information provided in the submission what sterilization method is used to sterilize the sterilizing grade filter: (b)(4)
   - We note from the information provided in the submission that the product (b)(4)

3. It is unclear from the information provided in the BLA submission whether there were any deviations from the protocol and acceptance criteria during the drug product process validation runs. Please clarify. If there were, please provide a summary of deviation reports or indicate their locations if existed in the submission.

B. Regarding the drug substance manufacturing at (b)(4) in (b)(4):

1. We note from the information provided in the BLA submission that you provided a cleaning validation summary (including validation data) for the (b)(4) and a description of equipment cleaning procedures and testing. Also, you indicated in the submission that equipment sterilization validation was performed prior to the PPQ studies and cleaning studies were conducted concurrently with the PPQ studies (3.2.S.2.5.1 Overview of Process Validation Studies), but we cannot locate any cleaning and sterilization/sanitization validation summary and results for both dedicated and non-dedicated product contact equipment (listed in Tables 3 and 4 in 3.2.A.1. Facilities and Equipment-Drug Substance). Please provide the validation

summary and results for cleaning and sterilization/sanitization of the product contact equipment.

2. Please provide a rationale for not including (b)(4) in the testing plan for your blank run to evaluate cleaning performance of (b)(4) processes in addition to what you proposed in the submission.

3. You indicate in the submission that small scale (b)(4) studies are conducted for (b)(4) but no data is submitted. Please provide the results pertaining to cleaning and sanitization of the (b)(4).

4. We note that you validated (b)(4) used in the drug substance manufacturing, but (b)(4) is not evaluated in any way such as there is no testing for (b)(4). Please comment. Please also indicate in process controls for (b)(4)

5. It is unclear from the information provided in Table 8 on page 21 of the section 3.2.S.2.5 Process Validation and/or Evaluation why normal operating range for (b)(4) even though your process validation results are in the range of (b)(4). Please clarify.

C. Regarding the diluent manufacturing at (b)(4):

1. (b)(4)
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2. Please provide a validation summary and results for the integrity testing of the diluent container closure system (b)(4) tests that you listed in the submission).

The review of this submission is on-going and issues may be added, expanded upon, or modified as we continue to review this submission.

Please submit your responses to this information request as amendments to this file by November 15, 2012 referencing the date of this request. If you anticipate you will not be able to respond by this date, please contact the Agency immediately so a new response date can be identified.

The action due date for this file is February 4, 2013.

If you have any questions, please contact me at (301) 827-6116.

Sincerely,

Leigh A. Pracht
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