To: Leigh Pracht , HFM-392 and files of BLA125426/0 and IND 13551

From: Roman Drews, HFM-392

Through: Timothy Lee, HFM-392
Acting Chief, Laboratory of Hemostasis, DH, OBRR

Subject: Review of *in vitro* comparability studies proposed by Inspiration Biopharmaceuticals following the addition of a (b) (4) process for the Drug Substance of Coagulation Factor IX (Recombinant) [IB1001]

Background

Inspiration Biopharmaceuticals (Inspiration) submitted a draft protocol to demonstrate comparability between the Coagulation Factor IX (Recombinant) (rFIX) (b) (4) manufactured by the current commercial process described in the BLA and that manufactured by a modified manufacturing process. The modification comprises of the addition of a (b) (4) This is the only manufacturing change that has been planned by Inspiration. The viral filtration step will require re-validation after the introduction of the (b) (4)

(b) (4)

The goal of modifying the DS manufacturing process is to reduce the overall level of Chinese hamster ovary (CHO) host cell proteins (HCP) in the DS with a specific emphasis on removing the HCP that caused immunological responses in patients during the clinical trial.

The results of the scaled-down study and the first full-scale run indicate that the level of HCP in the (b) (4) has been reduced to (b) (4) of rFIX (b) (4) as measured by an improved (b) (4) assay (b) (4) This level is around (b) (4) lower than that presented in the BLA of several (b) (4) lots of this product, which Inspiration code-named IB1001.

The submitted protocol also outlines studies that will be performed in support of future amendments to BLA 125426/0 and IND 13551 with the intention of lifting the IND off clinical hold.

Analytical Approach to assess the Removal of HCP by the (b) (4)

Inspiration proposed to use a combination of analytical tools to assess the reduction of the overall level of HCP and removal of the HCP that induced immunogenic responses in subjects in clinical trials. These include:

(b) (4)

Comments:
The adequacy of the coverage of HCP spectrum by the (b) (4) used in the (b) (4) assay was not fully demonstrated. Therefore, to support product licensure, Inspiration needs to develop an assay that uses (b) (4) To address the Clinical Hold concerns and show the effectiveness of the corrective action, i.e., the ability of the (b) (4) to remove HCP, Inspiration should perform the following additional experiments:

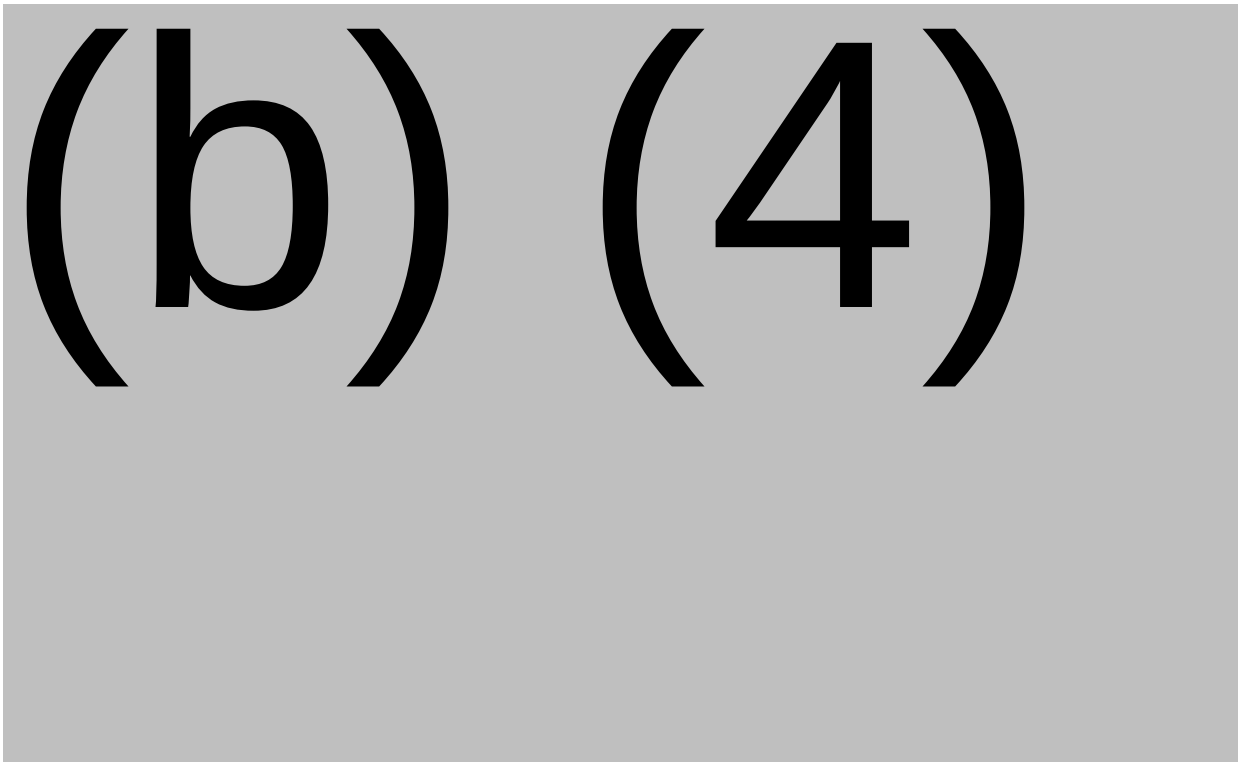
- (b) (4) .
- (b) (4)

Analytical Approach to Demonstrate Comparability of (b) (4) before and after the addition of the (b) (4)

In general, the plan proposed by Inspiration is acceptable. Table 3 shows the scope of the proposed study that comprises of lot release assays and (b) (4) The table also shows the results of the proposed tests that will be submitted to the IND (Q1 of 2013), and that to the BLA (Q2 of 2013).

2 pages determined to be not releasable: (b)(4)

(b) (4)



Comments:

- Inspiration should submit to the BLA a validation report of an (b) (4)
- Assessment of the (b) (4) of rFIX in IB 1001 (e.g., by (b) (4) should be provided in the IND and BLA amendments.

Data Submission Plan

IND

In 1Q 2013, Inspiration plans to submit an IND amendment to address the CMC issues described in the Clinical Hold Letter, which will include the following:

- Release test data of IB1001 (b) (4) made from the modified commercial process (HCPs reduced/removed) including (b) (4)
- (b) (4)
- Additional HCP data on the (b) (4) full-scale modified commercial process (b) (4) batches compared to representative (b) (4) batches from the clinical study. Data from a non-clinical PK study (rat) comparing (b) (4) from the commercial process with the modified commercial process. The materials for modified commercial process will come from the full-scale non-GMP demonstration batch which will be shown to be representative

  of the GMP batches made from the modified commercial process. Materials from the commercial process will be from a previously released GMP batch.
- Release data from a 500 IU drug product lot manufactured with non-GMP drug substance mentioned above from the full-scale modified commercial process
- The full-scale (b) (4) batches and 500 IU DP (worst case) lot from the modified commercial process will be enrolled in the factor IX long-term stability programs and updates will be reported to FDA on a regular basis.

Comments:

The data from the re-validation of viral filtration step (at least for one virus, e.g., (b) (4) should be submitted in the IND amendment

BLA

An amendment to the pending BLA is estimated to be submitted in 2Q 2013. The CMC data will include:

- Release data from the modified commercial (b) (4) process including at least three full-scale GMP (b) (4) compared to release data from batches used for clinical studies.
- (b) (4)
- Additional HCP C/C data on at least three full-scale GMP batches from modified commercial process batches compared to representative batches from the clinical study. These HCP C/C approaches are those described in Section 3.
- Re-assessment of (b) (4) from the modified commercial process.
- Drug substance process re-validation studies that support (b) (4) (b) (4) within the factor IX process. This will include (b) (4) focused on the (b) (4)
- GMP (b) (4) drug product for all dosage strengths will be enrolled in the factor IX long-term stability program and stability updates will be reported to FDA on a regular basis. At the time of filing, at least 3 months of data from the long-term stability program will be available from (b) (4) drug product representative of the modified commercial process.

Recommendation

The following comments should be communicated to Inspiration:

1. With regard to the proposed IND amendment, please include the following:
    - (b) (4)
    - (b) (4)
    - The data from the re-validation study of the viral filtration step using at least one model virus, such as (b) (4)

- (b) (4)

2. In your response to FDA's Information Request dated 25 July 2012, you reported an (b) (4) recognition of HCP by the (b) (4) , as determined by comparison of the (b) (4) analysis. 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) and include the validation report in the BLA amendment.