**M E M O R A N D U M**

**Department of Health and Human Services**
**Public Health Service**
**Food and Drug Administration**
**Center for Biologics Evaluation and Research**

To: File of STN 125426/0 and Leigh Pracht, HFM-380

From: Roman Drews, HFM-392

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

Subject: Final review of CMC information in the Biologics License Application by Inspiration Biopharmaceuticals Inc. for Coagulation Factor IX (Recombinant) – Complete Response Letter

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IB1001 is a recombinant coagulation factor IX intended for control and prevention of bleeding episodes and peri-operative management in patients with hemophilia B. The IB1001 final drug product (FDP) is formulated as a sterile, non-pyrogenic lyophilized powder intended for intravenous injection. It is provided in single-use glass vials containing the labeled amount of factor IX activity, expressed in international units (IU). FDP is manufactured in three nominal dose presentations – 500, 1000, and 1500 IU.

During the course of the BLA review, Inspiration reported formation of antibodies, at persistent and growing titers, against a process-related impurity, Chinese Hamster Ovary (CHO) cells host cell proteins (HCP) in Hemophilia B patients during the ongoing clinical study IB 1001-01. Because of safety concerns, CBER placed study IB 1001-01 on clinical hold and informed Inspiration that the product will not be approved in its current form, i.e., a Complete Response (CR) letter will be issued for the pending BLA. The corrective and preventive actions proposed by Inspiration include changes to the manufacturing process, i.e., an addition of a (b) (4) and optimization of the assay for residual HCP (b) (4) The adequacy of the proposed corrective actions that include the re-validation of the modified (b) (4) process, and its effect on the Safety, Purity and Efficacy of the product has to be evaluated when the completed data are provided for the Agency's review.

In addition to the aforementioned deficiencies that prevent BLA approval, several other CMC (Product and Facility) deficiencies were identified during the first review cycle. Therefore, the review committee recommends issuing Inspiration a CR letter listing all the deficiencies in this BLA.

## Background

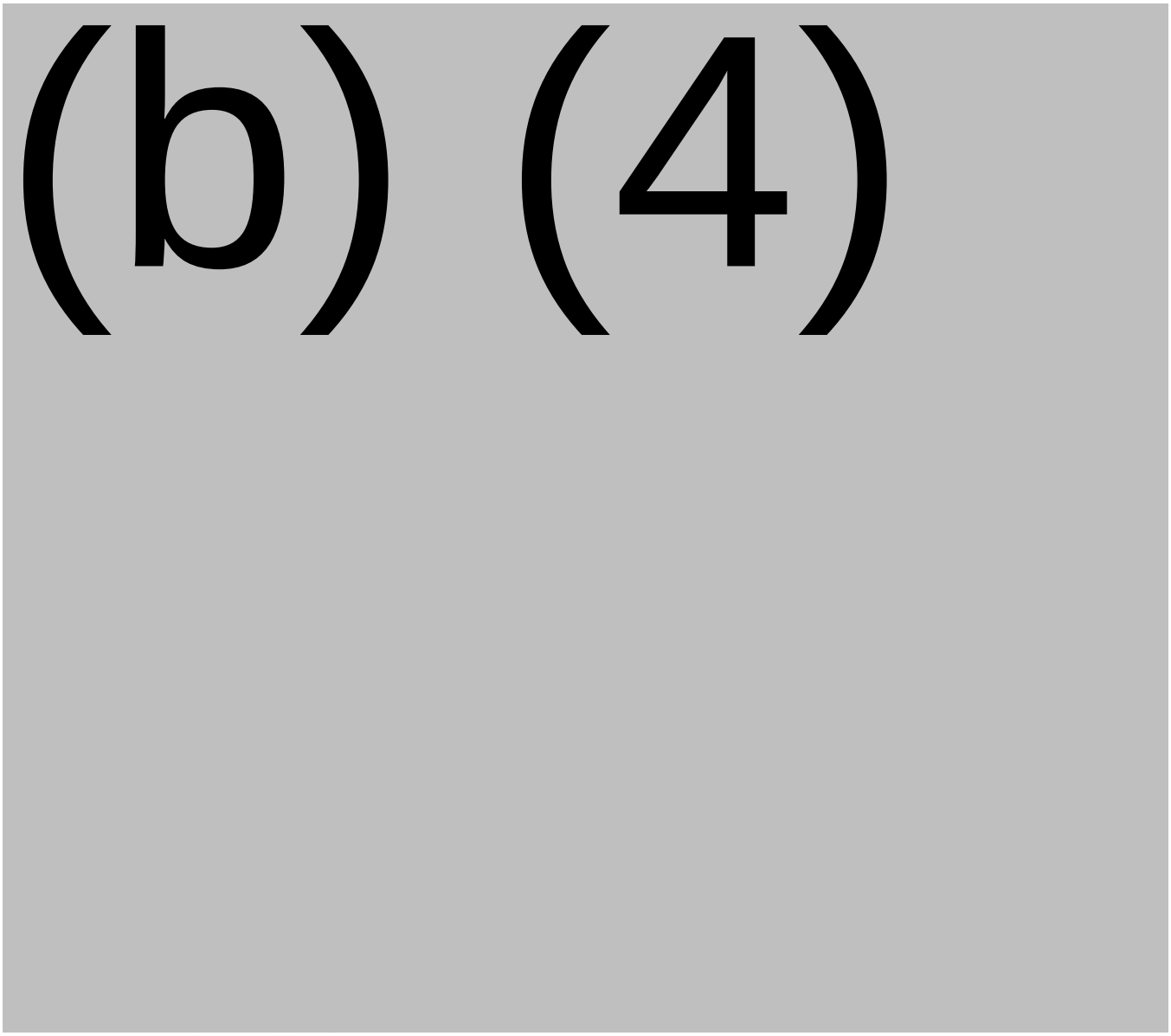
Structure and Mode of Action

Endogenous Coagulation Factor IX
Coagulation Factor IX (FIX) is a vitamin K dependent serine protease zymogen. Naturally occurring, human plasma derived FIX is a approximately 56 kDa single chain molecule that undergoes extensive post-translational modifications – glycosylation (N-linked Asn 157, Asn-167, O-linked Ser53, Ser61, Thr159, Thr169, Thr179), beta-hydroxylation (Asp64), sulfation (Tyr155), phosphorylation (Ser158), and Vitamin K dependent γ-carboxylation of up to 12 Glutamic acid residues, so called Gla-domain. Calcium binding to the Gla-domain results in a conformational change in the protein that is essential for FIX function in the process of blood coagulation. Upon initiation of blood coagulation FIX is converted into its active form FIXa by FVIIa/TF complex or Factor XIa. During this process the highly glycosylated 11 kDa activation peptide is cleaved off (R145-R180) resulting in two-chain molecule comprising of covalently linked light and heavy chains. The N-terminal light chain (18 kDa) is composed of a Gla-domain and two epidermal-growth-factor-like domains. The C-terminal heavy chain (28 kDa) contains trypsin –like protease domain that carries FIXa enzymatic activity. Upon activation FIXa forms a complex with FVIIIa that in turn activates FX (tenase complex) in the presence of Calcium ions and on phospholipid surface. Absence of functional FIX is associated with severe hemophilia B, caused by an X-linked recessive trait carried by females with one defective FIX gene. Hemophilia B occurs in one of 32 000 men, and represents 15-20% of hemophiliacs.

IB1001
The manufacture of IB1001 includes cell culture, harvest, and purification, i.e. the typical steps used in the biotechnology industry.

IB1001 is a 415 amino acid, 55 kDa, single chain glycoprotein purified recombinant analogue of human FIX that is expressed in Chinese Hamster Ovary (CHO) cells. Naturally occurring human plasma derived factor IX exists in one of two allelic forms - Thr 148 is the predominant form (80%) whereas Ala 148 (20%) is the minority form. The IB1001 primary amino acid sequence is identical to the Thr148 allelic form of plasma derived FIX. Similarly to native FIX, IB1001 has up to 12 but no less than 10 γ-carboxylated Gla residues, is composed of 13% of carbohydrate, and has 11 disulfide bonds. (b) (4) . The primary structure of recombinant factor IX (rFIX), IB1001 is shown below.

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




Process Validation and Evaluation

The review of DS Process Validation and Evaluation is based on the amended Section 3.2.S.2 submitted three months after the submission of the original BLA. The IB 1001 DS manufacturing facility (b) (4) used by Inspiration underwent non-process related changes after the validation of the DS commercial process. The facility modernization and its impact on the validation studies was discussed with the Agency during the BLA meeting with Inspiration held on November 15, 2011. At the meeting, it was agreed that Inspiration would perform three confirmatory DS batches post facility remodeling. In addition, the Agency agreed that data from one batch would be submitted in the BLA, and the data from two conformance batches would be provided in the aforementioned amendment to Section 3.2.S.2 three months after submitting the BLA. On May 30th, 2012, Inspiration reported to CBER a formation of antibodies with the persistent and growing titer against a process related impurity, Chinese Hamster Ovary

(CHO) cells host cell proteins, (HCP) in Hemophilia B patients during the ongoing clinical study IB 1001-01. Subsequently, CBER placed study IB 1001-01on clinical hold and informed Inspiration that the product will not be approved in its current form, i.e. the complete response letter will be issued for the pending BLA application. The corrective and preventive action proposed by Inspiration includes changes to the manufacturing process, i.e. (b) (4) and an optimization of the residual HCP (b) (4) assay (b) (4) The adequacy of the proposed action that include re-validation of the modified (b) (4) process, and the final effect on the Purity of the product has to be evaluated when complete data will be provided for the Agency's review.

Principles of the Validation Studies
As stated by Inspiration, " the process validation effort for IB 1001 DS process is based on a life cycle approach and through process understanding". Inspiration based its process validation on the following principles (*in italics*):

- *Process Parameters (input) and Performance Parameters (output) were classified. The operational ranges for Process Parameters were identified based on historical production data. The Performance Parameters were further categorized into: In-Process Controls, In-process Limits, and in Process Specifications. A Parameter Risk Assessment and Parameter Justification reports were generated for each unit operation. Based on these exercise, and historical and scientific/characterization studies, Inspiration assigned commercial manufacturing operational ranges and criticality of the parameters*.

  Reviewer comment: The firm did not provide adequate data to justify proposed process and performance parameters and their ranges, i.e. the relevant developmental data and data from the small scale studies including summaries of Parameter Risk Assessment and Parameter Justification reports were not submitted in to the BLA. In particular, data demonstrating a link between process performance of unit operation and product quality attributes were not established.

- *The Process Control Strategy is provided in the Evaluation Report for the process validated in* (b) (4) . *The final classification of the parameters as critical or non-critical, the validated operational ranges, as well as justification of the ranges is provided in Section 3.2.S.2.4.*

  Reviewer comment: As stated above, Inspiration did not provide sufficient information to justify the proposed Process Control Strategy for the IB 1001 process.

- *As stated by Inspiration, regardless of the designation as critical or non-critical, all failures to meet the established operational limits will result in a deviation under the outlined quality system.*
  Reviewer comment: I agree with Inspiration that this strategy is acceptable and should help to maintain the consistency of the manufacturing process.

- *Process Performance Qualification studies were performed according to the Validation Plan i.e. performance of unit operations have to meet the pre-determined acceptance criteria and DS batches have to meet all the batch release criteria. At least three consecutive DS conformance batches were manufactured during the pre-improvement and post-improvement studies.*

- Reviewer comment: The batches were successfully manufactured at set points of the unit operation control parameters.

- *The risk assessment was presented for the facility changes, as described in Section 3.2.A.1.*

  Reviewer comment: Agree with the firm's conclusions that there is a potentially a minimum impact of the facility improvement on the outcome of the process validation study.

- *Additional, including small-scale, studies were performed to support* (b) (4) *, and removal rates of process and product impurities*

- Reviewer comment: The adequate data were not provided to support the validity of the studies.

- *Retrospective full scale* (b) (4) *studies have been conducted and prospective small-scale* (b) (4) *studies have been initiated to evaluate adequacy and impact of cleaning procedures on the* (b) (4) *performance.*

- Reviewer comment: The retrospective studies are adequate. There is no sufficient information provided to confirm that small scale studies mimic commercial process conditions

- *Evaluation of extractable and leachable was only based on risk assessment and vendor specific information.*

- Reviewer comment: The provided information is not adequate since Inspiraton did not perform any in-house studies that are specific for IB 1001 process.

- *A Continued Process Verification Protocol for the monitoring of the process through life of the product has been implemented and outlined in Section 3.2.S.2.5.5.*

- Reviewer comment: The outlined plan is adequate

The process validation studies are outlined in the tables attached below:

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

(b) (4)

Potency of rFIX

The potency of the reference material and several batches of rFIX used in clinical studies has been determined in an inter laboratory study performed at three international laboratories versus (b) (4)

Each laboratory used (b) (4) assay with the different reagents and instruments. The (b) (4) was used to determine potency.

(b) (4)

The acceptable results, demonstrating good correlation between laboratories are presented in the table below.

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

Evaluation of Adventitious Agents Safety (3.2.A.2)

Inspiration adequately addressed risk and implemented sufficient actions to mitigate and prevent a potential contamination of the product with the adventitious agents. The following measures have been implemented:

- The risk of contamination with TSE agents is minimized by the selection of appropriate raw materials.
- The Master Cell Bank (MCB), Working Cell Bank (WCB), and end of production cells (EPCs from the WCB) were tested for endogenous and adventitious viruses according to ICH Q5A.
- Solvent/Detergent (S/D) treatment and nanofiltration using an(b) (4) virus retention filter were implemented as deliberate steps for viral inactivation/removal, and their effectiveness was demonstrated by appropriate studies.
- (b) (4) e chromatography was validated for virus removal.
- (b) (4)
- Manufacturing occurs within distinct process areas designed to provide viral segregation of process operations and purified materials.

Materials of Biological Origin

There are no raw materials of human origin used in the manufacture of rFIX. There are also no raw materials of animal origin that are used directly in the commercial manufacturing process. (b) (4) The chromatography resins and Polysorbate 80 are not of biological origin. The risk of BSE/TSE and adventitious viruses has been minimized by the sourcing of the raw and submitted certification documents.

(b) (4)

Cell Source and Cell Banks Testing

The adequate safety data were provided by Inspiration with regards to the development of cell substrate and cell banks testing. The review of these data has been provided in another part of this memorandum.

Viral Testing of (b) (4)

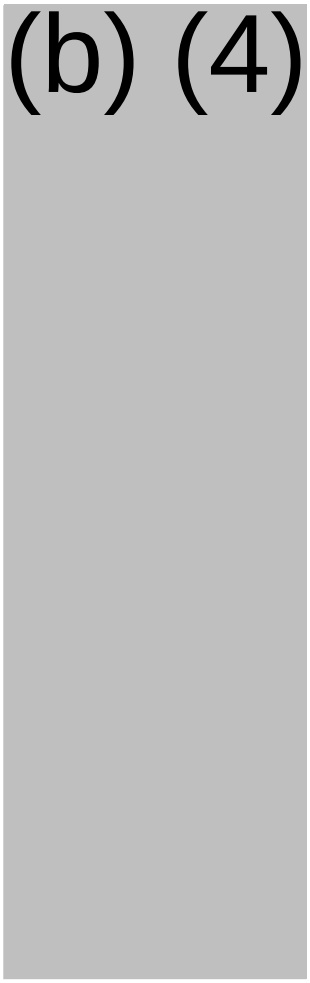
Inspiration followed the ICH Q5A guideline principles to routinely test all cGMP lots for the absence of adventitious viruses in the (b) (4) . This includes testing (b) (4)

Viral Segregation of Process Operation

Inspiration stated that, in addition to implemented logistic measures (flows for personnel, materials, and waste) viral reduction related operations are well segregated, in particular the establishment of two boundaries in the facility for viral segregation: pre-viral /post-viral boundaries for the relevant unit operations. The adequacy of the viral segregation for DS manufacturing process should be confirmed during the pre-approval inspection.

Viral Clearance Studies

The attached flow below chart shows the manufacturing process for rFIX DS. The steps marked in red were investigated for their viral clearance capacity.




Two dedicated viral clearance steps were implemented by Inspiration: Solvent/Detergent treatment and (b) (4) filter. Two steps have different mechanism of action. In addition, the (b) (4) chromatography column, (b) (4) was selected to demonstrate its capacity to remove tested viruses. The selection of steps is in the agreement of the ICH Q5A guideline.

Also, selection of tested model and relevant viruses is acceptable since provided a broad range of the physicochemical properties among the tested species.

(b) (4)

(b) (4)

(b) (4)

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Solvent/Detergent (S/D) Treatment

(b) (4)

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

(b) (4)

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Extractables and Leachables (E&L)

Inspiration submitted risk assessment based on vendors E&L studies. The risk assessment is not adequate because is not based on the IB 1001 process specific data. Therefore, the risk associated with levels of E&L in the final product and their potential impact on safety has not been evaluated.

## Final Drug Product

Description and Composition

IB 1001 final drug product (FDP) is formulated as a sterile, nonpyrogenic, lyophilized powder preparation intended for intravenous (IV) administration. The product is provided in single vials containing the labeled amount of factor IX activity expressed in international units (IU). Each vial contains nominally 500, 1000, or 1500 IU of rFIX. The quantitative composition of FDP is shown in Table 1.

Table 1: Composition of IB1001 Drug Product

| Component[a] | Functions | Quantity per vial (after reconstitution/per mL) | | | Quality Standard |
|---|---|---|---|---|---|
| IB1001[b] | Active | 500 IU (100 IU/mL) | 1000 IU (200 IU/mL) | 1500 IU (300 IU/mL) | Internal specifications |
| Excipients | | | | | |
| (b) (4) Histidine | (b) (4) | (b) (4) | 7.75 mg (1.55 mg/mL) | 7.75 mg (1.55 mg/mL) | (b) (4) |
| Mannitol | | | 150 mg (30 mg/mL) | 150 mg (30 mg/mL) | |
| (b) (4) Trehalose Dihydrate | | | 50 mg (10 mg/mL) | 50 mg (10 mg/mL) | |
| Sodium chloride | | | 19.285 mg (3.857 mg/mL) | 19.285 mg (3.857 mg/mL) | |
| Polysorbate 80[c] | | | 0.375 mg (0.075 mg/mL) | 0.375 mg (0.075 mg/mL) | |
| (b) (4) | | (b) (4) | | | |

(b) (4)

[c] Polysorbate 80, from (b) (4) origin.

(b) (4)

- The labeled potency should be based on the actual lot potency, not nominal potency, as proposed by Inspiration.

The primary container-closure system for FDP is an (b) (4) clear glass vial (20 nm, 10 mL) and (b) (4) grey chlorobutyl rubber stopper (20 mm). An overseal with a colored polypropylene flip-off cap is applied to protect the closure. The more detailed description of the container closure is provided in the Section 3.2.P.7 of the BLA.

The solvent for reconstitution of one vial of FDP is 5mL of sterile Water for Injection (WFI) provided prefilled in 10 mL (b) (4) glass syringe. The sterile WFI is compliant with the (b) (4) . The detailed information about manufacture of WFI is provided in Section 3.2.P Drug Product (b) (4)

Determination of Compatibility
Inspiration provided the adequate data demonstrating compatibility of the reconstituted FDP with the diluent and the container. Three vials of each of two 1500 IU lots (lots (b) (4) and (b) (4) ) were reconstituted with WFI injected from the (b) (4) pre-filled syringe. The reconstituted solution was passed through the sterile vial adaptor that contains 15 µm filter, loaded into syringe, and passed through an infusion set. The more detailed description of the tested system is provided in Table 1. The tests were performed by (b) (4) using the release assays and included measurement of the collected reconstitution volume. The test results had to meet the release specifications to determine the compatibility.

Table 1: Systems Used for Compatibility Testing

| | |
|---|---|
| 1 | SWFI: 5 mL in prefilled syringe (b) (4) |
| 2 | DP High Potency (1500 IU) Lots (b) (4) |
| 3 | Vial Adaptor (b) (4) |
| 4 | Sterile Infusion Set (b) (4) |
| 5 | Sterile Syringe (5 mL) |
| 6 | Alcohol Swab |

The scope of testing is provided in table 2 attached below. The results of testing are provided in Tables 3-5. The results are unremarkable.

Table 2: Test and Rationale for Each Test

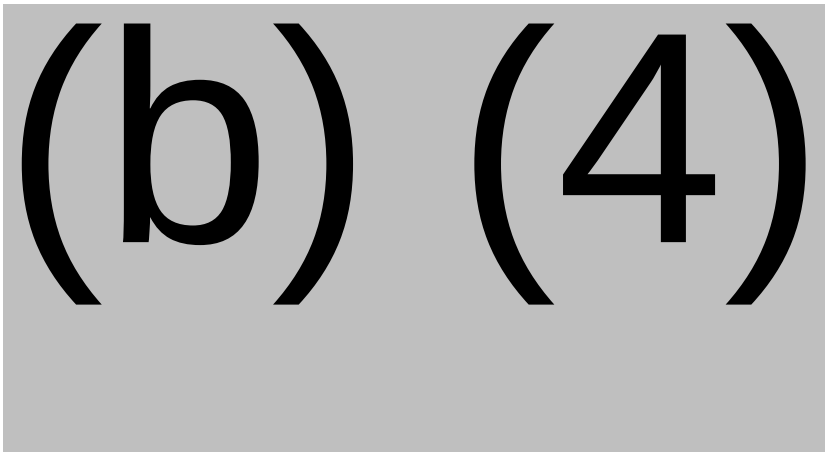
| Test | Rationale |
|---|---|
| Visual Appearance | Particulates have not been introduced due to patient noncompliance with reconstitution instructions |
| Solubility Time | The method of introducing diluent into the DP vial may vary depending on the water container |
| Factor IX Potency (b) (4) (b) (4) | (b) (4) |
| Protein Concentration | At least 5mL diluent is introduced to the final DP vial or FIX could adsorb to devices |

(b) (4)

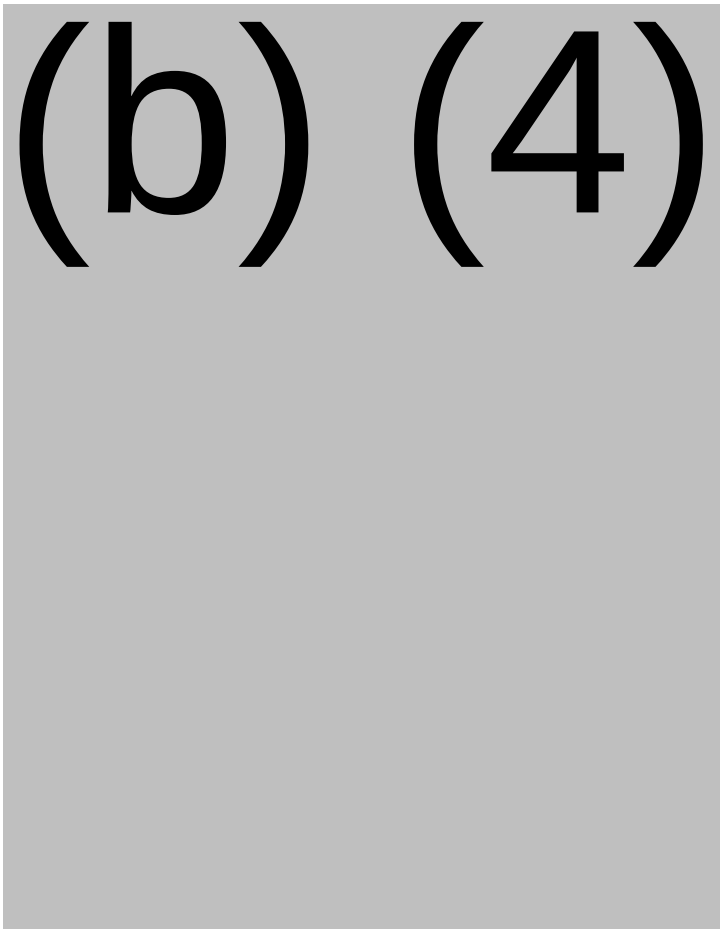
Manufacturers
FDP is manufactured, tested, and release for Inspiration and commercial distribution using contract manufacturers and contract laboratories. The names and responsibilities of these contractors are captured in the table below:

(b) (4)

Batch Formula
(b) (4)




Manufacturing Process
The flow diagram of the FDP manufacture is attached below. The adequacy of validation study and control of critical steps for the process has been reviewed by Ms. Rabia Ballica, reviewer for this BLA from Division of Manufacturing and Product Quality (DMPQ).



Control of Excipients

(b) (4) specifications for all excipients used in the formulation of IB1001 drug product are in compliance with (b) (4). In tables 1- 9 Inspiration provided list of analytical procedures used for release testing of the (b) (4) excipients that is performed at (b) (4). The list of tests is comprehensive and acceptable. In addition, the copies of Certificate of Analysis deriving from vendors and (b) (4) were submitted in the BLA. The submitted data are unremarkable.

Table 1: Excipient Specifications

| Excipient | Specification |
|---|---|
| (b) (4) Histidine | (b) (4) |
| Mannitol | |
| (b) (4) Trehalose dihydrate | |
| Sodium chloride | |
| Polysorbate 80 (b) (4) | |
| (b) (4) | |
| (b) (4) | |

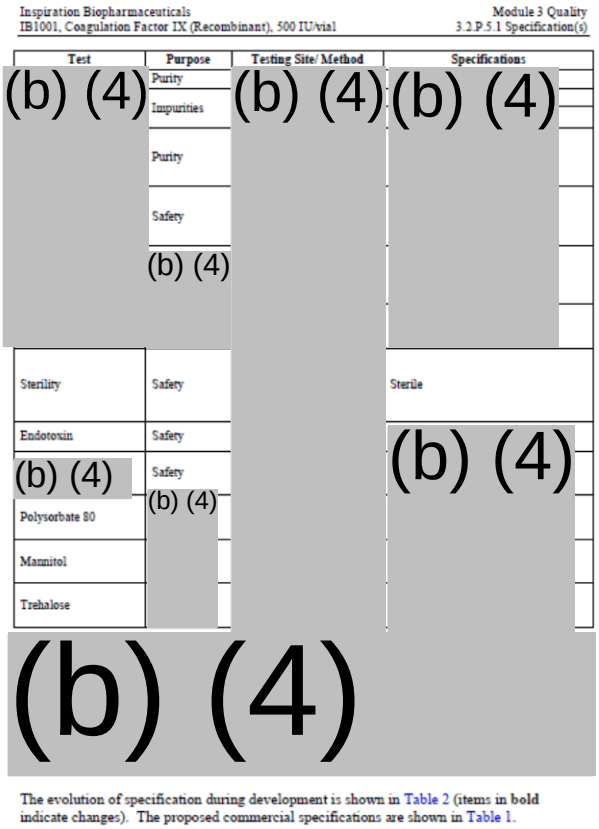
Specifications - Final Drug Product

3.2.P.5.1 Specification(s) (IB1001, Coagulation Factor IX (Recombinant), 500 IU, Powder for Solution for Injection)

Table 1 lists the IB1001 500 IU drug product specifications at release and for stability.

Table 1: IB1001 500 IU Drug Product Release and Stability Specifications

| Test | Purpose | Testing Site/ Method | Specifications |
|---|---|---|---|
| Appearance: Cake Solution | Safety | (b) (4) | White cake with no dark particles<br>Clear colorless solution free of visible particles |
| Reconstitution Time | Safety | | (b) (4) |
| Residual Moisture | Safety | | |
| (b) (4) | Purity/ Potency | | |
| (b) (4) | Quality | (b) (4) | (b) (4) |
| | Quantity | | |
| | Purity | | |
| | Purity/ Identity | | |
| | Impurities | | |
| | Purity | | |
| | Impurities | | |



Inspiration Biopharmaceuticals
IB1001, Coagulation Factor IX (Recombinant), 500 IU/vial

Module 3 Quality
3.2.P.5.1 Specification(s)

| Test | Purpose | Testing Site/ Method | Specifications |
|---|---|---|---|
| (b) (4) | Purity | (b) (4) | (b) (4) |
| | Impurities | | |
| | Purity | | |
| | Safety | | |
| | (b) (4) | | |
| Sterility | Safety | | Sterile |
| Endotoxin | Safety | | (b) (4) |
| (b) (4) | Safety | | |
| Polysorbate 80 | (b) (4) | | |
| Mannitol | | | |
| Trehalose | | | |
| (b) (4) | | | |

The evolution of specification during development is shown in Table 2 (items in bold indicate changes). The proposed commercial specifications are shown in Table 1.

The specifications for the release of FDP (500 IU strength) and Stability are provided in the tables attached above. The scope of testing, with regards to the selection of analytical procedures and measurement of product quality attributes is acceptable. However, as discussed below, the proposed acceptance limits for certain specification tests are too wide and are not supported by the manufacturing experience.

Justification of Specification

Inspiration stated that the proposed commercial specifications are based on the testing results of (b) (4) lots of which 31 were used in the clinical trials. The (b) (4) early lots were manufactured at (b) (4) facility and remaining lots were manufactured in the currently used (b) (4) facility. To establish specification limits, Inspiration used process capability analysis and along with the three standard deviations approach. Inspiration stated that certain historical data were reprocessed to improve the quality/consistency for meaningful justification of specifications. This includes (b) (4) based assays. According to Inspiration, data reprocessing did not invalidate the original results they met the quality standards applicable at the time of issuance. However, the details concerning data reprocessing were not submitted and its impact on specification limits is difficult to assess. Also, the proposed FDP specifications for some quality attributes are wider than (b) (4) standard deviations (SD) and are not fully justified by the historical data presented in this BLA. Inspiration stated that these limits are not higher than clinical lots limits are supported by (b) (4) .

- Inspiration should provide additional information to explain “data re-processing” approach to the historical data set.

- In addition, the proposed acceptance limits for many specification tests ( as discussed below) are too broad and are not representative of historical values.

Acceptance Limits

The specification tests and their discussions for their acceptance criteria are provided below.

**3.2.P.5.6.1 Appearance and Reconstitution Time**

The proposed acceptance criteria are:

- Appearance of the lyophilized cake: White cake with no dark particles
- Reconstituted solution: Clear colorless solution free of visible particles
- Reconstitution time: (b) (4)

The proposed acceptance criteria are acceptable.

**3.2.P.5.6.2** Residual Moisture

The proposed acceptance criterion for residual moisture is:

- Residual moisture: (b) (4)

Table 4: Statistical Analysis of Historical Residual Moisture Data (Unit: %)

(b) (4)

The acceptance criteria are acceptable.

**3.2.P.5.6.3** Factor IX Potency

The proposed acceptance criteria for the Factor IX potency are

(b) (4) J/vial for 500 IU/vial drug product
U/vial for 1000 IU/vial drug product
IU/vial for 1500 IU/vial drug product

The lower potency limits correspond to (b) (4) of the target potency and are acceptable. The upper potency limits for the nominal potency of 500 IU and 1500 IU strength are not acceptable because they exceeded the (b) (4) of the target potency that is traditionally used for FIX products. The upper limit for 1000 IU strength is within (b) (4) range and is acceptable.

Table 5: Statistical Analysis of Historical Potency Data (Unit: IU/vial)

(b) (4)

(b) (4)

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

(b) (4)

(b) (4)

(b) (4)

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**3.2.P.5.6.15 Endotoxin**

The proposed commercial acceptance criterion for endotoxin is:

- Endotoxin (b) (4)

(b) (4)

The historical data shows that the tested values are well below the proposed limit of (b) (4) . The limit is based on(b) (4) that defines Endotoxin levels for Coagulation Factor IX. Inspiration should base the specification limits on its manufacturing experience.

(b) (4)

**3.2.P.5.6.17 Polysorbate 80**

The proposed commercial acceptance criteria for Polysorbate 80 after reconstitution are:

- Polysorbate 80:(b) (4)

The proposed acceptance criteria are acceptable.

**3.2.P.5.6.18** Mannitol

The proposed commercial acceptance criteria for Mannitol after reconstitution are:

- Mannitol:(b) (4)

The proposed acceptance criteria are acceptable.

**3.2.P.5.6.19** Trehalose

The proposed commercial acceptance criteria for Trehalose after reconstitution are:

- Trehalose: (b) (4)

The proposed acceptance criteria are acceptable.

Comparison of Analytical testing at (b) (4)

(b) (4)

(b) (4)

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FDP Stability

Inspiration provided stability data for all three dosage strengths, 500 IU, 1000 IU, and 1500 IU. The 500 IU and 1500 IU dosage strengths studies comprised of (b) (4) lots manufactured in (b) (4) facility (initial manufacturing site for FDP) and (b) (4) lots manufactured in (b) (4) facility. The long-term term stability studies were continued up to (b) (4) data point for (b) (4) products and up to 18 months for (b) (4) products (at the date of BLA submission). The 1000 IU dosage strength was bracketed between 500 IU and 1500 IU and stability study was limited to (b) (4) lots manufactured in (b) (4) facility. Based on stability data from lots manufactured at (b) (4) and (b) (4) facility, Inspiration proposed the following shelf-life periods:

(b) (4)

Inspiration stated that (b) (4) lots were manufactured at commercial scale, used almost the same container closure (b) (4) ), and biochemical studies demonstrated comparability between materials manufactured at two different facilities. In addition, stability data between lots manufactured at (b) (4) and (b) (4) showed similar trends over the storage conditions and data points.

Since this BLA will not be approved at this (i.e. the first review cycle) and manufacturing process for drug substance will be changed when compare to the current process, the final decision about product expiry should be based on the data deriving from the finalized stability studies for (b) (4) product and stability data for FDP manufactured from the from next generation of drug substance.

Stability Specifications

I found a scope of the proposed testing acceptable. The acceptance criteria should be adjusted according to the changes recommended by this reviewer to FDP release specifications.

Table 8: Stability Tests

| Test ID | Attribute | Acceptance Criteria |
|---|---|---|
| 1 | • Appearance: Cake<br>• Solubility Time<br>• Solution | • White cake with no dark particles<br>• (b) (4)<br>• Clear, colorless solution free of visible particles |
| 2 | Residual Moisture | |
| 3 | Factor IX Potency | |
| 4 | (b) (4) | (b) (4) |
| 5 | | |
| 6 | | |
| 7 | | |
| 8 | | |
| 9 | | |
| 10 | | |
| 11 | | |
| 12 | | |
| 13 | Sterility | Sterile |
| 14 | (b) (4) | (b) (4) |

Protocols

The testing protocols and storing conditions, including shelf-life, accelerated, and stress conditions are acceptable and in agreement with the recommendations of ICH Q5C guideline. Tables 11-15 show details of the referenced protocols. The photo-stability study was performed for 1500 IU strength only and showed photo-sensitivity of the tested product. In use studies showed that product is stable up to (b) (4) when reconstituted in room temperature.

Table 11: Stability Protocol for IB1001 Drug Product Lots Stored at 5 ± 3°C

| Storage Condition | Months and Test ID per Test Point | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 0 | 6 | 12 | 15 | 18 | 21 | 24 | (b) (4) |
| 5 ± 3°C | (b) (4) | | | | | | | |

Table 12: Stability Protocol for IB1001 Drug Product Lots Stored at 25 (b) (4) C

| Storage Condition | Months and Test ID per Test Point | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | 0 | 2 | 4 | 6 | 9 | 12 | 15 | 18 | 21 | 24 | (b) (4) |
| 25 (b) (4) C | (b) (4) | | | | | | | | | | |

(b) (4)

Stability lots; 500 IU dosage strength

Table 4: History of the Low Strength IB1001 Drug Product Stability Lots

(b) (4)

Stability lots; 1000 IU dosage strength

Table 2: Current Stability Data from the IB1001 Medium Strength Stability Lots

| Drug Product Lot Number | Nominal Strength | Storage Condition and Months of Stability Data | |
|---|---|---|---|
| | | 5°C | 25°C |
| (b) (4) | 1000 IU | 9 | 9 |
| | 1000 IU | 6 | 6 |

(b) (4)

NA: Not applicable

Stability lots; 1500 IU dosage strength

Table 6: Current Stability Data from the IB1001 High Potency Lots

| Drug Product Lot No. | Nominal Potency | Storage Condition and Months of Stability Data | |
|---|---|---|---|
| | | 5°C | 25°C |
| (b) (4) | (b) (4) | (b) (4) | (b) (4) |
| | 1500 IU | 18 | 18 |
| | 1500 IU | 12 | 12 |
| | 1500 IU | 12 | 10 |
| | 1500 IU | 9 | 9 |

NA: Not applicable

Results

All tested samples met the specification requirements when stored at the shelf-life conditions. The 1500 IU dosage strength samples also stay within specification limits when stored at stress conditions at (b) (4). As expected, the 500 IU and 1000 IU failed Potency stability requirements when stressed at (b) (4).

The following trends were statistically significant for all tested dosage strengths and condition storage:

- Decrease of Solubility Time
- Increase of Residual Moisture
- Increase of Potency (at (b) (4) only)
- Decrease or Increase of (b) (4) ( because of data set variability)
- Decrease in (b) (4) (related to Potency values)
- (b) (4)
- (b) (4)
- 
- 

## Conclusions and Recommendations

The review of the original BLA revealed that several outstanding issues related to the clearance of host cell proteins, process validation, control strategy for several unit operations, and final release specification testing have not been resolved satisfactorily during the first review cycle. Therefore, I recommend issuing Inspiration a Complete Response letter containing the following deficiency items:

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

   (b) (4)

2. As 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, 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 has not been provided. Specifically, the understanding of the causes of process variations, ability to detect the variations, and assessment of the potential impacts of the variation on process and product quality attributes were not shown.

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.

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

   (b) (4)

(b) (4)

4. The current (b) (4) campaign is based solely on the (b) (4) Please establish additional (b) (4) criteria that are based on the (b) (4)

5. 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) are too broad and not justified by historical data.

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

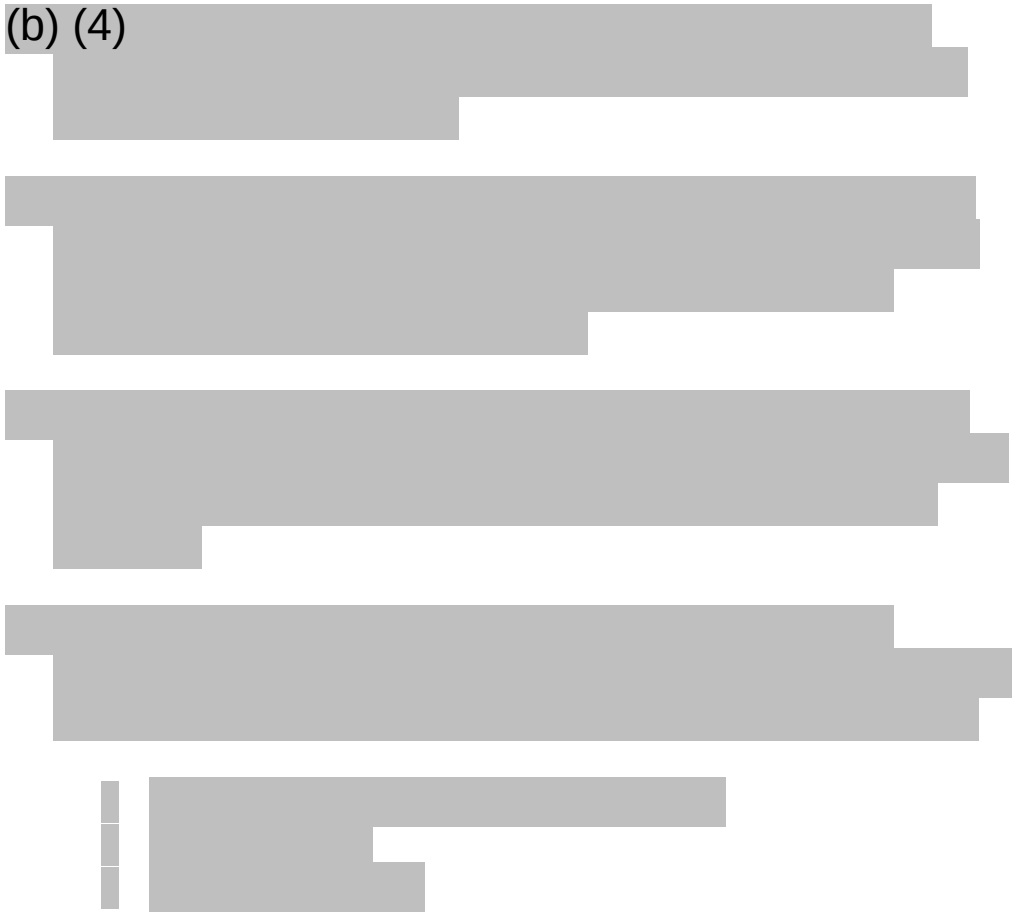
6. With regard to the in-process controls for the (b) (4) step, please:

   (b) (4)

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

   (b) (4)

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




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

9. Please provide, in tabulated 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: content of loaded and cleared impurity by the tested unit operation, log clearance values for the individual unit operation, and calculation of the total log clearance achieved by the entire purification process for each of the referenced impurities.

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

a. Please provide more specific (e.g. side-by-side comparison between the original and modified results) information 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) *Release and Stability Specification* 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:


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)

(b) (4)

*f.* Please identify th (b) (4)

11. 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 drug substance (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.

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

    a. Please provide more specific (e.g. side-by-side comparison between the original and modified results) information 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 Specification* 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)

(b) (4)

(b) (4)

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

14. 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.

15. With regard to the comparability plan for DS manufactured using the current and modified purification processes, submitted on October 11, 2012, please submit 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)

16. 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)

# Appendix I

Development of antibodies against CHO Host Cell Proteins (HCP);

## Background

During the course of the BLA review, Inspiration reported via telecon (May 2012) formation of antibodies against a process related impurity, Chinese Hamster Ovary (CHO) cells host cell proteins (HCP) during the ongoing clinical Study IB1001-01.

Subsequently, Inspiration submitted amendment STN 125426/0.5 containing preliminary investigational data regarding identification of immune-reactive HCPs and corrective action that includes implementation of a new, more sensitive, (b) (4) assay to detect HCP levels at (b) (4) .

According to the firm's last update, 18 of 68 patients (26%) tested by (b) (4) assay were positive for the presence of antibodies against HCP (anti-HCP). Moreover, Inspiration observed an increase in the number of positive patients and, in some patients, significant growth of the anti-HCP titer over the duration of clinical studies. The patients were tested in 3 groups. In Q1 of 2011 there was one positive patient out of 23 tested (4%); in Q3 of 2011 there were four total positive patients out of 35 tested (11%). In a third batch tested in Q1 of 2012 there were 14 additional positive titer patients for a total of 18 out of 68 tested (26%). For four patients, the baseline status is unknown. Two subjects with the highest titers developed reactivity in 2010, along with a third patient that has maintained a low titer over the duration of the study. The titers varied from 316,885 to 163, as established by the Inspiration (b) (4) assay.

No related adverse events (AE) or serious adverse events (AEs) have been reported by Inspiration. In addition, there were no signs of inhibition of the clinical effect of IB1001 on the treatment and prevention of bleeding. The firm stated that that there is no association with a particular lot of the final product and the formation of anti-HCP.

## Safety concerns

The formation of anti-HCP antibodies raises the following safety concerns:

- HCP can act as an adjuvant and trigger formation of antibodies against rFIX in Hemophilia B patients

- The antibodies against HCP may cross –react with human counterpart proteins which may lead to adverse reactions

## PROPOSED CORRECTIVE and PREVENTIVE ACTIONS

(b) (4)

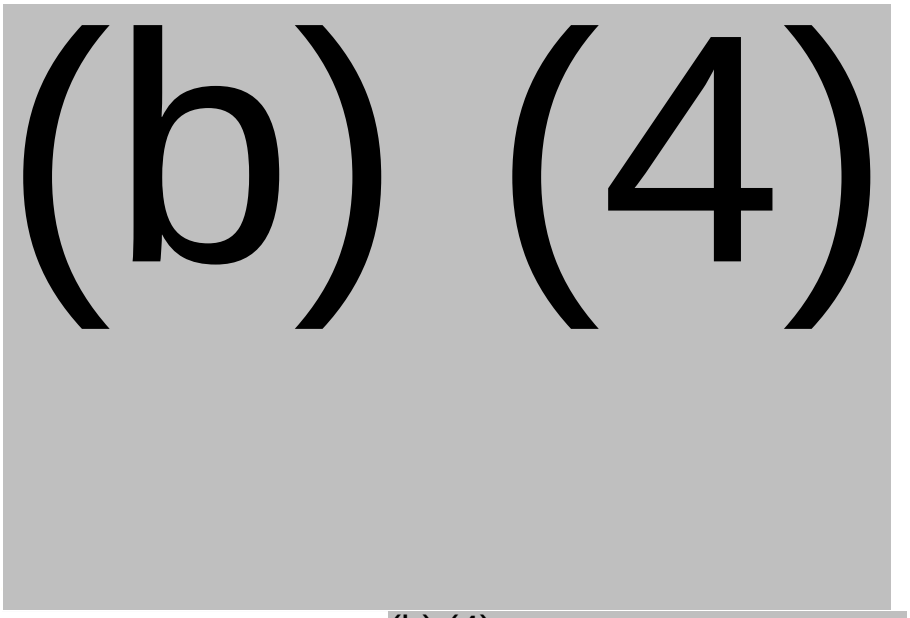
1 page determined not to be releasable: (b)(4)

(b) (4)

(b) (4)

**Proposed Changes to Manufacturing Process**

To lower the level of CHO HCP, Inspiration has proposed improvements in the manufacturing process that will include addition of (b) (4) A preliminary, small scale study demonstrated reduction of HCP in the (b) (4) as demonstrated by the (b) (4) attached below.




In addition, Inspiration considers (b) (4) steps to further reduce the level of HCP. The DS lots manufactured by the modified manufacturing process will be subjected to a comparability exercise that will be comprised of biochemical and nonclinical studies.

**Optimization of the Residual HCP (b) (4) assay**

Inspiration has replaced the currently used (b) (4) assay used for the measurement of residual HCP. The current assay is based on a (b) (4) commercial kit. The new assay uses (b) (4) . According to Inspiration, the sensitivity of the assay and HCP coverage has increased. However, the sensitivity of commercial assays is usually below an in-house developed assay, i.e., an assay based on (b) (4)

**FDA REGULATORY ACTION**

- Inspiration's IND was placed on clinical hold on June 26, 2012.
- The company was informed that the product will not be approved in its current form, i.e., the complete response letter will be issued for the pending BLA application (Action Due Date is on February 2nd, 2013).

**SUMMARY and CONCLUSIONS**

- The cluster of patients that developed antibodies with persistent and growing titer against CHO-HCP is an unusual event for this class of products.
- Up to now, Inspiration has provided limited data from the ongoing CMC investigation, including:
  - preliminary identification of the immunoreactive proteins
  - the initial root cause investigation and plan of corrective action

- change of the HCP (b) (4) assay
- plan of the comparability study

- The adequacy of the proposed studies will be reviewed by FDA in the second review cycle for the pending BLA application ( projected date : Q1/2-2013)

## Appendix 2

Draft comparability plan

**Background**

On October 11, 2012, Inspiration submitted a draft protocol to demonstrate comparability between the Coagulation Factor IX (Recombinant) (rFIX) drug substance (DS) 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 (b) (4) 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) times 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:

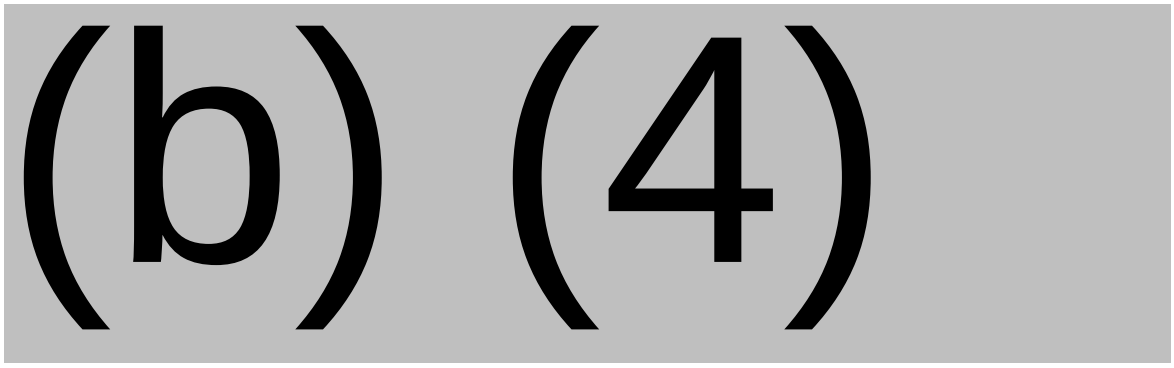
(b) (4)

Reviewers 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)

(b) (4)

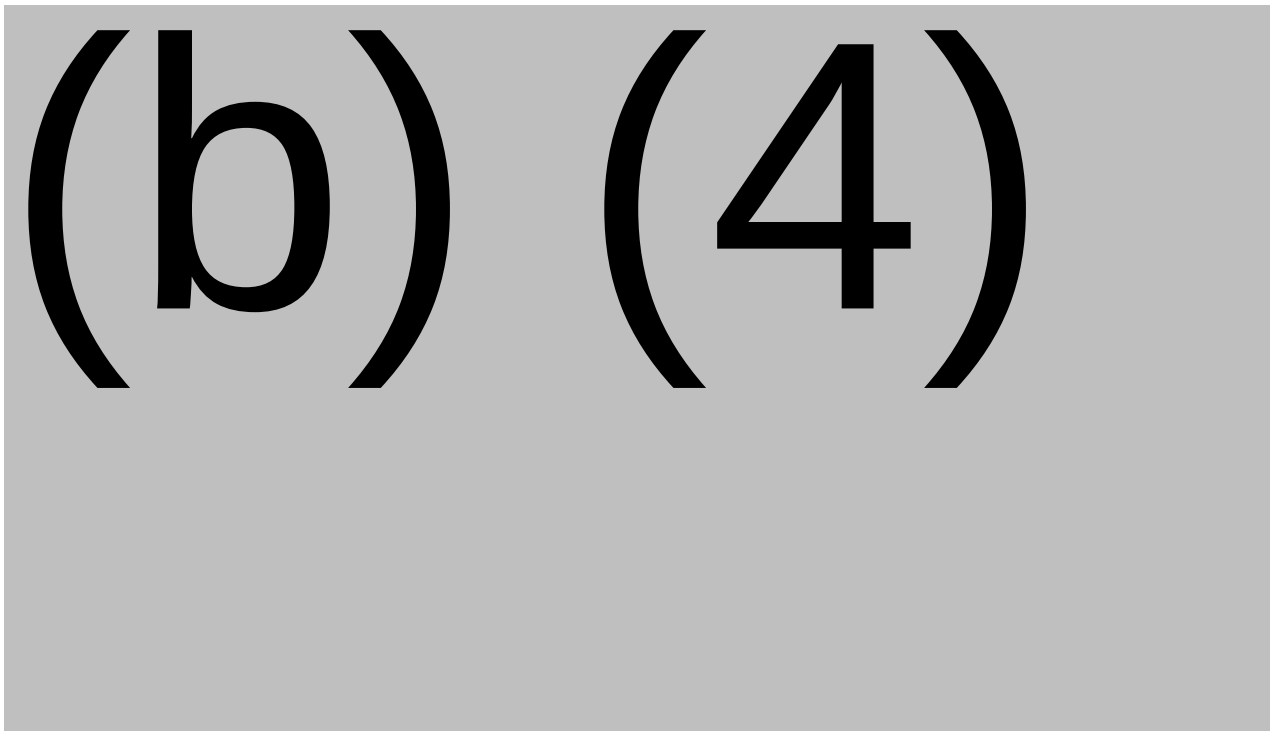
:




**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 heightened biochemical characterization. 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)




Comments:

- Inspiration should submit to the BLA a validation report of an (b) (4) to measure HCP, which uses a (b) (4)

**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) compared to release data the (b) (4) made from the filed commercial process. (b) (4) (b) (4) (b) (4) are considered adequate for resumption of clinical studies considering the minor change to the process and risk assessment that the (b) (4) step is not expected to negatively affect the product quality attributes.
- (b) (4)
- Additional HCP data on the (b) (4) full-scale modified commercial process (b) (4) compared to representative (b) (4) 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.

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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) s 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 virus validations focused on the (b) (4)
- GMP (b) (4) and 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) and drug product representative of the modified commercial process.

**Recommendation**

The following comments were 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 usin (b) (4) and include the validation report in the BLA amendment.