



## DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration  
Center for Biologics Evaluation and Research  
Office of Compliance and Biologics Quality  
Division of Manufacturing and Product Quality

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**To:** BLA STN 125444/0, Coagulation Factor IX (Recombinant), Fc Fusion Protein [ALPROLIX™]  
**From:** Ellen Huang, CSO, OCBQ/DMPQ/MRB II, HFM-676  
**Through:** Marion Michaelis, Branch Chief, OCBQ/DMPQ/MRB II, HFM-676  
**Cc:** Nancy Kirschbaum, Ph.D., Chair, OBRR/DH/LH, HFM-392  
Edward Thompson, RPM, OBRR/DBA/RPMB, HFM-380  
**Subject:** Review of the BLA submitted by Biogen Idec Inc., Lic. # 1697, for the treatment of hemophilia B for: control and prevention of bleeding episodes, routine prophylaxis to prevent or reduce the frequency of bleeding episodes, perioperative management (surgical prophylaxis)  
**Due Date:** December 28, 2013

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### REVIEW RECOMMENDATIONS

I recommend additional information requests be sent to the firm.

### REVIEW SUMMARY

Biogen Idec Inc. (Biogen Idec) submitted a BLA under STN 125444/0 for the licensure of recombinant coagulation factor IX Fc fusion protein (rFIXFc) [ALPROLIX™] for the treatment of hemophilia B. The BLA was submitted by Biogen Idec and received by CBER on December 28, 2012. The proposed indication is for the treatment of hemophilia B, for control and prevention of bleeding episodes, routine prophylaxis to prevent or reduce the frequency of bleeding episodes or perioperative management (surgical prophylaxis). The reconstituted drug product solution is for intravenous injection.

CBER performed Pre-License Inspection (PLI) at the Biogen Idec facility in ----(b)(4)----  
----- from -----(b)(4)----- to support the review of STN 125444/0. The -----(b)(4)----- facility is used for the manufacture of the drug substance and the inspectional findings are documented in the Establishment Inspection Report (EIR).

Information Requests (IR) questions from DMPQ were communicated to the firm on January 22, 2013 and the firm provided a response on February 5, 2013 in Amendment STN 125444/0/5. A second IR was sent to the firm on July 1, 2013 and the firm provided a response on August 9, 2013 in Amendment STN 125444/0/22 and will be reviewed as an Addendum.

As this is a recombinant product, this review was conducted under FDA's *Guidance for Industry for the Submission of Chemistry, Manufacturing, and Controls Information for a Therapeutic Recombinant DNA-derived Product or a Monoclonal Antibody Product for In Vivo Use*. Under this guidance, limited information is required to be submitted regarding facility and equipment. As such, my review is based on this guidance document.

## NARRATIVE REVIEW

### Items Reviewed

- STN 125444/0
- Amendment STN 125444/0/5

I reviewed the manufacturing processes of rFIXFc to include the drug substance (----- (b)(4) -----) performed at Biogen Idec's ----- (b)(4) ----- facility and drug product (formulation, filling, and lyophilization) performed at the contract manufacturer --(b)(4)-- ----- facility, as well as the manufacturing of the diluent performed at the contract manufacturer ----- (b)(4) ----- facility.

My review focused on the facilities, equipment, sterilization, lyophilization, container closure integrity testing, and the filling and packaging. The following facilities in Table 1 are associated with the manufacture of rFIXFc drug substance (DS), drug product (DP), and diluent.

**Table 1: Facilities Associated with Manufacturing of rFIXFc Drug Substance, Drug Product, and Diluent**

Name and Address	Responsibilities	Last FDA Inspection
Biogen Idec, Inc. ----- (b)(4) ----- ----- FEI ----- (b)(4) -----	----- (b)(4) ----- ----- ----- ----- ----- ----- ----- ----- ----- -----	---- (b)(4) ----
Biogen Idec, Inc. 14 Cambridge Center Cambridge, MA 02142 FEI # 1220951	----- (b)(4) ----- ----- ----- ----- ----- -----	3/4-3/15/2013

Name and Address	Responsibilities	Last FDA Inspection
	Diluent QC testing Warehousing DP QC testing Product warehousing	

Name and Address	Responsibilities	Last FDA Inspection
<div>[ --(b)(4)-- ]</div>		

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Biogen Idec's -----(b)(4)----- facility was inspected from -----(b)(4)-----.  
Other facilities inspections were waived or the facilities were not subject to an inspection.  
Please refer to the inspection waiver memo.

### **Product Description**

rFIXFc is a fully recombinant coagulation factor IX (FIX) Fc fusion protein consisting of human coagulation FIX covalently linked to the Fc domain of human immunoglobulin G1 (IgG1). rFIXFc is produced in human embryonic kidney (HEK) (b)(4) cells that have been -----(b)(4)-----  
-----.

rFIXFc is formulated as a sterile, non-pyrogenic, preservative-free, white, lyophilized powder for IV administration in a single-use vial. It is available in single-use vials containing the labeled amount of FIX activity, expressed in IU. Each vial contains nominally 500, 1000, 2000, or 3000 International Units (IU) of rFIXFc for reconstitution with provided diluent.

### **Overview of Manufacturing**

The rFIXFc DS is manufactured at the Biogen Idec in -----(b)(4)-----  
------. The rFIXFc drug product (DP) and diluent for reconstitution are  
manufactured for Biogen Idec by -----(b)(4)-----  
------. The DP is manufactured at the -(b)(4)- facility located in -----(b)(4)----  
------. The diluent (0.325% [w/v] sodium chloride) is produced at the -----(b)(4)-----  
----- site. The rFIXFc DP is provided in a 10 mL vial as a  
lyophilized powder. The diluent is provided in a prefilled syringe. Both components are  
packaged into a product kit along with a syringe plunger rod and vial adapter.

No raw materials of direct animal origin are used in either the cell banking or the rFIXFc manufacturing processes.

### **DRUG SUBSTANCE**

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Biogen Idec Inc.  
Coagulation Factor IX (Recombinant), Fc Fusion Protein

BLA STN 125444/0

Fourteen (14) Pages Determined to be Non-Releasable: (b)(4)

## DRUG PRODUCT

### **Establishment Description**

Other product categories in clean room (b)(4) are:

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The -----(b)(4)----- facility does not manufacture the following product types:

- beta-lactams
- cytotoxic products
- live or attenuated virus
- microorganisms

Since -----(b)(4)----- works exclusively as a contract manufacturer, all additional products are beyond the pre-clinical status, i.e., are either under clinical investigation or are approved for marketing.

**Manufacturing Process for DP**

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Biogen Idec Inc.  
Coagulation Factor IX (Recombinant), Fc Fusion Protein

BLA STN 125444/0

Three (3) Pages Determined to be Non-Releasable: (b)(4)

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All of the specifications for the DP can be found in Table 13 of *eCTD 2.3P – Drug Product -----(b)(4)----- – power for injection – Biogen Idec*.

**Release and Stability Specifications**

The firm also provided the release and stability specifications for the DP. Table 8 below summarizes the specifications that are under DMPQ's purview.

**Table 2 Release and Stability Acceptance Criteria**

	Release Acceptance Criteria	Stability Acceptance Criteria
Appearance	White to off-white powder to cake	White to off-white powder to cake

	Release Acceptance Criteria	Stability Acceptance Criteria
Residual Moisture	(b)(4)	(b)(4)
Appearance, after reconstitution	----- (b)(4) ----- ----- ----- -----	----- (b)(4) ----- ----- ----- -----
Reconstitution Time	----- (b)(4) -----	----- (b)(4) -----
Endotoxin	----- (b)(4) ----- ----- ----- ----- -----	----- (b)(4) ----- ----- ----- ----- -----
Sterility	--- (b)(4) ---	(b)(4)
Container Closure Integrity	(b)(4)	--- (b)(4) ---

The proposed shelf life of the DP by the firm is 24-months. The stability study included a bracketed approach that included three lots of (b)(4) IU/vial, three lots of 3000 IU/vial and one lot each of 500, 1000, and 2000 IU/vial. All stability specifications were met that were under DMPQ's purview.

All of the specifications for the DP can be found in section 5 of *eCTD 2.3.P – Drug Product* ----- (b)(4) ----- – *power for injection – Biogen Idec.*

#### ***Reviewer's Comments***

- During review of the process consistency validation, it was noted that often the action limit or in-process specification for endotoxin was much higher than the actual results and did not reflect the process capabilities. The Product Office made the same observation and requested the firm to change their endotoxin in-process specification and release limits. Refer to IR sent on July 1, 2013.

#### **Process Validation for DP**

For process validation the firm completed process consistency, media fill, sterile filter, and hold time validations.

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All rFIXFc DP lots met release specifications. The firm also provided the critical parameter results.

Assessment of the effect of vial placement in the lyophilizer on product quality attributes was not possible during the Process Consistency Validation runs due to the GMP nature of runs. The impact of vial location on product quality attributes was extensively assessed in at-scale technical runs. No differences in product quality attributes were observed between different positions within a shelf and different shelves in the lyophilizer.

The firm also provided critical and major manufacturing deviations during process validation in section 5.5 of *eCTD 3.2.P.3.5 – Drug Product – Process Validation and/or Evaluation*. The deviations appeared to have no product impact.

***Reviewer's Comments***

- As mentioned previously for the DS process consistency section, further clarification from is needed to understand the -----(b)(4)----- to manufacture the DP. Additionally, it appears that DS Batches -----(b)(4)----- were not from the DS conformance lots. A telecon with the sponsor will be held on August 20, 2013 to discuss this further.
- The firm did not provide any information regarding lyophilization validation. Also, as noted in the DP Container Closure system section, the firm has (b)(4) vial vendors. It was not clear if lyophilization included vials from (b)(4) manufacturers. Refer to **IR Question 4** for this request.

**Media Fill Validation**

The firm provided a summary of the (b)(4) media fills required to ---(b)(4)--- the process of DP on filling line -----(b)(4)----- site (refer to Table 10). All (b)(4) media fills passed the protocol acceptance criteria for a successful media fill. rFIXFc uses a (b)(4) vial which is ---(b)(4)--- by the media fills listed in Table 10 covering vials sizes between ----(b)(4)---.

**Table 3 Media Fill Details**

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The viable monitoring requirements during the filling period and the microbial monitoring results for the (b)(4) media fills were provided. All requirements were met. However, there was an exception of the microbiological monitoring for media fill -----(b)(4)----- . An objectionable organism (growth of spore forming germ) was found on a personnel.

Additional details about the media fill are found in section 5.9 of *eCTD 3.2.P.3.5 – Drug Product – Process Validation and/or Evaluation*.

***Reviewer's Comments:***

- It is not clear if the firm performed an investigation for the objectionable organism found on an operator and the outcome. I recommend this to be sent to the firm as an IR.
- While the firm stated they are using (b)(4) vials, it is unclear what the fill volume is for the DP. The firm was asked to provide this information in **IR Question 7** below.

**Sterile Filter Validation**

The validation studies performed on the sterilizing filter used in the manufacture of the DP included product ---(b)(4)--- determination, -----(b)(4)-----, microbial challenge, and extractable substances (under the Product Office purview). All study acceptance criteria were met confirming that the sterilizing filter is compatible with the product -----(b)(4)----- . There were no deviations or exceptions documented during the filter validation studies. The validated filtration parameter ranges -----(b)(4)----- respectively. All validation studies were executed at controlled -----(b)(4)----- . Additional details about the media fill are found in section 5.10 of *eCTD 3.2.P.3.5 – Drug Product – Process Validation and/or Evaluation*.

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**Table 4 Acceptance Criteria for Microbial Challenge Testing**

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*Reviewer's Comments*

- It was not clear if the bacterial challenge included the “worst-case” sterilization conditions and if the firm evaluated if the product is inhibitory or stimulator towards growth of ----(b)(4)----- I recommend this be sent to the firm as an IR.

Hold Time Validation

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### *Reviewer's Comments*

- ## Containment/Cross-Contamination

All rFIXFc DP contact equipment, including the filling needles, is dedicated and is cleaned according to an approved SOP before use. Filters and tubing used in the rFIXFc DP aseptic filling process are --(b)(4)--. At the completion of a campaign, product changeover is performed according to approved procedures prior to introducing another product into that area. In addition, personnel are trained in procedures that prevent cross-contamination, including proper gowning procedures, material and product flow, aseptic handling, handling of product waste, etc.

Product change-over is performed between each product manufacturing campaign. The changeover activities include the following:

- Upon successful completion, the area is released for manufacture of the next product.

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Access to the manufacturing area is controlled. Personnel enter the production area through air locks. Gowning and personal sanitization requirements are defined in approved SOPs, and must be adhered to by all personnel entering the manufacturing facilities area. The firm provided personnel, material, and waste flow diagrams in eCTD 3.2.A.1 -----(b)(4)----- – powder for injection -----(b)(4)-----  
----- – Facility and Equipment Drawings – (b)(4) and they appear appropriate.

***Reviewer's Comment***

- Also, it is not clear how the filled product is physically transported to the lyophilizer. I recommend asking the firm to clarify this.

**Equipment Cleaning Validation**

In general, equipment used for manufacturing is easy to clean with smooth surfaces. Preferably stainless steel equipment is used (with the exception of single use equipment). New active ingredients and excipients introduced into the -(b)(4)- facility are evaluated with respect to their physico-chemical and pharmacological properties prior to production according to an established cleaning validation policy. Based on the results of this evaluation, cleaning procedures are established for the equipment.

Cleaning validation for rFIXFc DP is covered by an established matrix cleaning validation. The worst case substance is considered an appropriate substitute for rFIXFc DP based on a risk analysis of chemical class and physico-chemical properties. Re-qualification of cleaning validation of the worst case substance is performed --(b)(4)--, and is generally conducted on ----(b)(4)----. Cleaning of the lyophilizer is covered by the cleaning validation.

***Reviewer's Comment***

- A summary of the firm's cleaning validation for manufacturing equipment was requested. Refer to **IR Question 1b** below in the "Review Question" section.

**Environmental Monitoring (EM)**

The firm performs viable and non-viable monitoring to ensure sterile manufacturing of rFIXFc DP. Details on the environmental controls in place at the manufacturing facility are defined and maintained in --- (b)(4) --- SOPs.

**Viable Monitoring**

Surfaces in Grade (b)(4) (Class (b)(4)), Grade (b)(4) (Class (b)(4)) and Grade (b)(4) (Class (b)(4)) areas are monitored at established locations. ----(b)(4)---- are used on surfaces and on personnel (hands and arms). Surface monitoring is performed --(b)(4)-- of production of a batch in Grade (b)(4) areas, --(b)(4)-- during production of a batch in Grade (b)(4) areas, and routinely monitored --(b)(4)-- the LAF protected areas for Grade (b)(4) areas. In -(b)(4)- areas both the laminar flow area and the surrounding Grade (b)(4) area are monitored on a routine basis. Personnel monitoring is conducted on a routine basis for all personnel who enter the clean room environment Grade (b)(4) and Grade (b)(4). All personnel are sampled on fingers, thumbs, and arms. Incubation, evaluation and germ identification of -(b)(4)- is performed according to established SOPs.

Viable air monitoring is performed in Grade (b)(4) areas where the DP is sterile filtered and filled, in the surrounding Grade (b)(4) and Grade (b)(4) areas on defined sampling points. Grade (b)(4) areas are also routinely monitored --- (b)(4) --- the LAF protected areas according to valid - (b)(4) - SOPs.

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Non-Viable Particulate Monitoring

--- (b)(4) --- non-viable particulate monitoring is performed at designated locations in Class (b)(4) and Class ----- (b)(4) ----- during operations. In Class - (b)(4) - ----- monitoring is performed during operations. Particle counts for particles (b)(4) and particle (b)(4)  $\mu\text{m}$  are monitored.

The limits for non-viable particulate monitoring during operations are set according to the requirements of the current version of ----- (b)(4) -----, and are established in valid - (b)(4) - SOPs. Table 12 includes the limits for non-viable particulate monitoring.

**Table 5 Limits for Non-Viable Particulate Monitoring**

Room classification	Parameter	Maximum permitted no. of particles/ft <sup>3</sup>	unit
-- (b)(4) --			

Equipment/Systems for DP

rFIXFc DP contact equipment is dedicated and/or single use. Operations in which the product or sterilized components are exposed to the environment are performed under Grade ----- (b)(4) ----- . A list of major and support equipment used in the manufacture of rFIXFc DP is provided in Tables 13 and 14.

**Table 6 Major Equipment Used in the Manufacture of rFIX Drug Product**

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--(b)(4)--

**Table 7 Support Equipment Used in the Preparation of rFIXFc Fill Materials**

Function	Major Equipment
Washing of vials	----- (b)(4) -----
Sterilization of equipment and packaging materials	---- (b)(4) ----
Depyrogenation of vials	---- (b)(4) ----
Filling of rFIXFc formulated solution	----- (b)(4) -----
Lyophilization of Vials	---- (b)(4) ----
Washing of equipment	----- (b)(4) ----- -----

<sup>1</sup> Equivalent equipment may be used

The ----- (b)(4) ----- and are cleaned according to defined procedures based on the results of the cleaning validation (final rinse is with (b)(4)). After cleaning the ----- (b)(4) ----- using a validated cycle.

Filters used for filtration of rFIXFc ----- (b)(4) ----- . Filter testing is performed ----- (b)(4) ----- of the filters according to the filter specifications. Post-use testing of filters is also performed.

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***Reviewer's Comment:***

- The firm mentions that equivalent equipment can be used. The firm was asked to clarify this in **IR Question 11** below.
- It is not clear if there is any new equipment implemented as a result of rFIXFc drug product. I recommend seeking clarification from the firm.

### **Container Closure for DP**

The rFIXFc DP is lyophilized in a -----(b)(4)----- glass vial. Vials from -----(b)(4)----- vials have the same specifications. Vials are closed with a 20 mm chlorobutyl elastomer stopper, with a -----(b)(4)----- . The stoppered vials are sealed with 20 mm aluminum seals with a -----(b)(4)----- flip off cap, of various colors, dependent on vial strength. The rFIXFc DP kit also includes a 20mm vial adapter transfer device for use during reconstitution from -----(b)(4)----- [510(k) approved Class II medical device --- (b)(4) ---]. Details of these components are in Table 15 below.

**Table 8 FIXFc Powder for Injection, Container Closure System**

Component	Description of Material	Manufacturer
Vial	----- (b)(4) ----- ----- -----	----- (b)(4) ----- ----- -----
Stopper	----- (b)(4) ----- ----- ----- ----- ----- ----- ----- -----	----- (b)(4) ----- ----- ----- ----- ----- ----- ----- -----
Seal (no product contact)	20 mm, Aluminum crimping seal, ----- (b)(4) ----- flip off cap: (b)(4) - Yellow ((b)(4)) (b)(4) - Royal Blue (500 IU/vial) (b)(4) - Green (1000 IU/vial) (b)(4) - Red (2000 IU) (b)(4) - Mist Grey (3000 IU/vial) Delivered “ready to sterilize”	----- (b)(4) ----- ----- ----- ----- ----- ----- ----- -----

The firm also provided extractable and leachable testing, which is under the Product Office’s purview. The specifications and drawings for each of the components were provided. Additionally, the firm provided the DMF number for the vials and stoppers. Details about the container closure system can be found in in eCTD 3.2.P.7 *Drug Product* – ----- (b)(4) ----- – *powder for injection* – *Container Closure System*.

### ***Reviewer’s Comment***

- It is not clear how the vial and stopper are qualified. I recommend seeking clarification on this.

### **Preparation of Components for DP**

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***Reviewer's Comment***

- The firm was asked for a summary of the sterilization validation for these components. Refer to **IR Question 1a**.
- I confirmed on FDA's website that the vial adapter is 510(k) cleared.

**Container Closure Integrity for DP**

For CCIT for the DP, the firm used the ----(b)(4)---- method. The procedure was performed at a contract manufacturing organization, -----(b)(4)-----, according to approved procedures. Three finished lots of rFIXFc (b)(4) IU/vial DP were tested, and all passed the pre-defined acceptance criteria. All strengths of rFIXFc use the same container closure components prepared and assembled in the same manner; therefore, this study is applicable to all strengths of rFIXFc.

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The results from the testing showed that there was no detectable level of ----- (b)(4) ----- in any of the test articles. The results also showed that the positive visual and --- (b)(4) --- controls were ----- (b)(4) ----- after the test performance as expected. Negative controls showed no visible levels of coloration.

***Reviewer's Comments***

- The actual CCIT validation report was requested in **IR Question 5a**.
- The firm used a positive control of -(b)(4)-. Typically, a positive control of -(b)(4)- is used. The firm was asked to provide their rationale for why -(b)(4)- was selected as the positive control and why it is appropriate. Also, the firm was asked if they had shown the presence of ----- (b)(4) ----- positive control size in your study. Refer to **IR Question 5b and 5d**.
- The firm stated the acceptance criterion for this study as, “any visual incursion of -(b)(4)- into the test vials constitutes a failure.” The firm was asked if they have qualified the operators to be able to detect small leaks approaching worst case and if the concentration of (b)(4) is sufficient to be detected by visual inspection. Refer to **IR Question 5c**.
- Since the firm has (b)(4) vial vendors, the firm was asked if CCIT was performed on (b)(4) vials. Refer to **IR Question 5e**.
- Also, I asked the firm if any part of the container closure system that is product contact contains latex. Refer to **IR Question 5f**.

**Container Closure Integrity for Stability Testing for DP**

Container Closure Integrity is conducted in lieu of sterility for stability testing as allowed per ICH Q5C using a ----- (b)(4) ----- method. rFIXFc DP vials and positive controls consisting of breached rFIXFc DP vials are placed ----- (b)(4) -----

----- after reconstitution with 5 mL 0.325% sodium chloride (NaCl) (rFIXFc Diluent) per vial to determine if ---- (b)(4) ----.

Sample ---- (b)(4) ---- must be below that of the detection limit (DL) preparation (rFIXFc drug product spiked to ----- (b)(4) -----) to pass the test. Positive and negative controls are used to ensure validity of the assay. Positive controls were prepared using ----- (b)(4) -----.

The validation for the Container Closure Integrity assay can be found in eCTD 3.2.P.5.3.17 Drug Product - ----- (b)(4) ----- – powder for injection – Validation of Analytical Procedures-Safety-Container Closure Integrity.

***Reviewer's Comments***

- Overall, the validation appears acceptable. However, the -----(b)(4)----- was not provided. I recommend requesting this information.
- It is not clear why the firm is using a different test methods for CCIT during stability versus testing the initial container closure. I recommend seeking clarification from the firm.

### **Shipping DP**

DP vials are packaged into -----(b)(4)----- shipping container. For shipment, DP vials are loaded into a -----(b)(4)----- storage container. The storage container maintains temperature of -----(b)(4)----- . The container is shipped by a -----(b)(4)----- to the finished goods manufacturing site. Temperature and shipping qualification studies were completed. Typical shipping routes for DP are from --- (b)(4) --- USA. ----(b)(4)----- testing was used to simulate a typical international shipment.

The temperature qualification was designed to expose the shipper to a -----(b)(4)----- temperature profile. During this qualification, the temperature was monitored, and confirmed to maintain -----(b)(4)----- duration. As part of the shipping qualification, DP was exposed to -----(b)(4)----- testing which simulate the stresses of warehouse handling, vehicle loading and un-loading, and transportation by ----(b)(4)----. The acceptance criteria included temperature control, visual inspection, and CCIT. All acceptance criteria were met.

Additionally, as part of shipping qualification, CCIT was used to confirm that the container closure system remains intact. This testing is performed as part of shipping qualification in lieu of sterility testing per ICH Q5C. CCIT was performed on DP vials after they have been subjected to the hazards of shipping, such as -----(b)(4)----- . Sample ----(b)(4)---- of the test sample was below the detection limit. For the CCIT test method, please refer to the “Container Closure Integrity for Stability Testing” section above.

Additional information about the shipping studies can be found in eCTD 3.2.P.3.3.3 *Drug Product* - ----(b)(4)---- – *powder for injection* – *Shipping Information*.

### **Reviewer’s Comments**

- According to ----(b)(4)----, depending on the distribution cycle, various test schedules are employed to simulate shipping conditions. I recommend asking the firm specifically what testing was performed.

### **DILUENT**

The rFIXFc diluent is an aseptically filled, --- (b)(4) --- sterilized 0.325 w/v % sodium chloride solution used for the reconstitution of all strengths of the rFIXFc lyophilized DP. The diluent is supplied as a 5 mL fill in a single-use prefilled syringe.

### **Establishment Description**

Manufacturing of rFIXFc diluent is performed at -----(b)(4)----- . The rFIXFc diluent is filled in -----(b)(4)----- . The physical



facilities at (b)(4) consist of material preparation areas, (b)(4) areas, material and personnel airlocks, and (b)(4) filling areas. All surface finishes are made of impervious materials, which facilitate cleaning and maintenance.

The facility was designed as a multi-product manufacturing facility. Products are filled on a (b)(4) within a clean room area. All production steps where product is exposed to the environment are performed under (b)(4).

Other product categories filled in clean room (b)(4) are:

(b)(4)

The (b)(4) facility does not manufacture the following product types:

- beta-lactams
- cytotoxic products
- live or attenuated virus
- microorganisms

Since (b)(4) works exclusively as a contract manufacturer, all additional products are beyond the pre-clinical status, i.e., are either under clinical investigation or are approved for marketing.

**Manufacturing Process for Diluent**

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(b)(4)

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One (1) Page Determined to be Non-Releasable: (b)(4)

A number of in-process controls and testing is performed for the diluent, including bioburden, filled syringes, ---(b)(4)--- sterilization, and finished product.

In-process controls and tests for bioburden are taken at the following points.

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**Release and Stability Specifications for Diluent**

Below are release and stability specifications under DMPQ's purview.

Attribute	Release Acceptance Criteria	Stability Acceptance Criteria
Appearance	Clear, colorless solution, essentially free of visible particles	Clear, colorless solution, essentially free of visible particles
Endotoxin	---(b)(4)---	---(b)(4)---
Final Container Sterility	No Growth	No Growth

All of the specifications for the diluent can be found in section 5 of *eCTD 2.3.P – Drug Product* -----(b)(4)----- – *Diluent* – --(b)(4)--.

**Process Validation for Diluent**

For process validation the firm completed process consistency, ----(b)(4)---- sterilization, media fill, filter, and hold time validations.

**Process Consistency Validation**

Three commercial scale lots of diluent were manufactured during the validation campaign. Diluent lots were manufactured to --(b)(4)-- the proposed commercial process which ranged in volume from ----(b)(4)---- (approximately -----(b)(4)-----). The identity and sizes of the individual process validation lots are summarized in Table 16.

**Table 9 Process Validation Overview**

[ --(b)(4)-- ]

[ --(b)(4)-- ]

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

All three validation lots were successfully manufactured. In-process and release test results for all three validation lots met the pre-defined acceptance criteria. In-process parameters were monitored and in-process samples were analyzed to document the consistency and reliability of the process.

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

There were four deviations during the process validations. Two of them were related to batch --(b)(4)--, which was aborted. These deviations were related to sampling errors. One of the deviations was for batch --(b)(4)--, which was also aborted since a long, black particle was found in the NaCl solution after --- (b)(4) ---. The root cause was not definitive, but the firm suspects that the particle was from the raw material and the lot of NaCl was discarded. The last deviation affected lot --(b)(4)-- where the sample for viable count testing was tested at ----- (b)(4) -----.

There is no impact since the sample was tested after a greater hold time.

For additional details about the process validation, other parameters measured, and deviations, refer to eCTD 3.2.P.3.5 *Drug Product – Diluent for ----- (b)(4) ----- – diluent – ----- (b)(4) ----- – Process Validation and/or Evaluation.*

----- (b)(4) -----  
----- (b)(4) -----  
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----- (b)(4) -----  
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***Reviewer's Comment:***

- ## Media Fills

------. All acceptance criteria were met.

- Since the diluent is ---(b)(4)----sterilized, media fills are not required. However, I reviewed the summary of their media fill and found it acceptable.

(b)(4)

(b)(4)

(b)(4)

The validation of hold times related to the diluent manufacturing process at (b)(4)- in (b)(4) met the protocol acceptance criteria. One lot of rFIXFc diluent was produced (b)(4)-. Of note, lot (b)(4)- passed the bioburden specification of -----(b)(4)----- for the in-process testing -----(b)(4)-----.

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validity of the study, and samples tested meet the specifications presented in the original hold time protocol. All bioburden results were -(b)(4)- syringes and the endotoxin results were -(b)(4)-.

***Reviewer's Comments***

- Generally firms perform three or more hold time studies. However, for the diluent, the firm only performed a hold time study on one lot. I recommend asking the firm to provide their rationale on why two lots are acceptable.

**Heating, Ventilation and Air Conditioning (HVAC)**

All rooms involved in manufacturing have proper pressure differentials to facilitate the flow of air from critical to less critical areas. All operations where product is exposed are performed --- (b)(4) ---.

The HVAC system provides conditioned air to the clean room areas. Supply air for the clean room areas consists of up to (b)(4) re-circulated air and minimum (b)(4) fresh air.

For air filtration, HEPA filters are used. HEPA filters are included in an existing program for performance testing and maintenance. HEPA filters in (b)(4) areas of clean rooms are integrity tested ---- (b)(4) ----. In addition, ----- (b)(4) ----- are equipped with audible and optical alarms.

**Containment/Cross-Contamination**

-(b)(4)- uses facility design features, equipment design, operating procedures, in-process controls, training, and changeover to prevent contamination and cross-contamination. In addition, -(b)(4)- maintains temporal and/or spatial separation of operations and product.

All rFIXFc diluent contact equipment is dedicated, and is cleaned according to an approved SOP before use. Filters and tubing used in the rFIXFc diluent aseptic filling process are ---- (b)(4) ----. At the completion of a campaign, product changeover is performed according to approved procedures prior to introducing another product into that area. In addition, personnel are trained in procedures that prevent cross-contamination, including proper gowning procedures, material and product flow, aseptic handling, handling of product waste, etc.

**Cleaning Validation**

New active ingredients and excipients introduced into the -(b)(4)- facility are evaluated with respect to their physical-chemical and pharmacological properties prior to production according to an established cleaning validation policy. Based on the results of this evaluation, cleaning procedures are established for the equipment.

Cleaning validation for the rFIXFc diluent solution is covered by an established matrix cleaning validation based on a risk analysis of chemical class and physical-chemical properties. NaCl is currently classed as a ----- (b)(4) ----- . Based on the results of this evaluation, cleaning procedures are established for the equipment. The approach to cleaning validation incorporates the use of product-specific, validated analytical assays. Re-qualification of cleaning validation is performed -(b)(4)-, and is generally conducted

on (b)(4) production run. Filters and tubing used in the formulation and filling processes are -(b)(4)-.

In general, equipment used for production is easy to clean with smooth surfaces. Only stainless steel and glass equipment is used (with the exception of single use equipment). All product contact equipment is cleaned before use.

#### Product Changeover

Product changeover is performed between each product manufacturing campaign. The changeover activities include the following:

- Areas/rooms, equipment, and support requiring cleaning and verification that cleaning is complete.
- Cleaning acceptance criteria and verification that acceptance criteria were met after cleaning.
- Identification and verification of miscellaneous items to be discarded or stored.
- Portable equipment to be stored and verification of storage, including location.
- Filter replacement on specified equipment.

Upon successful completion of change-over activities, the area is released for manufacture of the next product.

#### Environmental Monitoring

The firm performs viable and non-viable monitoring to ensure sterile manufacturing of rFIXFc diluent. Details on the environmental controls in place at the manufacturing facility are defined and maintained in -(b)(4)- SOPs.

#### Viable Monitoring

Surfaces in Grade (b)(4) (Class (b)(4)), Grade (b)(4) (Class (b)(4)) and Grade (b)(4) (Class (b)(4)) areas involved in manufacturing are monitored at established locations. Surface monitoring is performed ----- (b)(4) ----- in Grade (b)(4) areas and is performed --- (b)(4) --- during production of a batch in Grade (b)(4) areas. Grade (b)(4) areas are also routinely monitored ---- (b)(4) ---- the LAF protected areas. Personnel monitoring is conducted on a routine basis for all personnel who enter the clean room environment Grade (b)(4) and Grade (b)(4). All personnel are sampled on fingers, thumbs, and arms. ----- (b)(4) ----- is performed according to established SOPs.

Viable air monitoring is performed in Grade (b)(4) areas where the product is sterile filtered and filled, in the surrounding Grade (b)(4) and Grade (b)(4) areas on defined sampling points. Grade (b)(4) areas are also routinely monitored --- (b)(4) --- the LAF protected areas according to valid -(b)(4)- SOPs. Air sampling in Grade (b)(4) and Grade (b)(4) is performed via ----- (b)(4) ----- . In Grade (b)(4) areas air sampling is additionally performed with -- (b)(4) -- during setup and during filling operation. Air monitoring is performed --- (b)(4) --- in Grade (b)(4) areas. In Grade (b)(4) areas air monitoring is performed ----- (b)(4) ----- is performed according to established SOPs.

#### Non-Viable Particulate Monitoring

Continuous non-viable particulate monitoring is performed at designated locations in Class (b)(4) and Class (b)(4) on -----(b)(4)----- during operations. In Class (b)(4) ----- monitoring is performed during operations. Particle counts for particles -(b)(4)- and particle -(b)(4)- are monitored. The limits for non-viable particulate monitoring during operations are set according to the requirements of the current version of -(b)(4)- of the -----(b)(4)-----, and are established in -(b)(4)- SOPs. The limits are listed in Table 17 below.

**Table 10 Limits for Non-Viable Particulate Monitoring**

[  
--(b)(4)--  
]

Equipment for Diluent

rFIXFc diluent contact equipment is dedicated and/or single use. Operations in which the product or sterilized components are exposed to the environment are performed under Grade -----(b)(4)----- . A list of major equipment used in the manufacture of rFIXFc diluent is provided in Table 18. In addition, Table 19 provides a summary of the support equipment used to prepare rFIXFc fill materials. Support equipment is not product dedicated as they are non-product contact equipment.

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

[  
--(b)(4)--  
]

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

[  
--(b)(4)--  
]



[illegible]

- The firm mentions that equivalent equipment can be used. The firm was asked to clarify this in **IR Question 11** below.
- It is not clear if there is any new equipment implemented as a result of rFIXFc diluent. I recommend seeking clarification from the firm.

The rFIXFc DP was designed to be reconstituted with 5mL of 0.325% NaCl using a vial adapter. Based on the design requirements, a 5 mL -----(b)(4)----- glass barrel with luer-cone and groove needle attachment (luer lock syringe) was selected. Each syringe is closed with a ----(b)(4)----- bromobutyl plunger and a tamper evident closure system -----(b)(4)----- closure is comprised of a bromobutyl tip cap, a ----(b)(4)----- luer lock, and a ----(b)(4)----- tamper-evident cap.

**Table 11 rFIXFc Diluent Container Closure System**

Primary Packaging Material	Manufacturer DMF No.	Type of Material
Syringe Barrel	----- (b)(4) ----- -----	<ul style="list-style-type: none"> <li>• 5 mL syringe with luer cone and groove</li> <li>• ---- (b)(4) ----- glass, clear</li> <li>• Compliant with ----- (b)(4) -----</li> </ul>
(b)(4) Closure System: (Seal and Tip Cap)	----- (b)(4) ----- ----- ----- -----	<ul style="list-style-type: none"> <li>• Tip cap: bromobutyl rubber, -(b)(4)-, grey, compliant with ----- (b)(4) -----</li> <li>• Tamper-evident seal (no product contact), ---- (b)(4) ----</li> <li>• Luer lock (no product contact), ---- (b)(4) ----</li> </ul>
Plunger	--- (b)(4) --- -----	<ul style="list-style-type: none"> <li>• ---- (b)(4) ---- bromobutyl rubber</li> <li>• Compliant with ----- (b)(4) -----</li> </ul>

The firm provided a description on how the components are prepared, the specifications for the components, drawings, DMF number, extractable/leachable testing (Product's Office purview), and CCIT in eCTD 3.2.P.7 *Drug product – Diluent for ---- (b)(4) -----* ----- – *Container Closure System*.

***Reviewer's Comment***

- It is not clear how the syringe barrel, (b)(4) closure system, and plunger are qualified. I recommend seeking clarification on this.

**Preparation of Components for Diluent**

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----- (b)(4) -----  
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***Reviewer's Comment***

- The firm provided the -----(b)(4)----- studies in their response to **IR Question 1a.**

**Container Closure Integrity for Diluent**

CCIT on the rFIXFc diluent was performed by means of a -----(b)(4)----- test, with an optical inspection. The procedure was performed at a contract manufacturing organization, -----(b)(4)-----, according to approved procedures. A minimum of (b)(4) units from each of (b)(4) finished lots of rFIXFc diluent syringe were tested and all passed the predefined acceptance criteria.

The test method was the same as for the DP (refer to “Container Closure Integrity for DP”). The results from the testing showed that there was no detectable level of ---(b)(4)----- in any of the test syringes. The results also showed that the positive visual and capillary controls were -----(b)(4)----- after the test performance as expected. Negative controls showed no -----(b)(4)-----.

**Shipping Diluent**

Diluent syringes are stored and shipped at -(b)(4)- conditions. Diluent syringes are shipped to the label and packaging site utilizing a -----(b)(4)----- storage container. The storage container maintains temperature of -----(b)(4)----- . The container is shipped by a combination or -(b)(4)- to the finished goods manufacturing site. Typical shipping routes for diluent syringe are from -----(b)(4)----- USA. Standardized -----(b)(4)----- testing was used to simulate a typical international shipment.

The temperature qualification was designed to expose the shipper to a -----(b)(4)----- temperature profile. During this qualification, the temperature was monitored, and confirmed to maintain -----(b)(4)----- . The acceptance criteria for the diluent syringe shipper temperature qualification temperature control, visual inspection, and container closure integrity. All acceptance criteria were met.

Additional information about the shipping studies can be found in in eCTD 3.2.P.3.3.3 *Drug Product - -----(b)(4)----- – powder for injection – Shipping Information.*

***Reviewer's Comments***

- According to --(b)(4)--, depending on the distribution cycle, various test schedules are employed to simulate shipping conditions. I recommend asking the firm specifically what testing was performed.

**LABELING AND PACKAGING**

Labeling and packaging activities utilize batch records and SOPs and are conducted at Biogen Idec or at a designated manufacturing site as listed in Table 1. Following manufacture, unlabeled drug vials and syringes are labeled by ---(b)(4)--- labeling ---(b)(4)---. The rFIXFc DP is then assembled as a kit containing a DP vial, diluent syringe, plunger rod, and vial adapter. The DP kit is intended for use with commercially available ancillary components for infusion.

The rooms utilized are intended for use as labeling and packaging rooms, and are designed with smooth durable surfaces for easy cleaning. The materials of construction consist of -----(b)(4)-----  
-----  
The rooms are climate controlled  
and monitored to ---(b)(4)--- temperature, and less than -(b)(4)-. The rooms share air handling systems -----(b)(4)-----, and there is no class designation for air quality.

Biogen sends documentation to the manufacturing site authorizing the specific labeling or packaging operation. The documentation includes the package lot number, expiration date, and any specified packaging components allocated to a particular lot. Lot specific batch records are created for each operation at each manufacturing site.

Unlabeled vials and syringes are segregated and documented in the inventory systems. Product allocation is documented in the packaging batch records for the particular lot. Product use is verified by production and Quality personnel and documented in the batch record. Completed batch records are QA reviewed by the manufacturing site and Biogen.

Biogen then sends authorization to the manufacturing site to ship finished goods to a designated distribution center. All finished goods are shipped -----(b)(4)-----.

Automated equipment is used during labeling operations. Preprinted labels are electronically verified to ensure that the correct label version is used. The labels are then imprinted with Lot #, actual activity (IU), and Expiry and are machine verified prior to being applied to the container. Each container is then scanned to ensure label presence.

The kitting operation consists of a manual process. The labeled vial, labeled syringe, plunger rod, and vial adapter are -----(b)(4)-----  
-----.

The kit is labeled using automated labeling equipment. Preprinted labels are electronically verified to ensure that the correct label version is used. The labels are then imprinted with Lot and Expiry, and machine verified prior to being applied to the kit. Each kit is then scanned to ensure label presence. The kit is manually inserted into a preprinted carton along with a package insert. The carton is then imprinted with Lot and Expiry and machine verified. The cartons are manually loaded into a corrugated shipping container and palletized. The corrugated container is labeled with preprinted labels containing all product information including Lot #, actual activity (IU) and Expiry. Finished goods are stored at 2 to 8 °C. Biogen provides authorization to the manufacturing site to ship finished goods to a designated distribution facility. Finished goods are shipped at 2 to 8°C.

### *Reviewer's Comments*

- The firm did not provide how they ensure label reconciliation and accuracy of their labeling process. Additionally, it is not clear where and when identity testing is performed. Per 21CFR610.14, “the contents of a final container of each filling of each lot shall be tested for identity after all labeling operations shall have been completed.” I recommend asking the firm for clarification as an IR.

## REVIEW QUESTIONS

Review question one was communicated to the sponsor on January 22, 2013. On February 5, 2013, CBER received responses from the sponsor in amendments STN 125444/0/5. IR Questions 2-13 was communicated to the firm on July 1, 2013 and CBER received responses from the firm in amendment STN 125444/0/22 on August 9, 2013. These responses will be reviewed as an Addendum. A summary of our review questions (in *Italics*), Biogen Idec’s responses (in regular text) and my comments (in **bold**) are below:

- 1. Please provide the following information to support your established procedures for prevention of contamination and cross-contamination:*
  - a. A description and summary of the validation for sterilization of equipment and components used for manufacturing the DS, DP, and diluent. The information provided should also include a summary supporting validation for the ---(b)(4)--- sterilization of the diluent.*

### Drug Substance

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Drug Product

Major equipment used in the manufacturing process of rFIXFc DP is described below. All major equipment was qualified or re-qualified for use in the manufacture of rFIXFc DP.

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(b)(4) -----  
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Eleven (11) Pages Determined to be Non-Releasable: (b)(4)

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(b)(4)-----  
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Drug Product and Diluent

rFIXFc drug product and diluent cleaning validation is performed by ---(b)(4)-----  
------. In Amendment STN 125444/0/5, the firm provided Cleaning  
Validation Document Number 50099-03 (Powder for Injection Equipment) and  
Cleaning Validation Document Number 50083 (Diluent equipment) to support the  
manufacture of rFIXFc and diluent at -(b)(4)-.

According to Cleaning Validation Document Number 50099-03 (Powder for  
Injection Equipment), the worst case substance was evaluated base on the  
chemical classes (------(b)(4)-----  
-----). The physic-chemical aspects (i.e. -----(b)(4)-----),  
analytical method (i.e. LOD/LOQ, sampling method), and frequency of  
production were evaluated. rFIXFc was determined to have better ---(b)(4)---  
compared to other products manufactured at -(b)(4)- and was not considered the  
hardest to clean. -(b)(4)- also performed a risk analysis under the pharmacological  
criterion that ensures that no residues of the previous batch can cause a  
pharmacological effect in the subsequent batch. The cross contamination of  
------(b)(4)----- into FIXFc was determined to be the worst case and  
the maximum allowable carryover was ---(b)(4)---.



According to Cleaning Validation Document Number 50083 (Diluent equipment) (b)(4) was identified as the -----(b)(4)----- of the group of inorganic compounds. -----(b)(4)----- equipment is easily cleaned with the -(b)(4)- cleaning procedures using PW and WFI. For production of the Diluent for FIXFc dedicated equipment is used. The firm concluded since the Diluent for FIXFc contains -----(b)(4)----- there is no risk regarding the pharmacological aspect.

***Reviewer's Comments: I find the firm's response acceptable.***

- b. *A summary of your facility cleaning validations; information provided should include your facility organisms and your disinfectant effectiveness studies*

Drug Substance

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One (1) Page Determined to be Non-Releasable: (b)(4)

The firm also provided SOP 10107 (Cleaning and Disinfection of Rooms and Equipment in the Production Area), which describes the cleaning and disinfection procedure for rooms and equipment and the frequency. The firm uses ----(b)(4)-----  
----- disinfectants.

**Reviewer's Comments:** The procedures appear acceptable.

- c. Please clarify how you segregate product/processes that are performed pre-virus clearance from those performed post-virus clearance for your drug substance. Please also indicate how pre- and post-viral areas are separated with respect to placement of air handling units (AHU). Please provide a drawing with the floor plan that includes the AHUs.

For the drug substance, the segregation of pre-virus clearance and post-virus clearance operations within the ----(b)(4)---- suite is achieved through the application of -(b)(4)- primary control aspects:

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

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------(b)(4)-----  
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#### Standard Operating Procedures

Personnel, product, and material flow procedures are in place to prevent cross contamination and segregation of pre and post viral reduction steps. Material flow SOPs provide for the segregation of product pre and post viral reduction. All product flow through the LSM facility is -----(b)(4)-----. In addition, operational procedures specify -----(b)(4)-----.

Within the purification suite the personnel gowning SOPs require operators to be in full clean room jumpsuits with booties and hair covering (i.e., head, beard). In addition, for segregations of unit operations including pre- and post-viral reduction steps, all manufacturing personnel are required to wear and change gloves between unit operations.

Additionally, spill containment procedures outline actions necessary to contain and remediate spills. The spill containment procedures require that all other operations ongoing in the purification suite remain closed while the spill is contained, treated, and the area is returned to normal operating conditions.

#### Air Handling Units

------(b)(4)-----  
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***Reviewer's Comments: I had concerns about this response. This system should have been validated as -(b)(4)-. I requested the inspection team to further evaluate this during the inspection and to confirm that the system is ---(b)(4)---. The firm was cited on having inadequate segregation and that the manufacturing system is ---(b)(4)--- to the environment in Observation 1.***

*d. A description and a summary of media fill simulations for your drug product*

The firm provided a summary of their medial fill simulation for rFIXFc. The information provided was also provided in section 5.9 of eCTD 3.2.P.3.5 – *Drug Product – Process Validation and/or Evaluation*.

**Reviewer's Comments: At the time I requested this information, I did not noticed that it was provided in in the BLA. This information was reviewed under the "Media Fill Validation" section of the "Process Validation for DP" section.**

- e. *A summary of the environmental monitoring program for your drug product, including acceptance limits and frequency of sampling for viable and non-viable particles.*

The firm provided a summary of their EM program for the DP. Most of this information provided was also provided in section 2.4.6 of eCTD 3.2.A.1 – *Appendices – Facilities and Equipment Report - -----(b)(4)-----*. One additional information that was provided was the viable monitoring limits/sampling frequency for classified production areas (Table 16 of Amendment STN 125444/0/5).

**Reviewer's Comments: Most of my review of the EM program is under the "Environmental Monitoring" section of the "Containment/Cross-Contamination" section. I also reviewed Table 16 and found it appropriate.**

2. *Regarding depyrogenation:*

- a. *Please provide a description of all of the depyrogenation ovens that will be used for the vials, syringe barrel, and plunger.*
- b. *Please provide the depyrogenation validation studies for the plunger for the diluent.*

3. *Regarding sterilization:*

- a. *Please provide a description of each autoclave used for the drug product or diluent and each sterilization method. Please also describe what is sterilized in each autoclave.*
- b. *Please clarify if the production sterilization loads are fixed/defined or flexible/undefined. If the loads are flexible, please explain the flexibility and restrictions of the load.*
- c. *Please clarify if submitted sterilization validation studies were specifically for equipment and components used during rFIXFc manufacture. If not, please explain how the loads that were validated compare to the loads that will be used for rFIXFc.*

4. *Regarding lyophilization:*

- a. *Please provide the study report for validation of the lyophilization process and a description of the lyophilizer(s). Please ensure the validation report includes all deviations and how each deviation was resolved.*

- b. Please clarify if a validation study was performed for each dosage strength and fill volume. If not, please justify why this is acceptable.*
    - c. Please clarify if validation studies were performed using vials from each qualified vendor. If not, please justify why this is acceptable.*
- 5. Regarding the ----(b)(4)---- test for container closure integrity testing (CCIT):*
  - a. Please provide the validation report(s) for CCIT for the drug product and diluent.*
  - b. You stated that the positive control was (b)(4). Please provide your rationale for why this size was selected as the positive control and why it is appropriate.*
  - c. You stated the acceptance criterion for this study as, “any visual incursion of -(b)(4)- into the test vials constitutes a failure.” Please clarify if you have qualified the operators to be able to detect small leaks approaching worst case and if the concentration of (b)(4) is sufficient to be detected by visual inspection.*
  - d. Please clarify if you have shown the presence of (b)(4) with the (b)(4) positive control size in your study.*
  - e. Please clarify if CCIT was performed on vials from (b)(4) qualified vendors for the drug product and please specify which vial size(s) were tested.*
  - f. Please clarify if any part of the container closure system that is product contact contains latex.*
- 6. The submission states that -----(b)(4)----- during drug product and diluent manufacture. Please clarify for which part of each process the ---(b)(4)----- is used.*
- 7. Please provide the fill volume and vial sizes for all dosage strengths.*
- 8. Please provide the fill volume and syringe size for the diluent.*
- 9. Please clarify if the drug product and diluent manufacturing processes are performed in closed or open systems.*
- 10. Regarding visual inspection:*
  - a. Please clarify if the inspection is manual, semi-automated, or automated.*
  - b. Please describe the visual inspection procedure performed for the drug product and diluent. Information provided should include, but not be limited to, what defects are being evaluated, what are the acceptance criteria, and the criteria for accepting or rejecting a lot.*
- 11. You state, “equivalent equipment may be used” for the manufacturing of the drug product and diluent (module 3.2.A.1). Please clarify what equivalent equipment will be used and if those pieces of equipment are validated specifically for manufacturing rFIXFc.*
- 12. Please clarify the bioburden in-process specification for the -----(b)(4)----- process. Table 23 in module 2.3.S states an acceptance limit of (b)(4).*

13. *Please clarify if vials are -----(b)(4)----- . If they are, please clarify if any -----(b)(4)----- studies have been performed.*

## CONCLUSION

In summary, I recommend the following additional information requests be sent to the firm.

1. Regarding the media fill for the drug product, there was an exception of the microbiological monitoring for media fill ----(b)(4)----. An objectionable organism (growth of spore forming germ) was found on a personnel. Please clarify if you have performed an investigation for the objectionable organism and a summary of your investigation.
2. Regarding the Bacterial Challenge Testing for the sterile filtration validation for the drug product,
  - a. Please clarify if it included the “worst-case” sterilization conditions. If not, please provide your rationale on why this is acceptable.
  - b. Please clarify if you have evaluated if the product is inhibitory or stimulator towards growth of --- (b)(4) ---. If so, please provide the results. If not, please provide a justification on why this is acceptable.
3. Regarding the hold time validations for the drug product, you only performed studies on two lots. For the diluent, you performed hold time studies on one lot. Please provide your rationale on why one or two lots are acceptable.
4. Please explain how the filled product is physically transported to the lyophilizer and how you prevent the contamination of the product during this process.
5. For the container closure integrity testing (CCIT) for stability testing of the drug product, please provide the pressure and vacuum cycle.
6. Please clarify why you used different test methods for CCIT during stability versus testing the initial container closure.
7. For all of your microbiological cycles in your sterilization validations please provide the BI locations (a graphical representation is acceptable) and your rationale on the placement.
8. Regarding ----(b)(4)---- sterilization
  - a. Please clarify which --- (b)(4) --- was used for the first summary (Document Number 5009120).
  - b. The second summary provided (Document Number 5009120) included a microbiological cycle. Please clarify what organism was used for this microbiological cycle, the population of the BI, and the D-value. Please clarify if there was any growth for the BIs placed in the load and if/what positive and negative control was used. Furthermore, it appeared that only (b)(4) BIs were used. Please justify why this amount of BIs is sufficient.

- c. In Document Numbers 5017449 and 5017450 you state that -----(b)(4)-----  
----- is the worst case material. Please provide justification why this is the worst case load and how it compares to the load of the subject diluent.
- d. (b)(4) BIs were used in the requalification (Document Numbers 5017449 and 5017450). Please justify why this amount of BIs is sufficient.
9. Please clarify what distribution cycle and actual testing was performed for your shipping validations for the drug product and diluent. Please justify how the simulated testing conditions are worst-case compared to actual shipping conditions.
10. Please clarify if any new equipment were implemented as a result of the drug product or diluent.
11. Please provide how you ensure label reconciliation and accuracy of your labeling process.
12. Please clarify when and where identity testing of the drug product and diluent is performed.
13. Please provide a description of the vial, vial stopper, syringe barrel, -----(b)(4)----- system, and syringe plunger qualification program and the latest qualification results.