



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

To: BLA STN 125487/0, Coagulation Factor VIII (Recombinant), Fc fusion protein (rFVIIIIFc)

From: Jie He, M.S., 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
Leigh Pracht, RPM, OBRR/DBA/RPMB, HFM-380
Ellen Huang, Consult, CSO, OCBQ/DMPQ/MRB II, HFM-676

Subject: Review of the BLA submitted by Biogen Idec Inc., Lic. #1697, to provide for marketing of Coagulation Factor VIII (Recombinant), Fc fusion protein (rFVIIIIFc).

Due Date: June 7, 2014

REVIEW RECOMMENDATIONS

I recommend additional information requests be sent to the firm.

REVIEW SUMMARY

Biogen Idec Inc. (Biogen) submitted an original application under STN 125487/0 for the licensure of Antihemophilic Factor (Recombinant), Fc Fusion Protein (rFVIIIIFc), Recombinant Factor VIII Fusion Protein (rFVIIIIFc) for the treatment of hemophilia A. The BLA was received by CBER on March 8, 2013. rFVIIIIFc drug substance is produced at the ---b(4)----- scale at Biogen Idec facilities located in Cambridge, Massachusetts. The rFVIIIIFc drug product (DP) is manufactured for Biogen Idec by ---b(4)----- . The Sterile Water for Injection (SWFI) pre-filled syringes are manufactured under contract by ---b(4)-----

rFVIIIIFc is formulated as a sterile, non-pyrogenic, preservative-free, lyophilized, white to off-white powder to cake for intravenous (IV) administration in a single-use vial. Each single-use vial contains nominally 250, 500, 750, 1000, 1500, 2000, or 3000 International Units (IU) of rFVIIIIFc for reconstitution with liquid diluent (SWFI), which is provided in a pre-filled syringe.

A recommendation for waiver of pre-license inspection memo was signed by OBRR/DH and OCBQ/DMPQ on July 8, 2013.

A categorical exclusion of environmental assessment memo was signed by OCBQ/DMPQ on July 16, 2013.

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.

I. NARRATIVE REVIEW

Items Reviewed

- STN 125487/0

I reviewed the manufacturing processes of rFVIII-Fc to include the drug substance ---b(4)----- performed at Biogen Idec's Cambridge, Massachusetts facility and the 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)-----

My review focused on the facilities, equipment, sterilization, lyophilization, container closure integrity testing, and the filling and packaging. The review is organized as the following sections:

- I. NARRATIVE REVIEW**
- II. DRUG SUBSTANCE**
- III. DRUG PRODUCT**
- IV. DILUENT**
- V. LABELING AND PACKAGING FOR FINISHED GOODS**
- VI. REVIEW QUESTIONS**

Product Description

Recombinant coagulation factor VIII Fc (rFVIII-Fc) is a fully recombinant fusion protein consisting of a single molecule of B domain deleted human coagulation factor VIII (FVIII) covalently linked to the dimeric Fc domain of human immunoglobulin G1 (IgG1) with no intervening sequence. rFVIII-Fc is produced in stably transfected HEK293 cells.

rFVIII-Fc is a heterodimer comprised of FVIII-Fc single chain and Fc single chain associated through -b(4)--- bonds at the hinge regions of the Fc fragments as well as extensive noncovalent interactions between the Fc fragments. rFVIII-Fc confers the procoagulation function of clotting factor VIII for effective hemostasis. The presence of the Fc domain enables rFVIII-Fc to bind to the neonatal Fc receptor (FcRn), which serves

a critical role in IgG homeostasis by protecting Fc containing molecules from catabolism and extending their plasma half-life.

rFVIIIIFc is formulated as a sterile, non-pyrogenic, preservative-free, lyophilized, white to off-white powder to cake for IV administration in a single-use vial. Each single-use vial contains nominally 250, 500, 750, 1000, 1500, 2000, or 3000 IU of rFVIIIIFc for reconstitution with liquid diluent (SWFI), which is provided in a pre-filled syringe.

Facilities Associated with Manufacturing of rFVIIIIFc Drug Substance, Drug Product, and Diluent

Name and Address	Responsibilities	Last FDA Inspection
Biogen Idec Inc. 14 Cambridge Center, Cambridge, MA 02142 FEI# 1220951 DUNS #: 121376230	Drug substance manufacturing Drug substance QA/QC release and stability testing and in- process testing Raw material QA/QC testing and release Drug substance and cell bank storage Drug product and Diluent QC testing and product warehousing	3/4-3/15/2013
---b(4)----- ----- ----- ----- -----	---b(4)----- ----- ----- ----- ----- ----- ----- ----- -----	--b(4)-----
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The facilities inspections were waived or facilities were not subject to an inspection. Refer to the inspection waiver memo for details, as appropriate.

The rFVIIIFc DS is manufactured at the Biogen Idec facility in Cambridge, MA. The rFVIIIFc DP and diluent for reconstitution are manufactured for Biogen Idec by (b)(4)------. The DP is manufactured at the (b)(4)------. The diluent is produced at the (b)(4)------. The rFVIIIFc DP is provided in a 10 mL vial as a lyophilized powder. The diluent is provided in a prefilled syringe in 3 mL form. Both components are packaged into a product kit along with a syringe plunger rod and vial adapter.

II. DRUG SUBSTANCE

The rFVIIIFc drug substance is manufactured at the Biogen Idec –b(4)--- production -b(4)----- facility located in Cambridge, Massachusetts. The Cambridge facility is comprised of ---b(4)------. Biogen claims

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

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Heating, Ventilation and Air Conditioning (HVAC) System

Potential product contamination from the manufacturing environment is minimized through the use of separate air handling systems, High Efficiency Particulate Air (HEPA) filters, single-pass air systems in specific manufacturing rooms, and room air pressure differentials.

Five air handling units serve the Building b(4)manufacturing areas. The rooms supporting each ---b(4)----- area have a dedicated air handling unit, and the -b(4)----- area has one dedicated air handling unit. -b(4)----- also has one dedicated air handling unit. Drawing and diagrams are provided in the submission. The air handling system serves two distinct areas: non-GMP office space and GMP clean space. The GMP clean space is classified as -b(4)-----, and is routinely monitored. Classified areas have ceiling-mounted terminal HEPA filters.

Room pressure differentials are generally utilized to move air from zones with higher cleanliness levels and room classifications to those areas with relatively lower classification or cleanliness levels. Air in any Class -b(4)--- processing room is not re-circulated into another Class -b(4)----- processing room. Differential pressures in

manufacturing areas are continuously monitored and alarmed to maintain the proper room environment and desired air flow direction.

Air handler design is 100% outside air single pass through the unit. Outside air is conditioned in the unit and filtered with HEPA filters. Air is exhausted out of the facility by designated fans. The facility also uses re-circulated air through ducted fan powered HEPA filters dedicated to the room.

Utilities

The firm has the following utilities: purified water, water for injection, clean steam, and compressed gas used for manufacturing rFVIII-Fc. Biogen provided description and preventative programs of these utility systems in the BLA. Since this is a FDA approved facility, detailed information is not discussed in this memo.

Containment/Cross-Contamination

Multiproduct Facility

The Biogen Idec Cambridge facility was approved as a multi-product facility for production of the following FDA licensed products:

Licensed Products Manufactured at the Cambridge Facility

Product	Reference
Interferon beta-1a (Avonex)	BLA 103628
Alefacept (Amevive)	BLA 125026
Ibritumomab tiuxetan (Zevalin)	BLA 125019

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Prevention of Contamination

To prevent product contamination and cross-contamination, Biogen Idec utilizes facility and equipment design features, campaign-dedicated equipment, standard operating procedures, and in-process testing. Procedures followed include testing cell lines to International Conference on Harmonization (ICH) standards, and performing documented changeover procedures between manufacture of different products.

The Cambridge facility utilizes spatial separation to prevent contamination. There are separate areas with separate air handling units. The manufacturing areas are accessed through gowning rooms and material/equipment airlocks. Each of these controlled-access areas has its own glass wash, autoclave, and clean in place (CIP) equipment, except for the --b(4)----- area, which utilizes single-use glassware or disposable items, and does not require a CIP system. Equipment design features include use of closed systems, e.g., ---b(4)-----, and equipment that can be cleaned and sterilized as appropriate. In addition, equipment is designed and operated to minimize bioburden, e.g., sterilizable --b(4)-----.

The segregation of pre-virus clearance and post-virus clearance operations within the purification suite for DS is achieved through the application of the following control aspects:

1. Equipment Dedication - Product contact equipment is dedicated on a campaign basis for specific unit operations/process step, excluding small parts. Following each use, the small parts are cleaned offline using cleaning agents that demonstrate virucidal effectiveness. Prior to the start of a new manufacturing campaign all product contact equipment is cleaned using a method that has demonstrated effectiveness for viruses.
2. Closed Systems - Where possible, facilities and processes are designed to prevent the need for any open (exposed to the environment) product manipulations. Required open operations involving product are performed in facilities designed to provide protection from environmental contamination (e.g. biosafety cabinet), and only one open operation is performed at a time in any manufacturing area. Where possible, equipment is designed such that product sampling is performed with closed vessels and open sampling is not required within the processing rooms.
3. Room Dedication and Facility Design - The manufacturing facilities are designed to provide segregation of upstream and downstream process stages. The following operations are segregated: cell culture glass wash, purification glass wash, media

4. Standard Operating Procedures - Gowning procedures are in place and designed to prevent contamination from personnel. In addition, operators are required to wear a new set of gloves when entering each purification process room. Gloves are disposed of, upon exiting, and new pair of gloves is required for each re-entry into a process room if there is active processing or preparation activities are on-going in a purification suite.
5. Air Handling Unit - In Building b(4) each purification suite (Suite –b(4)-----) in Purificationb(4)area is made up of b(4) independent environmental rooms designated b(4) and a common area. Air from the AHU is supplied to the environmental room for positive pressurization to the common area which is also positive to the common hallway. Each environmental room within a suite operates independent of each other and each suite operates independent of each other in terms of air flow. There is no air flow from one environmental room to another environmental room. The pre- and post- viral downstream unit operations are segregated and performed in different environmental rooms.

All rooms with the exception of office space are monitored at specified frequencies for confirmation of room classification. Action levels for EM excursions are established throughout the facility in accordance with b(4)----- Critical open activities are performed in either biosafety cabinets b(4)----- or laminar flow curtained areas (b(4)-----). During these activities, in addition to room monitoring, personnel monitoring is performed. Facility EM data obtained to date indicate that the environment is maintained in a state of control and appropriate for the activities performed.

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 b(4)

All manufacturing rooms and equipment are cleaned and sanitized based on established procedures with specified frequencies depending on the room classification.

Cleaning validation has been completed for all process equipment used for manufacturing rFVIIIFc drug substance in the Biogen Idec manufacturing facility, located in Cambridge, MA. A complete cleaning validation summary was submitted.

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The firm provided personnel, raw material, product, equipment, and waste flow diagrams in eCTD 3.2.A.1 Facilities and Equipment Report – Cambridge - *Facility and Equipment Diagrams– Cambridge*. A description of the flow for raw materials, product flow, and equipment flow was in section 1.5.3.2 of *eCTD 3.2.A.1 Facilities and Equipment Report*.

Reviewer's comment

- The flow of clean and soiled equipment appear adequate. The flow of personnel appears adequate, but there is insufficient information, such as gowning policies, to determine if personnel are allowed to move between rooms where different products may be manufactured concurrently. Biogen agreed to provide additional information regarding these practices during a telecon held with FDA on 10/23/2013. Amendment 24 was received by CBER on 10/31/2013 which contains additional information on rFVIII Fc manufacturing area, equipment, movement and traceability of equipment, EM data and in-process –b(4)----- test results for DS. This amendment will be reviewed in a separate memo.

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

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The rFVIIIc DP is a sterile lyophilized powder for injection intended for intravenous administration. It is supplied in aseptically filled single use glass vials which contain nominally 250, 500, 750, 1000, 1500, 2000, and 3000 IU per vial. The vials are 10 mL glass vials sealed with a 20 mm rubber lyophilization stopper and aluminum flip-off crimp seal. Prior to lyophilization, the nominal fill volume target for all dosage strength vials is the same. The composition of the formulation excipients prior to lyophilization is the same for all dosage strengths; only the quantity of rFVIIIc varies. The powder for injection is reconstituted with nominal 3 mL SWFI supplied in a sterile prefilled syringe. All seven

of the rFVIII-Fc drug product strengths are compounded from the rFVIII-Fc drug substance. Excipient ---b(4)----- during the manufacturing of the rFVIII-Fc drug product. When reconstituted with 3mL SWFI, the product contains the following excipients: b(4) sucrose, b(4)-- sodium chloride, -b(4)- L-histidine, -b(4)- calcium chloride, and -b(4)----- polysorbate 20. Detailed nominal composition of each different dosage are provided in the submission.

Establishment Description

Biogen Idec utilizes -b(4)----- as a contract manufacturer for rFVIII-Fc, Powder for Injection drug product. The following manufacturing related activities are performed at the -b(4)- facilities during the production of rFVIII-Fc drug product:

- Drug Substance Receipt at the Manufacture Site
- Drug Product Manufacturing
- Component and Equipment Preparation
- Quality Control Testing
- In-Process Testing
- Bulk Packaging
- Product Storage

In addition to the primary site for DP manufacturing, in-process testing/release testing at ----- b(4)----- sites may be used as back-up/secondary sites for DP in-process testing, and sterility testing for release. ---b(4)----- sites are alternate for in-process visual inspection. There is no information provided in the submission regarding if these alternative sites were used during manufacturing of the conformance lots. A list of facilities involved in DP manufacturing is listed in the table below:

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

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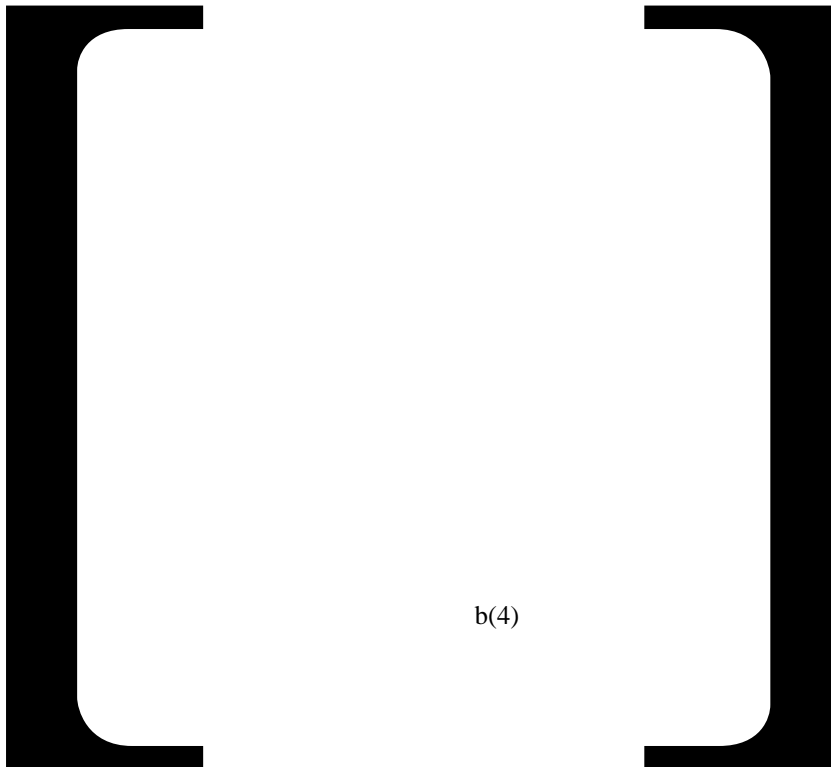
Reviewer's comment

- The BLA did not provide information on if the alternative sites in –b(4)---- were used for in-process testing for the manufacturing the conformance lots. The firm will be asked to clarify specifically what the listed alternate site(s) were used.

Manufacturing Process for DP

The figure below is a graphical depiction of the DP manufacturing process.

rFVIII-Fc Powder for Injection Process Flow and Room Classification Diagram



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All of the specifications for the DP can be found in Table 17 of *eCTD 2.3P – Drug Product eftrenonacog alfa – power for injection – Biogen Idec*.

Release and Stability Specifications

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

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
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	No Growth	Not tested
Container Closure Integrity	Not tested	Conforms

All of the specifications for the DP can be found in section 5 of *eCTD 2.3.P – Drug Product eftrenonacog alfa – power for injection – Biogen Idec*.

Reviewer's Comments

- During review of the process consistency validation, it was noted that often the action limit –b(4)----- 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 –b(4)----- and release limits. Refer to **IR Question 18**.
- No detailed description was provided regarding visual inspection for ---b(4)----- and final DP. Refer to **IR Question 7**.

Process Validation for DP

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

Process Consistency Validation

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All rFVIII-Fc DP lots met release specifications. The firm also provided the critical parameter results.

Reviewer's Comments

- The firm provided no information on the type/model of the lyophilizer(s) used, no information on initial and processing lyophilization validation, and no information on the validated lyophilization cycle as well. Refer to **IR Question 3** for this request.
- It was not clear if the lyophilization cycles used for the prospective and retrospective conformance lots manufactures were the same. The first is asked to clarify. Refer to **IR Question 4**.
- Retrospective validation batches were used, and product office has determined that these batches are not acceptable, and Biogen is asked to manufacture additional batches. Refer to **IR Question 24**.

Media Fill Validation

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

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Hold Time Validation

The validation of the hold times employed a bracketing strategy, in concert with the overall validation strategy. Hold times were tested ---b(4)-----
----- Hold time recommendations apply to all drug product strengths (250 IU to 3000 IU). The overall validation strategy -----b(4)-----
-----; however, worst-case conditions for hold time are considered to be the minimum load as worst-case product contact surface area to volume ratios are encountered at the minimum processing volumes. Hold times were considered acceptable if all the pre-defined acceptance criteria are met, including the final release of the drug product.

Reviewer's Comments

- Hold time studies were performed on -b(4)----- The proposed hold times are generally much longer than the conformance batch range. The firm is asked to establish maximum intermediate hold times based on conformance batch experience. Refer to **IR Question 22**.

Heating, Ventilation and Air Conditioning (HVAC) System

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 in laminar air flow areas.

The heating, ventilation and air conditioning (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 laminar flow (LAF) areas of clean rooms are integrity tested -(b)(4)-. In addition, laminar flow units are equipped with audible and optical alarms.

Utilities

The facility has the following utility systems: purified water, water for injection, clean steam, and compressed gas used for manufacturing rFVIII-Fc DP. Biogen provided description and preventative programs of these utility systems in the BLA. Since this is a FDA approved facility, detailed information is not discussed in this memo.

Reviewer's Comment

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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 rFVIII Fc DP contact equipment, including the -b(4)-----, is dedicated and is cleaned according to an approved SOP before use. Filters and tubing used in the rFVIII Fc DP aseptic filling process are single use. 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. All production steps where product is exposed to the environment are performed under laminar flow.

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 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.

A product specific cleaning validation is performed for rFVIII Fc drug product equipment. The approach to cleaning validation incorporates the use of product-specific, validated analytical assays. Requalification of cleaning validation is performed --(b)(4)--, and is generally conducted on one production run. All equipment with direct product contact is dedicated to rFVIII Fc. Filters and tubing used in the formulation and filling processes are single use.

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Container Closure for DP

The rFVIII^h DP is lyophilized in a --b(4)----- glass vial. Vials from --b(4)-----) were qualified to ensure continuity of supply--b(4)-- vials have identical specifications and meet the ISO 10R standard. Drawings of --b(4)-- vials are provided. b(4) vials use the same glass formulation. The vials are closed with a 20 mm lyophilization stopper with ---b(4)----- . After the lyophilization process is

complete, the stoppered vials are sealed with 20 mm aluminum seals with a -----
-----(b)(4)----- flip-off cap of various colors to differentiate the different vial strengths.

The rFVIIIc DS kit also includes a vial adapter transfer device for use during
reconstitution from ---b(4)-----

rFVIIIc Powder for Injection, Container Closure System

Component	Description of Material	Manufacturer
Vial	--b(4)----- ----- glass, clear, ---b(4)-----.	-b(4)--- ----- ----- -----
Stopper	Rubber -b(4)---, grey, 20 mm Iyo, ---b(4)----- ----- ----- ----- ----- -----	---b(4)--- ----- ----- -----
Seal (no product contact)	20 mm, Aluminum crimping seal, -----(b)(4)----- flip-off cap: -b(4)- – Yellow (250 IU) -b(4)- – Red (500 IU/vial) -b(4)- – Garnet (750 IU/vial) -b(4)- – Green (1000 IU/vial) -b(4)- – Dark Green (1500 IU/vial) -b(4)- – Royal Blue (2000 IU) -b(4)- – Mist Grey (3000 IU/vial) --b(4)-----	---b(4)----- -----

Vial Specifications

Attribute	Specification
Description	Clear glass tubing vial
Vial Height, mm	-b(4)-----
Body Outer Diameter, mm	-b(4)-----
Lip Inner Diameter, mm	---b(4)-----
Lip Outer Diameter, mm	--b(4)-----
Lip Height, mm	--b(4)----
Physical Inspection	--b(4)-----

Certificate of Analysis	---b(4)-----
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Specifications for the stoppers

Attribute	Specification
Description	Gray lyophilization stopper 20 mm with -b(4)----- -----
Site of Production	--b(4)-----
Certificate of Analysis	--b(4)----- -----
Visual Identity	-b(4)-----
Identification	--b(4)----- -----
Color	--b(4)-----
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--b(4)-----	--b(4)-----
Stopper Height, mm	--b(4)-----
Stopper thickness, mm	--b(4)-----
Stopper Top Diameter, mm	--b(4)-----
Plunger Diameter, mm (at widest point)	--b(4)-----
Physical Inspection	--b(4)-----

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--b(4)-----

Specifications for the Seals

Attribute	Specification
Description	Aluminum seal, plastic flip-off button, various colors
Certificate of Analysis	--b(4)-----
Physical Inspection	--b(4)-----
Seal Height, mm	--b(4)-----
Seal Inner Diameter, mm	--b(4)-----

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

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

The firm also provided extractable and leachable testing, which is under the Product Office's purview. Details about the container closure system can be found in in eCTD 3.2.P.7 Drug Product

Reviewer's comment

Biogen claimed in the submission that b(4) type of vials have identical specifications, but there is no specification for the vial bottoms of b(4)--- vial provided. Since this is a critical aspect and may impact the lyophilization process, the firm will be asked to provide information on this.

Reconstitution Components –Vial adapter

The rFVIII-Fc drug product kit includes a vial adapter transfer device for use during reconstitution. The vial adapter transfers diluent from the syringe into the lyophilized rFVIII-Fc drug product vial for reconstitution, and after completion of the reconstitution process, drug product is transferred back into the syringe through the vial adapter.

The 20mm vial adapter from ---b(4)-----
----- and is CE marked. Vial adapters are supplied by the manufacturer as a sterile component individually packaged in a PETG blister pack with Tyvek® lid.

Container Closure Integrity for DP

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

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

Shipping DP

Objective of the drug product shipping qualification study is: 1) maintain temperature control, and 2) ensure transport packaging protects the drug product from shipping hazards such as ---b(4)----- during commercial shipment. DP vials are packaged into -b(4)-- -----

-----, The container is shipped by a combination or truck/air to the finished goods manufacturing site. Temperature and shipping qualification studies were completed. Typical shipping routes for DP are from -b(4)----- Standardized -b(4)----- testing was used to simulate a typical -b(4)----- shipment.

The temperature qualification was designed to expose the shipper to a summer ambient 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 ground and air. The acceptance criteria included temperature control, visual inspection, and CCIT. All acceptance criteria were met.

IV. DILUENT

The rFVIIIc diluent is sterile Water for Injection (SWFI), and is used for the reconstitution of all strengths of the rFVIIIc lyophilized DP. The sSWFI prefilled syringes are manufactured under contract by ---b(4)----- The diluent is supplied as a 3 mL fill in a single-use prefilled syringe. The container closure system consists of a ---b(4)----- closure system (-b(4)-----) composed of a tip cap with a Luer lock and a tamper-evident seal.

Names of Ingredients	Unit and/or Percentage	Reference to Standards
Water for Injection	3.0 mL	--b(4)-----

Establishment Description

The SWFI prefilled syringes are manufactured under contract by -b(4)----- Manufacturing responsibilities by facility are outlined in the table below:

Site name and Address	Responsibilities
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[b(4)]

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
-b(4)-----	---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 3.2.P.5*

Process Validation for Diluent

For firm stated that results of the process validation studies confirm that the unit operations associated with the diluent manufacturing process can be utilized to consistently produce SWFI prefilled syringes that meet the predefined release specifications. Biogen states the validated filling process is consistent, reproducible, and reliably produces a drug product (solvent) of the desired quality. No validation data was included in the submission, and they referred to Drug Master File # -b(4)-- 'Sterile Water for Injection as Manufactured in -b(4)-----

--b(4)-----

--b(4)-----

Reviewer's Comment:

- Validation reports were not provided, as required by FDA's *Guidance for Industry for the Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products*. Refer to **IR Question 1 and 2**.

-b(4)-----

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

--b(4)-----

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

Heating, Ventilation and Air Conditioning (HVAC)

The heating, ventilation, and air conditioning (HVAC) system provides conditioned air to the clean room areas. For air filtration HEPA filters with required efficiency are used. HEPA filters are included in an existing program for performance testing and maintenance. HEPA filters in LAF areas of clean rooms are integrity tested -b(4)-----.

All laminar flow units are equipped with audible and visual alarms.

Utilities

The facility has the following utility systems: purified water, water for injection and clean steam used for manufacturing WFI diluent. Biogen provided description and preventative programs of these utility systems in the BLA. Since this is a FDA approved facility, detailed information is not discussed in this memo.

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 rFVIII Fc diluent contact equipment is dedicated, and is cleaned according to an approved SOP before use. Filters and tubing used in the rFVIII Fc diluent aseptic filling

process are single use. 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

The SWFI prefilled syringes are produced with dedicated or single-use product contact equipment. Only –b(4)----- equipment is used (with the exception of single-use equipment). A specific cleaning validation for WFI is considered not necessary, since there are no ingredients that could accumulate for the subsequent batch.

Disinfectant qualification

The cleaning and disinfection of the production area of grade b(4) is conducted to maintain the cleanliness of equipment and rooms. Routine cleaning procedures are designed to ensure the removal or elimination of cross contamination such as particles, dust, fats and oils. Routine disinfection is designed to reduce or eliminate microorganisms that have entered the room. Established cleaning procedures ensure a regular cleaning and disinfection of equipment, such as machines, machine parts, instruments, assemblies, etc. Room cleanings are conducted routinely. The frequency of cleaning is based on room classifications as defined in the cleaning procedures.

Product Changeover

Product changeover is performed between each product manufacturing campaign.

Line cleaning also includes cleaning procedures for production equipment and premises. Commonly used equipment such as autoclaves, ovens, syringe washers, etc. are checked between product fills for clearance of components used for the previous product. The identity of raw materials is verified, and the release status is checked prior to their use in production. In addition, the identity and cleanliness status of equipment used in filtration and filling is verified and documented. Prior to filling, the identity of the container/closure system components is verified and documented. Personnel conducting line cleaning and clearance procedures are properly trained. Any deviations that occur during line cleaning are immediately addressed and properly documented. Personnel are trained in procedures that prevent cross-contamination, including proper gowning procedures, material and product flow, handling of product waste, etc.

Environmental Controls

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

Equipment for Diluent

rFVIIIc 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

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

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

b(4)

CCIT on the rFVIIIc diluent was performed by means of a -----(b)(4)-----
----- . The procedure was performed at a contract manufacturing
organization, -----b(4)-----,
according to approved procedures. A minimum of –b(4)---- from each of 3 finished lots
of rFVIIIc diluent syringe were tested and all passed the predefined acceptance criteria.

Reviewer's comment

- ### Shipping for Diluent

For shipping, diluent syringes consists of 3 mL glass syringes and are packaged into protective plastic trays that are stacked inside of a corrugated shipping container. Diluent syringes are stored and shipped at –b(4)– conditions. Diluent syringes are shipped to the label and packaging site utilizing –b(4)– storage container. The storage container maintains temperature of –b(4)– for

The temperature qualification was designed to expose the shipper to a summer ambient temperature profile. During this qualification, the temperature was monitored, and confirmed to maintain -b(4)----- for up to -b(4)---- duration. As part of the shipping qualification, the diluent syringe was exposed to -b(4)-----
-----which simulate the stresses of warehouse handling, vehicle loading and unloading, and transportation by ground and air. The acceptance criteria for the diluent syringe shipper temperature qualification temperature control, visual inspection, and container closure integrity. All acceptance criteria were met.

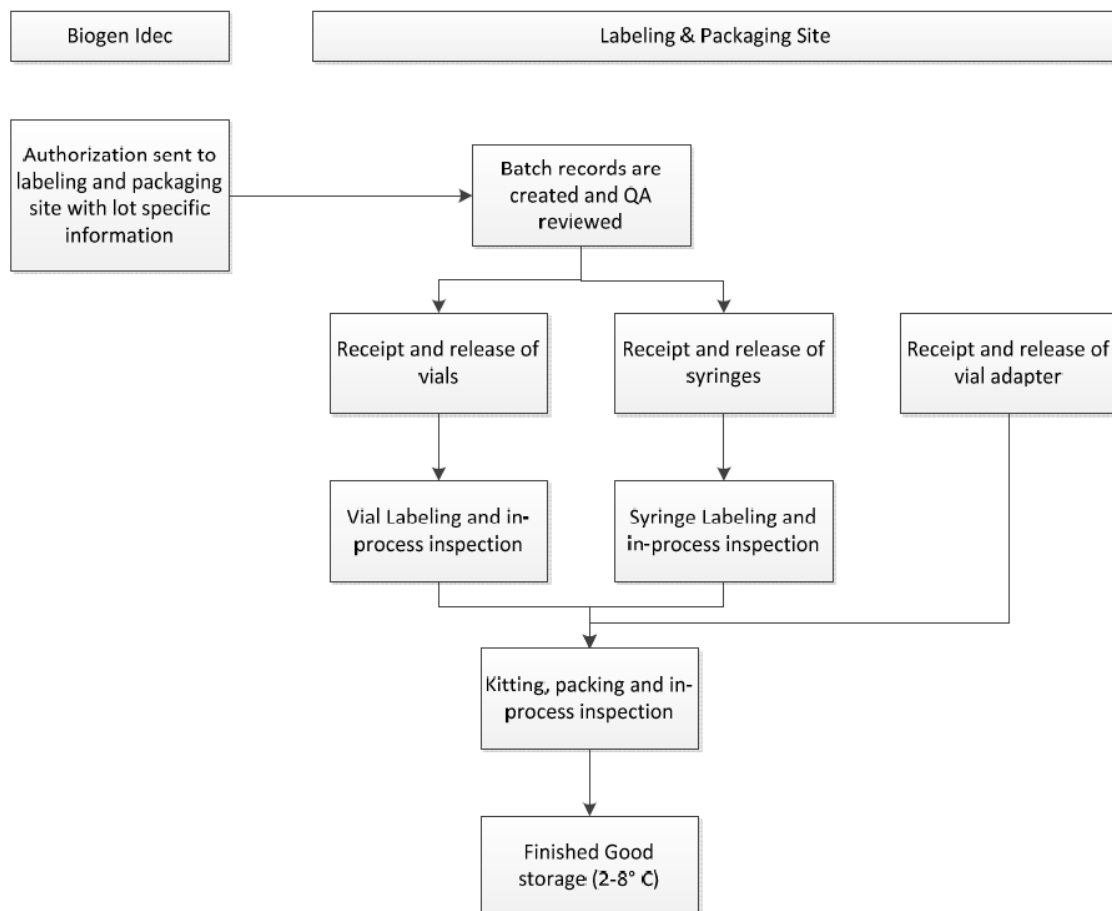
For finished rFVIII-Fc product, labeling and packaging activities utilize batch records and SOPs and are conducted mainly at the same –b(4)----- facility where DS is manufactured. Biogen Idec has listed other designated manufacturing site for this process when needed. Following manufacture, unlabeled drug vials and syringes are labeled by automated labeling equipment. The rFVIII-Fc 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)-----

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Process Description

The chart below describes the packaging process flows:



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 refrigerated –b(4)–.

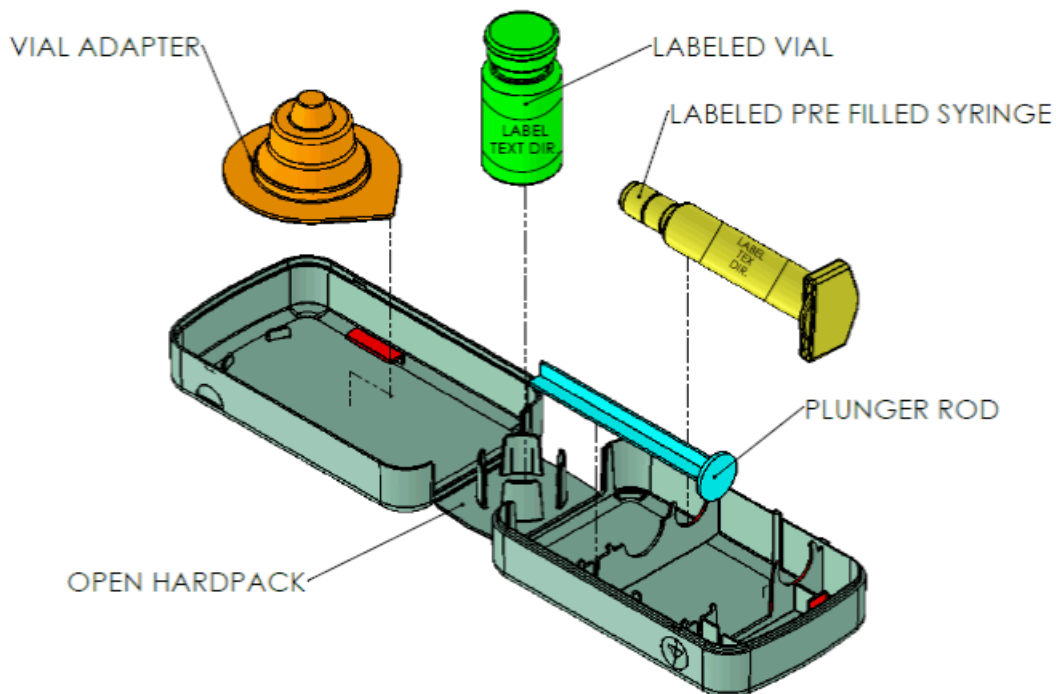
Drug Product Vial and Diluent Syringe Labeling

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.

Kitting

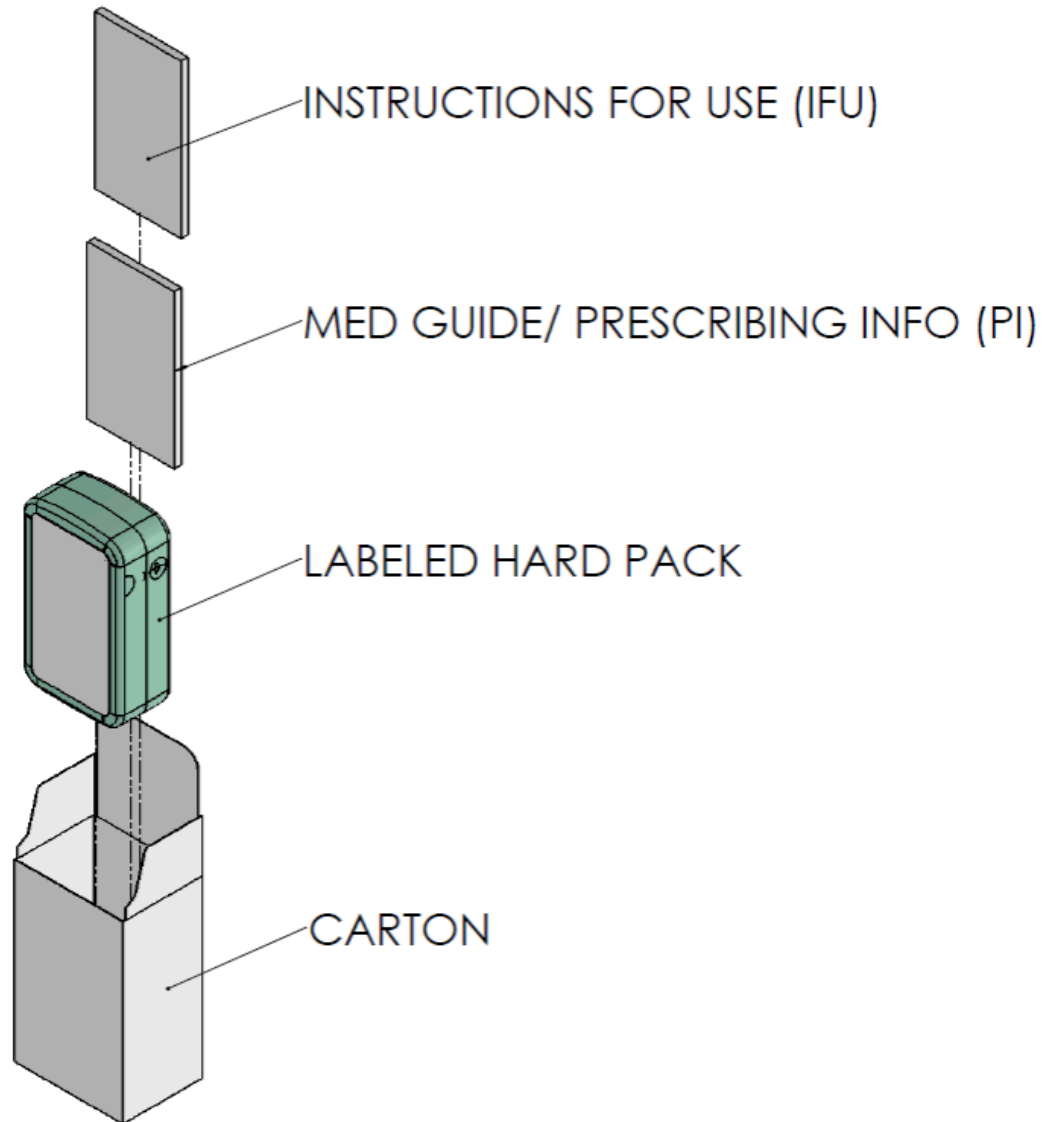
The kitting operation consists of a manual process. The labeled vial, labeled syringe, plunger rod, and vial adapter are manually inserted into a kit tray. Each kit is weight-checked to ensure accurate kit contents.

EXPLODED VIEW OF LOADED HARD PACK



Final Packaging

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 comment

- No detailed description was provided regarding visual inspection for in-process control and final diluent. Refer to **IR Question 7.**

Shipping Finished Goods

Finished goods consist of the DP vial, diluent syringe, syringe plunger rod, and vial adapter. Finished goods are stored at 2 to 8°C and are shipped by refrigerated truck (2 to 8°C) to designated distribution sites. Distribution sites distribute the finished goods in insulated shipping containers that utilize a combination of refrigerants to maintain –b(4)–
------. Temperature and shipping qualification studies were completed.

Actual representative truck and air transport shipments were performed as part of this study in order to demonstrate the robustness of the finished good. The study was designed to subject the finished good to a variety of truck and air transport conditions. In order to verify that the shippers maintain temperature for the duration of a typical shipment, the insulated shippers were subjected to both summer and winter ambient temperature profiles using an environmental chamber. The testing exposes the insulated shipping containers to a variety of high and low ambient temperatures designed to stress the shipment.

The acceptance criteria for the finished goods shipper qualification included temperature control, visual inspection, and DP and diluent syringe CCIT. 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– Shipping Information.

VI. REVIEW QUESTIONS

Review questions were communicated to the sponsor on September 11, 2013 as part of a multi-discipline information request and the firm has not yet provided a complete response as written of this memo. Selected CMC portion of the IR related to DMPQ review issues are listed below:

Chemistry, Manufacturing and Controls (Facilities and Equipment)

1. Regarding ----(b)(4)-----:
 - Please provide the ----(b)(4)----- validation studies for the –b(4)----- of vials used for the drug product, and for the syringe barrel and plunger used for the diluent.
 - Please provide a description of all of the -----(b)(4)----- that will be used for the vials, syringe barrel and plunger.
2. Regarding sterilization:
 - Please provide a description of all autoclaves used for sterilization of product contact equipment and/or components. Please provide the sterilization validation studies.
 - Please provide a description of the autoclave used to sterilize the diluent. Please provide the –b(4)----- sterilization validation studies for the diluent.
3. Regarding lyophilization:
 - Please provide the study report(s) for validation of the lyophilization process and a description of the lyophilizer(s).
 - Please explain your approach to validating the lyophilization cycle. Required information will include the results of empty chamber temperature mapping studies for each lyophilizer you intend to employ to manufacture drug product. Please provide a summary of those studies. Please also ensure you describe your sampling method (e.g., extended sampling, sampling pattern, which shelves sampled and sample locations, number of samples taken at each location), lot size of each run, fill volume of each run, product strength of each run, and testing results (e.g., residual moisture, potency, reconstitution time).

- Please clarify if validation studies were performed using vials from each qualified vendor. If not, please justify why this is acceptable.
 - Please confirm that the lyophilization cycle is –b(4)--. Please provide detailed information on any changes made for any of the validation runs.
 - Please provide your validation final report for the corresponding validation runs.
 - Please clarify if a study was performed for each dosage strength and fill volume. If not, please provide a justification for why this is acceptable.
 - Please provide the final fill volumes and vial sizes for all dosage strengths.
 - Please provide the drug product –b(4)----- for all dosage strengths.
 - Please explain how the filled product is physically transported to the lyophilizer and how you prevent contamination of the product during this process.
4. Please clarify if there are any differences in the lyophilization cycle and product testing among drug product lots: --b(4)-- -----
-----.
5. Regarding the –b(4)----- test for container closure integrity testing (CCIT):
- Please provide the validation report for CCIT of the drug product and diluent.
 - You stated that the positive control was –b(4)-. Please provide your rationale on why this size was selected as the positive control and why it is appropriate.
 - You stated the acceptance criterion for this study as, “—b(4)-----
----- Please clarify if you have qualified the operators to be able to detect –b(4)-----

 - Please clarify if CCIT was done on vials from b(4) vendors for the drug product.
 - Please clarify if any part of the container closure system that is product contact contains latex.
 - For CCIT for stability testing, please provide the –b(4)-----
 - Please clarify why you used different test methods for CCIT for stability testing versus initial release.
6. Please clarify if –b(4)----- during either drug product or diluent manufacture. Please also clarify if the drug product is stoppered ----(b)(4)----.
7. Regarding visual inspection:
- Please clarify if the inspection is manual, semi-automated, or automated.
 - Please describe the visual inspection procedure performed for the drug product and diluent. Information provided should include, but not be limited to, defects evaluated, acceptance criteria, and criteria for accepting or rejecting a lot.
 - Please provide the qualification of your visual inspection process.
8. You state, “equivalent equipment may be used,” for the manufacturing of the drug product and diluent (module 3.2.A.1). Please clarify which equivalent equipment will be used and if those pieces of equipment are also validated for manufacturing rAHFFc.

9. Regarding hold time validation for drug product, two lots (--b(4)-----) were studied (module 2.3.P. Table 23) and product intermediates were held for significantly less time than the claimed maximum. Please adjust maximum hold times to reflect conformance lot manufacturing experience.

10. Please provide your drug substance and drug product process validation protocols.

Chemistry, Manufacturing and Controls (Product)

18. Please revise acceptance criteria for the following release tests, as indicated:

- Please establish acceptance criteria for ----- -b(4)----- in accordance with clinical and commercial scale manufacturing experience, calculated according to an appropriate statistical paradigm. The proposed acceptance criteria of ---b(4)-- ----- for drug product do not reflect historical manufacturing experience.
- Please establish an acceptance criterion for endotoxin that reflects manufacturing capability and is consistent with the drug product release specification. The proposed acceptance criterion of -b(4)----- neither reflects conformance batch results, --b(4)----- nor is consistent with the highest proposed drug product release specification of -b(4)-----.
- Please establish a provisional acceptance criterion for percent -b(4)----- drug product release since this was the statistically based, calculated value. Please commit to re-evaluation of the acceptance criterion after accumulating additional commercial release data, with the aim of lowering the value.

19. Please establish in-process specifications (IPS) for -b(4)----- that reflect manufacturing capability.

22. Please establish maximum process intermediate hold times based on conformance batch manufacturing experience, not laboratory studies, e.g.:

[b(4)]

29. Please be advised that only the manufacturing areas through which conformance batch/lot manufacture has been successfully performed will be licensed