



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 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
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Cc: Nancy Kirschbaum, Ph.D., Chair, OBRR/DH/LH, HFM-392
Edward Thompson, RPM, OBRR/DBA/RPMB, HFM-380

Subject: Addendum 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: March 29, 2014

REVIEW RECOMMENDATIONS

I recommend approval base on the review of the firm's response and additional information submitted.

Additionally, I recommend the following items should be evaluated on the next inspection:

- -----(b)(5), (b)(7)(e)-----

- -----(b)(5), (b)(7)(e)-----

- -----(b)(5), (b)(7)(e)-----

- -----(b)(5), (b)(7)(e)-----

----- (b)(5), (b)(7)(e) -----

REVIEW SUMMARY

Biogen Idec Inc. (Biogen Idec or Biogen) 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 (DP) solution is for intravenous injection.

CBER performed Pre-License Inspection (PLI) at 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).

Please refer to my discipline review memo for a review of the BLA STN 125444/0 and Amendment STN 125444/0/5. This review memo is an addendum that covers the Amendments STN 125444/0/22, STN 125444/0/25, STN 125444/0/27, STN 125444/0/28, STN 125444/0/34, STN 125444/0/36, STN 125444/0/37, STN 125444/0/39, STN 125444/0/40, STN 125444/0/41, STN 125444/0/44, STN 125444/0/45, STN 125444/0/48, STN 125444/0/50, STN 125444/0/52, and STN 125444/0/54. FDA sent a letter to Biogen Idec on November 25, 2013 to indicate that Amendment STN 125444/0/was considered a major amendment.

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

- Amendments STN 125444/0/22, STN 125444/0/25, STN 125444/0/27, STN 125444/0/28, STN 125444/0/34, STN 125444/0/36, STN 125444/0/37, STN 125444/0/39, STN 125444/0/40, STN 125444/0/41, STN 125444/0/44, STN 125444/0/45, STN 125444/0/48, STN 125444/0/50, STN 125444/0/52, and STN 125444/0/54.

- ## **Review of Amendment STN 125444/0/22**

rFIXFc DP-Vial

(b)(4)

(b)(4)

(b)(4)

(b)(4)

b. Please provide the depyrogenation validation studies for the plunger for the diluent.

(b)(4)

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

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

Reviewer's Comments: I reviewed this requalification and it appears acceptable. All acceptance criteria were met, including a -(b)(4)- reduction of endotoxin for the plungers.

2. *Regarding sterilization:*

- a. *Please provide a description of each autoclave used for the DP or diluent and each sterilization method. Please also describe what is sterilized in each autoclave.*

Drug Product

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

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

Diluent

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

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

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

Reviewer's Comments: Overall, the response is acceptable. However, the firm mentions that for the DP the "sterilization process the autoclave chamber can be equipped with ----- (b)(4) ----- onto which the goods are loaded according to defined fixed load patterns." It is not clear what the firm means by ---- (b)(4) ----. Refer to IR Question 2 below in Amendment STN 125444/0/25.

- 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.*

Defined autoclave loading patterns are used for routine production cycles to ensure that all loads are arranged in a similar pattern and do not exceed the maximum loading established during qualification. Loading patterns are described in procedures and include criteria such as the type of goods validated and the placement of goods within the autoclave. The loads used for qualification/re-qualification purposes follow a ---- (b)(4) ---- concept in which all materials to be autoclaved are assessed and the worst case goods are identified. Based on this assessment the autoclave loads for qualification/re-qualification are defined to represent the worst case. This autoclave qualification and ---- (b)(4) ---- approach allows certain flexibility in routine productions cycles and has been validated by an initial validation using three individual validation runs.

All autoclaves and sterilization production cycles used for manufacturing rFIXFc DP vials and the associated diluent syringe (process validation and routine commercial production) are based on the parameters and the load patterns which were validated.

Reviewer's Comments: It is not clear how the firm is using a ---- (b)(4) ---- approach and how the firm determines the worst case goods. The firm states that this approach allows them flexibility. Refer to IR Question 2 below in Amendment STN 125444/0/25.

- 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.*

The existing initial validations and the submitted sterilization re-validation studies cover all equipment and components used for manufacturing rFIXFc DP vial and the associated diluent syringe. No new validation specific to rFIXFc were performed.

Reviewer's Comments: The firm stated no new validations for rFIXFc were performed. Therefore, I asked the firm to explain how they assess if the new equipment for rFIXFc is the worst case equipment. Refer to IR Question 2 below in Amendment STN 125444/0/25.

3. *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.*

Process consistency validation of the lyophilized process was demonstrated by the completion of validation protocols representing all dosage strengths (refer to Table 1). Three DP lots at the proposed highest strength and lowest dosage strength were manufactured. Additionally, one validation lot was manufactured for each of the intermediate concentrations.

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

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

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

The firm stated that process validation was conducted to demonstrate that the manufacturing process operates in a controlled manner which consistently produces product meeting pre-defined product quality attributes.

The lyophilizer that was validated in clean room ----- (b)(4) -----
-----, Equipment Requalification Report 5015215) at --- (b)(4) ---
----- facility contains (b)(4) shelves. Each shelf holds approximately (b)(4)

(b)(4)-----

(b)(4)-----

(b)(4)-----

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

Reviewer's Comment: It is not clear if the temperature distribution study is the empty chamber shelf temperature mapping study. If so, it is deficient since every Shelf (b)(4) was not temperature mapped. Additionally, (b)(4) TCs do not provide assurance that the shelf temperatures are uniform. Typically, each shelf is mapped in -----(b)(4)----- . Furthermore, there is a large variation allowed in temperature. Typically there should be limited variability (less than 1°C temperature variation of each shelf and less than 2°C shelf-to-shelf variation).

I also reviewed the process validation protocols and reports listed in Table 1. Regarding lyophilization, those reports only provide the set point, operating range, and actual results for the in meeting the lyophilization parameters. It is not clear where samples were taken (e.g. which shelf and shelf location).

Thus a telecon was held with the firm on August 20, 2013. The firm provided a response in IR Question 3 below in Amendment STN 125444/0/25.

- Reviewer's Comment:** Additional information is needed. In eCTD 3.2.P.7 (Container Closure System) the firm provided diagrams with specifications for each vial. However, it did not describe the bottom of the vial (e.g. heel radius). Differences in the bottom of the vial may impact the heat transfer that occurs during lyophilization. The firm was asked to provide a comparison of the vials, including the bottom of the vial. Refer to IR Question 4 below in Amendment STN 125444/0/25.

- (b)(4)

TR-PPD-003246 (rFIXFc Diluent Syringes Container Closure Integrity Results for PVR Lots) was for the diluent syringes and the test method was the same as for the DP. None of the test units showed ---(b)(4)---

Reviewer's Comments: In general, the response is acceptable. However, there are additional questions related to the positive control. Refer to below to **IR Question 4b**.

- 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.*

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

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

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

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

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

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

- 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.*

-(b)(4)- has trained their operators to perform this test according to their internal procedures. During execution of the simulated breach size study described in TR-PPD-003570, (b)(4) simulated breaches were reliably detected in all samples.

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

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

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

Reviewer’s Comments: It is acceptable that the firm has trained and qualified their operators. However, there is concern about their positive control (refer to IR Question 4b above).

- d. *Please clarify if you have shown the presence of (b)(4) with the (b)(4) positive control size in your study.*

The firm referred to report PDR-100-12-41, where all positive control units for (b)(4) separate tests reported as positive ----- (b)(4) -----.

Reviewer’s Comments: A summary of this report is above in IR Question 4a. My comments about the positive control are above in IR Question 4b.

- e. *Please clarify if CCIT was performed on vials from (b)(4) qualified vendors for the DP and please specify which vial size(s) were tested.*

Only 10 mL vials are used in the manufacturing of rFIXFc. ---- (b)(4) -----
-- vials are considered to be equivalent. Report PDR-100-12-41 details the CCIT for 3 lots of vials produced by ---- (b)(4) ----. Report TR-PPD-003676 describes the CCIT for one lot of vials produced by -- (b)(4) --.

Reviewer’s Comments: The response is acceptable. These reports were reviewed above in IR Question 4a and were found acceptable, with the exception about additional questions regarding the positive control.

- f. *Please clarify if any part of the container closure system that is product contact contains latex.*

The vial stopper is made of a chlorobutyl elastomer which does not contain dry natural rubber, which is the source of latex. The diluent syringe plunger and tip cap are made of a latex-free bromobutyl elastomer. The manufacturer's compound data sheets were also provided.

Reviewer's Comment: The response is acceptable.

5. *The submission states that -----(b)(4)----- during DP and diluent manufacture. Please clarify for which part of each process the ----(b)(4)----- is used.*

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

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

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

Reviewer's Comment: The response is acceptable. However, it is not clear if the product is filled under pressure or if it is oxygen sensitive. If so, using a ---(b)(4)----- test for CCIT is not appropriate since it is not sensitive enough to ensure the vacuum is maintained. The firm clarified during the August 20, 2013 telecon that the product is stoppered ----- (b)(4) ----- . The firm provided in writing that their product ----- (b)(4) ----- in STN 125444/0/34.

6. *Please provide the fill volume and vial sizes for all dosage strengths.*

Prior to lyophilization, the nominal fill volume for (b)(4)-2000 IU DP is (b)(4). The fill volume for the 3000 IU DP is (b)(4). The composition of the formulation

excipients prior to lyophilization is the same for all dosage strengths. The vial size for all dosage strengths is 10 mL.

Reviewer's Comment: The response is acceptable.

7. *Please provide the fill volume and syringe size for the diluent.*

The rFIXFc diluent solution is used for the reconstitution of all strengths of the rFIXFc DP. The syringe used for the diluent is a 5 mL -----(b)(4)----- glass barrel with luer-cone and groove needle attachment (luer lock syringe). The nominal fill volume is -(b)(4)- to ensure a deliverable volume of 5.0 mL to the DP.

Reviewer's Comment: The response is acceptable.

8. *Please clarify if the DP and diluent manufacturing processes are performed in closed or open systems.*

rFIXFc Drug Product:

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

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

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

rFIXFc Diluent:

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

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

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

Reviewer's Comment: The response is acceptable.

9. *Regarding visual inspection:*

- a. *Please clarify if the inspection is manual, semi-automated, or automated.*

The 100% visual inspections of the DP and diluent are performed manually.

Reviewer's Comment: The response is acceptable.

- b. *Please describe the visual inspection procedure performed for the DP 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.*

Description of the Visual Inspection Procedure

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

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

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

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

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

Defects being Evaluated

During visual inspection of rFIXFc DP, each packaging material component is evaluated for defects such as cracks, damages, inclusions, general deviations or particulate contaminations. The lyophilized product is evaluated for defects such as particulates, glass splinters and fibers, filling volume, discoloration and the quality of the lyophilized cake itself.

During visual inspection of rFIXFc diluent, each packaging material component is evaluated for defects such as cracks, damages, inclusions, general deviations or particulate contaminations. The liquid diluent itself is evaluated for defects such as particulates, glass splinters and fibers, filling volume, color and turbidity.

Acceptance criteria for visual inspection and the criteria for accepting or rejecting a lot:

Defects are classified as minor, major, or critical. Based on the classification, it is determined if the visually inspected unit is considered acceptable or rejected. The firm also provided a table (Table 2 in Amendment STN 125444/0/22) that indicated the criteria in place at --(b)(4)-- for evaluation of visual defects in relation to classification categories of minor, major, or critical. The generic (b)(4)- procedure allows for up to (b)(4) repeat visual inspections if the first inspection is

(b)(4)-----

Review of Amendment STN 125444/0/25

(b)(4)

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

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

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

Reviewer's Comment: From a DMPQ perspective, batch ----- (b)(4) ----- is acceptable to use for the PV for DP. It was manufactured after the three DS PV lots and was prospectively defined as part of the PV plan.

- d. *Please clarify if these lots were manufactured and tested exactly how the DS conformance lots were manufactured. If not, please provide the differences.*

Both batches (----- (b)(4) -----) were manufactured in the exact manner as the validation lots and processed through to drug substance. Both lots had the same in-process and release testing as used for all commercial rFIXFc lots. However, certain non-routine tests that are performed on validation lots were not performed on these two lots. Table 2 in Amendment STN 125444/0/25 detailed the breakdown of which testing was not performed.

Review Comments: I defer to the Product Office to assess the testing. It is acceptable that the same manufacturing process was used.

2. *Regarding sterilization*

- a. *In STN 125444/0/22, you mention that for the DP the “sterilization process the autoclave chamber can be equipped with ----- (b)(4) ----- onto which the goods are loaded according to defined fixed load patterns.” Please describe your ----- (b)(4) ----- and clarify what you mean by defined fixed load patterns.*

The materials and the equipment used for the DP process are sterilized using the ----- (b)(4) ----- . Depending on the size of the material and equipment they are

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

According to Figure 1 in Amendment STN 125444/0/25, there are ----- (b)(4) ----- load types. In total, up to (b)(4) carts with defined load patterns can be placed in different positions ((b)(4)) in the autoclave chamber per sterilization cycle. (b)(4) different possible loading combinations are shown in Table 3 in Amendment STN 125444/0/25. Based on the qualification, the order of the carts is allowed to vary.

Reviewer's Comment: The response is acceptable. As per the response below in IR Question 2b, the sterilization cycles are fixed and defined.

- b. *You also state that "the loads used for qualification/re-qualification purposes follow a --- (b)(4) --- concept in which all materials to be autoclaved are assessed and the worst case goods are identified. Based on this assessment the autoclave loads for qualification/re-qualification are defined to represent the worst case. This autoclave qualification and ---- (b)(4) ---- approach allows certain flexibility in routine productions cycles and has been validated by an initial validation using three individual validation runs." Please clarify your --- (b)(4) ---- approach and how you determine the worst case goods.*

The loading patterns for routine production cycles are fixed and define the permitted loading of carts, items (equipment and materials), their permitted positions and the related sterilization cycle.

Critical items which are used for initial qualification and re-qualification are defined according to a risk assessment taking the following aspects into consideration:

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

These critical items cover all items permitted for sterilization in routine production on the autoclave. The assessment of all individual production items to be sterilized, the relationship between all items and the tested worst case items during qualification/requalification is documented in this assessment and are documented in the 'single items' list (Figure 6 in Amendment STN 125444/0/25). Furthermore, these identified critical items are used for TC and BI placement during qualification/requalification.

-- (b)(4) -- uses a ---- (b)(4) ---- approach for validation and requalification of autoclave load patterns. For a maximum load during qualification/requalification, the autoclave is loaded with materials representing the maximum possible heat capacity.

Due to the variety of critical items necessary to be tested in a requalification, it may be necessary to divide the loading pattern into several validation loads to cover all materials according to the above mentioned single item list. All validated load patterns are considered worst case since they exceed the heat capacity of routine production cycles. Requalification activities are performed only for load patterns considered worst case. If additional load patterns are required, they will be qualified, and if the load pattern is considered the new worst case, requalification will be done using this load to ensure ---(b)(4)--- approach is still maintained.

Certain flexibility means that all items to be autoclaved are assessed regarding its criticality. After successful initial qualification of critical items, the position of the covered validated item types are defined in the routine production load patterns.

Reviewer's Comment: With the new equipment for rFIXFc, it appears the firm performed a risk assessment to determine if it was the worst case equipment. However, it is not clear if the risk assessment considers factors such as -----(b)(4)-----
----- etc.

A telecon was held with the firm on September 16, 2013. During that call, the firm clarified that these factors were considered under "material structural form." The response was found acceptable. -----(b)(5), (b)(7)(e)-----

3. *Regarding lyophilization*

- a. *Please explain your approach to validating your lyophilized cycle to demonstrate batch to batch uniformity and consistency. Please clarify if you have performed empty chamber temperature mapping of each shelf to determine hot and cold spots of each, if any. 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), batch size of each run, fill volume of each run, product strength of each run, and testing results (e.g. residual moisture, potency, reconstitution time).*

The approach to developing and validating the lyophilization cycle is aimed to ensure batch to batch uniformity and consistency by examining temperature mapping as a function of lyophilizer load as well as product location. This summary includes the sampling methods and testing throughout the various full scale lyophilizer runs along with other key characteristics of each run (batch size, fill volume, strength, etc.). The specific studies included:

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

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

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

- b. *Please describe in detail how the technical runs differ from your actual production lyophilization cycle.*

For Technical Run 1, ----- (b)(4) -----
----- than the final production cycle, respectively. For
Technical Runs 2 and 3 and the Technical Runs for (b)(4) and 2000 IU Cycle, the
----- (b)(4) ----- time was ----- (b)(4) ----- than the final
production cycle, respectively.

Reviewer's Comments: Again, this demonstrates that the Technical Runs were development work and did not represent the final production cycle. Thus, this data cannot be used to validate the final cycle; the data is supportive of selection of an appropriate lyophilization cycle only.

- c. *Please confirm that your lyophilization cycle is fixed.*

The firm confirmed that the lyophilization cycle depicted in Table 10 of STN 125444/0/25 is used for all rFIXFc DP strengths.

Reviewer's Comments: The response is not clear. During the telecon on September 16, 2013 the firm stated that they use ----- (b)(4) ----- to drive the cycle. Later the firm stated that they have a --(b)(4)-- cycle and that at ----- (b)(4) -----
----- . If the (b)(4) does not meet the acceptance criteria, ----- (b)(4) -----
----- . We stated that they have not provided data to ----- (b)(4) -----
----- . We recommended they use a fixed cycle and to use the (b)(4) for information only. This was again clarified during the October 8, 2013 telecon. The firm confirmed that they will be using only the validated --(b)(4) cycle for commercial product manufacture in STN 125444/0/36. The firm decided that the (b)(4) will not be enabled during commercial manufacturing operations.

- d. *Did you determine the -----(b)(4)----- temperature of your product?*

The ----- (b)(4) ----- of the lyophilized powder product has been measured and is provided in Table 8 below.

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

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

4. *Regarding the vials*

- a. *Please provide a side-by-side comparison of the vials. Please include specific dimensions of the base of the vial, heel radius, and thickness of the glass.*

The specific dimensions of (b)(4) vials are illustrated in Table 11.

(b)(4)-----

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

Reviewer's Comment: The response is not clear. It appears there is no specification for the bottom of the vial, which I have bolded in the table above. If the bottoms of the vials are different, it may affect the heat transfer for the lyophilization process. Discussions were held with the firm on October 8, 2013 regarding this. Refer to Amendment STN 125444/0/44.

- b. *Please clarify how each vial is manufactured.*

(b)(4) vials are made of ----(b)(4)---- tubular glass. The forming process takes place at the manufacturers -----(b)(4)----- respectively. (b)(4) have in-process controls in place to ensure the agreed quality. The sponsor referred to the DMF for additional detail.

Reviewer's Comment: The response is acceptable. I requested the DMFs.

I reviewed DMF----(b)(4)----- from -(b)(4)-. In Amendment -----(b)(4)-----, a description of the production flow for vial manufacturing was found. The vials are ----(b)(4)-----, and packaged. The vials are tested for -(b)(4)---

-----.

I was not able to obtain the DMF for -(b)(4)- as the DMF was not available. Although I was not able to review the DMF for the -(b)(4)- vial, the response is acceptable since the vials are (b)(4) made from tubular glass. The main

concern is the specifications for the bottom of the vial (refer to IR Question 4a above).

- c. *Please provide the final release data for the -(b)(4)- vials.*

Three DP lots have been filled into -(b)(4)- vials: -----(b)(4)----- (2000 IU/vial), and -(b)(4)- (3000 IU/vial). Release data for each is provided below in Table 16, Table 17, and Table 18, respectively in Amendment STN 125444/0/22. All test methods met the specifications.

Reviewer's Comment: I reviewed the release data and all results were acceptable. The response is acceptable.

Review of Amendment STN 125444/0/27

The following review questions were communicated to the sponsor on August 22, 2013. On September 12, 2013, CBER received responses from the sponsor in amendment STN 125444/0/27. A summary of my review questions (in *Italics*), Biogen Idec's responses (in regular text) and my comments (in **bold**) are below:

1. *Regarding the media fill for the DP, 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 person. Please clarify if you have performed an investigation for the objectionable organism and a summary of your investigation.*

During viable environmental monitoring an objectionable organism was detected on a personnel and this was identified as *Bacillus silvestris* (1 CFU/(b)(4)). A deviation was initiated and an investigation was performed according to procedures. The investigation concluded there was no assignable cause by the laboratory or manufacturing. Deviations are classified as minor if the product quality is not influenced and if there is no risk for the product. There was no evidence that this objectionable organism was transferred into the filled units or into critical zones of the production area. Below summarizes the investigation.

- Sample transport between the incubator in the sample-handover lock and the microbiological laboratory conformed to the requirements.
- Storage of samples, analysis, and materials used conformed to the requirements.
- The cleanroom was cleaned and disinfected according the SOP.
- Particle and flow monitoring in the cleanroom on the day the nonconformity occurred complied with the requirements.
- The visual inspection of the cleanroom did not reveal any conspicuous conditions.
- The process validation of the media fill was completed successfully.
- The training status of the persons conformed to the requirements.
- Both staff members who were in the clean room had a valid gowning validation.
- There was no evidence of incorrect behavior on the part of the staff members.
- There were no further nonconformities which could be related to the level excursion.

- All other results of the microbiological monitoring of the air, the surfaces and the personnel performed in Grade (b)(4) (class (b)(4)) and Grade (b)(4) (class (b)(4)) during this media fill conformed to the requirements.
- During 100% visual inspection and subsequent AQL testing no opalescent media fill units were identified.
- There was no evidence that the objectionable organism nor any other was transferred into the filled units or into critical zones of the production area.

According to the results of the microbiological investigation no special action was required since there was no trend detectable.

Reviewer's Comment: The response appears acceptable.

2. *Regarding the Bacterial Challenge Testing for the sterile filtration validation for the DP:*

- a. *Please clarify if it included the "worst-case" sterilization conditions. If not, please provide your rationale on why this is acceptable.*

The firm summarized what was submitted in the BLA, which included worst case time, pressure, filter area, and batch volume.

Reviewer's Comment: The firm did not address if filters experienced worst-case thermal stress mimic from -(b)(4)- sterilization. The firm was asked to clarify this on October 10, 2013. Refer to IR Question 2 in Amendment STN 125444/0/40.

- 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.*

The effect of rFIXFc against retention --- (b)(4) --- was evaluated as part of the Microbial Retention Validation, Project Number 10-8B5KJK by ----(b)(4)---- and reported in PVR-100-11-11. The product was found not to be antagonistic or stimulatory at (b)(4) hours of exposure. The firm also provided a table that summarized the results.

Reviewer's Comment: The response is acceptable.

3. *Regarding the hold time validations for the DP, 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.*

The hold time strategy includes a --- (b)(4) --- Compatibility Study tracking product quality ----- (b)(4) ----- challenge during process validation.

As rFIXFc is intended to be a multi-strength product, one hold time validation run was conducted --(b)(4)-- for each of the highest and lowest strengths to ensure that hold times were appropriate for the entire range of strengths. One lot of the minimum and maximum strength was deemed appropriate relative to product quality given the results of the ----(b)(4)---- study.

(b)(4)

Contamination of the DP is prevented by the -----(b)(4)-----
 ----- and the fact that the handling of the (b)(4) DP is performed in Grade (b)(4)
 (Class (b)(4)) air only. Vial filling, stopper placement, lyophilization, stopper closing,
 and crimping processes take place in a Grade -----(b)(4)-----

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

Viable and non-viable particulate monitoring is routinely performed.

The results gained from the product specific process validation, the validation of the aseptic process by media fill and the clean room qualifications support that the process and controls in place prevent contamination of the product.

Reviewer's Comment: The response appears acceptable.

5. *For the container closure integrity testing (CCIT) for stability testing of the DP, please provide the ----- (b)(4) ----- cycle.*

The description of the container closure integrity testing method which includes the ----- (b)(4) ----- cycles used for stability testing of the DP is given in Table 12 with acceptance criteria listed in Table 13.

Table 1 Stability Testing Container Closure Integrity Test Method Description

Testing Parameter/Component	Stability Testing Container Closure Integrity Test (---- (b)(4) ----- -----)
----- (b)(4) ----- Solution	-- (b)(4) --
Hold Time for Each Cycle	-- (b)(4) --
-- (b)(4) -- Cycle Set point	-- (b)(4) --
-- (b)(4) -- Cycle Set point	-- (b)(4) --
Positive Control Preparations	<ul style="list-style-type: none"> • (b) (4) ----- ----- • (b)(4) ----- -----
Reconstitution of Drug Product after (b)(4)	----- (b)(4) -----
Analytical Testing Method	----- (b)(4) -----

Table 2 Stability Testing Container Closure Integrity Test Acceptance Criteria

Parameter	Stability Testing Container Closure Integrity Test (----- (b)(4) -----)
Positive Control	----- (b)(4) -----
Test Articles	----- (b)(4) -----

Reviewer's Comment: The response is acceptable.

6. *Please clarify why you used different test methods for CCIT during stability versus testing the initial container closure.*

For routine testing and stability container closure integrity testing (CCIT), Biogen Idec utilizes the contract laboratory ----- (b)(4) -----
----- as it is domestically located. Only the initial container closure integrity testing for the purpose of qualifying the container closure system was performed at - (b)(4) ---
-----.

Both CCIT methods, which are considered equivalent, are based on the detection of -----(b)(4)----- into the DP containers. Both test methods incorporate the use of suitable controls along with the test samples. The CCIT methods for rFIXFc DP used at -----(b)(4)----- have been validated.

Reviewer's Comment: The response is not acceptable. The positive control for CCIT at -----(b)(4)-----. The firm was asked to clarify this difference during the October 8, 2013 telecon. Refer to IR Question 1 in Amendment STN 125444/0/37.

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.*

During microbiological cycles of initial qualifications, the position of the critical single items to be verified in the chamber, equipped with the BIs, are varied from cycle to cycle, as long as the size of the load items allows it. The aim is to verify each critical single item at (b)(4) different positions (----- (b)(4) -----). The items to be sterilized can be released for routine production cycles, if

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

In cases where the size of an item limits the options of positions in the loading pattern, these items need to be allocated to certain levels.

During the re-qualification cycles the critical single items equipped with BI are placed according to the validated load pattern.

If -(b)(4)- microbiological heat capacity challenge cycles are performed within the scope of the qualification (e.g. during initial qualifications), the position of the worst-case items equipped with BI must vary with each cycle (e.g. -----(b)(4)-----). If only one microbiological heat capacity challenge cycle is performed (e.g. for re-qualifications), the worst-case material sampled with BI must be positioned -----(b)(4)-----.

Depending on the respective production autoclave, stoppers and/or closure parts (if classified as critical single items) are verified during the microbiological heat capacity challenge as well. The stoppers/closure are -----(b)(4)----- . The heat capacity of the total load tested during validation/re-validation must exceed the heat capacity used during routine production cycles. The stoppers/closure parts to be verified during these heat capacity challenges must be positioned -----(b)(4)----- as they represent worst case position in the chamber.

The firm provided several diagrams with the BI locations.

Reviewer's Comment: I reviewed the diagrams and the response appears acceptable. BIs appeared to be in the worst case.

8. *Regarding ---(b)(4)--- sterilization*

- a. *Please clarify which ----(b)(4)---- was used for the first summary (Document Number 5009120).*

In summary Document No. 5009120, -----(b)(4)----- with the inventory number (b)(4) and equipment number ---(b)(4)--- was used. The ---(b)(4)--- type is -----(b)(4)-----.

Reviewer's Comment: The response is acceptable.

- 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 four BIs were used. Please justify why this amount of BIs is sufficient.*

The organism (spore suspension) used for the microbiological cycle was -----(b)(4)----- . The determination of the D-value in the product (diluent sodium chloride 0.325%) was performed at a temperature of -(b)(4)- -----.

There was no growth for the BIs placed in the load within the three performed runs. A negative as well as a positive control was used during the microbiological cycle. Each position was accompanied by one non-inoculated sample in --(b)(4)--- ----- to serve as a negative control. Not less than (b)(4) positive controls containing (b)(4) CFU were prepared for all samples and transferred into -(b)(4)-- -----.

A total number of (b)(4) BIs were used in the microbiological cycle. The number of positions equipped with BIs was determined depending on the size of the -----(b)(4)----- . The BIs were then evenly distributed throughout the different levels of the -----(b)(4)----- under discussion has (b)(4) loading levels. In that case, loading level -----(b)(4)----- are equipped with BI inoculated syringes ((b)(4) syringes at each position) to cover all loading levels released for routine production cycles for a total of (b)(4) BIs.

Reviewer's Comment: The missing information for the study was provided and found acceptable.

- 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.*

Worst case load for requalification purposes is defined to be the material with the maximum heat capacity. Currently, this is the material as mentioned above, with a total heat capacity of ---(b)(4)---. In comparison to that load, the heat capacity of the maximum load for Diluent for rFIXFc is calculated to be ---(b)(4)---. Since the maximum heat capacity of the -----(b)(4)----- is above the subjected diluent,

the defined requalification load covers the load configurations of the Product Diluent for rFIXFc.

Reviewer's Comment: The response appears acceptable for requalification purposes. The initial qualification for ---(b)(4)--- sterilization was with the 5 mL diluent syringe and was reviewed and found acceptable (refer to my primary review memo and IR Question 8a and 8b above).

- d. (b)(4) BIs were used in the requalification (Document Numbers 5017449 and 5017450). Please justify why this amount of BIs is sufficient.

(b)(4) positions are equipped with BI inoculated syringes ((b)(4) syringes at each position) to cover all loading levels released for routine production cycles for a total of (b)(4) BIs. The justification is provided with the answer to question 8b.

Reviewer's Comment: The response appears acceptable. The firm clarified a total of (b)(4) BIs were used.

9. Please clarify what distribution cycle and actual testing was performed for your shipping validations for the DP and diluent. Please justify how the simulated testing conditions are worst-case compared to actual shipping conditions.

Testing was performed utilizing -----(b)(4)----- in accordance with -----(b)(4)----- test methods. The distribution cycle was based on the hazard elements that the DP may potentially be exposed to during the Commercial Supply Chain. The distribution cycle for DP and diluent is outlined below.

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

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

----- (b)(4) ----- was used because the anticipated supply chain is well understood and the testing more accurately reflects the anticipated commercial supply chain. The testing for (b)(4) was developed based on careful observations of the various hazard elements seen during distribution. (b)(4) ensures the DP and diluent are exposed to a variety of hazards including ----- (b)(4) -----

----- . Assurance Level I assures the worst case distribution cycle since it is comprised of a high level of test intensity. Schedule B (---- (b)(4) ----) was conducted at Assurance Level II since procedures require ----- (b)(4) ----- during transport or warehousing.

***Reviewer's Comment:* It is not clear how the simulated testing conditions compared to actual shipping conditions with regards to temperature, time, and conditions. The firm was asked to clarify this on October 10, 2013. Refer to IR Question 4 in Amendment STN 125444/0/40.**

10. *Please clarify if any new equipment were implemented as a result of the DP or diluent.*

All rFIXFc product contact equipment (DP and diluent) is dedicated or single use; hence it was newly ordered and implemented for each. The design and the materials of this product dedicated equipment e.g. the vessels, ----- (b)(4) -----, the filling needles and the filters, the tubings and the gaskets are well known and did not require new sterilization validations.

There is no new shared equipment (autoclaves, depyrogenation tunnels, lyophilizers, etc.). The existing initial validations and the submitted sterilization re-validation studies cover all equipment and components used for manufacturing rFIXFc DP vial and the associated diluent syringe.

***Reviewer's Comment:* The response is acceptable.**

11. *Please provide how you ensure label reconciliation and accuracy of your labeling process.*

Labeling operations are performed at ----- (b)(4) ----- and -(b)(4) -----.

The incoming materials department identifies labeling material by product, item number/code, specification number and or lot number/expiration date per appropriate internal procedures. The Internal Quality Assurance (IQA) department samples, inspects and releases each receipt of labeling material per appropriate internal procedures.

Appropriate label control is maintained after IQA release. Released labels are issued to the production room. Prior to applying the labels to the primary container on validated equipment setup per appropriate internal procedures, the labels are printed with lot number, expiration date and any additional variable text per the production batch record. After printing, the labels are 100-percent inspected with an --(b)(4)----- system to assure the lot number, expiration date, additional variable text and item number/code of the labels are verified to be present, correct and legible. The labels are then applied to the primary containers. Label

presence inspection is performed after the label application to detect unlabeled primary containers. Any containers with labels that failed the (b)(4) or label presence inspection are ejected from the line.

Therefore, in accordance with 21 CFR 211.125(c) and 211.122 (g)(2), since 100-percent examination of labels is performed using -----(b)(4)-----
----- inspects and rejects the labels, both facilities do not perform labeling reconciliation. All excess labeling printed with lot number, expiration date, and additional variable text shall be destroyed. Returned labeling shall be maintained and stored in a manner to prevent mix-ups and provide proper identification.

Reviewer's Comment: The response appears acceptable.

12. Please clarify when and where identity testing of the DP and diluent is performed.

Identity testing of rFIXFc DP and diluent is performed by Biogen Idec QC laboratories in -----(b)(4)----- Cambridge, MA at the time of release for all DP and diluent lots manufactured by --(b)(4)-- as per approved specifications.

Reviewer's Comment: It is not clear if identity testing is performed after labeling as per 21CFR610.14. The firm was asked to clarify this on October 10, 2013. Refer to IR Question 3 in Amendment STN 125444/0/40.

13. Please provide a description of the vial, vial stopper, syringe barrel, (b)(4) closure system, and syringe plunger qualification program and the latest qualification results.

Product contact container closure components are qualified according to the following processes:

- Reviewing vendor data to ensure compliance with compendial requirements and appropriate safety testing, such as -----(b)(4)-----;
- Establishing compatibility through stability studies of DP with the components;
- Determining the presence of extractable and leachable substances;
- Establishing container closure integrity;
- Ensuring that the assembled components (as DP) are not negatively impacted during shipping and handling by the performance of suitably-designed shipping studies.
- Incoming goods testing is established by the contract manufacturing organization, in this case, -----(b)(4)-----.

The following is a summary of the qualification that is under DMPQ's purview that was not presented in the original BLA:

Vendor Data Review

The vial stopper is constructed of ---(b)(4)--- rubber and is -----(b)(4)----- on top and bottom surfaces, with trace quantities of ---(b)(4)--- on the stopper flange. The vendor's data for this component was provided. The vial stopper referenced here complies with -----(b)(4)----- . The material is also tested according to the biological reactivity tests in -----(b)(4)-----.

The diluent syringe plunger and the tip cap inside the (b)(4) are both made from the same -----(b)(4)-----, and the vendor's data are shown in Attachment

2. The syringe plunger and tip cap both comply with -----(b)(4)-----.
The material is also tested according to the biological reactivity tests in ---(b)(4)---
The vendor's CoC/CoA was also provided in the amendment.

Material receipt testing

According to the supplier qualification system which is utilized at -(b)(4)-, each new supplier and each new production site for currently approved suppliers of primary packaging materials is qualified via established audit processes at -(b)(4)-. Suppliers are re-qualified on a periodic basis as defined by -(b)(4)- process.

A qualification/requalification of the primary packaging material is periodically conducted. For the packaging material (elastomeric closures and glass), the requalification was performed every (b)(4) years according to the aforementioned audit process. The latest results for the requalification of the vial and vial stopper, syringe barrel, the tip cap of the (b)(4) closure system, and syringe plunger was provided and conformed.

In accordance with US CFR §211.84, -(b)(4)- implemented a new qualification/requalification system for packaging materials on 1 July 2013. This new risk-based procedure specifies whether and to what extent (i.e., full analysis) testing is performed after quality-relevant change(s) are implemented to new packaging materials (e.g. from a new supplier) or to the existing packaging materials. All materials undergo a full analysis utilizing a risk-based approach with testing on at least a ---(b)(4)--- interval.

The -----(b)(4)----- of the glass and characteristic tests for the elastomers will be done on a representative material that will be within the scope of the future requalification tests. This is justified by the fact that after their production, the tubular glass and elastomers do not change during the subsequent processing steps at the suppliers. Other attributes will be tested on the representative materials per the supplier and production sites based on the relevant material type and quality. This ensures that the tests documented on the supplier certificates for the relevant materials of each supplier and production site are verified and evaluated.

The full analysis of the new packaging materials and the ----(b)(4)---- concept within the scope of the future qualification/requalification ensures that there will be adequate verification of the supplier with regard to the correctness of the certified data. It also ensures that the supply of packaging materials conform to the quality guidelines in accordance with the regulatory compendia.

With regard to the rFIXFc DP and the diluent the new qualification/requalification system of Packaging Materials will be used for all future testing. Requalification in accordance with the new qualification system per CFR §211.84 is not yet available.

Reviewer's Comment: The response appears acceptable. The latest requalification conformed. From a high level, it appears acceptable that -(b)(4)- is using a risk-based process for their new qualification/requalification program. -----(b)(5), (b)(7)(e)-----

-----**(b)(5), (b)(7)(e)**-----

Additionally, it is not clear if the firm is following the 21 CFR 820s for the diluent syringe since that is considered a combination product. Refer to Amendment STN 125444/0/54 for the firm's clarification.

Review of Amendment STN 125444/0/28

During the late cycle meeting on September 12, 2013, FDA communicated concerns regarding the submission. On September 19, 2013, CBER received responses from the sponsor in amendment STN 125444/0/28. A summary of the Product Office and my review questions regarding the process validation (in *Italics*), Biogen Idec's responses (in regular text) and my comments (in **bold**) are below:

1. *There is a concern about your process validation conformance lots for the following reasons:*

- a. *There is insufficient data to support manufacturing on -----(b)(4)-----.*
Specifically, the conformance lot data submitted was not manufactured under prospective validation and was not carried on beyond the cell culture process.

As clarified at the late cycle review meeting, batch ---(b)(4)--- was the prospectively defined validation batch for -----(b)(4)----- . Batch ---(b)(4)--- ---- was included in the cell culture process validation report for -----(b)(4)----- (refer to BLA 125444/0000 Section 3.2.S.2.5.3.2 Process Consistency Validation – Cell Culture). As the purification process was already validated, this batch was not included in the purification reports, however, in-process characterization testing and additional characterization of the (b)(4) batch was performed. All in-process characterization and additional characterization results for the (b)(4) were found to be consistent across batches. Additionally, batch ---(b)(4)--- was carried through into DP. To support the validation of (b)(4), data was provided in the Amendment for the in-process testing, -----(b)(4)-----, and release results. The results are provided side by side with (b)(4) results for comparative purposes. Also provided in the Amendment were release and stability test results for DP produced with ---(b)(4)---. Subsequent to (b)(4) validation, an additional (b)(4) batches have been produced on (b)(4) to support product launch. All (b)(4) lots met release specifications for ----(b)(4)----.

Reviewer's Comment: The process was carried through to the DP. Since this is a recombinant product, limited equipment information was provided. Of note, the firm did provide the equipment cleaning acceptance criteria in Amendment STN 125444/0/5 and it was the same for ----(b)(4)----. From a DMPQ perspective, this is acceptable.

- b. *Drug substance (DS) batches -----(b)(4)----- were not manufactured as part of the DS conformance batches and were used for the drug product (DP) conformance lots in support of this BLA. Additionally, it is not clear if these batches were manufactured under the process validation master plan or under prospective validation.*

As communicated at the late-cycle review meeting, this item was resolved in responses submitted to BLA 125444 on September 5, 2013.

***Reviewer's Comment:* In discussions with the Product Office, their response was concluded to be acceptable.**

Review of Amendment STN 125444/0/34

On September 16 and 19, 2013, two telecons were held with the sponsor. Please refer to FDA's minutes for details regarding these telecons. On September 27, 2013, CBER received responses from the sponsor in amendment STN 125444/0/34. A summary of my review questions (in *Italics*), Biogen Idec's responses (in regular text) and my comments (in **bold**) are below:

- 1. Please provide a summary of your understanding of what is required from our telecons.*

The firm understood that FDA requested:

- A lyophilizer empty chamber temperature mapping study
- Product quality attributes (potency and moisture content) and temperature mapping -----(b)(4)----- for the following:
 - Commercial lyophilization cycle, with a minimum loaded lyophilizer with vials containing the minimum fill volume, corresponding to the (b)(4) strength
 - Commercial lyophilization cycle, fully loaded lyophilizer with vials containing maximum fill volume, corresponding to the 3000IU strength

These two runs could be commercial runs with extended sampling or -(b)(4)- runs with --(b)(4)-- vials.

The firm also understood that they could not extend the cycle if the ---(b)(4)--- test did not meet the requirements or if extended release of the material would need to be reported to the Agency. The firm also stated that even though the vials are stoppered ----(b)(4)---- the product is -----(b)(4)-----.

***Reviewer's Comment:* FDA did not ask the firm to perform extended sampling during the technical runs. I had suggested that the firm takes samples from actual commercial lots. However, during the September 19, 2013 telecon, the firm expressed sterility concerns in performing extended sampling during commercial lots. Since sampling during the technical runs is similar sampling during commercial runs, the two technical runs are acceptable.**

Regarding the (b)(4), it appears that the firm did not understand our comment. The firm can use the (b)(4) for information only, but the (b)(4) results cannot be used to drive the cycle time until they have validated it (established correlation with the shelf temperature). This was communicated to the firm during the October 8, 2013 telecon. Per Amendment STN 125444/0/36, the firm has committed to running a (b)(4) duration cycle and the (b)(4) will not be used during production. -----(b)(5), (b)(7)(e)-----

2. Please provide the original empty chamber mapping study.

All three runs met the acceptance criteria.

already performed the requalification. The firm submitted the requalification in Amendment STN 125444/0/39. Refer to IR Question 1 under Amendment STN 125444/0/39 for a review of the requalification.

3. *Please provide your protocols for the technical runs.*

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

For TR-PPD-004872, the firm will use a ----- (b)(4) -----, which represents the minimum load, of (b)(4) IU rFIXFc product. For TR-PPD-004873, --(b)(4)-- shelves will be loaded (maximum load) with --(b)(4)-- and be -(b)(4)- with 3000 IU rFIXFc product. Both technical runs will include product temperature mapping and extended sampling. The mapping and sampling will come from the ----- (b)(4) -----
----- . The extended sampling includes ----- (b)(4) -----
----- .

***Reviewer's Comment:* Overall, the approach appears acceptable. However, during the October 8, 2013 telecon, we provided some feedback. First, we asked the firm to submit in writing that shelf (b)(4) will be used for the minimum production load. Please refer to Amendment STN 125444/0/36 for this commitment.**

Also, during the call I noted that there was no acceptance criterion for the product temperature mapping and requested the firm to include an acceptance criterion for this in their protocol. Furthermore, the firm confirmed that the temperature mapping and samples will all come from vials filled with product.

The firm performed the two additional Technical Runs and submitted it in Amendment STN 125444/0/45.

Review of Amendment STN 125444/0/36

On October 8, 2013, a telecon was held with the sponsor. Please refer to the minutes for details regarding this telecon. On October 11, 2013, CBER received a meeting summary from the firm in amendment STN 125444/0/36. A summary of my review questions (in *Italics*), Biogen Idec's responses (in regular text) and my comments (in **bold**) are below:

1. *Please provide a summary of your understanding of the October 8, 2013 telecon.*

The firm provided their meeting summary, which included the following:

- DP vial: Biogen intends on using ----- (b)(4) ----- vials for commercial use. During the telecon, Biogen stated that they will be using the -(b)(4)- vials during the technical runs. In their summary, they stated instead that only the -(b)(4)- vials will be used during the technical runs. FDA stated additional information is

- needed to confirm the equivalency of the (b)(4) vials. Biogen stated they would provide detailed vial descriptions and dimensions.
- Lyophilizer requalification: The firm indicated that they recently completed the requalification. -----(b)(4)-----
----- Acceptance criteria were also tightened. The firm will submit the report by October 18, 2013.
 - Lyophilizer Technical Runs: The firm indicated that shelf -----(b)(4)----- shelf and is used for the minimum run during routine operations. The firm also agreed to add temperature mapping acceptance criteria to the protocol and that samples will be taken from actual product. The firm also clarified they understood that only the validated (b)(4) cycle will be used for commercial product manufacture and that changes to the cycle will require a supplement. The firm also stated that they would clarify that the maximum load will include --(b)(4)-- vials -(b)(4)- with product.
 - CCIT: The firm understood that FDA was requesting the acceptability of a (b)(4) positive control and the differences between the -----(b)(4)----- CCIT test method.

Reviewer's Comment: Overall, the firm captured the essence of the telecon. Please refer to FDA's minutes for additional details discussed during the telecon and the official minutes.

Review of Amendment STN 125444/0/37

On October 8, 2013, a telecon was held with the sponsor. Please refer to the minutes for details regarding this telecon. On October 15, 2013, CBER received responses from the sponsor in amendment STN 125444/0/37. A summary of my review questions (in *Italics*), Biogen Idec's responses (in regular text) and my comments (in **bold**) are below:

1. *The positive control for the ---(b)(4)--- test used at -(b)(4)- was (b)(4), which is not consistent with current literature regarding the detection capabilities of CCIT. The average microbe is 4-6 μ m and if your limit of detection is around (b)(4), there is concern that the test cannot detect -(b)(4)- of an average microbe. Please address this concern. Furthermore, the positive control used at --(b)(4)-- (stability) is (b)(4) for the ---(b)(4)--- test. Please address why you are able to detect a leak at (b)(4) for stability testing of the vials versus the (b)(4) for qualifying the vials and syringes.*

The container closure integrity (CCI) method developed and validated at -(b)(4)-, which has demonstrated capability to detect breaches down to (b)(4) in size, was used for the purposes of container closure qualification for rFIXFc DP. Since that time, a CCI method developed and validated by -----(b)(4)----- has been used for all shipping validation and stability testing of rFIXFc DP vials. The ---(b)(4)--- CCI assay, which was validated to reliably detect breaches of (b)(4) or greater, has been conducted on more than (b)(4) vials of rFIXFc DP for various shipping and stability studies (refer to Table 15), and all vials tested have passed.

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

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

(b)(4)-----

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

The firm committed to repeating the container closure qualification study with a validated method capable of detecting breaches of (b)(4). In addition, they committed to conducting any future CCI testing using a validated method capable of detecting breaches of (b)(4).

***Reviewer's Comment:* I find the CCI acceptable for the DP vial using the test method at -----(b)(4)----- positive control). The large number of samples ((b)(4) vials) evaluated by ---(b)(4)---, provides additional assurance that the DP final container is integral.**

However, it is unclear if the firm has similar data for the diluent syringe. During the October 21, 2013 telecon, the firm stated they did not. The firm committed to re-qualifying the CCIT for the diluent syringes by the end of January 2014. The firm provided this data is Amendment STN 125444/0/50.

Review of Amendment STN 125444/0/39

On September 16, September 19, and October 8, 2013, telecons were held with the sponsor. Please refer to the minutes for details regarding these telecons. On October 17, 2013, CBER received the requalification of the lyophilizer in amendment STN 125444/0/39. A summary of my review questions (in *Italics*), Biogen Idec's responses (in regular text) and my comments (in **bold**) are below:

1. Please submit your requalification of the lyophilizer.

The firm provided the final qualification report, (b)(4)_5038699, for the lyophilizer -----(b)(4)----- was assessed at (b)(4) different locations in -----(b)(4)----- for a total of (b)(4) locations for the empty chamber temperature mapping study.

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

The following review questions were communicated to the sponsor on October 10, 2013. On October 22, 2013, CBER received responses from the sponsor in amendment STN 125444/0/40. A summary of my review questions (in *Italics*), Biogen Idec's responses (in regular text) and my comments (in **bold**) are below:

- Biogen confirms that any changes made to implementing qualified, equivalent equipment will be appropriately reported to the Agency.

2. Please clarify if the sterile filters used for the Bacterial Challenge Testing mimic the actual process that they are used for. Specifically, if the sterile filters you use for production are (b)(4) sterilized prior to use, did the filters used during validation also experience this sort of worst-case -(b)(4)- stress during testing?

[illegible]

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3. *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.” Please clarify if identity testing will be performed after labeling has been completed.*

A final container from each filling of each lot will be tested for Identity upon the completion of all Biogen Idec labeling and packaging operations. Identity will be confirmed by -----(b)(4)----- visual inspection of the product. The visual inspection includes confirmation of unique individual product and container closure characteristics including cake appearance and cap color.

Reviewer’s Comment: The response is acceptable.

4. *Regarding your shipping validations for the DP and diluent, please compare the simulated testing conditions to the actual shipping conditions with regards to temperature, time, and conditions.*

For shipment, the DP and diluent syringe are loaded into a -----(b)(4)----- storage containers. The container maintains temperature of -----(b)(4)----- . The container is shipped by a combination of --(b)(4)-- to the finished good packaging site. Typical shipping routes for DP are from -----(b)(4)----- USA with duration of ----(b)(4)----. The --(b)(4)-- minimum/maximum temperature ranges from -----(b)(4)----- and from -----(b)(4)-----.

Simulated temperature testing in a chamber was based on representative DP/diluent syringe shipments as well as worst case --(b)(4)-- temperature profiles. The simulated temperature testing performed modeled 1) representative shipments for the standard shipping duration, 2) variable --(b)(4)-- temperature profiles for the maximum time duration, and 3) worst-case varying --(b)(4)-- temperature profiles. During this qualification, the temperature was monitored, and confirmed to maintain --(b)(4)-- (DP) and --(b)(4)-- (diluent syringe) for up to --(b)(4)-- duration.

The firm also simulated shipping conditions. The simulated distribution cycle was based on actual hazards that the DP and diluent syringe may potentially be exposed to during the Commercial Supply Chain. The simulated distribution cycle for DP and diluent syringe are in comparison with supply chain actual hazards are in Table 19 below. Simulation Testing was performed utilizing -----(b)(4)----- (User Defined) in accordance with -----(b)(4)----- test methods.

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

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

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

***Reviewer's Comment:* The response is acceptable. The simulated testing conditions are worst case or comparable to actual shipping conditions.**

Review of Amendment STN 125444/0/41

The following review questions were communicated to the sponsor on October 18, 2013. On October 23, 2013, CBER received responses from the sponsor in amendment STN 125444/0/41. A summary of my review questions (in *Italics*), Biogen Idec's responses (in regular text) and my comments (in **bold**) are below:

- 1. Please clarify your acceptance criteria for the requalification report of the lyophilizer provided in Amendment STN 125444/0/39. For example, one of the acceptance criteria for method 2 states -----(b)(4)-----*

(b)(4)-----

(b)(4)-----

(b)(4)-----

***Reviewer's Comment:* The clarification is acceptable. However, evaluating the mean value does not provide sufficient support to demonstrate the lyophilizer is in control. Refer to IR Question 2 below for the firm's comments to evaluate this concern.**

2. *In general, taking the (b)(4) value of thermocouples is not appropriate for an acceptance criterion for empty chamber shelf temperature mapping. Please address this concern.*

Biogen Idec asked (b)(4)- to provide us with data obtained during the qualification study showing the maximum difference between -----(b)(4)-----
----- for each of the steps of the qualification cycles. The data received from (b)(4)- is provided below in Table 19.

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

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

All acceptance criteria were met. The firm provided an addendum to the original qualification report.

***Reviewer's Comment:* The response is acceptable. Evaluating the maximum difference between the temperature reading of an -----(b)(4)-----
----- is acceptable. There should be limited variation of each shelf and from shelf-to-shelf (industry standard is $\pm 2^{\circ}\text{C}$). Although the firm allowed -----(b)(4)-----, the net difference was ---(b)(4)---. I found the firm's criterion acceptable.**

Review of Amendment STN 125444/0/44

On October 8, 2013, a telecon were held with the sponsor requesting additional information regarding the vial. On November 15, 2013, CBER received this information in amendment STN 125444/0/44. A summary of my review questions (in *Italics*), Biogen Idec's responses (in regular text) and my comments (in **bold**) are below:

1. *Please provide information to show that the -----(b)(4)----- vials are equivalent.*

Vial dimensional information for (b)(4) vials from the -----(b)(4)-----
----- used in DP manufacturing are provided in Table 21 and Table 22. The vial body diameter specifications and tolerances for the (b)(4) vials are presented in Table 21. The vial bottom thickness, bottom radius, and bottom concavity measurements presented in Table 22 were requested from each vendor and the dimensions were provided by the vial suppliers for multiple lots. The values reported here represent the averages from three distinct lots of --(b)(4)-- vials and four distinct lots of -(b)(4)- vials, as collected during IPC measurements.

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

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

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

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

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

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

The vial bottom thickness dimension specified in the --(b)(4)-- standard is --(b)(4)--; for (b)(4) vendors, the average bottom thickness measurements were found to be --(b)(4)--, with similar standard deviations, maximum, and minimum values.

The average values of the bottom radius measurements are provided in Table 22 for ----- (b)(4) ----- vials. The average bottom radius value for the -(b)(4)- vial is similar to that of the -(b)(4)- vial; furthermore, the maximum and minimum values for the -(b)(4)- vial are within the range of maximum and minimum values reported for the -(b)(4)- vial.

The average values of the vial bottom concavity measurements are provided in Table 22 for ----- (b)(4) ----- vials. (b)(4) vials conform to the (b)(4) standard of a maximum value of (b)(4) for bottom concavity. The bottom concavity vial dimension

has been shown not to impact sublimation of the DP, as reported in the literature.

The firm concluded that based on information found in scientific literature and the vial dimensions reported in Table 21 and Table 22, the -----(b)(4)----- vials can be considered comparable.

The firm also noted that three GMP DP lots were produced using -(b)(4)- vials and placed on stability, ---(b)(4)--- IU/vial), -(b)(4)- (2000 IU/vial), -(b)(4)- (3000 IU/vial). The (b)(4) IU/vial and 2000 IU/vial represent the lowest and highest strength at the (b)(4) fill volume. The 3000 IU/vial is the only strength with (b)(4) fill volume. Stability data for these lots were provided in the recent Stability Update to the BLA submitted on 27 September, 2013 (SN0034).

Reviewer's Comment: I have contacted the vendor to confirm the specifications for the vials and it is consistent with what the firm provided in IR Question 4a in Amendment STN 125444/0/25. The specification for the bottom thickness is a minimum of (b)(4) mm, the bottom radius is (b)(4) mm, and the bottom concavity is a maximum of (b)(4) mm.

The actual lot data for bottom thickness show that the -(b)(4)- vials are very similar to the -(b)(4)- vials. The bottom thickness has the same average and similar standard deviation. The bottom radius for the -----(b)(4)----- vials are also similar. The actual lot data show that the -(b)(4)- vials are manufactured with a -----(b)(4)----- vials (which were used for the lyophilization validations).

However, it is difficult to compare the bottom concavity since the vendors are using different locations to measure this specification. The firm provided a paper where the author performed a study that showed no statistically significant difference in measured sublimation rates in vials with different concavities with the presence of a -----(b)(4)----- . I reviewed this paper and it appears to be a well-designed experiment.

Given that the specifications for the vials are identical, the lot data indicates that the bottom thickness and bottom radius are similar, and the firm has provided a paper demonstrating that the bottom concavity does not impact the sublimation rates; I find the (b)(4) vials sufficiently similar that the likelihood that lyophilization would progress differently -----(b)(4)----- is low, and therefore they are acceptable for use.

Review of Amendment STN 125444/0/45

On September 16, September 19, and October 8, 2013, telecons were held with the sponsor. Please refer to the minutes for details regarding these telecons. On November 20, 2013, CBER received the technical report studies of the lyophilizer in amendment STN 125444/0/45. A summary of my review questions (in *Italics*), Biogen Idec's responses (in regular text) and my comments (in **bold**) are below:

- 1. Please provide the technical reports for the lyophilization process.*

Six (6) Pages Determined to be Non-Releasable: (b)(4)

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

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

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

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

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

Review of Amendment STN 125444/0/48

On November 22, December 2, and December 4, 2013, telecons were held with the sponsor. Please refer to the minutes for details regarding these telecons. IR questions were sent to the communicated to the firm during the telecons. On December 18, 2013, CBER received responses to the IR in amendment STN 125444/0/48. A summary of my review questions (in *Italics*), Biogen Idec's responses (in regular text) and my comments (in **bold**) are below:

1. *You stated in your protocols (in Amendment 45) that "some thermocouples may give inconsistent data during the lyophilization run and may not meet the above criteria." Did any TCs give inconsistent data? If so, please provide that data and why it is acceptable.*

None of the TCs used to monitor the product temperatures malfunctioned or showed any inconsistent data for both technical runs. All of the product temperature TCs gave consistent data and were used in the assessment of both technical runs.

Reviewer's Comment: The response is acceptable.

2. *Please provide the amended technical reports with corrected -----**(b)(4)**-----*
-----.

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

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

4. *Good lyophilization practice entails keeping the product temperature below the (b)(4) of the product during ----(b)(4)----. Please explain your rationale for your ---(b)(4)--- cycle being below ----(b)(4)----. Please provide your rationale why it is acceptable that the product temperature is above the (b)(4) during ----(b)(4)----. Please also provide the literature reference that supports your rationale.*

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

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

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

Reviewer's Comment: The response is acceptable. The articles the firm referenced indicates that -----(b)(4)----- products should be at temperatures -----(b)(4)-----, which is what the firm's ----(b)(4)---- cycle is set to. Looking collectively at the articles that the firm provided, the data from the technical reports, and data from the process validation lots, it appears acceptable that the ----(b)(4)---- cycle is operating

-----**(b)(4)**-----**. From the technical runs provided in Amendment STN 125444/0/45, I found the results from the extending sampling acceptable. All product quality attributes meet the acceptance criteria and statistically there was no statistical significant difference between each sampling location. Furthermore no melt back or collapse has been observed for the -(b)(4)- lots the firm inspected.**

5. *Please explain why there is such a large difference in temperature between the (b)(4)-*
-----.

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

Reviewer's Comment: The response is acceptable. -----(b)(4)**----- discussed that the -----**(b)(4)**-----
-----**. This is the observed case for rFIXFc.****

6. *Historically, please clarify if you have observed any melt back. Please also provide how many lots were visually inspected.*

Based on 100 % visual inspection of (b)(4) DP lots produced using the proposed rFIXFc commercial lyophilization cycle, the firm has not observed any instances of cake collapse or melt back. The firm provided a table that contains the visual inspection results for the lots produced using the commercial cycle. Additionally, photographs of examples of rFIXFc dry powder cakes from lot ---**(b)(4)**--- and lot **-(b)(4)-** (3000 IU) strength were provided.

Reviewer's Comment: The response is acceptable. **-(b)(4)- lots, which include over **-(b)(4)-** vials, have been inspected and no melt back or collapse have been observed.**

7. *Please clarify how many vials were sampled and tested for the process validation lots.*

The firm provided a table that showed the number of vials that were taken for testing and the number of vials that have been tested for the process validation lots. The number of vials listed included release testing for every lot and stability testing, where applicable. Additionally, the percentage of the lot that was placed on stability was listed.

Reviewer's Comment: The response is acceptable. The firm manufactured **(b)(4) process validation lots. Of the **(b)(4)** vials manufactured, **(b)(4)** vials have been**

tested to date. A total of (b)(4) vials were sampled (includes release and stability testing).

8. *There appears to be a lag time between the -----(b)(4)------. Please address how you have ensured that the -(b)(4)- vials have completed the --(b)(4)----- cycle at the end of the -(b)(4)- cycle.*

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

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

(b)(4)

(b)(4)

(b)(4)

- The product temperatures at the end of each cycle step were provided. All measured T_p met the acceptance criteria. The raw temperature data for the last (b)(4) hours of the ----(b)(4)---- phase of the fully loaded technical run was also provided.

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(b)(4)

(b)(4)

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in amendment STN 125444/0/50. A summary of my review questions (in *Italics*), Biogen Idec's responses (in regular text) and my comments (in **bold**) are below:

1. *Please provide the re-qualification for CCIT of the diluent syringes.*

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

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

The container closure integrity qualification was repeated using the --- (b)(4) ----- method and documented in Report TR-AT-006082. Over (b)(4) diluent syringes from the (b)(4) different lots ((b)(4) syringes in total) were tested and all samples passed CCIT. All test samples did not have visible ---- (b)(4) ----- was less than the test sample spiked with (b)(4) at the DL. Additionally, all positive controls had an ---- (b)(4) ----- to test sample test samples spiked with (b)(4) at the DL. The firm concluded that the syringe container closure component provides a suitable barrier to maintain the quality and sterility of its contents.

***Reviewer's Comment:* The response is acceptable. The firm has demonstrated that the --- (b)(4) --- container closure integrity method is capable of detecting breaches (b)(4) in the rFIXFc diluent syringes. And the re-qualification report showed all test units did not have visible (b)(4).**

Review of Amendment STN 125444/0/52

Information request questions were communicated to the firm on February 12, 2014. On February 24, 2014, CBER received the firm's responses in amendment STN 125444/0/52. A summary of my review questions (in *Italics*), Biogen Idec's responses (in regular text) and my comments (in **bold**) are below:

1. *Please explain your qualification program for the 100% visual inspection of the drug product. Specifically, please provide details about the test set used to qualify the operators.*

In STN 125444/0/52, the firm provided a summary of -(b)(4)- visual inspection training process. Operators must undergo and pass -(b)(4)- eye exam. Additionally, new operators are trained using established procedures and a training kit. Each training kit includes all possible defects (provided in Table 1 of the amendment). The components used in the training kits are not the actual vials and syringes used for rFIXFc.

After a training period of at least (b)(4) days, the practical exam using a qualification test kit can be taken. Each visual inspection test kit contains a set of ---(b)(4)--

Staff members who fail the visual inspection test may not conduct any visual inspections until the test is successfully repeated. If the first test was not passed, (b)(4) days of further training must be performed by the staff member, before the test can be repeated. Additionally, if the staff member fails the first test, an eye exam is required to ensure the repeat test failure is not due to defective vision.

If the second test is not passed, the Production Leader of Visual Inspection and the Team Manager or Shift Coordinator may determine whether the staff member is allowed to participate in the test again. If the staff member fails three tests, he cannot perform any visual inspections.

For manual visual inspection, each operator must successfully complete 6 sets of acceptable quality limits (AQL) testing and pass a test using a qualification test kit.

Re-qualification is performed on an -(b)(4)- basis.

Reviewer's Comment: Overall, the qualification program for visual inspection appears acceptable. However, -----(b)(5), (b)(7)(e)-----

Review of Amendment STN 125444/0/54

Information request questions were communicated to the firm on February 19, 2014. On February 27, 2014, CBER received the firm's responses in amendment STN 125444/0/54. A summary of my review questions (in *Italics*), Biogen Idec's responses (in regular text) and my comments (in **bold**) are below:

1. *Please note that the Final Rule for 21 CFR Part 4 – Regulation of Combination Products became effective July 22, 2013. The pre-filled diluent syringe is considered a combination product (21 CFR 3.2(e)). It appears that you have chosen to demonstrate compliance with the drug CGMPs. Please provide a summary of how you have complied with the following provisions of the Quality System (QS) regulation for the pre-filled diluent syringe:*
 - a) 21 CFR § 820.20. *Management responsibility*
 - b) 21 CFR § 820.30. *Design controls*
 - c) 21 CFR § 820.50. *Purchasing controls*

d) 21 CFR § 820.100. Corrective and preventive action

Per STN 125444/0/54, Biogen Idec and -(b)(4)-, and the diluent syringe component suppliers meet the controls of the 820s. Biogen Idec is responsible for providing technical and quality oversight of the contract manufacturing organization (CMO) selected to manufacture the pre-filled diluent syringe and subsequently any companies utilized by the CMO to manufacture and supply components of the pre-filled diluent syringe.

In their response, the firm listed procedures that define management responsibilities, design control, purchasing controls, and corrective and preventive actions under the Quality Management System. In addition, for design controls, the response discussed design and development planning, design inputs, design outputs, design review, design verification, design validation, design transfer, and design changes.

Reviewer's Comment: The firm appears to have a system in place to meet the intent of the 820s. The response is acceptable.

Bibliography

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

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

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