



MEMORANDUM

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

To: File (STN 125487/0)
Leigh Pracht, Regulatory Project Manager, RPMB/DBA/OBRR

From: Ze Peng, PhD, LH/DHRR/OBRR

Through: Mark Weinstein, PhD, Assoc. Dep. Dir. for Science, OBRR

Subject: Final Review of Stability information in Biogen Idec's original BLA for Antihemophilic Factor (Recombinant Fc Fusion Protein)

Cc: Nancy Kirschbaum, PhD, Committee Chair, LH/DHRR/OBRR

Executive Summary

This memorandum summarizes the review of stability information in an original Biologics License Application (BLA) under STN 125487/0 submitted by Biogen Idec (Biogen) for Antihemophilic Factor (Recombinant Fc Fusion Protein) [rFVIIIIFc]. The available stability data provided in the original BLA submission and the amendments dated 29 August 2013, 19 December 2013, and 18 April 2014 support the stability of rFVIIIIFc drug product (DP); therefore, I recommend approval of the BLA under STN 125487/0.

Stability studies on rFVIIIIFc drug substance

Stability data support the following expiry period of rFVIIIIFc drug substance (DS): ----
b(4)----- . This expiry period is supported by the following batches:

[*b(4)*]

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

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

Stability studies on rFVIII Fc drug product

Stability data support the following shelf life of rFVIII Fc DP: *Up to 24 months under storage at $5 \pm 3^{\circ}\text{C}$. Within this period, the product can be stored at room temperature (i.e., $\leq 30^{\circ}\text{C}$) for a single period, not to exceed the expiration date, of up to 6 months, and then discarded.* This shelf-life is supported by the stability data generated from the following conformance lots and clinical lots:

rFVIII Fc conformance DP lot No.	DP Strength	Storage temperature	Available data
--b(4)---	250 IU/vial	5 ± 3°C	18 months
		30 -°C -b(4)---	--b(4)---
		--b(4)---	--b(4)---
--b(4)---		5 ± 3°C	18 months
		30 -°C -b(4)---	--b(4)---
		--b(4)---	--b(4)---
--b(4)---		5 ± 3°C	18 months
		30 -°C -b(4)---	--b(4)---
		--b(4)---	--b(4)---
--b(4)---	3000 IU/vial	5 ± 3°C	18 months
		30 -°C -b(4)---	--b(4)---
		--b(4)---	--b(4)---
--b(4)---		5 ± 3°C	18 months
		30 -°C -b(4)---	--b(4)---
		--b(4)---	--b(4)---
--b(4)---		5 ± 3°C	18 months
		30 -°C -b(4)---	--b(4)---
		--b(4)---	--b(4)---

--b(4)-----*: the manufacturing process is comparable to the proposed commercial one

No critical trends were detected from stability data for up to 18 months under the long-term storage condition of $5 \pm 3^{\circ}\text{C}$. The available stability data for the storage condition of 30°C --b(4)-----also met acceptance criteria. Although the long-term stability data for the conformance lots are not available for up to 24 months at this time, Biogen provided --b(4)--- stability data ($5 \pm 3^{\circ}\text{C}$ and 30°C --b(4)-----) on the following seven clinical rFVIII Fc DP lots.

rFVIII Fc clinical DP lot* No.	DP Strength	Storage temperature	Available data
--b(4)---	250 IU/vial	$5 \pm 3^{\circ}\text{C}$	24 months
		30°C --b(4)---	--b(4)---
		--b(4)---	--b(4)---
--b(4)---	500 IU/vial	$5 \pm 3^{\circ}\text{C}$	24 months
		30°C --b(4)---	--b(4)---
		--b(4)---	--b(4)---

rFVIII ^h clinical DP lot* No.	DP Strength	Storage temperature	Available data
--b(4)----	750 IU/vial	5 ± 3°C	18 months
		30 °C -b(4)----	--b(4)----
		--b(4)----	--b(4)----
--b(4)----	1000 IU/vial	5 ± 3°C	24 months
		30 °C -b(4)----	--b(4)----
		--b(4)----	--b(4)----
--b(4)----	1500 IU/vial	5 ± 3°C	18 months
		30 °C -b(4)----	--b(4)----
		--b(4)----	--b(4)----
--b(4)----	2000 IU/vial	5 ± 3°C	24 months
		30 °C -b(4)----	--b(4)----
		--b(4)----	--b(4)----
--b(4)----	3000 IU/vial	5 ± 3°C	24 months
		30 °C -b(4)----	--b(4)----
		--b(4)----	--b(4)----

These clinical lots qualify to support this shelf-life because the process in the manufacture of these lots is comparable to the proposed commercial one. Additionally, the in-use stability studies support the holding time after reconstitution to be limited for 3 hours at room temperature ($\leq 30^{\circ}\text{C}$).

Biogen undertook stability studies for the --b(4)-----

Stability studies on the diluent

Stability data support the following shelf-life of diluent (i.e., sterile Water for Injection (sWFI)): --b(4)--- when stored at $5 \pm 3^{\circ}\text{C}$. Within this period, the diluent can also be stored at room temperature ($\leq 30^{\circ}\text{C}$) for up to 6 months. Up to --b(4)--- of long-term stability data are available for the conformance lots --b(4)-----, and all the test results under the long-term storage condition of $5 \pm 3^{\circ}\text{C}$ met the acceptance criteria.

Background

rFVIII^h is a long-acting, fully recombinant fusion protein, which consists of a human FVIII covalently linked to the Fc domain of human immunoglobulin G1. It is produced in a human embryonic kidney (HEK) 293 cell line with molecular mass of 220kDa. The FVIII in FVIII^h is comparable to B-domain deleted FVIII regarding its primary amino acid sequence and post-translational modifications.

The manufacturing process of rFVIII^h includes a detergent (i.e., --b(4)-----) viral inactivation step, affinity chromatography, and nanofiltration (pore size, 15 nm) viral clearance steps. There are no human or animal derived additives used in the production and formulation steps. rFVIII^h is formulated as a sterile, white to off white lyophilized

powder for intravenous injection only. When reconstituted with its diluent sWFI, this product contains nominally 250, 500, 750, 1000, 1500, 2000 or 3000 IU of rFVIII activity per vial.

Summary of Review

Flow chart of the manufacture process of rFVIII Fc

rFVIII Fc drug substance

1. ---b(4)-----
2. ---b(4)-----
3. ---b(4)-----
4. ---b(4)-----

5. ---b(4)-----
6. ---b(4)-----
7. ---b(4)-----
8. ---b(4)-----
9. ---b(4)-----
10. ---b(4)-----

rFVIII Fc drug product

11. Formulation
12. Sterile filtration
13. Filling, lyophilization, Stoppering, and Crimping
14. Visual inspection, and packaging

The rFVIII Fc DS is manufactured in a ---b(4)----- at Biogen's facility in
Cambridge, Massachusetts, and then ---b(4)-----

Stability (Sections 3.2.S.7 and 3.2.P.8)

1. Drug substance

- 1) Qualification of the rFVIII Fc drug substance manufactured through
manufacturing process-b(4)-

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

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

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

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

No other controlled parameters were changed. In general, these changes are used for ensuring process consistency and robustness. For the concentration of -b(4)-----, Biogen found the concentration of ---b(4)----- was near the lower end of the effective range based on referenced literature. Therefore, they -b(4)----- concentration by approximately -b(4)--- in the proposed commercial process. This concentration is still within the recommended range based on referenced literature.

The impact on the product quality was further evaluated using the rFVIII Fc DS manufactured before and after this modification. The data indicate that there is no significant impact on product quality. Additionally, the DS formulation did not change over the manufacturing development. We consider none of the modifications to be major changes. Therefore, the rFVIII Fc DS manufactured through process b(4) is comparable to the one manufactured through the proposed commercial manufacturing process.

- 2) Stability data for the rFVIII Fc drug substance manufactured through the proposed commercial manufacturing process

-b(4)- rFVIII Fc DS batches in the stability studies were manufactured through the proposed commercial manufacturing process. The information on these batches is listed as follows:

[b(4)]

The parameters used in assessing stability include ---b(4)--- -----

Additionally, upon our request, Biogen in their amendment dated 29 August 2013 committed to report the –b(4)– results determined by –b(4)– in the updated stability protocol. This response is acceptable.

Regarding the long-term storage condition at –b(4)–, all results met the acceptance criteria for up to –b(4)– and no significant trends were detected. For the accelerated storage condition at –b(4)–, and the results of this parameter were out of specification (OOS) in all –b(4)– conformance batches at the –b(4)– time points. In addition, there was a downward trend for both –b(4)–, and the test results of –b(4)– were also OOS at the –b(4)– time points. For the stressed storage condition at –b(4)–, although the test results of these two parameters were still within the acceptance criterion.

Product reviewer’s comment: The available stability data support the long-term storage condition of the drug substance at –b(4)–. We request more data from Biogen to support their proposed shelf life of rFVIII Fc DS: –b(4)–.

This comment was sent to Biogen on 17 August 2013, and we received their responses in amendments on 29 August 2013 and 19 December 2013, respectively. We consider that the establishment of the period of expiration of a DS depends mainly on the long-term stability of the process validation batches, which are manufactured by the commercial process. Thus, the updated stability data on rFVIII Fc DS provided in the amendment dated 19 December 2013 only support an expiration period of –b(4)– under storage at –b(4)–

In addition, Biogen proposed a specification of acceptability for rFVIII Fc DS –b(4)– which is quite different from that proposed in Biogen’s stability study of –b(4)–. The available data from long-term storage showed that –b(4)– with no significant –b(4)– trend over time. We request that Biogen tighten the acceptance criterion of –b(4)– in the stability studies based on the long-term stability data.

This comment was sent to Biogen on 17 August 2013, and we received their response on 29 August 2013, which is summarized as follows:

Biogen’s response: Biogen stated that the specifications listed on relevant data tables reflect the clinical specifications in effect prior to commercial specification implementation. The acceptance criterion for –b(4)– in DS is listed in Section 3.2.S.4.1 and 3.2.S.4.5.

Product reviewer’s comment: Biogen confirmed that the acceptance criterion for –b(4)– in the stability study on DS is –b(4)– which is the same as the one set for rFVIII Fc DS. The response is acceptable.

2. Drug product

Biogen introduced a bracketing design in the stability studies for the following reasons. The design of a protocol that incorporates bracketing assumes that the stability of the intermediate condition samples is represented by those at the extremes. rFVIII Fc DP is supplied as 250 IU, 500 IU, 750 IU, 1000 IU, 1500 IU, 2000 IU, and 3000 IU per vial. The composition of the rFVIII Fc DP is the same for the seven product presentations except for the content of the active ingredient. These bracketing stability studies are designed in accordance with the International Conference on Harmonisation (ICH) guidance, *Guidance for Industry: Q1D Bracketing and Matrixing Designs for Stability Testing of New Drug Substances and Products*, January 2003.

1) Stability study for the process validation lots of rFVIII Fc drug product

- Lots tested

DP lot No.	DP Strength	DS batches used	Proposed storage condition	Data available
-b(4)-	250 IU	-b(4)-	2-8°C -b(4)-	6 months
-b(4)-		-b(4)-	30°C/-b(4)-	6 months
-b(4)-		-b(4)-	-b(4)-	6 months
-b(4)-		-b(4)-	2-8°C -b(4)-	6 months
-b(4)-		-b(4)-	30°C/-b(4)-	6 months
-b(4)-		-b(4)-	-b(4)-	6 months
-b(4)-		-b(4)-	2-8°C -b(4)-	3 months
-b(4)-		-b(4)-	30°C/-b(4)-	3 months
-b(4)-		-b(4)-	-b(4)-	3 months
-b(4)-	3000 IU	-b(4)-	2-8°C -b(4)-	3 months
-b(4)-		-b(4)-	30°C/-b(4)-	3 months
-b(4)-		-b(4)-	-b(4)-	3 months
-b(4)-		-b(4)-	2-8°C -b(4)-	3 months
-b(4)-		-b(4)-	30°C/-b(4)-	3 months
-b(4)-		-b(4)-	-b(4)-	3 months
-b(4)-		-b(4)-	2-8°C -b(4)-	3 months
-b(4)-		-b(4)-	30°C/-b(4)-	3 months
-b(4)-		-b(4)-	-b(4)-	3 months

-b(4)-

The -b(4)- rFVIII Fc DP lots are manufactured through the proposed commercial manufacturing process; therefore, the stability data from these lots are acceptable to demonstrate the shelf-life of rFVIII Fc DP.

Parameters tested: Appearance of lyophilized product, Reconstitution Time, Appearance of solution, Residual Moisture, -----b(4)-

----- for Purity and Impurity, Endotoxin, Container Closure Integrity, and Particulates. Additionally, upon our request, Biogen in their amendment dated 29 August 2013 committed to report the

potency results determined by both One-stage clotting assay and Chromogenic assay in the updated stability protocol. This response is acceptable.

Biogen tests the final product of rFVIII^h for Sterility. However for stability studies, Biogen uses the alternative container closure integrity testing in lieu of Sterility testing, in accordance with the relevant FDA guidance (*Guidance for Industry: Container and Closure System Integrity Testing in Lieu of Sterility Testing as a Component of the Stability Protocol for Sterile Products, February 2008*).

The acceptance criteria are the same for release specifications and for stability specifications except for Residual Moisture, -----b(4)-----
Biogen proposes that the limit of Residual Moisture be set at –b(4)-----
----- in the specifications for release and for stability, respectively. For
-b(4)-----, Biogen proposes that the limit be –b(4)-----
for the release specification and stability, respectively.

Product reviewer’s comment: -b(4)----- is essential for the increased circulatory lifetime of the rFVIII^h product. This parameter should be monitored not only in the final product but also in the stability studies. We will request that Biogen include this parameter in the ongoing stability studies and relevant stability protocols.

We sent this comment to Biogen on 17 August 2013, and received their response in an amendment on 29 August 2013. Their response is summarized as follows:

Biogen’s response: The test for –b(4)----- has been added as a parameter in all on-going stability studies and –b(4)---- data will be included in the stability update in December 2013.

Product reviewer’s comment: This response is acceptable.

- Proposed shelf-life of rFVIII^h drug product

As described in the following, the stability data submitted in amendment dated 19 December 2013 can only support the rFVIII^h DP stored at $5 \pm 3^{\circ}\text{C}$ for up to 24 months but not –b(4)----- proposed by Biogen. Within this period, the product is allowed to be stored at room temperature (i.e., $\leq 30^{\circ}\text{C}$) for a single period of up to 6 months not to exceed the expiration date.

- Stability results

Stability data for the long-term storage (2 – 8°C) are available for up to 6 months in the original BLA submission. All the results are within the acceptance criteria; no significant trend is detected. Stability data for the storage at 30°C/-b(4)----- also met the acceptance criteria.

The potency data (chromogenic assay) for these lots stored at 2 – 8°C are listed as follows:

Lot No.	Strength (IU/vial)	Storage time (months)			
		0	1	3	6
-b(4)-----	250	-b(4)-----	-b(4)-----	-b(4)-----	-b(4)-----
-b(4)-----	250	-b(4)-----	-b(4)-----	-b(4)-----	-b(4)-----
-b(4)-----	250	-b(4)-----	-b(4)-----	-b(4)-----	-b(4)-----
-b(4)-----	3000	-b(4)-----	-b(4)-----	-b(4)-----	-b(4)-----
-b(4)-----	3000	-b(4)-----	-b(4)-----	-b(4)-----	-b(4)-----
-b(4)-----	3000	-b(4)-----	-b(4)-----	-b(4)-----	-b(4)-----

A slight -b(4)----- in residual moisture is observed under the accelerated condition (-b(4)-----). However, the test results for this parameter are -b(4)- still within the acceptance criteria -b(4)---- during the -b(4)----- storage period. The results of other parameters also meet the acceptance criteria.

The potency data for these lots stored at -b(4)--- are listed as follows:

Lot No.	Strength (IU/vial)	Storage time (months)			
		-b(4)-----	-b(4)-----	-b(4)-----	-b(4)-----
-b(4)-----	250	-b(4)-----	-b(4)-----	-b(4)-----	-b(4)-----
-b(4)-----	250	-b(4)-----	-b(4)-----	-b(4)-----	-b(4)-----
-b(4)-----	250	-b(4)-----	-b(4)-----	-b(4)-----	-b(4)-----
-b(4)-----	3000	-b(4)-----	-b(4)-----	-b(4)-----	-b(4)-----
-b(4)-----	3000	-b(4)-----	-b(4)-----	-b(4)-----	-b(4)-----
-b(4)-----	3000	-b(4)-----	-b(4)-----	-b(4)-----	-b(4)-----

The stability data for the accelerated storage condition support the stability of rFVIII Fc DP. There are only 6-month stability data for long-term storage provided in this submission from the process validation lots. To support the proposed shelf-life for rFVIII Fc DP, Biogen needs to supply updated stability data for these six lots.

We sent this comment to Biogen on 17 August 2013, and received their responses in amendments on 29 August 2013 and 19 December 2013, respectively. In the amendment dated 19 December 2013, Biogen submitted the long-term stability data for up to -b(4)----- under the storage conditions of 5 ± 3°C or 30°C/-b(4)----. They also submitted the stability data for up to -b(4)--- under the accelerated condition of -b(4)-----. All the data met the acceptance criteria. We consider that the shelf-life of a DP depends mainly on the long-term stability of the process validation batches, which are

manufactured by the commercial process. Thus, the updated bracketing stability data on rFVIIIIFc DP provided in the amendment dated 19 December 2013 support a shelf life of 18 months under storage at $5 \pm 3^{\circ}\text{C}$. Within this period, the product is allowed to be stored at room temperature (i.e., $\leq 30^{\circ}\text{C}$) for a single period of up to 6 months not to exceed the expiration date.

- 2) Stability study for the rFVIIIIFc drug product using drug substance manufactured through either the commercial manufacturing process or process –b(4)–

- Information for the lots tested

In addition to the abovementioned bracketing stability studies, Biogen also performed stability studies on one lot for each rFVIIIIFc DP dosage strength. For these DP lots, the rFVIIIIFc DS used were manufactured through either the commercial process or process b(4). With reference to the amendment dated 19 December 2013, the detailed information on these DP lots is listed as follows:

DP lot No.	DP Strength (IU/vial)	DS batches used (Type of process)	Proposed storage condition	Data available
–b(4)–	250	–b(4)–	2-8°C –b(4)–	24
			30°C/–b(4)–	b(4)
			–b(4)–	b(4)
–b(4)–	500	–b(4)–	2-8°C –b(4)–	24
			30°C/–b(4)–	b(4)
			–b(4)–	b(4)
–b(4)–	750	–b(4)–	2-8°C –b(4)–	18
			30°C/–b(4)–	b(4)
			–b(4)–	b(4)
–b(4)–	1000	–b(4)–	2-8°C –b(4)–	24
			30°C/–b(4)–	b(4)
			–b(4)–	b(4)
–b(4)–	1500	–b(4)–	2-8°C –b(4)–	18
			30°C/–b(4)–	b(4)
			–b(4)–	b(4)
–b(4)–	2000	–b(4)–	2-8°C –b(4)–	24
			30°C/–b(4)–	b(4)
			–b(4)–	b(4)
–b(4)–	3000	–b(4)–	2-8°C –b(4)–	24
			30°C/–b(4)–	b(4)
			–b(4)–	b(4)

As previously mentioned, the rFVIIIIFc DS manufactured through process b(4) is comparable to the one through the proposed commercial manufacturing process. These seven rFVIIIIFc DP lots are manufactured at the proposed commercial facility –b(4)–. Therefore, all seven rFVIIIIFc DP lots are qualified to support their proposed shelf-life.

- Stability results

Stability data for the long-term storage (2 – 8°C) are available for up to 24 months. All the results are within the acceptance criteria, and we have not detected any significant trend. Stability data for storage at 30°C/-b(4)--- also met the acceptance criteria.

An increase in Residual Moisture is observed under the accelerated condition (-b(4)-----). However, the test results for this parameter met the acceptance criterion (i.e., --b(4)-----). The test results of -b(4)-----, and are within the acceptance criteria -b(4)----- The results of other parameters also meet the acceptance criteria.

Product reviewer’s comment: The shelf-life of rFVIII Fc DP is mainly dependent on long-term stability data. Based on the stability data for these seven clinical lots and the process validation lots mentioned above, they can only support a shelf-life of 24 months under storage at $5 \pm 3^{\circ}\text{C}$. Within this period, the product is allowed to be stored at room temperature (i.e., $\leq 30^{\circ}\text{C}$) for a single period of up to 6 months not to exceed the expiration date.

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

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

We sent this comment to Biogen on 17 August 2013, and received their response in an amendment on 29 August 2013. In this amendment, Biogen clarified that the temperature range for “---b(4)-----”. This response is adequate.

4) Photostability

We agree with Biogen that the exposure of rFVIII Fc DP to light should be minimized based on their photostability study. Biogen performed a study on the photostability of rFVIII Fc DP using the process validation lots ---b(4)----- They found that -b(4)-----

in these -b(4)- dosage strengths after unprotected vials were exposed to an overall illumination of ---b(4)-----

ICH guideline Q1B: *Photostability Testing of New Drug Substances and Products*.

5) Stability for the use of –b(4)----- glass vial

Biogen undertook an additional stability study for the –b(4)----- final container provided by –b(4)---, because the final containers used in the above mentioned stability studies are –b(4)----- vials. –b(4)-----vials meet the requirements of the ----b(4)----- glass. The strength dosage of lot (lot –b(4)---) used in the additional study was b(4) IU per vial, the –b(4)- among the introduced ones, and the one that represents the worst case scenario. Therefore, it is acceptable to use one b(4) IU lot for this study. In the original BLA submission, Biogen provided stability data for 1 month, and the test results met the acceptance criteria. During the mid-cycle review, we requested Biogen to provide more stability data to support the introduction of the –b(4)----- final container, --b(4)----- glass vial.

We sent this comment to Biogen on 17 August 2013, and received their responses in amendments on 29 August 2013 and 19 December 2013, respectively. In the amendment dated 19 December 2013, Biogen included a –b(4)---IU/vial lot (Lot –b(4)---) in this study in addition to a –b(4)--IU/vial lot (--b(4)---). They submitted the stability data for up to –b(4)----- under the storage conditions of $5 \pm 3^{\circ}\text{C}$ or $30^{\circ}\text{C}/\text{--b(4)--}$, and for up to –b(4)----- under the accelerated condition of –b(4)-----. All the data met the acceptance criteria. The trend and variance of the stability are also similar for rFVIIIIFc filled in –b(4)----- vials. Thus, the shelf-life proposed for rFVIIIIFc filled in –b(4)- vials can be extended to those filled in –b(4)---vials.

6) Reconstitution (in-use) stability

Biogen submitted reconstitution stability data under section 3.2.P.2.6 Compatibility. The data are considered to be incomplete although the submitted data met the acceptance criteria. For instance, the pH of the solution after reconstitution needs to be well controlled because pH can affect the stability of the active ingredient. During the mid-cycle review, we requested Biogen to include pH in the reconstitution stability study. In addition, -b(4)---- should also be included in the study because ---b(4)----- is essential for the increased circulatory lifetime of the rFVIIIIFc product *in vivo*. We also requested Biogen to provide a complete protocol for the reconstitution stability.

We sent these comments to Biogen on 17 August 2013, and received their response in an amendment on 29 August 2013. In the response, Biogen planned to execute a reconstitution stability study of b(4) GMP rFVIIIIFc DP lots, b(4) IU/vial and b(4) IU/vial strengths which will include pH and –b(4)----- testing and results will be assessed against the commercial stability protocol. Data from

the reconstitution stability study was resubmitted in the amendment dated 19 December 2013.

As the amendment indicated, pH and –b(4)----- test were included in the stability protocol, and the relevant reconstitution stability data was provided under Section 3.2.P.8. All the test results met the acceptance criteria, which support the proposed reconstitution time: –b(4)----- at room temperature ($\leq 30^{\circ}\text{C}$) after reconstitution. Considering the safety of reconstituted rFVIII Fc DP, we requested Biogen to –b(4)--- the holding time from –b(4)-- to 3 hours after reconstitution, which Biogen agreed with. This comment has been implemented in the updated Package Insert in the amendment dated 8 May 2014.

3. Stability of the diluent, sterile Water for Injection

There are three consecutive conformance lots (lots –b(4)-----
-----) in the stability studies. These lots are being investigated under the long-term storage conditions ($5 \pm 3^{\circ}\text{C}$ for –b(4)-----; $30 \pm 2^{\circ}\text{C}$ b(4)----- for –b(4)----) and the accelerated condition (–b(4)-----). The container closure system used in the stability study is identical to the one used commercially. The parameters used in the long-term stability study include Appearance of solution, ---b(4)-----

----- Sterility, Container closure integrity test.

–b(4)---- of long-term stability and –b(4)----- of accelerated stability data are available (with reference to the amendment dated 19 December 2013). There are no significant changes detected, and the test results for the parameters are within the acceptance criteria except for –b(4)-- -----

----- The test results for the same parameter were still OOS at the –b(4)---- time point. Biogen concluded it is because parts of the glass surface are no longer –b(4)-----
-----, and indicated that the resulting localized increase in –b(4)----- is not a risk to product quality.

Product reviewer’s comment: The stability data for the diluent provided in the amendment dated 19 December 2013 support the shelf-life of the diluent to be less than –b(4)---- when stored at –b(4)----- . To be consistent with the storage of rFVIII Fc DP, we request Biogen to revise your proposed shelf life of the diluent to be –b(4)---- under the storage of $2 \pm 8^{\circ}\text{C}$. Within this period, the diluent may be stored at room temperature (up to 30°C) for up to 6 months when packaged with rFVIII Fc DP.

Biogen completely accepted the above FDA comment in their amendment dated 18 April 2014. The revised labeling for diluent will be reflected in the updated Prescribing information and the post-approval stability protocol. This response is adequate.

Recommendation

The stability data provided in the original BLA submission, and the amendments dated 29 August 2013, 19 December 2013, and 18 April 2014 support the product stability of rFVIIIIFc DP. Therefore, I recommend approval of the BLA under STN 125487/0.