

Final Review of Stability Information Memo, February 2014 - ALPROLIX

MEMORANDUM

Department of Health and Human Services
Public Health Service
Food and Drug Administration

Center for Biologics Evaluation and Research

To: File (STN 125444/0)
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From: Ze Peng, PhD, LH/DH/OBRR

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

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

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

Executive Summary

This memorandum summarizes the review of stability information in an original Biologics License Application (BLA) under STN 125444/0 submitted by Biogen Idec (Biogen) for Coagulation Factor IX (Recombinant), Fc Fusion Protein [rFIXFc]. The proposed proprietary name of this product is *ALPROLIX*. The available stability data provided in the original BLA submission and the amendments dated 9 August 2013 and 27 September 2013 support the proposed shelf-life of rFIXFc drug product (DP); therefore, I recommend approval of the BLA under STN 125444/0.

Stability studies on rFIXFc drug substance

Stability data support the currently proposed expiry period of rFIXFc drug substance (DS): *Up to --(b)(4)-- under the storage of ---(b)(4)---*. Within this period, rFIXFc DS ---

(b)(4)--- is allowed to be stored at -----(b)(4)----- . This expiry period is supported by the following batches:

rFIXFc DS	Storage temperature	Available data
Validation batch: -----(b)(4)-----	--(b)(4)--	--(b)(4)--
	--(b)(4)--	--(b)(4)--
Post-validation batch: -----(b)(4)-----	--(b)(4)--	--(b)(4)--
	--(b)(4)--	--(b)(4)--
Post-validation batch: -----(b)(4)-----	--(b)(4)--	--(b)(4)--
	--(b)(4)--	--(b)(4)--

The stability data indicate that no critical trends are detectable for up to --(b)(4)-- under the long-term storage condition (---(b)(4)---). Although the long-term stability data for the validation/post-validation batches are not yet available for as long as --(b)(4)--, Biogen provided --(b)(4)-- long-term stability data on two clinical batches, --(b)(4)----- . These data qualify to support the expiry period of rFIXFc DS because the process in the manufacture of these two clinical batches is comparable to the proposed commercial one. Moreover, Biogen committed in their amendment dated 9 August 2013 to submit the updated stability data for the validation/post-validation batches in future annual reports (ARs), and to notify FDA immediately upon the occurrence of any confirmed out-of-specification (OOS) result.

In addition, regarding the use of either -----(b)(4)----- for storage, the stability data indicate that changes observed in each product attribute are similar between the -----(b)(4)----- for the referenced validation/post-validation batches, and are not statistically significant. Thus, both -----(b)(4)----- are suitable for the storage of commercial rFIXFc DS.

Stability studies on rFIXFc drug product

Stability data support the currently proposed shelf life of rFIXFc drug product (DP): *Up to 36 months under the storage of 5 ± 3°C. Within this period, the product is allowed to be stored at room temperature (i.e., ≤ 30°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 following conformance lots:

rFIXFc DP lot No.	DP Strength	Storage temperature	Available data
		5 ± 3°C	18 months
		--(b)(4)--	18 months
--(b)(4)--		--(b)(4)--	12 months
	--(b)(4)--	5 ± 3°C	24 months
		--(b)(4)--	24 months
--(b)(4)--		--(b)(4)--	12 months
		5 ± 3°C	24 months

--(b)(4)--		--(b)(4)--	24 months
		--(b)(4)--	12 months
		5 ± 3°C	24 months
--(b)(4)--	2000 IU/vial	--(b)(4)--	24 months
		--(b)(4)--	12 months
		5 ± 3°C	18 months
		--(b)(4)--	18 months
--(b)(4)--		--(b)(4)--	12 months
	3000 IU/vial	5 ± 3°C	24 months
		--(b)(4)--	24 months
--(b)(4)--		--(b)(4)--	12 months

RH: Relative humidity

No critical trends were detected from stability data for up to 24 months under the long-term storage condition of 2 - 8°C. The available stability data for the storage condition of -----(b)(4)----- also met acceptance criteria. Although the long-term stability data for the conformance lots are not available for up to 36 months at this time, Biogen provided 36-month stability data (2 - 8°C and -----(b)(4)-----) on three clinical rFIXFc DP lots --(b)(4)-- (500 IU/vial), --(b)(4)-- (1000 IU/vial), and --(b)(4)-- (3000 IU/vial). These clinical lots qualify to support this shelf-life because the process in the manufacture of these three lots is comparable to the proposed commercial one. To further support the currently proposed shelf-life of rFIXFc DP, Biogen committed to place all conformance lots on stability at 30 °C for 6 months after storage at 2 – 8°C for 30 months as described in the amendment dated 27 September 2013. They will submit the updated stability data in the future ARs, and notify FDA immediately upon occurrence of any confirmed OOS result. Additionally, the in-use stability studies support the holding time after reconstitution to be limited for 3 hours at room temperature (≤ 30°C).

Biogen undertook an additional stability study for the alternative final container: --(b)(4)-vial besides (b)(4) (formerly -(b)(4)-) vials. The available stability data from three GMP rFIXFc DP lots --(b)(4)-- IU/vial), --(b)(4)-- (2000 IU/vial), --(b)(4)-- (3000 IU/vial) indicated that the shelf-life proposed for rFIXFc DP filled in (b)(4) vials can be extended to those filled in -(b)(4)- vials.

Stability studies on the diluent

Stability data support the currently proposed shelf life of diluent (i.e., sterile 0.325% sodium chloride in Water for Injection (w/v)): *36 months when stored at 2 – 25°C. Within this period, the diluent can also be stored at room temperature (≤30°C) for up to 6 months.* Up to 36-month of long-term stability data are available for the conformance lots -(b)(4)- and -(b)(4)-, and all the test results met the acceptance criteria.

Background

rFIXFc is a long-acting, fully recombinant fusion protein, with molecular mass of 98 kDa, which consists of a full length Coagulation Factor IX covalently linked to the Fc domain of human immunoglobulin G1. It is produced in a human embryonic kidney (HEK) - (b)(4)- cell line. The FIX portion of this product has a primary amino acid sequence that is identical to the Thr148 allelic form of plasma derived FIX, and has structural and functional characteristics similar to endogenous FIX.

The manufacturing process of rFIXFc includes (b)(4)- chromatography and nanofiltration (pore size, (b)(4)-) viral removal steps. There are no human or animal derived additives used in the production and formulation steps. rFIXFc is formulated as a sterile, white to off white lyophilized powder, and used only for intravenous injection. When reconstituted with its diluent, sterile 0.325% sodium chloride in Water for Injection (w/v), this product contains 500, 1000, 2000 or 3000 IU of rFIX activity per vial.

Summary of Review

Flow chart of the manufacture process of rFIXFc drug product

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

rFIXFc drug product

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

-(b)(4)--Sterile filtration
-(b)(4)--Filling, lyophilization, Stoppering, and Crimping
-(b)(4)--Visual inspection, and packaging

rFIXFc DS is manufactured at a -----**(b)(4)**----- at Biogen's facility located in ----
-----**(b)(4)**-----, and then shipped to -----**(b)(4)**-----
----- facility located at -----**(b)(4)**----- for further manufacture of
rFIXFc DP.

The diluent used for reconstitution of rFIXFc DP is also manufactured by ----**(b)(4)**-----
----- but in their facility located at ----**(b)(4)**-----

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

1. Drug substance

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

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

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

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

Product reviewer’s comment: The available stability data for the validation/ post-validation batches support the long-term storage condition of -----(b)(4)----- . Although these data are not available for as long as ----(b)(4)---, Biogen provided --- (b)(4)--- long-term stability data for two clinical batches, -----(b)(4)----- ---. These data qualify to support the expiry period of rFIXFc DS because the process in the manufacture of these two clinical batches is comparable to the proposed commercial one. Moreover, Biogen committed in their amendment dated 9 August 2013 to submit the updated stability data for the validation/post-validation batches in the future ARs, and to notify FDA immediately upon the occurrence of any confirmed OOS result. Therefore, the proposed ----(b)(4)---- expiry period of rFIXFc DS is acceptable.

In addition, regarding the use of either -----(b)(4)----- for storage, the stability data indicate that changes observed in each product attribute are similar between the -----(b)(4)----- for the referenced validation/post-validation batches, and are not statistically significant. Thus, both -----(b)(4)- ----- are suitable for the storage of commercial rFIXFc DS.

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. rFIXFc DP is supplied as -----(b)(4)-----, 500 IU, 1000 IU, 2000 IU, and 3000 IU per vial. Prior to lyophilization, the composition of the rFIXFc DP is ----- --(b)(4)----- . These bracketing stability

studies are designed in accordance with 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 conformance lots of rFIXFc drug product

- Lots tested

Based on the stability data provided in the original submission and the amendment dated 27 September 2013, the lot information is updated as follows:

DP lot No.	DP Strength (IU/vial)	DS batches used	Storage condition	Available data
--(b)(4)--		--(b)(4)--	----(b)(4)----	18 months
			----(b)(4)----	18 months
			----(b)(4)----	12 months
			----(b)(4)----	24 months
--(b)(4)--	--(b)(4)--	--(b)(4)--	----(b)(4)----	24 months
			----(b)(4)----	12 months
			----(b)(4)----	24 months
--(b)(4)--		--(b)(4)--	----(b)(4)----	24 months
			----(b)(4)----	12 months
			2-8°C ----(b)(4)----	24 months
--(b)(4)--	2000	--(b)(4)-- --(b)(4)--	----(b)(4)----	24 months
			2-8°C ----(b)(4)----	12 months
			----(b)(4)----	18 months
--(b)(4)--	3000	--(b)(4)-- --(b)(4)--	----(b)(4)----	18 months
			----(b)(4)----	12 months
			2-8°C ----(b)(4)----	24 months
--(b)(4)--		--(b)(4)-- --(b)(4)--	----(b)(4)----	24 months
			----(b)(4)----	12 months

*: Clinical batch: The manufacturing process is comparable between the referenced clinical batches and process validation batches.

The proposed commercial manufacturing process is used to manufacture these rFIXFc DP lots. The stability data from these lots are therefore qualified to demonstrate the shelf-life of rFIXFc DP.

Parameters tested: Appearance of lyophilized product, Reconstitution Time, Appearance of solution, Residual Moisture, (b)(4), Protein ;Concentration, FIX Potency measured by One-stage aPTT Assay, -----(b)(4)-----

----- for Purity and Impurity, -----(b)(4)----, Activated FIXFc, Endotoxin, Container Closure Integrity, and Particulates.

Biogen tests the final product of rFIXFc for Sterility, whereas for stability studies, Biogen uses the alternative container closure integrity testing in lieu of Sterility testing. This is acceptable 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 between release specifications and stability acceptance criteria except for Residual Moisture, -----(b)(4)----
 -----(b)(4)----- . Biogen proposes that the limit of Residual Moisture be set at -----
 (b)(4)----- in the specifications for release and stability, respectively. For (b)(4)
 species, Biogen proposes that the limit of this parameter be set at -----(b)(4)----- for
 the specifications for release and stability, respectively. For -----(b)(4)-----, Biogen
 proposes that the limit of this parameter be set at -----(b)(4)----- for the
 specifications for release and stability, respectively. Considering the potential minor
 change of the rFIXFc DP during the long-term storage, it is acceptable for Biogen to
 have slightly different acceptance criteria regarding the referenced three parameters.

- Proposed shelf-life of rFIXFc drug product

The rFIXFc DP can be stored at 2 – 8°C for up to 36 months. Within this period, the product is allowed to be stored at room temperature (i.e., ≤ 30°C) for a single period of 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 24 months. All the results are within the acceptance criteria. No significant trend was detected. Stability data for the storage at -----(b)(4)---- also met the acceptance criteria. The FIX potency results (measured using FIX One-Stage Clotting assay) for these lots do not show adverse trending. Activated FIXFc is minimal (i.e., -(b)(4)- mol%, the limit for this parameter is -(b)(4)- mol%) under storage at 2 – 8°C or -----(b)(4)----- . The potency data (FIX One-Stage Clotting assay) for these lots stored at 2 – 8°C are listed as follows:

FIX Potency results* for the conformance lots stored at 2 – 8°C

Lot No.	Strength (IU/vial)	Storage time (months)							
		0	1	3	6	9	12	18	24
-(b)(4)-	-(b)(4)-	-(b)(4)-							
-(b)(4)-	-(b)(4)-	-(b)(4)-							
-(b)(4)-	-(b)(4)-	-(b)(4)-							
-(b)(4)-	2000	100% (1906 IU)	110%	104%	112%	106%	106%	110%	109%
-(b)(4)-	3000	100% (3310 IU)	92%	91%	93%	94%	88%	99%	ND

-(b)(4)- 3000 100% (2931 IU) 101% 104% 101% 101% 103% 100% 104%

*: The potency at each time point is expressed as the percentage of the respective potency result of 0 time point; ND: Not done

An -(b)(4)- trend for 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 12-month storage period. The test results of (b)(4) species are (b)(4) for up to 12 months, which is within the acceptance criteria for stability ((b)(4)). The trend for -----(b)(4)----- and that of -----(b)(4)----- during the 12-month period. The test results are still within the acceptance criteria.

Under the storage of ---(b)(4)---, there is a --(b)(4)--- trend for FIX potency whereas the level of activated FIXFc is still minimal, i.e., ---(b)(4)---. Two OOS results for FIX potency were observed at the 12-month time point. The results were (b)(4)/vial for lot (b)(4) and (b)(4) IU/vial for lot (b)(4). The rest of results met the acceptance criteria. The potency data for these lots stored at ---(b)(4)--- are listed as follows:

FIX Potency results* for the conformance lots stored at ---(b)(4)---

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

(b)(4)-----

The shelf life of rFIXFc DP is mainly dependent on the long-term stability data but not the stability data derived under the accelerated condition. Thus, two OOS results for FIX potency under the accelerated condition do not affect the proposed shelf-life of rFIXFc DP. The available data on these conformance lots support the 24-month long-term storage condition.

2. Stability study for the clinical lots of rFIXFc drug product

- Information for the lots tested

In addition to the abovementioned bracketing stability studies, Biogen also performed stability studies on one lot each for 500 IU, 1000 IU, and 3000 IU rFIXFc DP strengths. The data derived from these clinical lots qualify to support the shelf-life of rFIXFc DP because their manufacturing process is comparable to the proposed commercial one. Based on the stability data provided in the amendment dated 27 September 2013, the information on these clinical lots is updated as follows:

DP lot No.	DP Strength (IU/vial)	DS batches used	Storage condition	Available data
------------	-----------------------	-----------------	-------------------	----------------

		(Clinical)		
			2-8°C ---(b)(4)---	36
			------(b)(4)-----	36
-(b)(4)-	500	-(b)(4)-	------(b)(4)-----	12
			2-8°C ---(b)(4)---	36
			------(b)(4)-----	36
-(b)(4)-	1000	-(b)(4)-	------(b)(4)-----	12
			2-8°C ---(b)(4)---	36
			------(b)(4)-----	36
-(b)(4)-	3000	-(b)(4)-	------(b)(4)-----	12

- Stability results

Stability data for the long-term storage (2 – 8°C) are available for up to 36 months. All the results are within the acceptance criteria. No significant trend was detected. Up to 36-month stability data for the storage at ------(b)(4)----- are also met acceptance criteria.

An -(b)(4)- trend for Residual Moisture is observed under the accelerated condition (---(b)(4)---). However, the test results for this parameter are --- (b)(4), within the acceptance criteria ((b)(4)). Similarly, the test results of -----(b)(4)-----, respectively, all within the acceptance criteria ((b)(4)). The results of other parameters also meet the acceptance criteria.

Product reviewer’s comment: 36-month stability data from the clinical lots under the long-term storage (2 – 8°C) qualify to support the shelf-life of rFIXFc DP because the manufacturing process is comparable between the production of these clinical lots and the conformance lots. Together with the available stability data from conformance lots, they support Biogen’s currently proposed shelf-life of rFIXFc DP:

rFIXFc DP can be stored at 2 – 8°C for up to 36 months. Within this period, the product is allowed to be stored at room temperature (i.e., ≤ 30°C) for a single period of 6 months not to exceed the expiration date.

3. Stability for aged rFIXFc drug product

To further support the currently proposed shelf-life of rFIXFc DP, Biogen committed in the amendment dated 27 September 2013 to place all conformance lots on stability at room temperature (30 °C) for 6 months after storage at 2 – 8°C for 30 months. Initially, Biogen proposed that the shelf-life of rFIXFc DP to be 24 months under the storage condition of 2 – 8°C. This shelf-life was supported by a stability study for aged rFIXFc DP. This study included the clinical lots (b)(4) (500 IU/vial) and (b)(4) (3000 IU/vial). Stability data are available for the storage condition of 2 – 8°C for 18 months and then at 30°C for 6 months. All data met acceptance criteria. Because Biogen did not claim

the strength of (b)(4) IU in the labeling, it is acceptable for Biogen not to include (b)(4) IU rFIXFc DP strength lot in this study.

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

Biogen performed a -----(b)(4)----- study using the conformance lots -----
(b)(4)----- (3000 IU/vial) to support transient exposure of rFIXFc DP at the
temperature between -----(b)(4)----- . The data showed that the test results of
these lots were within the acceptance criteria after the -----(b)(4)-----

-----.

The ----(b)(4)----- material was placed on stability at 2 – 8°C, and the study is
ongoing. The stability data are available for 6 months. The data for all key attributes are
consistent with the initial -----(b)(4)----- results, which continuously support
transient exposure of rFIXFc DP at the temperature between -----(b)(4)----- (e.g.,
shipment).

5. Photostability

Data from a photostability study indicated that the exposure of rFIXFc DP to light should
be minimized. Biogen performed a study on photostability of rFIXFc DP using
conformance lots -----(b)(4)----- and ---(b)(4)--- (3000 IU/vial). They found an
upward trend for -----(b)(4)-----, and significantly -----(b)(4)----- and FIX
potency in these two strengths after unprotected vials were exposed to an overall
illumination of -----(b)(4)-----
----- . I will request Biogen to include the ---
(b)(4)--- test in the stability protocol for photo-stressed rFIXFc DP.

I sent this information request (IR) to Biogen on 1 July 2013, and received the response
from Biogen on 9 August 2013. Their response is summarized below:

Biogen’s response: Testing of ----(b)(4)---- was added to the stability program on
both rFIXFc DS and DP as described in an amendment dated 4 February 2013. The
method validation of ----(b)(4)---- was provided in this amendment.

Product reviewer’s comment: This response is acceptable.

6. Stability for the use of alternative final container- ----(b)(4)----- glass vial

Biogen undertook an additional stability study for the alternative final container: -(b)(4)-
vial besides -(b)(4)- (formerly -(b)(4)-) vials used in abovementioned stability. -(b)(4)-
vials meet the requirement of the --(b)(4)----- glass. The
stability data on the rFIXFc DP filled in -(b)(4)- vials need to be provided if Biogen is
planning to use -(b)(4)- vials to be alternative final containers.

I sent this IR to Biogen on 1 July 2013, and received the responses from Biogen on 9 August 2013 and 27 September 2013, respectively. Their responses are summarized below:

Biogen's response: Biogen has placed three GMP rFIXFc DP lots in -(b)(4)- vials on stability. These lots are -----(b)(4)----- (2000 IU/vial), --(b)(4)-- (3000 IU/vial). Lots -----(b)(4)----- represent the lowest and highest strength at the (b)(4)mL fill volume. Lot (b)(4) is the only strength with (b)(4) mL fill volume.

For the long-term storage condition under 2 – 8°C, the stability data for (b)(4) vials are available for 9 months. The test results of lots ----(b)(4)----- IU/vial) and (b)(4) (2000 IU/vial) are similar to those for (b)(4) vials. The stability of the 3000 IU/vial strength did not change significantly for either the (b)(4) vials or the (b)(4) vials. The same is true for the storage conditions at 30°C/ -----(b)(4)-----.

The stability studies are ongoing, and will last for up to ---(b)(4)--- and 12 months for long-term and accelerated storage conditions, respectively. The updated stability data will be reported in future ARs, and OOS results if any will be reported to FDA immediately.

Product reviewer's comment: The 9-month stability data for both long-term and accelerated storage conditions indicate that the trend and variance of the stability are similar for rFIXFc DP filled in ----(b)(4)---- vials. Thus, the shelf-life proposed for rFIXFc DP filled in -(b)(4)- vials can be extended to those filled in -(b)(4)- vials.

7. In-use (reconstitution) stability

In Section 3.2.P.8, the in-use stability data provided in the original submission and in an amendment dated 27 September 2013 indicated that rFIXFc DP is stable at 25°C within -(b)(4)- after reconstitution. However, only one 1000 IU strength clinical lot ---(b)(4)--- manufactured at a ---(b)(4)--- scale was included in the *In-use* stability study, and it cannot represent all strengths of rFIXFc DP. During the mid-cycle review, I requested that Biogen include at least one -(b)(4)- strength lot and one 3000 IU strength lot in the *In-use* stability study, and that these lots should be manufactured at a -(b)(4)- scale. Biogen responded in an amendment dated 9 August 2013, in which they explained that the requested reconstitution data were provided in Section 3.2.P.2.6.1, *Pharmaceutical development, Compatibility and In-Use stability study*. This study included one -(b)(4)-strength conformance lot (lot -(b)(4)-) and one 3000 IU strength clinical lot (lot -(b)(4)-).

Product reviewer's comment: As this amendment indicated, Biogen did not put the requested two strength lots under Section 3.2.P.8. However, the test results on these two lots 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 rFIXFc product, for the prescribing information (PI) of rFIXFc DP, we will request Biogen to reduce the holding time from -(b)(4)- to 3 hours after reconstitution.

This comment has been implemented in the updated PI, which was provided in an amendment dated 7 February 2014.

3. Stability for the diluent, sterile Water for Injection

There are two conformance lots (------(b)(4)-----) and one clinical (-(b)(4)-) in the stability studies on diluent (sterile 0.325% sodium chloride in Water for Injection). The manufacturing process is the same between clinical lot -(b)(4)- and other two conformance lots. Thus, this clinical lot qualifies for supporting the shelf-life of diluent.

These lots are being investigated under the long-term storage conditions (------(b)(4)-----) and accelerated condition (------(b)(4)-----). In addition, lots (b)(4)----- are stored at -----(b)(4)-----, whereas lot -(b)(4)- is stored at -----(b)(4)----- . The container closure system used in the stability is identical to the one used commercially. The parameters used in the long-term stability study include Appearance of solution, ---(b)(4)---, Endotoxin, Particulates, and Sterility. The -(b)(4)- is a critical parameter for diluent used for reconstitution of rFIXFc final product, and I requested Biogen to include this parameter in the referenced stability protocols for diluent. In the late-cycle meeting dated 12 September 2013, Biogen agreed with FDA to add -(b)(4)- in the stability protocol for the diluent, and will establish the specification of -(b)(4)- after sufficient data are generated. This response is acceptable.

Biogen submitted up to 24-month of long-term stability and 6-month of accelerated stability data in the original submission. There are no significant changes detected, and all the test results are within the acceptance criteria. They proposed that the shelf-life of diluent to be as follows:

36 months when stored at 2 – 25°C. Within this period, the diluent can also be stored at room temperature ($\leq 30^{\circ}\text{C}$) for up to 6 months.

The shelf life of the diluent is mainly dependent on the long-term stability data. For this reason, I requested Biogen to provide the updated data for these three lots. They responded as amendments on 9 August 2013 and 27 September 2013, in which they submitted up to 36-month of long-term stability data for these three lots. Biogen also committed to submit the updated stability data on these lots in future ARs, and to notify FDA immediately upon occurrence of any confirmed OOS result.

Product reviewer's comment: Up to 36-month of long-term stability data are available for these three lots, and all the test results met the acceptance criteria. These data are sufficient to support the proposed shelf-life of the diluent; therefore, their responses are acceptable.

Recommendation

The stability data provided in the original BLA submission, and the amendments dated 9 August 2013 and 27 September 2013 support the product stability of rFIXFc DP. Therefore, I recommend approval of the BLA under STN 125444/0.