



To: File (STN 125611/0) & Edward Thompson, RPMBI/DRPM/OTAT

From: Nobuko Katagiri, Katerina Alexaki & Chava Kimchi-Sarfaty, CMC Reviewers
Hemostasis Branch (HB)/ Division of Plasma Protein Therapeutics (DPPT)/
Office of Tissues and Advanced Therapies (OTAT)

Through: Tim Lee, Acting Chief, HB/DPPT/OTAT

Subject: Final Review of CMC information in Novo Nordisk, Inc.'s original BLA for
Coagulation Factor IX (Recombinant), GlycoPEGylated [N9-GP] [REBINYN]

Contents

1. EXECUTIVE SUMMARY	3
2. BACKGROUND	3
2.1. OVERVIEW OF HEMOPHILIA B	3
2.2. GENERAL INFORMATION ABOUT COAGULATION FACTOR IX	4
3. REVIEW HISTORY	4
3.1. MANUFACTURING AND TESTING FACILITIES	4
3.2. MANUFACTURING PROCESS OF DRUG SUBSTANCE AND PRODUCT	5
3.3. A BRIEF DESCRIPTION OF MANUFACTURING PROCESS	7
3.4. MANUFACTURING PROCESS DEVELOPMENT	8
4. DRUG SUBSTANCE	9
4.1. MASTER CELL BANK AND WORKING CELL BANKS	9
4.2. CONTROL OF MATERIALS	9
4.3. IN-PROCESS CONTROLS	11
4.4. CRITICAL PROCESS STEPS	14
4.5. PROCESS VALIDATION AND/OR EVALUATION	19
4.6. EXTENDED PROCESS AND HOLDING TIMES	25
4.7. CHARACTERIZATION	25
4.8. VIRAL CLEARANCE	27
4.9. IMPURITY PROFILE	28
4.10. CONTROL OF DRUG SUBSTANCE	30
4.11. CONTAINER CLOSURE	31
4.12. STABILITY	32



5.	HISTIDINE SOLUTION.....	33
5.1.	CONTAINER AND CLOSURE.....	34
5.2.	MANUFACTURING.....	34
5.3.	PROCESS VALIDATION.....	35
5.4.	STABILITY.....	36
5.5.	PHOTO-STABILITY.....	36
5.6.	HISTIDINE SOLUTION SPECIFICATIONS.....	36
6.	DRUG PRODUCT.....	37
6.1.	DESCRIPTION AND COMPOSITION OF THE ADYNOVATE DRUG PRODUCT.....	37
6.2.	FLOW DIAGRAM OF THE MANUFACTURING PROCESS.....	37
6.3.	A BRIEF DESCRIPTION OF MANUFACTURING PROCESS.....	38
6.4.	IN-PROCESS CONTROL.....	38
6.5.	CONTAINER CLOSER FDP.....	39
6.6.	PROCESS VALIDATION AND/OR EVALUATION.....	39
6.7.	CONTROL OF EXCIPIENTS.....	40
6.8.	CONTROL OF DRUG PRODUCT.....	40
6.9.	BATCH ANALYSIS.....	42
6.10.	IMPURITY PROFILE.....	43
	All impurity profiles are (b) (4) FDP. Therefore, section 4.9. IMPURITY PROFILE, of this review memo covers the impurity profile of (b) (4) FDP.	43
6.11.	IN-PROCESS CONTROLS.....	43
6.12.	CONTAINER CLOSURE SYSTEM.....	43
6.13.	Stability.....	44
6.14.	LABELING.....	47
7.	Recommendation.....	47



1. EXECUTIVE SUMMARY

This memorandum summarizes the review of CMC information in the original Biologics License Application (BLA) under STN 125611/0 submitted by Novo Nordisk, Inc. (Novo) for Coagulation Factor IX (Recombinant), GlycoPEGylated. Novo uses the *International Nonproprietary Name*, nonacog beta pegol, mostly for the bulk drug substance (BDS), as well as the abbreviation, N9-GP, for the product. Its proposed proprietary name, *REBINYN*, was determined to be acceptable based on the review by Oluchi Elekwachi from the *Advertising and Promotional Labeling Branch* in the *Office of Compliance and Biologics Quality*. The proposed indications are for adults and children with hemophilia B for: a) on-demand treatment and control of bleeding episodes; b) perioperative management of bleeding; and c) routine prophylaxis to reduce the frequency of bleeding episodes. The last indication is not granted because of exclusivity by Shire/Baxalta's RIXUBIS.

N9-GP is a recombinant version of human Coagulation Factor IX (rFIX) on which a 40-kilodalton (kDa) polyethylene glycol (PEG) molecule is attached. The addition of the 40-kDa PEG moiety to rFIX is intended to increase its circulatory half-life. The rFIX protein is expressed in Chinese Hamster Ovary (CHO) cell line (b) (4) and purified by several chromatographic steps, which also includes viral inactivation by detergent treatment. The 40-kDa PEG moiety is enzymatically attached to the N-linked glycans on rFIX with (b) (4) as a linker. The GlycoPEGylated product is then purified by (b) (4).

The molecular weight of GlycoPEGylated rFIX is approximately 98 kDa. Its structure was characterized and compared to licensed rFIX products. The study includes comparisons of (b) (4)

. A one-stage clotting assay is used to determine the biological activity of GlycoPEGylated rFIX, and its specific activity is found to be approximately 152 IU/mg. The final drug product (FDP) is formulated as a sterile lyophilized powder, and presented in three dosage strengths of nominal activity of 500, 1000, or 2000 IU of rFIX per vial. Upon reconstitution with the diluent (10 mM Histidine), it is used for intravenous administration only.

STN 125611/0 was reviewed under the standard schedule of the PDUFA V Program. Novo submitted the BLA on 16 May 2016, and the action due date is 3 June 2017.

These reviewers found the information provided in the original submission and Novo's responses to our information requests (IRs) to be sufficient to support the identity, quality, purity, safety, and potency of the product; therefore, from a product reviewers' point of view, we recommend the approval of BLA STN 125611/0.

2. BACKGROUND

2.1. OVERVIEW OF HEMOPHILIA B

Hemophilia B is a blood clotting disorder due to the deficiency or dysfunction in FIX. FIX is encoded by the *F9* gene, which is found on the X chromosome. As a result, hemophilia B is almost exclusively found in males, although heterozygous females may exhibit a mild form of the disease. The incidence of hemophilia B is estimated to be



approximately 1 case per 25,000 - 30,000 male births. Hemophilia B has a wide geographic distribution and is found in all racial and ethnic groups. Hemophilia B is classified by the level of FIX coagulant activity (CA) in the individual's plasma as: severe (CA: < 1% of normal), moderate (CA: 1% – 5%) or mild (CA: 5% - 30%).

The hallmark of hemophilia is hemorrhage into the joints (typically the ankles in children, and the ankles, knees, and elbows in adolescents and adults) resulting in permanent deformities, misalignment, loss of mobility, and extremities of unequal lengths. With mild hemophilia, hemorrhage most likely occurs with trauma or surgery. The availability of virus-cleared, plasma-derived FIX concentrate, and its recombinant analogues, as effective treatment for bleeds and prophylaxis, has significantly improved the outcome in the treatment of this disorder. The affected individuals can now achieve a close to normal life span, and enjoy a greatly improved quality of life.

Treatment of hemophilia B requires regular infusions with FIX-containing preparations. FDA-approved products for the treatment of hemophilia B include recombinant FIX (BENEFIX, IXINITY, and RIXUBIS), plasma-derived FIX concentrates (MONONINE and ALPHANINE), or plasma-derived FIX complex (PROFILNINE and BEBULIN). Also available are two long-acting rFIX fusion proteins, ALPROLIX (with Fc region of IgG), and IDELVION (with albumin), which allow the individual to infuse less frequently (on average, once every 7 days) in routine prophylaxis regimens.

The development of neutralizing anti-drug antibodies (often called “inhibitors” in coagulation literature) occurs in 3 - 5% of hemophilia B individuals. This is the most serious complication in the management of hemophilia B, and represents a major source of morbidity and mortality. The neutralizing anti-drug antibodies to a particular product often, though not always, cross-react with other FIX products, as well as the patient's endogenous FIX.

2.2. GENERAL INFORMATION ABOUT COAGULATION FACTOR IX

The activated form of FIX is a vitamin K-dependent serine protease in the blood coagulation system, responsible for converting FX to its active form, FXa. Factor IX is synthesized as a 461 amino acid precursor (primarily in the liver) and then secreted into plasma. FIX zymogen undergoes extensive co-translational and post-translational modifications, such as glycosylation (~17 % carbohydrate by weight) and γ -carboxylation. It has a 46-amino acid N-terminal propeptide (which includes a 28-amino acid signal sequence) that is cleaved off during cellular processing of FIX. FIX circulates in plasma as a single-chain zymogen of 415 amino acids. During blood clotting, the zymogen is activated by two distinct mechanisms: either by FXIa (intrinsic pathway) or FVIIa/tissue factor (extrinsic pathway). The activation of FIX results in the excision of the activation peptide (amino acid 145 – 180) that converts FIX into its active form, FIX $\alpha\beta$, where two polypeptide chains are linked together by a disulfide bond.

3. REVIEW HISTORY

3.1. MANUFACTURING AND TESTING FACILITIES

The manufacture and testing of N9-GP bulk drug substance (BDS) and N9-GP final drug product (FDP) are performed at several facilities (3.2.S.2.1 *Manufacturer*) which are listed in Table 1.



Table 1. Facilities involved in the manufacturing/ testing activities of N9-GP

Facility	Manufacturing/ Testing Activities
Novo Nordisk A/S (b) (4)	(b) (4)
Novo Nordisk A/S (b) (4)	(b) (4)
(b) (4)	(b) (4)
(b) (4)	(b) (4)
(b) (4)	(b) (4)

3.2. MANUFACTURING PROCESS OF DRUG SUBSTANCE AND PRODUCT

1. (b) (4)

(b) (4)



(b) (4)

(b) (4)

(b) (4)

(b) (4)

5. HISTIDINE SOLUTION

The histidine solution in a prefilled syringe is manufactured under contract by (b) (4).

The solvent is intended for reconstitution of the lyophilized drug product prior to use and does not possess therapeutic properties. The solvent appears clear and colorless. The final molarity of the histidine solution is 10 mM. The histidine solution in accompanying the N9GP FDP will be in a 4 mL presentation, filled in to a 5 mL syringe. The composition of the Histidine solution is shown in Table 10.

Table 10. Composition of the histidine solution



(b) (4)

(b) (4)

5.1. CONTAINER AND CLOSURE

The syringe barrel for the histidine solution in prefilled syringes is made of (b) (4) glass Type^(b) as defined in (b) (4). The syringe barrel is siliconised inside with (b) (4). The rubber plunger for the Histidine Solution in prefilled syringes is made of bromobutyl rubber Type^(b) as defined in (b) (4). The rubber plunger is siliconised with (b) (4).

The container closure system for the Histidine Solution in prefilled syringes consists of three parts: Tip closure, luer lock adapter and plastic sleeve. Only the tip closure part have direct contact to the histidine solvent, and is made of bromobutyl rubber Type^(b) as defined in (b) (4).

Compatibility of the container closure system was confirmed based on the stability data of the histidine solution. The container closure system had been tested for extractables and leachables at the 3 mL and 10 mL syringe presentation of Histidine Solvent, which have already approved for another drug product. The 5 mL presentation is covered under this bracketing approach. The leachable study included an accelerated and a long-term approach.

The container closure system and potential leachables from this are not considered to pose a safety concern. It is concluded that the prefilled syringe is considered suitable for its intended use with no safety concerns related to the level of leachables identified.

5.2. MANUFACTURING

(b) (4)

(b) (4)

(b) (4)

6. DRUG PRODUCT

6.1. DESCRIPTION AND COMPOSITION OF THE ADYNOVATE DRUG PRODUCT

N9-GP is full-length form of rFIX consisting of 461 amino acids covalently conjugated with a 40-kDa PEG reagent at its N-glycan(s). It is supplied in single-use vials containing nominal potencies of 500, 1000, or 2000 IU of GlycoPEGylated rFIX. Each vial of N9-GP is labeled with the actual value of FIX potency, which will be within (b) (4) of the targeted one. Sodium chloride, histidine, sucrose, mannitol, polysorbate 80, and slight amount of (b) (4) serve as excipients and/or stabilizers.

The presentation consists of one lyophilized drug product vial, one diluent (histidine solution) vial, a MixPro® pre-filled diluent syringe containing 10 mM histidine solution and sterile vial adapter with 25 micrometer filter, which serves as a needleless reconstitution device to allow for the transfer of the diluent into the drug product vial.

Table 14. N9-GP FDP composition

Component	Function	Amount per mL for different dosage strengths after reconstitution*		
		500 IU (nominal)	1000 IU (nominal)	2000 IU (nominal)
N9-GP, GlycoPEGylated rFIX	Active ingredient	125 IU (b) (4)	250 IU (b) (4)	500 IU (b) (4)
Mannitol	Excipient	25 mg	25 mg	25 mg
Sucrose	Stabilizer	10 mg	10 mg	10 mg
Sodium chloride	Excipient/Electrolyte	2.34 mg	2.34 mg	2.34 mg
Histidine	Excipient/buffer	3.10 mg	3.10 mg	3.10 mg
(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Polysorbate 80	Excipient/ Surfactant	0.05 mg	0.05 mg	0.05 mg
(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)

* N9-GP after reconstitution contains histidine from histidine solution, the diluent.

6.2. FLOW DIAGRAM OF THE MANUFACTURING PROCESS

The flow diagram of the manufacturing process is detailed in section 3.2.P.3.3 *Description of Manufacturing Process* and is summarized here:

- 1) *REBINYN* BDS is the starting material



- 2) Compounding (b) (4)
- 3) Filtration
- 4) Filling
- 5) Lyophilization
- 6) Container closure
- 7) Visual inspection and QA release
- 8) Labelling and packaging

6.3. A BRIEF DESCRIPTION OF MANUFACTURING PROCESS

N9-GP FDP is manufactured at the Novo facility in (b) (4)

, the product is lyophilized. The vials are fully stoppered after the completion of lyophilization and then capped with a rubber stopper and sealed with a snap-off cap made of aluminum and plastic. Following visual and quality control testing, the vials are labeled and packaged with secondary packaging. Finished FDP is (b) (4)

protected from light at 2 - 8°C.

Reviewers' comment: The process is well controlled.

6.4. IN-PROCESS CONTROL

The critical steps established to ensure product quality are described in section 3.2.P.3.4 *Control of Critical Steps and Intermediates* and are listed in Table 15.

Table 15. The critical process steps and in-process controls for manufacturing of FDP N9-GP

Critical step	In-process control	Control limits
Compounding	(b) (4)	(4)
Filtration		
Filling		
Lyophilization		
Capping		

¹ Analysis performed on sample taken prior to sterile filtration. By using (b) (4) in series it is ensured that the final



filter receives no more than (b) (4) in accordance with the (b) (4)
(b) (4) points out that a sample amount of (b) (4) can be used for general microbial counts.

² The filling weight must be controlled within (b) (4) of the set point for filling volume. A minor difference in density between the strengths 500 IU/vial and 1000 IU/vial compared with 2000 IU/vial results in a minor difference in the control limits.

Reviewers' comment: The parameters established and their acceptance criteria are considered to be appropriate and acceptable.

6.5. CONTAINER CLOSER SYSTEM FOR FDP

The container closure system used for the storage of N9-GP FDP consists of a vial made of colorless glass, a lyophilization stopper made of rubber and a snap-off cap made of aluminum and plastic (secondary packaging material). The glass vial complies with (b) (4) glass), (b) (4) glass) and (b) (4) the lyophilization stopper complies with (b) (4) rubber) and (b) (4) rubber); the snap-off cap complies with the release specification for examination of the cap and internal height of the aluminum cap.

Reviewers' comment: We defer the comments on this issue to Cmdr. Jeremy Wally from DMPQ. He included this topic in his review.

6.6. PROCESS VALIDATION AND/OR EVALUATION

We defer the comments on the lyophilization, media fill, and shipping validation to Cmdr Jeremy Wally from DMPQ. He included these topics in his review.

(b) (4)

Table 2 of section 3.2.P.3.5 *Process Justification Summary for Drug Product* lists all the FDP batches, the (b) (4) batches that correspond to them, and additional information regarding each of these batches. Batches tested for process validation comprise of 500 IU and 2000 IU.

The operational limits for each step are as follows:

- (b) (4)

For the mixing validation studies, samples were collected from the (b) (4) during the (b) (4) process.

Reviewers' comment: Product quality attributes were further evaluated in the manufacture of these batches. All the test results met the acceptance criteria. These data indicate that the extended holding times do not have a significant impact on the product quality. Process and quality controls for conformance lot manufacture complied with prospectively defined acceptance criteria for successful process validation.

6.7. CONTROL OF EXCIPIENTS

Excipients used are (b) (4) -Histidine, Mannitol, Polysorbate 80, Sodium chloride, (b) (4), Sucrose, (b) (4). All specifications are based on (b) (4), and Novo provided total microbial count limit per (b) (4).

Therefore, all the excipients used in the manufacture of N9-GP are well controlled, and acceptable.

6.8. CONTROL OF DRUG PRODUCT

The specifications of the N9-GP FDP are detailed in Table 16.

Table 16. FDP specifications: analytical procedures and acceptance criteria

Test	Analytical procedure	Acceptance criteria
Solid state		
Appearance of powder	Visual inspection (b) (4)	Complies ¹
Reconstitution time/solubility	Visual inspection (b) (4)	Complies ²
Water content	(b) (4)	(b) (4)
	(b) (4)	
Liquid state		
Appearance of solution	Visual inspection (b) (4)	Complies ⁴
(b) (4)	(b) (4)	(b) (4)
Identity	(b) (4)	Complies ⁵
Total impurities	(b) (4)	Release limit: (b) (4) Shelf life limit: (b) (4)
rFIX (b) (4)		Release limit: (b) (4) Shelf life limit: (b) (4)
rFIX (b) (4)		Release limit: (b) (4) Shelf life limit: (b) (4)
PEG profile	(b) (4)	Mono-PEG rFIX:



	(b) (4)	Release limit: (b) (4) Shelf life limit: (b) (4) (b) (4) rFIX: Release limit: (b) (4) Shelf life limit: (b) (4) rFIX: Release limit: (b) (4) Shelf life limit: (b) (4)
rFIX (b) (4)	(b) (4)	Release limit: (b) (4) Shelf life limit: (b) (4)
Protein content	(b) (4)	500 IU: (b) (4) 1000 IU: (b) (4) 2000 IU: (b) (4)
(b) (4)	(b) (4)	Release limit: (b) (4) Shelf life limit: (b) (4)
Potency	One-stage clotting assay M056	500 IU: Release limits: (b) (4) Shelf life limits: (b) (4) 1000 IU: Release limits: (b) (4) Shelf life limits: (b) (4) 2000 IU: Release limits: (b) (4) Shelf life limits: (b) (4) 500 IU: (b) (4) 1000 IU: (b) (4) 2000 IU: (b) (4)
Specific activity	Calculated from One-stage clotting assay and (b) (4) M056 (b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
Polysorbate 80	(b) (4)	(b) (4)
Sucrose	(b) (4)	(b) (4)
Mannitol	(b) (4)	(b) (4)
Particulate matter	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
Bacterial endotoxins	(b) (4)	(b) (4)



Sterility	(b) (4) CFR 610.12	Complies ⁷
------------------	-----------------------	-----------------------

¹Complies means that the lyophilized powder appears as a white to off-white

²Complies means that the lyophilized powder dissolves within 10 minutes at 20 - 25°C

³The (b) (4) method is based on the (b) (4) method. The (b) (4) method will be used on samples out of the (b) (4) calibration range or with threshold values higher than acceptance threshold for the (b) (4) method

⁴Complies means that the reconstituted solution appears as a clear and colorless liquid and free from particles that are clearly detectable. The visual inspection is performed according to (b) (4)

(b) (4). The analysis of Appearance of solution consists of three tests:

Clarity, Color and Foreign insoluble matter

⁵Complies corresponds to: (b) (4) of the sample is comparable to the (b) (4) of N9-GP reference material. The difference in retention time for rFIX, mono-(b) (4)-PEGylated rFIX of the N9-GP reference material and the samples must not be more than (b) (4) ""

⁶The unit IU/vial is (b) (4) (withdrawal volume)

⁷Complies means the product meets the requirement of test for sterility in (b) (4) /21 CFR 610.12

Reviewers' comment: The specification limits of N9-GP DFP are acceptable and support the consistency of the manufacturing process.

6.9. BATCH ANALYSIS

An overview of the batches produced during the development phase is provided in Table 1 of section 3.2.P.5.4 *Batch Analyses*. Among these were (b) (4) FDP Conformance Lots listed in Table 17.

Table 17. FDP Conformance Lots

Lot Number	Potency	Date of Manufacture	Batch size
(b) (4)	500 IU	(b) (4)	(4)
	500 IU		
	500 IU		
	1000 IU		
	2000 IU		
	2000 IU		

Reviewers' comment: The test results met all the specifications and acceptance criteria for the critical quality attributes for the conformance lots. These data confirm the consistency of the proposed commercial manufacturing process.



6.10. IMPURITY PROFILE

All impurity profiles are identical between (b) (4) FDP. Therefore, section 4.9. IMPURITY PROFILE, of this review memo covers the impurity profile of (b) (4) FDP.

6.11. IN-PROCESS CONTROLS

In-process controls (IPCs) are performed routinely to control the product quality attributes at various steps. Specifically IPCs were established for CQA-impacting process parameters.

All the methods used in the IPCs and in the release specifications have been validated, and the validation data are sufficient.

The complete review on the analytical method validation was performed by OCBQ and is summarized in their review memoranda with the exception of the following methods:

6.11.1. Appearance of the FDP powder and solution

These procedures are general descriptive methods which do not require validation for individual sample types.

6.11.2. Particulate matter of the FDP

The analytical procedure particulate matter (b) (4) is an assay for the determination of particulate matter in N9-GP FDP. The analytical procedure was validated in accordance with the harmonized procedure in the (b) (4). The method suitability is verified as follows: (i) performance check of the instrument and (ii) verification of the procedure for N9-GP FDP. Verification of the instrument performance is assured by routine calibration with standards traceable to NIST and by assessment of linearity. The verification of the procedure for N9-GP drug product was performed by assessment of accuracy and precision. Batch number (b) (4) was used for the verification of the procedure. Only FDP presentation of 2000 IU was used, as a worst case scenario.

The assay was found to be suitable for particle counting in N9-GP FDP.

6.12. CONTAINER CLOSURE SYSTEM

The primary container closure system for *Rebinyn* consists of a clear and colorless (b) (4) glass vial, a (b) (4) gray (b) (4) butyl rubber stopper, and aluminum crimp-cap with a polypropylene flip-off disk. Vials are made of glass Type (b) (4) and meet the requirements of current (b) (4). Rubber stopper complies with the requirements of current (b) (4). Container closure safety and performance were qualified through extractables, leachables studies and container closure integrity testing other than final product monitoring in the established stability program.

Reviewers' comment: We defer the review of this section to Cmdr Jeremy Wally from DMPQ.



6.13. STABILITY

Stability study for the primary, supportive and PPQ batches of N9-GP FDP are described in section 3.2.P.8 *Stability*. Novo submitted information regarding the stability of total (b) (4) PPQ batches, (b) (4) primary batches, and (b) (4) supportive batches of the FDP used in the phase III clinical trials. The information on these batches is listed in Table 18.

Table 18. Stability FDP batches, duration of the study and available data

(b) (4)



(b) (4)

Reviewers' comment: Some of the BDS that were used to make FDP, and are mentioned in this Table, were not reported in the BDS stability study.

Stability studies for N9-GP FDP focused on the two extreme dosage strengths: 500 and 2000 IU. The BDS used for manufacturing of FDP batches (b) (4) have been produced using 40-kDa PSC supplied by (b) (4)

Reviewers' comment: Novo showed comparability between the two 40-kDa PSC supplied by the (b) (4) different vendors and therefore it is acceptable.



The parameters used in assessing stability of FDP include: appearance of powder, reconstitution time, water content, appearance of solution, (b) (4), PEG profile including mono-, (b) (4) PEGylated rFIX (b) (4), total protein (b) (4) potency (one-stage clotting assay), specific activity (calculated), (b) (4) assay), total impurities including PEGylated rFIX (b) (4) and rFIX (b) (4), other rFIX (b) (4) and rFIX with shorter PEG (b) (4), bacterial endotoxins, and sterility.

Under long-term stability conditions, all stability results for all lots stored at 5°C for (b) (4) months, at 5°C for (b) (4) followed by (b) (4) months at 30°C, or at 30°C for (b) (4) months, comply with the specification, with the exception of potency and protein content. These two parameters showed a large variation due to the use of old secondary standard material (SRM) and therefore the results were recalculated using new SRM. Accordingly, specific activity was also recalculated. Recalculated results met the specification limits. Minor decrease in potency and minor increase in (b) (4), total impurities, (b) (4) mono-PEG rFIX were observed only in accelerated storage conditions (b) (4) and therefore, were determined as the stability indicating test parameters, to be followed to monitor aggregation or degradation of N9-GP FDP.

Results of “in-use (chemical stability)” and (b) (4) studies were submitted as a part of FDP stability studies. Increased (b) (4) of rFIX, and degradation of PEG moiety were demonstrated by (b) (4) when samples were stored in the primary packaging only, but were not observed when stored in secondary packaging.

Based on the stability studies conducted and the statistical evaluation of stability, a shelf life period of 24 months at 5°C, where the FDP may be kept at or below 30°C for a single period up to 6 months, is proposed for N9-GP FDP when stored in secondary packaging material, but should be protected from light when stored in primary packaging.

Reviewers’ comment: The (b) (4) stability data from the primary batches under the long-term storage condition are qualified to support the shelf-life of N9-GP FDP. N9-GP FDP can be stored at $5 \pm 3^\circ\text{C}$ for up to 24 months.

6.14. LABELING

The discussion regarding labeling is still on-going, and therefore will not be summarized here.

7. RECOMMENDATION

The manufacturing process of N9-GP is considered to be adequately validated and sufficiently controlled to ensure consistent manufacture of the commercial product that meets the release specifications. The measures taken by Novo to control adventitious agents in the manufacture of N9-GP are acceptable. We found the CMC information to support the quality, identity, purity, potency and safety of the product, and we recommend approval of this BLA.