Summary Basis for Regulatory Action Template

Date: February 15, 2019

From: Andrey Sarafanov, PhD, Chair of the Review Committee

***BLA* STN#:** 125671/0

Applicant Name: Novo Nordisk, Inc.

Date of Submission: February 27, 2018

PDUFA Goal Date: February 27, 2019

Proprietary Name: ESPEROCT

Established Name: Antihemophilic Factor (Recombinant), GlycoPEGylated-exei

Indication: For use in adults and children with hemophilia A for: (1) on-demand treatment and control of bleeding episodes, (2) perioperative management of bleeding, and (3) routine prophylaxis to reduce the frequency of bleeding episodes.

Recommended Action:
The Review Committee recommends approval of this Biologics License Application.

Review Office Signatory Authority:

Wilson W. Bryan, MD
Director
Office of Tissues and Advanced Therapies
Center for Biologics Evaluation and Research

☐ **I concur with the summary review.**

☐ **I concur with the summary review and include a separate review to add further analysis.**

☐ **I do not concur with the summary review and include a separate review.**

The table below indicates the material reviewed when developing the SBRA.

Document title	**Reviewer name, Document date**
CMC Reviews	
• CMC (product office)	Andrey Sarafanov, PhD, OTAT/DPPT Alexey Khrenov, PhD, OTAT/DPPT Mikhail Ovanesov, PhD, OTAT/DPPT Ze Peng, PhD, OTAT/DPPT Yideng Liang, PhD, OTAT/DPPT Mark Verdecia, PhD, OTAT/DPPT Haarin Chun, PhD, OTAT/DPPT
• Facilities review (OCBQ/DMPQ)	Hector Carrero, OCBQ/DMPQ Ekaterina Allen, PhD, OCBQ/DMPQ
• QC, Test Methods, Product Quality	Parmesh Dutt, PhD, OCBQ/DBSQC Karla Garcia, MS, OCBQ/DBSQC Jing Lin, PhD, OCBQ/DBSQC Tao Pan, PhD, OCBQ/DBSQC Charlene Wang, PhD, OCBQ/DBSQC
• QC, Sterility and Endotoxin	Hector Carrero, OCBQ/DMPQ
• Establishment Inspection Report (OCBQ/DMPQ)	Hector Carrero, OCBQ/DMPQ Ekaterina Allen, PhD, OCBQ/DMPQ
• Lot Release Protocol/Testing Plan	Marie Anderson, PhD, OCBQ/DBSQC
Clinical Reviews	
• Clinical (product office)	Najat Bouchkouj, MD, OTAT/DCEPT Bindu George, MD, OTAT/DCEPT
• Postmarketing safety Epidemiological review (OBE/DE)	Ohenewa Ahima, MD, OBE/DE
• BIMO	Anthony Hawkins, MS, OCBQ/BIMO
Statistical Review • Clinical data • Non-clinical data	Lin Huo, PhD, OBE/DB
Pharmacology/Toxicology Review • Toxicology (product office)	Gaya Hettiarachchi, PhD, OTAT/DCEPT
Clinical Pharmacology Review	Iftekhar Mahmood, PhD, OTAT/DCEPT
Labeling Review(s) • APLB (OCBQ/APLB)	Oluchi Elekwachi, PharmD, OCBQ/DCM/APLB Kristine Khuc, PharmD, OCBQ/DCM/APLB
Regulatory Project Management	Jean Dehdashti, MSc, RAC, OTAT/DRPM

1. INTRODUCTION

Novo Nordisk (Novo) submitted a biologics license application (BLA) under STN 125671/0 to seek U.S. licensure for their product, Antihemophilic Factor (Recombinant), GlycoPEGylated-exei, with the International Non-Proprietary Name of turoctocog alfa pegol. The proprietary name for the U.S. market is ESPEROCT.

The active ingredient of ESPEROCT is a recombinant (r) analog of B-domain truncated human coagulation factor VIII (FVIII), conjugated with a 40-kDa polyethylene glycol (PEG) molecule. The rFVIII variant is the same active ingredient in NOVOEIGHT, a licensed rFVIII product manufactured by Novo. The PEG moiety prolongs the circulatory half-life of rFVIII.

ESPEROCT is provided as a sterile lyophilized powder in five nominal dosage strengths of 500, 1000, 1500, 2000, and 3000 international units (IU) of FVIII activity per vial. ESPEROCT is intended for intravenous administration after reconstitution with (b) (4) of 0.9% sodium chloride solution provided in a prefilled syringe.

ESPEROCT replaces the deficient or missing FVIII in patients with hemophilia A. When PEGylated rFVIII (rFVIII-PEG) in ESPEROCT is activated by thrombin, the sequence with the PEG moiety is cleaved off, and the resulting activated FVIII (rFVIIIa) is similar in structure and function to native FVIIIa.

ESPEROCT is indicated for use in adults and children with hemophilia A for:

- On-demand treatment and control of bleeding episodes
- Perioperative management of bleeding
- Routine prophylaxis to reduce the frequency of bleeding episodes

To support the proposed indications, the BLA includes results from three studies to evaluate the safety and efficacy of ESPEROCT:

- Study 1, for on-demand and routine prophylaxis in adults and adolescents (≥12 years of age) with severe hemophilia A.
- Study 2, for perioperative management in adults and adolescents (≥12 years of age) with severe hemophilia A.
- Study 3, for treatment of bleeding and routine prophylaxis in previously treated pediatric patients (<12 years of age) with severe hemophilia A.

Studies 1, 2, and 3 adequately demonstrated the efficacy of ESPEROCT for on-demand, routine prophylaxis, and perioperative management of patients with severe hemophilia A with an acceptable safety profile and favorable benefit-risk assessment.

2. BACKGROUND

Hemophilia A is a hereditary bleeding disorder caused by deficiency or dysfunction of FVIII (historically referred to as Antihemophilic Factor). Hemophilia A has an X- linked, recessive inheritance pattern affecting 1 in 5,000 male births with rare occurrence in females. Severity of hemophilia A is classified based on a FVIII level with severe hemophilia being defined as <1% functional activity (1 IU/dL) and moderate hemophilia as FVIII levels that range from 1% to 5% (1-5 IU/dL). Replacement therapy is generally warranted for patients with severe hemophilia or moderate hemophilia with the severe bleeding phenotype. The goal of replacement therapy and prophylaxis is to reduce joint damage, and to reduce frequency of and/or to treat life-threatening bleeding episodes.

Currently, there are over 10 licensed plasma-derived or recombinant FVIII products for the treatment of hemophilia A. The FVIII products which are based on conventional variants of FVIII (full-size or B-domain deleted), all require frequent infusions. Therefore, there is a need for the development of new products based on modified FVIII, which have an extended half-life in blood circulation and require less frequent infusions. Several platform technologies have been used to extend the plasma half-life of therapeutic FVIII proteins; in the case of ESPEROCT, this involves the addition of a PEG moiety to the active molecule.

The development of neutralizing anti-drug antibodies (often called “inhibitors”) occurs in ~30 - 35% of previously-untreated patients (PUPs). This is the most serious complication in the management of hemophilia A, and represents a major source of morbidity and mortality. Neutralizing anti-drug antibodies to a product may cross-react with other FVIII products, as well as the patient’s endogenous FVIII. When therapeutic proteins are engineered with the introduction of neo-sequences, there are additional immunogenicity concerns. Similarly, the added PEG moiety could potentially elicit immune responses. These immune responses, which include hypersensitivity, have been evaluated in the review of ESPEROCT.

Regulatory History

FDA had multiple interactions with the Applicant throughout the reviews of the IND and BLA. ESPEROCT was developed under IND 14410, initiated in July 2010. The BLA was reviewed under the standard (12-month) review schedule of the PDUFA VI program. The BLA milestones are listed in Table 1.

Table 1: Review Milestones

Milestone	Date
Received	February 27, 2018
Filed	April 18, 2018

Milestone	Date
Mid-Cycle Communication	August 3, 2018
Blood Products Advisory Committee	Waived
PeRC Meeting	September 19, 2018
Late-Cycle Meeting	November 29, 2018
PDUFA Action Due Date	February 27, 2019

3. CHEMISTRY, MANUFACTURING, AND CONTROLS (CMC)

a) Product Quality

Molecular Structure and General Properties

The rFVIII protein in ESPEROCT is expressed in a Chinese Hamster Ovary (CHO) cell line using recombinant DNA technology. The human FVIII gene is genetically modified to express rFVIII in which the B-domain is replaced with a (b) (4) representing the (b) (4) regions of the B-domain. The linker contains the sites for (b) (4) cleavages, and O-glycosylation. The 40-kilodalton (kDa) PEG moiety is conjugated to the O-glycan. The resulting molecular mass of rFVIII-PEG is (b) (4).

The PEG moiety (b) (4) extends the molecule's circulatory half-life to (b) (4) hours, versus (b) (4) hours for native FVIII. In the blood, rFVIII-PEG is activated by thrombin cleavage, and the linker with the attached PEG moiety dissociates from rFVIIIa. This molecule is similar in structure and function to native FVIIIa.

Manufacture of ESPEROCT

The *Drug Substance* (DS) and *Drug Product* (DP) are manufactured at Novo's facilities in (b) (4), respectively. Eight other facilities, located in (b) (4), are responsible for storage and quality control of all materials and analytical testing, labelling, secondary packaging, and storage of finished product.

The manufacture of ESPEROCT starts with CHO cell culture maintained in a (b) (4) process. The rFVIII is then purified from the culture media in a process that consists of several chromatography steps (affinity chromatography, (b) (4) and sterile filtration. The process also includes two viral clearance steps: treatment with (b) (4) Triton X-100 to inactivate enveloped viruses, and filtration using a 20-nm (b) (4) to remove enveloped and non-enveloped viruses.

The rFVIII is PEGylated via the O-glycan in the B-domain (b) (4). The PEGylated rFVIII is then purified by (b) (4)

chromatography (b) (4) to produce the DS, which is stored at (b) (4). Upon completion of release testing, the DS is shipped to the (b) (4) site for further manufacture into the DP.

The DS is (b) (4) . This is followed by (b) (4) . Upon (b) (4) release testing, the DP vials are packaged with the diluent (0.9% sodium chloride solution in a prefilled syringe).

Quality Control Strategy

The strategy to control product quality was based on the determination of critical quality attributes (CQA) of ESPEROCT and process parameters which may impact CQA. The CQAs were rated according to a severity score (from 1 to 5). The most important CQA (severity scores of 4 - 5) were (b) (4) For DS manufacture, the risk assessment identified that essentially all steps of production have a potential impact on CQAs with high severity score (b) (4) For DP manufacture, the critical process steps were determined to be (b) (4)
For all production steps, respective in-process controls and analytical procedures with acceptable limits were developed to preserve the CQAs.

The manufacture of ESPEROCT is controlled by the following:

- raw materials quality;
- in-process control parameters;
- process performance qualification (PPQ);
- control of impurities;
- DS and DP release specifications; and
- stability monitoring.

Process Validation

Novo's validation strategy for the ESPEROCT manufacturing process is consistent with the recommendations of International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Guidelines Q7, Q8 and Q11. The validation strategy included (i) process design, (ii) process performance qualification (PPQ) and (iii) continued process verification.

The PPQ studies were performed at the intended commercial sites under prospective process validation protocols. The PPQ studies for DS included (i) (b) (4) approach. For all PPQ batches of DS and lots of DP, all in-process

controls and results of release testing versus respective specifications met the acceptance criteria.

Per FDA request to justify the (b) (4) approach, Novo provided stability trend analyses from a completed "accelerated" stability study (6-month (b) (4) for (b) (4) DP lots (500, 1000, 2000, and 3000 IU) including PPQ lots and a post-PPQ (b) (4) 1500 IU dosage strength. Comparable stability profiles were observed for all dosage strengths, thus supporting the process validation for all dosage strengths. Altogether, the PPQ data demonstrated consistency and reproducibility of the manufacturing process.

A Continued Process Verification plan was developed. According to the plan, extended monitoring of the manufacturing process performance will be continued with (b) (4) review of manufacturing data and risk assessment of test parameters.

Characterization of Structure and Function

The characterization program used an extensive panel of analytical methods to evaluate both the structure and function of the rFVIII-PEG protein.

Primary structure and post-translational modifications

These studies included (b) (4) The results confirmed comparability of the rFVIII to native FVIII.

Physico-chemical properties

This assessment included (b) (4) The results confirmed that the PEGylation process does not result in discernable changes in the primary, secondary, and tertiary structures of rFVIII.

Biological activity

This assessment included analysis of rFVIII-PEG interactions with Factor IXa and von Willebrand Factor (vWF), thrombin activation rate (with or without vWF), and rate of inactivation of rFVIIIa by (b) (4). The activity of rFVIII-PEG was assessed by either chromogenic substrate (CS) assay or one-stage clotting (OC) assay. The activity is expressed in IU relative to the (b) (4) World Health Organization (WHO) International Standard (IS) of FVIII. (b) (4) Thus, all

biochemical tests confirmed the structural and functional integrity of rFVIII-PEG.

Control of Impurities

1. *Product-related Impurities* include size and form variants of rFVIII including those originating from protein degradation or dissociation. (b) (4) The levels of these impurities are controlled by (b) (4) DP specifications.

2. *Process-related Impurities* include (b) (4) Removal of these impurities to sufficiently low levels was confirmed during process validation. (b) (4)

Evaluation of Safety Regarding Adventitious Agents

1. For the non-viral agents including bacteria, fungi, and mycoplasma, the potential of contamination is controlled through the use of: (i) appropriate environmental monitoring during the manufacture; (ii) validated cleaning/sanitization procedures of equipment; (iii) in-process controls, e.g., testing for (b) (4) ; and (iv) sterile filtration (using (b) (4) . The potential of ESPEROCT to be contaminated with non-viral adventitious agents is further reduced by testing the final product for Sterility and Endotoxin. Novo manufactures ESPEROCT according to GMP regulations.

2. The potential risk of adventitious viruses and transmissible spongiform encephalopathy agents is minimized because there are no raw materials or ingredients of human or animal origin used in the manufacturing process.

3. The potential of contamination by infectious viruses in cell culture is well controlled in the manufacture. The performed viral tests on the (b) (4) are consistent with the ICH Q5A(R1) guideline. All test results for viruses were negative except for (b) (4) . Furthermore, all viral tests were negative except for (b) (4) Novo routinely tests the (b) (4) process for adventitious viruses to ensure absence of viruses.

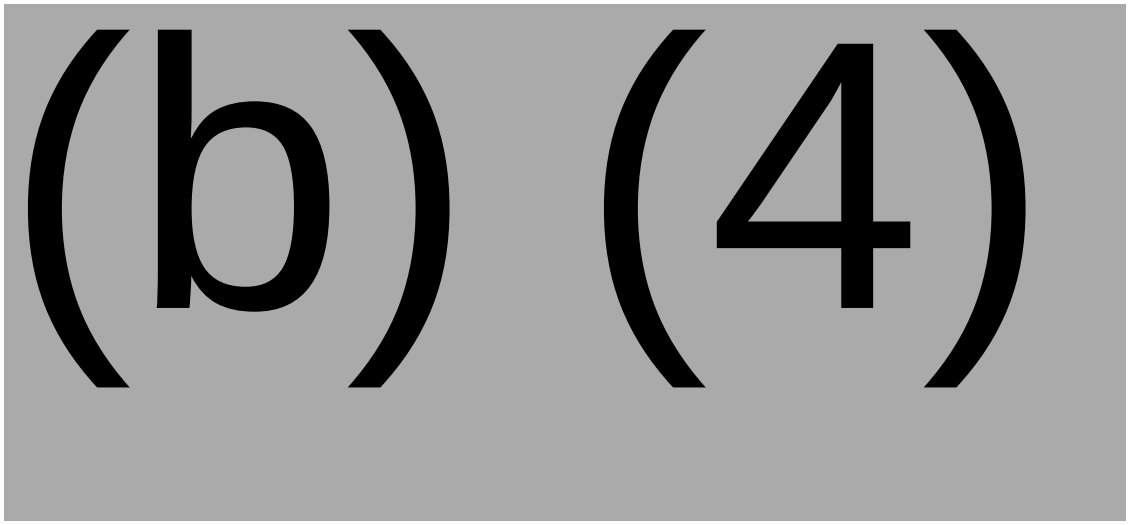
Additionally, the risk of viral contamination is mitigated by two viral clearance steps: treatment with (b) (4) Triton X-100 for the inactivation of enveloped viruses; and nanofiltration using 20-nm (b) (4) for the removal of enveloped and non-enveloped viruses. The Purification by (b) (4) step in the manufacturing process also contributes to virus removal. Novo evaluated these steps for viral clearance in relevant down-scale studies using model viruses with a wide range of physico-chemical properties. These viruses were (b) (4) These results demonstrate the effectiveness of the manufacturing process to clear viruses from ESPEROCT.

Control of Excipients

The excipients used in ESPEROCT are L-Histidine, Sucrose, Polysorbate 80, Sodium Chloride, L-Methionine, and Calcium chloride. All of these are of non-animal origin, have compendial specifications (b) (4) and are used in other medical products for parenteral use. Therefore, the excipients are considered to be safe.

Release Specifications for Drug Substance and Drug Product

The specifications for DS and DP are established in accordance with ICH Guideline Q6B. The parameters are selected from the CQA to ensure consistency of identity, purity, biological activity, and safety. Acceptance ranges/limits are established based on manufacturing capability, clinical outcome, analytical variability, and stability data.



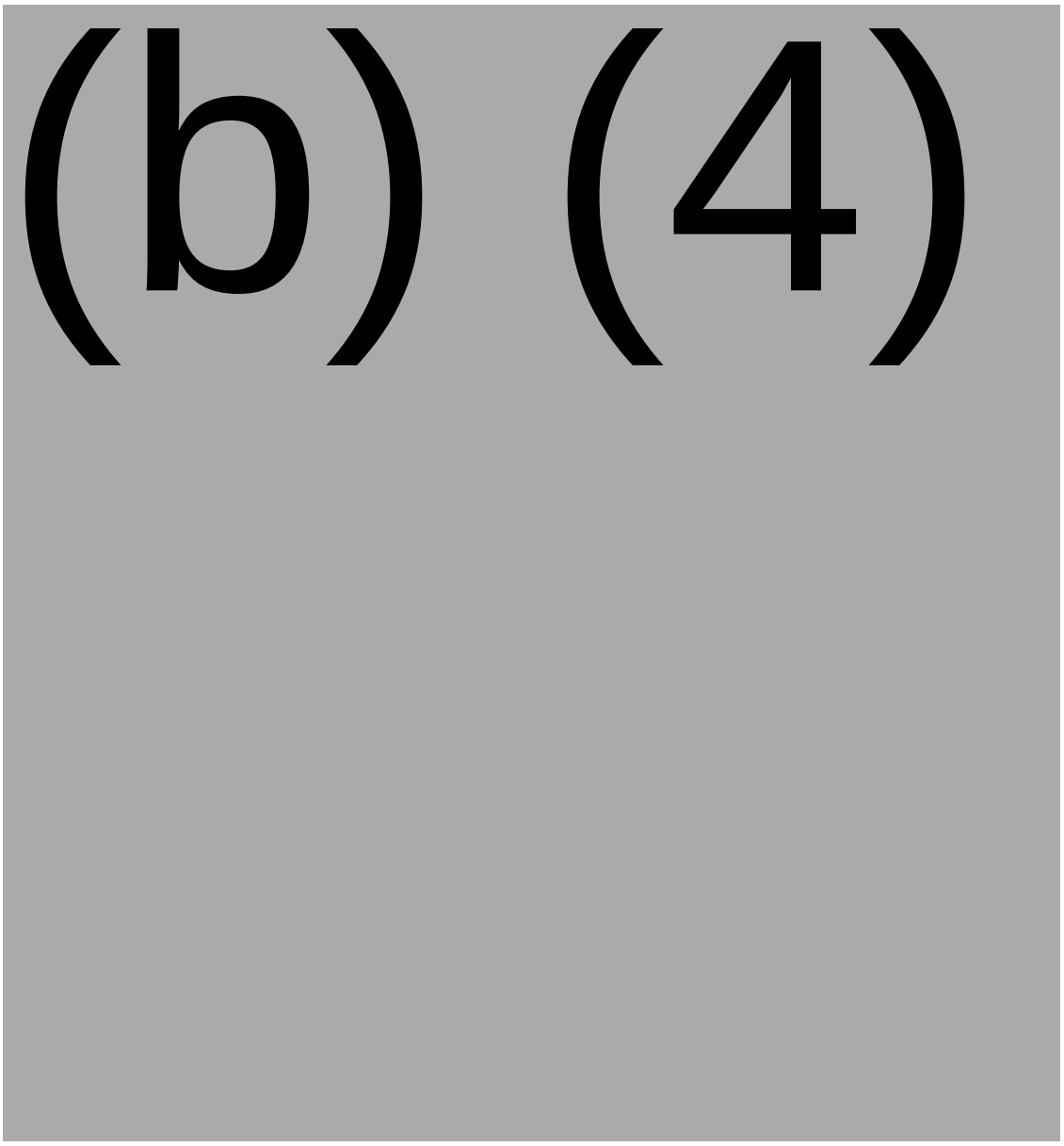


Table 3. Release Specifications for Drug Product

Test Parameter (Attribute)	Analytical Procedure	Acceptance Criteria
Appearance of powder	Visual inspection	White to off-white lyophilizate
Reconstitution time/solubility	Visual inspection	(b) (4)
(b) (4)	(b) (4)	(b) (4)

Test Parameter (Attribute)	Analytical Procedure	Acceptance Criteria
	(b) (4)	(b) (4)
Appearance of solution	Visual inspection	Clear and colorless liquid, free from particles that are clearly detectable.
(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
Protein content		(b) (4)
Identity	(b) (4)	(b) (4)
(b) (4)		(b) (4)
Purity		(b) (4)
Potency (IU/vial)	Chromogenic assay	(b) (4)

Test Parameter (Attribute)	Analytical Procedure	Acceptance Criteria
		(b) (4)
Particulate matter	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
Polysorbate 80	(b) (4)	(b) (4)
Calcium	(b) (4)	(b) (4)
Sucrose	(b) (4)	(b) (4)
Bacterial endotoxins	(b) (4)	(b) (4)
Sterility	(b) (4)	Sterile

Upon review of the original application, multiple deficiencies were found with both DS and DP specifications. The quantitative acceptance criteria were established arbitrarily. The justifications of specifications were not supported by adequate statistical analysis of manufacturing data, so the specifications did not allow for adequate control of the manufacturing process. Several parameters used to control glycans in DS specifications were found to be insufficient. Per the reviewers' request, Novo re-assessed the manufacturing data and justified and revised the acceptance limits. For several parameters, the limits were tightened and the acceptance criteria in DS specifications were changed from "For Information Only" to numeric ranges. All review concerns were addressed, and the specifications are found to be acceptable to control the identity, quality, purity, potency, and safety of ESPEROCT.

Analytical Methods

The analytical methods to control the DS/DP specifications described in compendia (b) (4), European Pharmacopoeia [Ph. Eur.] and (b) (4) were qualified (verified) and non-compendial methods were validated. The analytical methods and their validations and/or qualifications reviewed for the ESPEROCT DS and DP were found to be adequate for their intended use.

The potency of ESPEROCT is assigned using a chromogenic substrate FVIII activity assay. Comparison of the potency assignment using different commercially available chromogenic substrate- and one-stage clotting-based

assays revealed approximately (b) (4) variability between the assays. Most likely, these discrepancies were caused by PEGylation of rFVIII, which resulted in differences in how rFVIII-PEG and rFVIII interact with assay reagents. Because of this difference, under- and over-estimations of FVIII activity in post-infusion plasma samples can be expected in clinical settings. Over-estimation may lead to receiving less ESPEROCT by patients than needed. Specific measures are required to adequately convey this information to clinicians, the hemophilia community, and personnel involved in the care of the patients in order to facilitate adequate monitoring and prevent suboptimal dosing of ESPEROCT. To address this issue, specific communication and labeling strategies were developed by Novo based on the reviewers' recommendations.

To control the specifications parameters, Novo developed a Primary Reference Material (PRM) to serve as a reference for the determination of Identity, and as a calibrator for the Secondary Reference Material (SRM) for the determination of (b) (4) . The PRM (b) (4) were provided to link the PRM with the previously used standards. Appropriate protocols were developed to ensure stability and orderly replacement of the PRMs and SRMs over the product life-cycle. To address the (b) (4) stability trends noted by reviewers for early reference standards, Novo agreed to (b) (4) checks on PRM (b) (4) using the (b) (4) .

Container/Closure System

The container closure system for lyophilized DP, pre-filled syringe with diluent and vial adapter are packed together in ESPEROCT and constitute a drug (b) (4) , which has been previously approved for several of Novo's products.

1. The *Container/Closure System* for lyophilized product represents 5-mL (b) (4) glass vial (b) (4) closed with 13-mm chlorobutyl rubber stopper (b) (4) , aluminum cap, and plastic snap-off. Each vial contains a single 4-mL dose after reconstitution.

2. The *Container/Closure System* for the Solvent (0.9% sodium chloride solution) consists of a 5-mL (b) (4) glass syringe barrel (b) (4) a 5-mL Bromobutyl rubber plunger, and bromobutyl rubber tip cap (b) (4) conducted the container closure integrity testing (CCIT) of the pre-filled syringes at the (b) (4) site using a (b) (4) method; all acceptance criteria were met.

3. The *Vial Adapter* is a sterile, plastic disposable device in a blister package (Class II medical device, 510(K) number (b) (4) . Novo conducted the CCIT at the (b) (4) , employing the (b) (4) method; all acceptance criteria were met.

Leachables from the Container/Closure System for lyophilized product were tested under the real-time storage conditions (5°C ± 3°C) for 30 months (close to the shelf-life time of (b) (4) months). In the original application, the assessment of organic leachables was acceptable but elemental leachables (metals, etc.) were not assessed based on their absence in other lyophilized hemophilia drug products which use the same combination of the vial and rubber stopper. The reviewers had concern that different conditions may result in extraction of different leachables. To address this concern, Novo performed a study to analyze elemental leachables in the container system and showed their acceptable levels in the product.

(b) (4) PPQ lots of the solvent/delivery system were used for the process validations. Based on these studies, all components of the (b) (4) - the container/closure system for DP, pre-filled diluent syringe and vial adapter - were considered suitable for the use with ESPEROCT.

Stability

1. For *Drug Substance*, no significant stability trends were observed in stability studies, and the results support a shelf-life of (b) (4) months at (b) (4)

2. For *Drug Product*, the studies demonstrated consistent stability for 30 months at 5°C ± 3°C. Storage at room temperature was associated with gradual product degradation trends as evidenced by a decrease in potency and purity and an increase in protein (b) (4) time, thus supporting only 12 months of storage at ≤ 30°C (b) (4). The shelf-life of ESPEROCT was determined to be 30 months at 2°C to 8°C from the date of manufacture. Also, ESPEROCT may be stored at room temperature (≤ 30°C) for up to 12 months within the 30-month period but should not be returned to the refrigerator. After reconstitution, the product may be stored for 24 h at 5°C ± 3°C or 4 h at ≤ 30°C (b) (4) until use. These instructions are adequately reflected in the Prescribing Information. The established stability protocol provides sufficient control of DP stability post-approval. The DP Solvent, 0.9% Sodium Chloride, is stable for 60 months at 5°C (b) (4)

b) CBER Lot Release

Under the provision described in 60 FR 63048-63049 publication (December 8, 1995), routine lot-to-lot release by CBER is not required for ESPEROCT because it is a well-characterized therapeutic recombinant product. Thus, exemption of ESPEROCT from CBER Lot Release is justified.

c) Facilities review/inspection

Facility information and data provided in the BLA were reviewed by CBER and found to be sufficient and acceptable. The facilities involved in the manufacture of Antihemophilic Factor (Recombinant), GlycoPEGylated are listed in Table 4. The activities performed and inspectional histories are noted in Table 4 and further described below.

Table 4: List of Facilities and Inspectional History

Name/Address	FEI Number	DUNS Number	Inspection/ Waiver	Justification/ Results
Drug Substance Manufacturing Novo Nordisk (b) (4)	(b) (4)	(b) (4)	Pre-License Inspection	CBER/DMPQ (b) (4) VAI
Drug Product Manufacturing, Release Testing Novo Nordisk A/S (b) (4)	(b) (4)	(b) (4)	Waived	ORA (b) (4) NAI
Release Testing Novo Nordisk A/S (b) (4)	(b) (4)	(b) (4)	Waived	ORA (b) (4) NAI
Labeling Novo Nordisk A/S (b) (4)	(b) (4)	(b) (4)	Waived	CBER/DMPQ (b) (4) NAI
Diluent Manufacturing, Release Testing (b) (4)	(b) (4)	(b) (4)	Waived	ORA (b) (4) NAI
Release Testing (b) (4)	(b) (4)	(b) (4)	Waived	ORA (b) (4)

Name/Address	FEI Number	DUNS Number	Inspection/ Waiver	Justification/ Results
(b) (4)				VAI
Release Testing (b) (4)	(b) (4)	(b) (4)	Waived	ORA (b) (4) NAI

The Division of Manufacturing and Product Quality (DMPQ) conducted a pre-license inspection (PLI) at Novo Nordisk, Inc., (b) (4), in (b) (4) and a Form FDA 483 was issued at the end of the inspection. The firm responded to the observations and the corrective actions were reviewed and found to be adequate. All inspectional issues were resolved and the inspection was classified as voluntary action indicated (VAI).

ORA performed a surveillance inspection of the Novo Nordisk (b) (4) facility in (b) (4). No Form FDA 483 was issued and the inspection was classified as No Action Indicated (NAI).

ORA conducted a surveillance inspection of the (b) (4) facility in (b) (4). No Form FDA 483 was issued and the inspection was classified as NAI.

ORA performed a surveillance inspection of the (b) (4) manufacturing facility in (b) (4) and a Form FDA 483 was issued at the end of the inspection. All inspectional issues were resolved and the inspection was classified as VAI.

ORA conducted a surveillance inspection of the (b) (4) facility in (b) (4). No Form FDA 483 was issued and the inspection was classified as NAI.

d) Environmental Assessment

The BLA included a request for categorical exclusion from an Environmental Assessment under 21 CFR 25.31(c). The FDA concluded that this request is justified as the manufacturing of this product does not alter significantly the concentration and distribution of naturally occurring substances, and no

extraordinary circumstances exist that would require an environmental assessment.

e) Product Comparability

No changes were made in the manufacturing process, facilities and equipment between DP lots used in the Phase 3 clinical studies and conformance lots.

CMC Recommendation

The manufacturing process for ESPEROCT is considered adequately validated and sufficiently controlled to assure consistent manufacture of the commercial product that meets release specifications. The manufacturing process provides sufficient margin of safety regarding adventitious agents. The reviewers from the Division of Plasma Protein Therapeutics, OTAT, and the Division of Manufacturing and Product Quality and the Division of Biological Standards and Quality Control, OCBQ, conclude that the Applicant has provided sufficient data and information on CMCs to support the licensure of ESPEROCT.

4. NONCLINICAL PHARMACOLOGY/TOXICOLOGY

In hemophilia A (HA) dogs, an ESPEROCT dose level of 125 IU/kg normalized prolonged whole blood clotting time (WBCT) and thromboelastogram (TEG) reaction time from greater than 40 minutes (mins) to within the normal range (5-12 mins) for canines. The return to baseline WBCT and TEG values was delayed for HA dogs administered ESPEROCT compared to NOVOEIGHT, suggesting a prolonged duration of activity for ESPEROCT. These findings were supported by additional pharmacology studies conducted in standard tail vein transection (TVT), tail clipping, joint bleed, saphenous vein and (b) (4)-induced bleeding models in HA mice.

Repeat administration of ESPEROCT once every 4th day in immunocompromised rats over 52 weeks followed by a 12-week recovery period did not result in notable toxicities at dose levels up to 1200 IU/kg. Immunohistochemical (IHC) staining did not indicate the presence of the PEG moiety in brain tissues, including the choroid plexus or brain blood vessels, of animals after 52 weeks of repeat administration of 1200 IU/kg of ESPEROCT. However, the lowest detection limit for IHC was not determined and the presence of PEG below this detection limit cannot be excluded. No dose-dependent test article related histopathological changes were noted in any tissues compared to control animals. The no-observed-adverse-effect-level (NOAEL) was established at 1200 IU/kg for ESPEROCT administered intravenously every 4th day. This dose level is approximately 20-fold higher than the proposed prophylactic clinical dose levels (50-60 IU/kg twice weekly).

Genotoxicity, carcinogenicity, and reproductive and developmental toxicity studies were not conducted with ESPEROCT. This is acceptable based on the product class and the absence of adverse histopathological findings in the reproductive organs in the toxicology studies.

5. CLINICAL PHARMACOLOGY

The Pharmacokinetics (PK) of a single intravenous dose of 50 IU/kg ESPEROCT were evaluated in adult and pediatric subjects with hemophilia A (factor FVIII activity (FVIII:C) < 1%). The age of adult subjects ranged from 20-60 years and the age of pediatric patients ranged from 1-11 years [stratified into two age groups (1-5 years and 6-11 years)]. The plasma samples were analyzed using the one-stage clotting assay. The clearance of ESPEROCT was 2-fold higher in children compared to adults (2.4 vs 1.2 mL/hour/kg). The half-life of ESPEROCT was approximately 15 hours in children and 22 hours in adults. The in vivo recovery was approximately 44% lower in children than adults. The PK of ESPEROCT were comparable between two pediatric age groups but were not comparable between adults and pediatrics.

6. CLINICAL/STATISTICAL/PHARMACOVIGILANCE

a) Clinical Program

To support the clinical indication in pediatric and adult patients with hemophilia A for routine prophylaxis, on-demand treatment, control of bleeding and perioperative management, the clinical development program included three open label studies to evaluate the safety and efficacy of ESPEROCT:

- Study 1 (Main Phase), and its extension study (Extension Phase 1 referred to subsequently as Extension study) for on-demand and routine prophylaxis in adults and adolescents (≥12 years of age).

- Study 2, for perioperative management in adults and adolescents (≥12 years of age) with severe hemophilia A.

- Study 3, for treatment of bleeding and routine prophylaxis in previously treated pediatric patients (<12 years of age) with severe hemophilia A.

An ongoing Extension Phase 2 study, similar with respect to dosing and population as the Study 1 Extension Phase 1, was submitted to the BLA. The efficacy data from this Extension Phase 2 study are not available and therefore are not included in the efficacy results in the label; however, the safety data from the Extension Phase 2 study are included in the Prescribing Information.

Study 1: this study comprised of a Main Phase and an Extension Phase.

Main Phase: the safety and efficacy of ESPEROCT were evaluated in 186 subjects, 161 adults (18 to 65 years old) and 25 adolescents (12 to 17 years old). During the Main Phase of the study, 175 subjects received the prophylaxis regimen of 50 IU of ESPEROCT dosed every 4 days (Q4D), while 12 adults chose to receive on-demand treatment. (One subject changed from on-demand to prophylaxis and is counted in both groups). In the Main Phase, twelve (7%) of 175 subjects on the prophylaxis arm modified their regimen to Q3-4D (i.e., twice weekly) for ease of use. The Q3-4D dosing allowed subjects to adhere to a regimen that related to specific days of the week; 3rd day of the week followed by the 7th day of the week. All subjects received at least one dose of ESPEROCT and were evaluable for safety and efficacy. A total of 165 (89%) of 186 subjects completed the Main Phase of the study; 11 (92%) of 12 subjects were in the on-demand arm and 155 (89%) of 175 subjects were in the prophylaxis arm. The co-primary endpoints in the Main Phase are the incidence rate of FVIII-inhibitor ≥ 0.6 Bethesda Units (BU) and annualized bleeding rate (ABR) for subjects receiving prophylaxis treatment.

- Routine Prophylaxis: A total of 105 (60%) of 175 subjects in the prophylaxis arm experienced bleeding episodes of which 69% were spontaneous bleeding events. The median annualized bleeding rate (ABR) for all bleeds was 1.20 (Interquartile Range (IQR): 0.00;4.73) and the mean ABR was 3.26 (SD: 4.92).

- On-demand and control of bleeding: Out of the 968 bleeding episodes that required treatment in 117 subjects, 964 bleeds were rated. Additional 26 bleeds that occurred in 23 subjects were not treated. Untreated bleeding events were not included in the analyses of on-demand bleeding outcomes. The treatment response was assessed as “good” or “excellent” in 88.4% of all bleeds (when counting the missed ratings as failure).

- Safety: One adolescent subject developed FVIII inhibitors which resulted in an estimated inhibitor rate of 0.6% and a one-sided 97.5% upper confidence limit for the inhibitor rate of 3.8%. As this is below the pre-specified limit of 6.8 %, this co-primary endpoint was met.

Extension Phase of Study 1: compared two dosing regimens: 75 IU/kg every 7 days (Q7D) and 50 IU/kg every 4 days (Q4D). The randomization was open to subjects who experienced two or fewer bleeds during the last 6 months in the Main Phase of the study. Of the 186 subjects in the Main Phase of the study, 150 subjects continued into the Extension Phase. Of the 150 subjects entering the Extension Phase, 143 had received Q4D regimen in the Main Phase and 7 had received the on-demand therapy. Of the remaining 120 subjects who met the randomization eligibility criteria, 65 subjects chose not to be randomized and continued on 50IU/kg Q4 day regimen and 55 (46%) subjects were therefore

randomized (2:1) to two dose regimens: 75 IU/kg Q7D (38 subjects) and 50 IU/kg Q4D (17 subjects), respectively.

Outcomes of Main and Extension Phases of Study 1

- Routine Prophylaxis: Of the 143 subjects receiving Q4D regimen in the Main Phase, 120 were eligible for randomization in the Extension Phase 1. However, 88 remained on Q4D regimen without being randomized (23 subjects were ineligible and 65 chose not to be randomized). The remaining 55 (46%) of 120 subjects eligible for randomization chose to be randomized. Randomization was 2:1 to 75 IU/kg Q7D (38 subjects) and 50 IU/kg Q4D (17 subjects), respectively. A total of 139 subjects (93%) completed Extension Phase 1. Nine (24%) of 38 subjects discontinued the Q7D regimen and reverted back to the Q4D regimen (eight subjects due to bleeding and one subject due to investigator's choice). One additional subject in the Q7D arm discontinued the Q7D regimen due to an adverse event.

The table below shows the ABR across the Main and Extension Phases of Study 1 for the Q4 and Q7 day regimens.

Table 5: Study 1: ABR rates for Routine Prophylaxis for Q4 Day and Q7 Day regimen

Bleeding Outcome	**Main Phase (n=175)**	**Extension Phase (n=143)**		
		Non-randomized (n=88)	**Randomized (n=55)**	
		Q4 Day	Q4 Day (n=17)	Q 7 Day (n=38)
Mean ABR (SD)	3.26 (4.92)	3.98 (5.28)	1.68 (2.34)	3.37 (6.19)
Median ABR (IQR)	1.20 (0.00; 4.73)	1.74 (0.57; 6.02)	0.00 (0.00; 2.23)	0.00 (0.00; 2.36)

Note that the mean ABR for the nine subjects who switched from Q7D to Q4D was 11.8 and the mean ABR for the remaining 29 subjects on Q7D was 0.7. The mean ABR for the 65 subjects eligible for randomization who chose not to proceed with the Q7D regimen was 1.14 (SD 2.42), the mean ABR for the 38 subjects who were randomized was 3.37 (SD 6.19) suggesting that bleeding rates increased considerably in the randomized group as a result of less frequent dosing. Although not a cross-over design for comparison, the "migration" in ABR rates in the 38 subjects as compared to the 65 subjects and the half-life of the product suggest that a Q7D regimen places subjects at increased risk of bleeding and forms the basis for not including the Q7D regimen as a dosing

recommendation for routine prophylaxis in the label. The mean ABR rate of 0.7 for the 29 subjects reflects bleeding rates that are based on further selecting subjects with high bleeding rates, and supports tailoring the prophylaxis regimen on an individualized basis and forms the basis for the dosing recommendation in the label that adjustment of doses above the dosing frequency of Q4 days may be reasonable. In addition, the Q3-4 D regimen is also considered reasonable and forms the basis for the labelling recommendation for adjustment of doses below the dosing frequency of Q4 days.

- On-demand and control of bleeding: Out of the 1436 bleeding episodes in the Main Phase and Ext 1 of the trial, 1420 bleeds were rated. The treatment response was assessed as "good" or "excellent" in 87.7% of all bleeds.

Study 2: This study evaluated the safety and efficacy of ESPEROCT in 33 previously treated adolescents and adults who underwent 45 major surgeries. The dose level of ESPEROCT was selected to target FVIII activity as per World Federation of Hemophilia (WFH) guidelines. All subjects returned to the adult/adolescent trial (Study 1) after the surgery trial assessments were completed. The procedures included 15 joint replacements, nine arthroscopic orthopedic interventions, 17 other orthopedic interventions, and 4 non-orthopedic surgeries. The hemostatic effect of ESPEROCT was rated as "excellent" or "good" in 43 of 45 surgeries (95.6%), while the effect was rated as "moderate" in two surgeries (4.4%).

Study 3: In this study, the safety and efficacy of ESPEROCT was evaluated in 68 pediatric subjects who were evenly divided into two age groups, 0–5 and 6–11 years of age. Although all subjects were to receive the same prophylaxis regimen of approximately 60 IU/kg (50–75 IU/kg) twice weekly, the majority of subjects received 65 IU/Kg twice weekly. A total of 63 subjects (93%) completed the Main Phase and were continuing treatment with ESPEROCT in the ongoing Extension Phase. The primary endpoint of the trial was the incidence of inhibitory antibodies against FVIII ≥0.6 BU during the Main Phase of the trial (from 0-26 weeks of treatment). No FVIII inhibitors were observed. The mean ABR was 3.87 (SD: 9.68) for the 0-5 age group and 2.29 (SD: 2.86) for the 6-11 age group. The median ABR was 1.95 (IQR: 0.00; 2.79) and was comparable between the two age-groups. Out of the 70 bleeding episodes, 67 bleeds were rated. The treatment response was assessed as "good" or "excellent" in 78.6% of all rated bleeds.

Summary of Efficacy:
The routine prophylaxis indication in pediatric and adult subjects and on-demand treatment indication in adults and adolescents is supported by the efficacy results provided below in Table 6.

The on-demand treatment indication in pediatric subjects is based on the "good" and "excellent" responses of 78.6% observed in the pediatric study (Study 3).

The efficacy results to support the peri-operative indication in adult and adolescent subjects is based on the good and excellent hemostatic response rates of 95.6%.
The efficacy results to support the peri-operative indication in pediatric subjects are based on extrapolation of the efficacy data for on-demand treatment in pediatric subjects and PK data to support a target factor level for major and minor surgeries.

Table 6: Summary of Efficacy for Prophylaxis and On-demand treatment in Studies 1 and 3 Main Parts

	Prophylaxis*			On-demand**
Age Range	**0-6 years**	**6-11 years**	**12–70 years**	**18–70 years**
# of subjects	**N=34**	**N=34**	**N=175**	**N=12**
Mean treatment duration (years)	0.46	0.51	0.82	1.33
Treated bleeds				
# of subjects (%)	19 (56)	20 (59)	105 (60)	12 (100)
# of subjects with 0 bleed (%)	15 (44)	14 (41)	70 (40)	0
# of bleeds	30	40	436	532
Median ABR (IQR)	1.94 (0.00;2.08)	1.97 (0.00;3.91)	1.18 (0.00;4.25)	30.87 (18.64;38.51)
Mean ABR (SD)	3.87 (9.68)	2.29 (2.86)	3.00 (4.66)	31.90 (19.08)
All bleeds (treated & non-treated)				
# of subjects (%)	20 (59)	26 (77)	107 (61)	12 (100)
# of subjects with 0 bleed (%)	14 (41)	8 (24)	68 (39)	0
# of bleeds	41	65	458	536
Median ABR (IQR)	1.97 (0.00;3.99)	2.02 (1.93;5.99)	1.20 (0.00;4.73)	31.25 (18.64;38.90)
Mean ABR (SD)	5.00 (11.85)	3.76 (3.59)	3.26 (4.92)	32.15 (19.12)

*Prophylaxis regimen was 50-75 IU/Kg twice weekly for the pediatric age group <12 and 50 IU/Kg Q4D for subjects ≥12 years of age.
**On-demand arm did not include any pediatric subject <18 years of age

Bioresearch Monitoring
Bioresearch Monitoring (BIMO) inspection assignments were issued for three foreign and two domestic clinical study sites that participated in the conduct of Study 1. The inspections did not reveal any issues that impact the integrity of the data submitted in this BLA.

b) Pediatrics

This submission triggers the Pediatric Research Equity Act (PREA) and the Pediatric Equity Research Committee (PeRC) meeting was held on September 19, 2018. The Applicant has completed efficacy and safety evaluation through pediatric studies across all age groups; 34 subjects 0-5 years and 34 subjects 6-11 years. No deferrals or waivers are warranted as the pediatric studies were already conducted.

c) Other Special Populations

No information is available on specific populations such as geriatric, pregnant, or nursing adults.

d) Pharmacovigilance

Novo has proposed the following pharmacovigilance activities:

- Routine Pharmacovigilance for:
  - Identified risks of inhibitor development and allergic/hypersensitivity reactions
  - Missing information in previously untreated patients (PUPs), patients with HIV with high viral load and low CD4 cell count, patients with history of FVIII inhibitors, patients with history of thromboembolic events, and patients on immune tolerance induction (ITI) regimen

- Immunogenicity follow-up questionnaire for:
  - Identified risk of inhibitor development
  - Missing information in patients with history of FVIII inhibitors

- Hypersensitivity follow-up questionnaire for:
  - Identified risk of allergic/hypersensitivity reactions

- Ongoing study (Trial 3908) for missing information in PUPs

Note that "missing information" in the context of pharmacovigilance typically refers to information about certain groups of patients who were excluded from the clinical trials (based on their exclusion criteria), or patients in whom adequate data on their experience with the product are not yet available.

Additionally, Novo is planning to conduct a post-authorization safety study required by the European Medicines Agency (EMA), but not the FDA, for the identified risks of inhibitor development and allergic/hypersensitivity reactions.

7. SAFETY

The safety of ESPEROCT was evaluated in a total of 270 previously treated patients (PTPs) with severe hemophilia A [206 adult and adolescent (12-17 years) and 64 pediatric subjects <12 years of age]. The safety dataset included all subjects who received at least one dose of ESPEROCT. There were no deaths related to ESPEROCT. One adult subject died of pancreatic cancer which was unlikely related to the study product. The most frequently reported adverse reactions were rash in 14 subjects (5.2%), injection site reaction in seven subjects (2.6%), erythema in five subjects (1.9%), and pruritus in four subjects (1.5%). No

anaphylactic allergic reactions were observed. One previously treated subject developed confirmed neutralizing antibodies to FVIII (13.5 Bethesda Units). Moreover, two subjects had transient low titer FVIII antibody (<5 Bethesda Units) test results at one occasion. Two additional subjects with pre-existing low titer FVIII inhibitors were considered late screen failures and were subsequently withdrawn from the trial. There were no drug-related serious adverse reactions other than FVIII inhibitor development and hypersensitivity reactions. Anti-PEG antibodies of no clinical consequence were detected in 45 subjects, 32 of whom had pre-existing anti-PEG antibodies. Pre-clinical studies do not raise concerns related to PEG accumulation in the brain or renal tissues that warrant additional clinical long-term monitoring. Nine subjects developed anti-CHO HCP antibodies with no clinical consequence. The risk of FVIII inhibitors and allergic reactions will be conveyed in the Prescribing Information.

8. ADVISORY COMMITTEE MEETING

An advisory committee meeting was not convened per FDAAA [HR 3580-138 SEC. 918: REFERRAL TO ADVISORY COMMITTEE] because the product is not the first in its class; the safety profile, particularly with regard to long-term PEG accumulation associated with pre-clinical findings from a similar class of products, is not a concern, considering the pre-clinical findings for this product; the design of the clinical studies is similar to studies conducted to support other approved products of this class; the review of the application did not raise significant safety concerns that could not be addressed through information in the label; consultative expertise was not required; and no public health concerns arose upon review of this file.

9. OTHER RELEVANT REGULATORY ISSUES

No major regulatory issues were identified. Review of financial disclosure forms did not raise any concerns regarding study conduct.

10. LABELING

a) Proprietary Name

The proposed proprietary name, ESPEROCT, was reviewed by the Advertising and Promotional Labeling Branch (APLB) on April 06, 2018, and was found acceptable. CBER communicated the acceptability of the proprietary name to the Applicant on April 11, 2018. The four-letter suffix to the proper name (-exei) was accepted by APLB on May 17, 2018.

b) Prescribing Information/Carton and Container Labels

The prescribing information and the product package and container labels were reviewed, commented, and/or revised by the appropriate discipline reviewers and by the APLB from a promotional and comprehension perspective.

11. RECOMMENDATIONS AND RISK/ BENEFIT ASSESSMENT

a) Recommended Regulatory Action

The CBER review committee recommends APPROVAL of this BLA for Antihemophilic Factor (Recombinant), GlycoPEGylated-exei under the proprietary name ESPEROCT. The manufacturing process for ESPEROCT is considered adequately validated and controlled. Efficacy and safety clinical data for ESPEROCT support a favorable benefit/risk determination for use in adults and children with hemophilia A for:

- On-demand treatment and control of bleeding episodes;
- Perioperative management of bleeding;
- Routine prophylaxis to reduce the frequency of bleeding episodes.

b) Risk/ Benefit Assessment

The benefits of ESPEROCT include:

- On-demand ESPEROCT is effective for treatment of and prevention of spontaneous or traumatic bleeding in adult and children patients with Hemophilia A
- ESPEROCT is effective in the perioperative setting for reduction of bleeding during surgery.

The risks of ESPEROCT include:

- FVIII inhibitory antibodies, which were noted in the studies. The risk of development of inhibitory antibodies is considered an expected adverse event.

Based on the review of the submitted data, ESPEROCT appears safe and efficacious in adults and children with hemophilia A for the three indications being sought (on demand treatment and control of bleeding episodes; perioperative management of bleeding; routine prophylaxis to reduce the frequency of bleeding episodes in adults and children with hemophilia A). The benefit-risk profile of ESPEROCT in adults and children of all age groups with hemophilia A is favorable.

c) Recommendation for Postmarketing Activities

No postmarketing requirement (PMR) or postmarketing commitment (PMC) studies are recommended.