

Mid-Cycle Meeting Agenda/Summary

Application type and number: BLA 125671
Product name: Antihemophilic Factor (Recombinant), GlycoPEGylated-exei
Proposed Indication: For use in adults and children with hemophilia A for: on-demand treatment and control of bleeding episodes; perioperative management; and routine prophylaxis
Applicant: Novo Nordisk, Inc.
Meeting date & time: July 27, 2018; 1:00 – 2:00 PM EST
Committee Chair: Andrey Sarafanov, PhD
RPM: Jean Dehdashti, MSc, RAC

Meeting Attendees:

Discipline	Name [with credentials (not title)]	Attended meeting?
Regulatory Project Manager (RPM)	Jean Dehdashti, MSc, RAC	Y
Chair / CMC Reviewer	Andrey Sarafanov, PhD	Y
Clinical Reviewer	Najat Bouchkouj, MD	Y
CMC Reviewer	1. Alexey Khrenov, PhD 2. Mikhail Ovanesov, PhD 3. Ze Peng, PhD 4. Yideng Liang 5. Mark Verdecia	N Y N Y Y
CMC Inspector	Andrey Sarafanov, PhD	Y
Animal Pharmacology / Toxicology Reviewer	Gaya Hettiarachi, PhD	Y
Clinical Pharmacology Reviewer	Iftexhar Mahmood, PhD	N
OCBQ/DMPQ RPM	Ekaterina Allen, PhD	Y
OCBQ/DMPQ Reviewer	Hector Carrero	Y
OCBQ/DMPQ/PRB Reviewer	Cheryl Hulme	Y
OCBQ/DMPQ/Lead Inspector	Hector Carrero	Y
Statistical Reviewer of clinical data	Lin Huo	Y
Postmarketing Safety Epidemiological Reviewer	Ohenewa Ahima, MD	Y
OCBQ/APLB Reviewer (Proprietary Name Review [PNR])	Oluchi Elekwachi, PharmD	N
OCBQ/APLB Reviewer (Labeling)	Kristine Khuc, PharmD	Y
OCBQ/BIMO Reviewer	Anthony Hawkins, M.S.	Y
OCBQ/DBSQC	1. Marie Anderson, PhD 2. Parmesh Dutt, PhD 3. Karla Garcia, M.S. 4. Jing Lin, PhD 5. Tao Pan, PhD 6. Charlene Wang, PhD	Y Y Y Y Y Y

Discipline	Name [with credentials (not title)]	Attended meeting?
CDER/OSE/OMEPRM/DMEPA (Usability Studies) Consult	1. Idalia Rychlik, PhD 2. Hina Mehta, PhD	N N
<u>Other Attendees:</u>		
OTAT	Rachael Anatol, PhD	N
OTAT	Kim Benton, PhD	Y
OCBQ/DBSQC	Suzanne Carter, PhD	Y
OCBQ/DIS	Dennis Cato	Y
OBE/DB	Wambui Chege, MD	Y
OTAT/DPPT	Mahmood Farshid, PhD	Y
OTAT/DCEPT	Bindu George, MD	Y
OTAT/DCEPT	Tejashri Purohit-Sheth, MD	N
OTAT/DCEPT	Ilan Irony, MD	Y
OTAT/DPPT	Tim Lee, PhD	N
OTAT/DPPT	Natalya Ananyeva, PhD	Y
OCBQ/DMPQ	Tony Lorenzo	Y
OCBQ/DIS	Carla Jordan	Y
OTAT/DCEPT	Iwen Wu, PhD	Y
OTAT/DCEPT	Lei Xu, MD	N
OBE/DB	Renee Rees, PhD	Y

Discussion Summary:

Review committee presented their findings, as summarized below under item 1, Reviewer reports. Deficiencies were identified by the product Office, OTAT/DPPT, regarding release specifications, potency standards, and stability studies release specifications for the final drug product (FDP). These issues will be communicated with the sponsor during the External Mid-Cycle Communication, scheduled for August 8, 2018.

Jing Lin, OCBQ/DBSQC, discussed with the team if there are any standards available with respect to host cell protein (HCP) impurities and antibody coverage. Jing Lin will follow-up with Alexey Khrenov, OTAT/DPPT, as he is a subject matter expert in this area and will be able to address Jing's questions. An information request (IR) may follow, depending on the outcome of this discussion; however, these issues were identified as not being substantive and will not be discussed during the External Mid-Cycle Communication with the sponsor.

Report and Discuss:

1. Reviewer Reports

- **Andrey Sarafanov, Mikhail Ovanesov, Ze Peng, Yideng Liang, Mark Verdecia (DPPT); Marie Anderson, Tao Pan, Parmesh Dutt, Karla Garcia, Jing Lin, Charlene Wang (DBSQC); Ekaterina Allen, Hector**

DPPT Reviewer Report Summary:

i. Substantive issues identified:

- Potency:

- a. *Potency Assay.* Potency of (b) (4) Final Drug Product (FDP) is determined by a chromogenic assay as described in the (b) (4) “Assay of Human Coagulation Factor VIII”. The Potency is expressed in international units (IU), which are traceable to the WHO FVIII International Standard. The Potency assay has been optimized to reduce variability during phase 3 clinical development (standardization of the (b) (4) of samples prior to analysis).
- b. *Release Specification.* The specification limits for FDP are set per (b) (4), within (b) (4) of the nominal potency. The specification limits must be re-established based on actual potency values.
- c. *Potency Standards.* A lyophilized primary reference material (PRM) has been established for analytical use to serve as reference for determination of Identity and as calibrator for assignment of Protein content and Potency to the secondary reference material (SRM). The Potency of PRM was determined by calibration against the (b) (4) WHO International Standard FVIII Concentrate (b) (4) using a chromogenic assay. The PRM and SRM were manufactured by the commercial process as a (b) (4) IU FDP batch. Three former SRMs were used in non-clinical and phase 3 clinical studies; however, potency standard bridging data were not provided.
- d. *Potency Assay discrepancies* were investigated in a field study assessing the activity of this product (N8-GP) and Advate in spiked hemophilia A plasma samples. Some aPTT reagents can underestimate the activity by as much as 60% or overestimate by 20%. Some chromogenic assay kits can underestimate the activity by as much as (b) (4) or overestimate by (b) (4). The range of assay discrepancies should be described in the PI text. PI should also specify that the proprietary product-specific potency standard was used to generate reported pharmacokinetics data.

- Stability:

- a. *For long-term storage of BDS, FDP and in-use stability of FDP, only partial data are currently available. The company committed to submit the updated data between August 27-November 27, 2018;*
- b. *The FDP appears stable during storage at +4 °C but not at +30°C which is proposed as storage condition for a 12-month period within the shelf-life. Significant changes were observed upon 12 months of storage in such parameters as (b) (4) (increase), (b) (4) (increase) and Purity (decrease) including (b) (4) (increase). The stability specifications for these parameters are not supported by the provided release and stability data.*

The worst-case stability data were not provided to support the claim that “the FDP may be kept at or below 30°C for a single period up to 12 months”. The worst-case conditions should be 12 months of storage at +30°C followed by 18 months of storage at +5°C. Instead, Novo Nordisk provided data for 18 months of storage at +5°C followed by 12 months of storage +24°C (representing the best-case stability conditions).

Nominal potency values are incorrectly used as stability specifications. Stability specification for Potency should be set as the range (b) (4) of the actual Potency value at release.

- c. *For (b) (4), the trends we observed for (b) (4) (increase) and Potency/(b) (4) (increase). Most likely, the Potency assay is not suitable for Stability study.*
- ii. Date the primary discipline review will be complete: October 1, 2018, this will be also depended on availability of updates for Stability study.

DMPQ Reviewer Report Summary:

- i. No substantive issues have been identified by DMPQ. The pre-license inspection (PLI) is scheduled for (b) (4).
- ii. Date the primary discipline review will be complete: Projected for end of November 2018, however, this is dependent on the PLI findings.

DBSQC Reviewer Report Summary:

- i. No substantive issues identified to date. Update from DBSQC reviewers provided below.
 - Marie Anderson: A draft of the CBER Laboratory Quality Product Testing Plan (TP) has been written and routed for review. Comments due by COB Thursday, 19 Jul 2018.

- Tao Pan: All the lot release assays (chemistry), for both (b) (4) drug product have completely reviewed, except the (b) (4) assay for purity and identity with information request (IR) pending.
 - The following IRs were sent on 06/01/2018, response due July 27, 2018: 1) Request for SOP for visual inspection method; 2) Request validation data for (b) (4) for purity etc.
 - The following IR was sent on 07/07/2018, response due July 20, 2018: 1) Request for SOP for the determination of particulate matter.
 - Parmesh Dutt: In support testing for the drug product samples have been completed and sent for review by Team Lead and Branch Chief. Review of Method validation report not completely reviewed to date. Final review memo is expected to be completed by September 30, 2018. PD - 07/25/2018.
 - Karla Garcia: All assigned sections have been reviewed. IRs will be sent out by July 25, 2018.
 - Charlene Wang: All SOPs' and method validation issues are expected to be resolved through IR.
 - Response of pending IR (sent on 06/13/2018) is expected by 7/27/2018. Issue: Protein Content and (b) (4) validation issue for LOQ.
 - Jing Lin: No key findings and substantive issues were found
- ii. Date the primary discipline review will be complete:
- Marie Anderson: Not applicable.
 - Tao Pan: The primary discipline review (PDR) has been completed, except the response to the IRs.
 - Parmesh Dutt: PDR will be completed by September 30, 2018
 - Karla Garcia: Estimated completion date – November 5, 2018
 - Charlene Wang: Not applicable.
 - Jing Lin: October 03, 2018.

CDER Consult Reviewer Report Summary:

- i. No substantive issues identified. The CDER Division of Medication Error Prevention and Analysis has completed their review of the Summative Usability Test Report, Differentiation Tasks, and Human Factors Validation Test Conclusive Report, and has determined that the sponsor submitted Human Factors validation studies are acceptable.
 - ii. Date the consult review will be complete: Consult review completed on July 24, 2018.
- **Gaya Hettiarachi, CBER/OTAT/DCEPT – Animal Pharmacology / Toxicology**

i. No substantive issues identified.

- Key Finding: In (b) (4) rats who were administered N8-GP for 52 weeks at a dose level of 1200 IU/kg/dose every 4th day
 - PEG was not detected in brain tissue (including the choroid plexus) as measured using immunohistochemistry (Study #213109).
 - PEG concentrations were around or below the lower limit of quantification (b) (4) in plasma as measured using (b) (4) (Study #301333)
 - PEG concentrations were below the lower limit of quantification (b) (4) in cerebrospinal fluid as measured using (b) (4) (Study #301333)

ii. Date the primary discipline review will be complete: Review and memo will be completed and submitted to Branch Chief no later than November 1, 2018. The memo will be submitted to Division Director no later than December 1st, 2018.

• **Najat Bouchkouj, CBER/OTAT/DCEPT – Clinical**

i. No major issues have been identified to date. Review is ongoing. The following haven't been reviewed yet: In-depth review of CRFs; evaluation of control of bleeding, integrated summaries of efficacy and safety, PK and PUPs studies.

The following trials (3859, 3860, and 3885), in previously treated patients, have been reviewed and the primary results are as follows:

Trial 3859 (Pivotal trial, 186 subjects, 12-66 years old):

Both co-primary endpoints were met and were verified:

- Annualized bleeding rate for subjects receiving prophylaxis treatment: Based on observed bleeds: subjects on q3-4D prophylaxis during the pivotal part had a median ABR of 1.18. When subjects were randomized to either q4D or q7D prophylaxis in extension phase part 1, the median ABR was 0.00 for both regimens. When ABRs were calculated for patients on q3-4D or q7D up to the data cut-off for extension phase part 2, median ABRs were 0.85 and 1.82, respectively.
- The incidence rate of FVIII-inhibitors ≥ 0.6 BU: One subject (b) (4) 18 yo) developed FVIII inhibitors after 93 exposure days (ED), which results in an estimated inhibitor rate of 0.5%.
- Most frequent adverse reactions (Incidence $\geq 1\%$) included: Upper respiratory tract infections, elevated liver enzymes, rash, pruritis, headache, and arthralgia. Hypersensitivity (3 reactions in 2 subjects). One death occurred in a 67 y o subject with metastatic pancreatic carcinoma which is unlikely related to N8-GP. Total of 6 subjects were withdrawn from the trial due to AEs. No thromboembolic events were reported.

Trial 3860 (Surgery trial, 33 subjects with 45 surgeries, 15-69 years old): The primary endpoint was hemostatic effect during surgery.

- The hemostatic effect of N8-GP was rated as 'excellent' in 22 (48.9%) and as 'good' in 21 (46.7%) of the surgeries, giving a success rate of 95.6%. Two surgeries (4%) had the effect rated as 'moderate'.

Trial 3885 (Pediatric trial, 68 subjects, 1-11 years old): The primary endpoint was the incidence rate of FVIII-inhibitors ≥ 0.6 BU.

- No confirmed FVIII inhibitors developed during the trial.

Trial 3776 (PK trial, 26 subjects, 20-60 years old): Not reviewed.

Trial 4033 (Comparability study for PK and safety, 21 subjects, 25-71 years old): Not reviewed.

Trial 3908 (Previously untreated patients, 32 subjects, <6 years old): Not reviewed.

ii. Date the primary discipline review will be complete: December 2018.

- **Iftekhar Mahmood, CBER/OTAT/DCEPT – Clinical Pharmacology**

i. No substantive issues identified thus far and review is ongoing.

ii. Date the primary discipline review will be complete: December 2018.

- **Lin Huo, CBER/OBE/DB – Biostatistics**

i. No major issues identified thus far. Three trials (3859, 3860, and 3885) have been reviewed and the primary efficacy results are as follows:

- **Trial 3859 (Pivotal trial, 186 subjects, 12-66 years old).** Both co-primary endpoints were met.
 - The incidence rate of FVIII-inhibitors ≥ 0.6 BU. One out of 172 subjects at risk developed FVIII inhibitors, which results in an estimated inhibitor rate of 0.6% and a one-sided 97.5% upper confidence limit of 3.7% (below the pre-specified limit of 6.8%).
 - Annualized bleeding rate for patients receiving prophylaxis treatment. Based on observed bleeds: subjects on q3-4D prophylaxis during the pivotal part had a median ABR of 1.18. When patients were randomized to either q4D or q7D prophylaxis in extension phase part 1, the median ABR was 0.00 for both regimens. When ABRs were calculated for patients on q3-4D or q7D up to the data cut-off for extension phase part 2, median ABRs were 0.85 and 1.82, respectively.
- **Trial 3860 (Surgery trial, 33 subjects with 45 surgeries, 15-69 years old).** The primary endpoint was hemostatic effect during surgery.

The hemostatic effect of N8-GP was rated as ‘excellent’ in 22 (48.9%) and as ‘good’ in 21 (46.7%) of the surgeries, giving a success rate of 95.6%. Two surgeries (4%) had the effect rated as ‘moderate’.

- **Trial 3885 (Pediatric trial, 68 subjects, 1-11 years old).** The primary endpoint was the incidence rate of FVIII-inhibitors ≥ 0.6 BU. No confirmed FVIII inhibitors developed during the trial.

ii. Date the primary discipline review will be complete: December 2018.

- **Ohenewa Ahima, CBER/OBE/DE – Postmarketing Safety Epidemiological**

- i. No substantive review issues or major deficiencies that would require a PMR or REMS have been identified to date. The Sponsor has proposed a non-interventional post-authorization safety study (PASS) based on EU regulatory requirements; the proposal is currently under review.

ii. Date the primary discipline review will be complete: October 3, 2018

- **Anthony Hawkins, CBER/OCBQ/DIS – BIMO**

- i. No BIMO findings or substantive items to report at this time.

Pending: Receipt and review of three foreign and two U.S. clinical investigator site inspection reports, each covering clinical study protocol NN7088-3859; the CBER requested completion dates for the inspections are listed below.

Clinical Study Site for Inspection	CBER requested inspection completion date	Status of Inspection
KD Haemophilia Centre & Thrombosis Unit - London, Great Britain	09/04/2018	Inspection pending
Oxford Haemophilia Centre - Oxford, Great Britain	09/04/2018	Inspection pending
Centre for Haemophilia, Haemostasis and Thrombosis - Basingstoke, Great Britain	09/04/2018	Inspection pending
Children's Hospitals and Clinics of Minnesota - Minneapolis, Minnesota	08/31/2018	Inspection pending
Vanderbilt Clinical Trials Center - Nashville, Tennessee	08/31/2018	Inspection pending

- ii. Date the primary discipline review will be complete: The target timeframe for BIMO review of each of the above inspections is 30 days after CBER receipt of the completed inspection report (EIR package).

- **Jean Dehdashti, CBER/OTAT/DRPM – RPM (NDC Review)**
 - i. No substantive issues identified. The National Drug Codes (NDCs), barcodes, carton and container (bottle) labels, as per as per FDA/CBER draft job aid, *JA 900.08: National Drug Code and Bar code Labeling Review*, are acceptable.
 - ii. Date the primary discipline review will be complete: A review memo will be completed, including review of consistency of the Prescribing Information (PI), by January 28, 2019.
- 2. If the application will be discussed at an Advisory Committee (AC), review potential issues for presentation.
 - BLA 125671/0 has not and will not be discussed at an Advisory Committee (AC).
- 3. Determine whether Postmarketing Requirements (PMRs), Postmarketing Commitments (PMCs), or a Risk Evaluation Mitigation Strategy (REMS) are needed.
 - No substantive review issues or major deficiencies that would require a PMR or REMS have been identified to date. The Sponsor has proposed a non-interventional post-authorization safety study (PASS) based on EU regulatory requirements; the proposal is currently under review.
- 4. National Drug Code (NDC) assignments to product/packaging (excludes devices).
 - The National Drug Code (NDC) assignments, outlined in the table below, to the product presentations for the ESPEROCT drug product vial, kit components, and carton packaging are in compliance with NDC labeling requirements for all three NDC segments, as per FDA/CBER draft job aid, *JA 900.08: National Drug Code and Bar code Labeling Review*.

Presentation (Nominal Product Strength)	Carton NDC Numbers	Components
500 IU	NDC 0169 8500 01	ESPEROCT in single-use vial [NDC 0169 850111]; Pre-filled sterile saline diluent in syringe, 4 mL [NDC 0169 8008 98]; Vial adapter
1000 IU	NDC 0169 8100 01	ESPEROCT in single-use vial [NDC 0169 8101 11]; Pre-filled sterile saline diluent in syringe, 4 mL [NDC 0169 8008 98]; Vial adapter
1500 IU	NDC 0169 8150 01	ESPEROCT in single-use vial [NDC 0169 8151 11]; Pre-filled sterile saline diluent in syringe, 4 mL [NDC 0169 8008 98]; Vial adapter
2000 IU	NDC 0169 8200 01	ESPEROCT in single-use vial [NDC 0169 8201 11]; Pre-filled sterile saline diluent in syringe, 4 mL [NDC 0169 8008 98]; Vial adapter
3000 IU	NDC 0169 8300 01	ESPEROCT in single-use vial [NDC 0169 8301 11]; Pre-filled sterile saline diluent in syringe, 4 mL [NDC 0169 8008 98]; Vial adapter

5. Proper naming convention.

- Novo Nordisk has used the proper naming convention, Antihemophilic Factor (Recombinant), GlycoPEGylated, for this product throughout the BLA 125671/0 application. On May 17, 2018, FDA issued approval of sponsor proposed 4-letter suffix “exei”, therefore, the revised proper naming convention for this product is Antihemophilic Factor (Recombinant), GlycoPEGylated-exei

6. Status of inspections (GMP, BiMo, GLP) including issues identified that could prevent approval and the establishment inspection report (EIR).

- Manufacturing Facility: A PLI for the manufacturing of Antihemophilic Factor (Recombinant), GlycoPEGylated [ESPEROCT], drug product at Novo Nordisk facility in (b) (4), is scheduled to take place (b) (4). An inspection waiver for a PLI has been submitted for the manufacturing facilities listed in the table below:

Location	Activity	Most Recent Inspection
Novo Nordisk A/S (b) (4)	<ul style="list-style-type: none"> Manufacture of the Drug Product (formulation, filling and lyophilization) Final release testing (microbiological sterility, endotoxin) 	CDER (b) (4) Surveillance NAI
Novo Nordisk A/S (b) (4)	<ul style="list-style-type: none"> Final release testing (microbiological test) 	CDER (b) (4) Surveillance NAI

Location	Activity	Most Recent Inspection
(b) (4)	<ul style="list-style-type: none"> (b) (4) 	ORA (b) (4) Surveillance VAI
(b) (4)	<ul style="list-style-type: none"> Final release testing (microbiological test) 	CDER (b) (4) Surveillance VAI
(b) (4)	<ul style="list-style-type: none"> Final release testing (microbiological test) 	CDER (b) (4) Surveillance VAI

- Clinical Sites: BIOMO has issued review of three foreign and two U.S. clinical investigator site inspection reports, each covering clinical study protocol NN7088-3859; please see below.

Clinical Study Site for Inspection	CBER requested inspection completion date	Status of Inspection
KD Haemophilia Centre & Thrombosis Unit - London, Great Britain	09/04/2018	Inspection pending
Oxford Haemophilia Centre - Oxford, Great Britain	09/04/2018	Inspection pending
Centre for Haemophilia, Haemostasis and Thrombosis - Basingstoke, Great Britain	09/04/2018	Inspection pending
Children's Hospitals and Clinics of Minnesota - Minneapolis, Minnesota	08/31/2018	Inspection pending
Vanderbilt Clinical Trials Center - Nashville, Tennessee	08/31/2018	Inspection pending

Review Agenda Items

- Major target and milestone dates from RMS/BLA. Discuss pending dates of targets and milestones (e.g. Late-Cycle meeting, Advisory Committee, labeling discussion).
 - INTERNAL Mid-Cycle Meeting – July 27, 2018; 1 – 2 PM EST
 - EXTERNAL Mid-Cycle Communication (Teleconference)– August 8, 2018; 3 – 4 PM EST**
 - PLI – Week of August 20, 2018
 - PeRC Meeting – September 19, 2018, 9:00 – 12:00 PM (exact time-slot TBD one week prior to scheduled meeting).
 - INTERNAL Late-Cycle Meeting – November 2, 2018; 3 – 4 PM EST

- **EXTERNAL Late-Cycle Communication (Face-to-Face) – November 29, 2018; 3 – 4 PM EST**
- Weekly Labeling Meetings – Initiated 2 months prior to FDA reviewed draft package insert (PI) is sent to sponsor (projected goal date – January 15, 2018)
- PMC target date communication to RPM and PMC review committee of January 11, 2019
- **Target due date – February 15, 2019**
- **PDUFA Action Due Date – February 27, 2019**
- Post-approval de-briefing – April 12, 2019; 2 – 3 PM EST

Review schedule:

BLA Standard 12 Month Review	
STN: BLA 125671/0	
Applicant: Novo Nordisk	
Product: Antihemophilic Factor (Recombinant), GlycoPEGylated	
Short Summary: Original BLA for Antihemophilic Factor (Recombinant), GlycoPEGylated for use in adults and children with hemophilia A for: On-demand treatment and control of bleeding episodes; perioperative management of bleeding; and routine prophylaxis to reduce the frequency of bleeding episodes	
RPM: Jean Dehdashti	
Chairperson: Andrey Sarafanov	
Review Schedule	Target Date
DCC Receipt Date	Feb 27, 2018
Complete regulatory filing review; Assign review committee	Mar 9, 2018
Acknowledge receipt; Establish review schedule	Mar 13, 2018
First Committee Meeting	Mar 20, 2018
30 Day Late Components Due	Mar 29, 2018
AOM and Dataset	Apr 11, 2018
Walk-through	
Filing Meeting	Apr 13, 2018
Send Filing Determination Letter	Apr 27, 2018
Deficiencies Identified Letter	N/A
Proprietary Name Review	April 11, 2018
Request initial labeling review	Jul 30, 2018
INTERNAL Mid-Cycle Review Meeting	July 27, 2018
EXTERNAL Mid-Cycle Communication with Applicant	Aug 8, 2018
Send Information Requests as needed	
PeRC Meeting	Sep 19, 2018
Complete Discipline Reviews (Primary)	Oct 3, 2018
Complete Discipline Reviews (Secondary Review)	Oct 17, 2018
Send Discipline Review Letters as completed	Oct 30, 2018
INTERNAL Late-Cycle Meeting (Internal)	Nov 2, 2018
EXTERNAL Late-Cycle Meeting	November 29, 2018

Promotional labeling review (APLB)	Nov 29, 2018
Complete inspection reports	Dec 28, 2018
Circulate draft press release	Jan 28, 2019
Complete PMC Study, Labeling Review, Review Addenda	Jan 28, 2019
Complete Supervisory Review	Jan 28, 2019
Request Compliance Check, Lot Release Clearance	Feb 13, 2019
Send Press Release to OCOD	Feb 13, 2019
T-minus date	Feb 13, 2019
Send FDA Action Letter	Feb 27, 2019
Post-Action Debrief Meeting	Apr 12, 2019

8. Establish a labeling review plan and agree on future labeling meeting activities.

- Weekly Labeling Meetings – Initiated 2 months prior to FDA reviewed draft package insert (PI) is sent to sponsor (projected goal date – January 15, 2018)
 - *December 7, 2018 – First labeling meeting for all review committee members*
 - *December 14, 2018 – Sections and meeting required attendees to be determined*
 - *December 21, 2018 – Sections and meeting required attendees to be determined*
 - *December 28, 2018 – Sections and meeting required attendees to be determined*
 - *January 4, 2018 – Sections and meeting required attendees to be determined*
 - *January 11, 2018 – Sections and meeting required attendees to be determined*
 - *January 18, 2018 – Sections and meeting required attendees to be determined*
 - *January 25, 2018 – Sections and meeting required attendees to be determined*

9. Reminder to team that BLA 125671/0 is managed in eMRP, and that it is critical for all assigned committee members to complete assigned tasks in eMRP in the allocated timeframe to avoid any bottlenecks or issues in managing this submission.

10. Components Information Table was obtained and notification was sent to the Data Abstraction Team (DAT) if discrepancies were found per *SOPP 8401.5: Processing Animal, Biological, Chemical Component Information Submitted in Marketing Applications and Supplements*. If not complete, indicate date it will be completed.

- Notification sent on March 9, 2018, to CBER Data Abstraction Team (DAT) regarding processing of the animal, biological, and chemical component (ABC) information Submitted in BLA 125671/0.

11. New facility information is included in the application, requiring implementation of regulatory job aid (b) (4) [REDACTED]. If not complete, indicate date it will be completed.

- The new facility information, located in (b) (4) [REDACTED], responsible for the manufacturing of the drug substance, has been submitted and reviewed by DMPQ. The new facility information will be conformed post PLI.

12. Status of decisions regarding lot release requirements, such as submitting samples and test protocols and the lot release testing plan.

- Under the provision described in Federal Register (FR) 58:38771-38773 and the 60 FR 63048-63049 publication (8 December 1995), routine lot-to-lot release by CBER is not required for Antihemophilic Factor (Recombinant), GlycoPEGylated-exei [ESPEROCT], because it is a well-characterized recombinant product. Thus, exemption of ESPEROCT from CBER Lot Release is justified.

13. Unique ingredient identifier (UNII) code process has been initiated. See regulatory job aid (b) (4) for additional information.

- UNII code process initiated on March 9, 2018, and the UNII for Turoctocog alfa pegol is 9Y9727LS4D.

14. PeRC presentation date is set, and the clinical reviewer is currently in the process of reviewing all applicable BLA information for assessment of the PREA decision.

- The product is scheduled to go to PeRC on September 19, 2018, and in preparation for the meeting, the PeRC forms were sent no later than September 04, 2018.

15. Action Items:

- Jing Lin, OCBQ/DBSQC, will follow-up with Alexey Khrenov, OTAT/DPPT, to discuss the availability of standards for host cell protein (HCP) impurities and antibody coverage assays.

16. For applications subject to the PDUFA/BsUFA Programs:

a. Reach agreement on information to be included in the Mid-Cycle Communication telecon with the Applicant (see section below).

b. Dates for upcoming meetings:

- EXTERNAL Mid-Cycle Communication (Teleconference)– August 8, 2018; 3 – 4 PM EST
 - Chair, RPM, all assigned CMC committee members from OTAT/DPPT, and Clinical.
 - Agenda will be sent to sponsor 48 hours in advance of our scheduled call, preferably by Friday, August 03, 2018.

- INTERNAL Late-Cycle Meeting – November 2, 2018; 3 – 4 PM EST
- EXTERNAL Late-Cycle Communication (Face-to-Face) – November 29, 2018; 3 – 4 PM EST

Mid-Cycle Communication Agenda/Summary

1. Any significant issues/major deficiencies identified by the Review Committee to date.
 - Deficiencies identified regarding release specifications, potency standards, and stability studies.
2. Information regarding major safety concerns.
 - No major safety concerns identified thus far.
3. Preliminary Review Committee thinking regarding risk management.
 - Review committee has not identified the need for risk management thus far.
4. Any information requests sent and responses not received.
 - Division of Biostatistics (DB) information request (IR), issued on July 13, 2018, with a response due by August 03, 2018, regarding description used to obtain outputs in the draft package insert (PI), and remaining SAS analysis programs.
 - Division of Biological Standards and Quality Control (DBSQC) IR, issued on July 24, 2018, with a response due date of August 07, 2018, regarding additional information on the bacterial endotoxin and sterility qualification studies, as well as environmental monitoring results from the manufacturing facility.
 - Division of Clinical Evaluation and Pharmacology/Toxicology (DCEPT) IR, issued on July 31, 2018, with a response due date of August 09, 2018, regarding detailed information on subjects who were randomized to receive the Q3-4 D versus Q7D dosing.
5. Any new IRs to be communicated.
 - IRs regarding release specifications, potency standards and stability studies will be submitted after the teleconference.

6. Scheduled date for the Late-Cycle Meeting (LMC) and the LMC Materials:
 - The LCM between you and the review committee is currently scheduled for November 29, 2018, from 3 – 4 PM ET.
 - We intend to send the LCM meeting materials to you approximately 5 business days in advance of the LCM.
 - If this timeline changes, we will communicate updates to you.
7. Other projected milestone dates for the remainder of the review cycle, including changes to previously communicated dates.
 - PMC study target date of January 28, 2019
 - Labeling target date of January 28, 2019