

Late-Cycle Internal Meeting 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.
Date of LCM with Applicant: Thursday, November 29, 2018
Committee Chair: Andrey Sarafanov, PhD
RPM: Jean Dehdashti, MSc, RAC

Meeting Attendees:

Discipline/Organization	Name
Regulatory Project Manager (RPM)	Jean Dehdashti, MSc, RAC
Chair / CMC Reviewer	Andrey Sarafanov, PhD
Clinical Reviewer	Najat Bouchkouj, MD
CMC Reviewers	1. Alexey Khrenov, PhD 2. Mikhail Ovanesov, PhD 3. Ze Peng, PhD 4. Yideng Liang, PhD 5. Mark Verdecia, PhD
CMC Inspector	Andrey Sarafanov, PhD
Animal Pharmacology / Toxicology Reviewer	Gaya Hettiarachi, PhD
Clinical Pharmacology Reviewer	Iftekhar Mahmood, PhD
OCBQ/DMPQ RPM	Ekaterina Allen, PhD
OCBQ/DMPQ Reviewer	Hector Carrero
OCBQ/DMPQ/PRB Reviewer	Cheryl Hulme
OCBQ/DMPQ/Lead Inspector	Hector Carrero
Statistical Reviewer of clinical data	Lin Huo
Postmarketing Safety Epidemiological Reviewer	Ohenewa Ahima, MD
OCBQ/APLB Reviewer (Proprietary Name Review [PNR])	Oluchi Elekwachi, PharmD
OCBQ/APLB Reviewer (Labeling)	Kristine Khuc, PharmD
OCBQ/BIMO Reviewer	Anthony Hawkins, M.S.
OCBQ/DBSQC Reviewers	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

Discipline/Organization	Name
<u>Other Attendees:</u>	
OTAT/DRPM	Ebla Ali Ibrahim, MS
OTAT/DPPT	Natalya Ananyeva, PhD
OBE	Deepa Arya, MD
OTAT	Kim Benton, PhD
OTAT	Wislon W. Bryan, MD
OCBQ/DBSQC	Suzanne Carter, PhD
OCBQ/DIS	Dennis Cato
OBE/DB	Wambui Chege, MD
OTAT/DPPT	Mahmood Farshid, PhD
OTAT/DCEPT	Bindu George, MD
OTAT/DPPT	Basil Golding, MD, PhD
OCBQ/DIS	Carla Jordan
OTAT/DPPT	Tim Lee, PhD
OCBQ/DMPQ	Tony Lorenzo
OTAT/DCEPT	Tejashri Purohit-Sheth, MD
OBE/DB	Renee Rees, PhD
OTAT/DRPM	Ramani Sista, PhD
OTAT/DCEPT	Iwen Wu, PhD

Late–cycle internal meeting agenda:

1. Short summary of the submission. [Chair]

ESPEROCT is a purified recombinant human factor VIII (rFVIII) product with a 40 kDa polyethylene glycol (PEG) conjugated to the protein, with the 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.

The PEG is attached to the O-linked glycan in the truncated B-domain of rFVIII. The molecular mass of the ESPEROCT protein part is 166 kDa. The molecule consists of a heavy chain of (b) (4) and a light chain of (b) (4) held together by non-covalent interactions. The molecular mass of turoctocog alfa pegol is (b) (4) including post-translational modifications and the PEG moiety.

The drug product is a sterile lyophilised powder for solution for injection for intravenous use (single-use by intravenous bolus injection) and is manufactured in five product strengths:

- 500 IU/vial

- 1000 IU/vial
- 1500 IU/vial
- 2000 IU/vial
- 3000 IU/vial

ESPEROCT mode of action is based on the replacement of the deficient or absent FVIII in patients with haemophilia A. When ESPEROCT is activated by thrombin at the site of injury, the pegylated truncated B-domain is cleaved off, generating activated FVIII (FVIIIa), which is similar in structure to native FVIIIa. Activated rFVIII acts as a cofactor for activated factor IX (FIX) on the surface of activated platelets, and the complex catalyses the activation of factor X. By adding FVIII, the coagulation cascade can run uninterrupted ensuring that the end product, (b) (4). PEGylation increases the half-life of the protein.

2. Substantive issues raised during review.

a. **Andrey Sarafanov, Mikhail Ovanesov, Alexey Khrenov, Ze Peng, Yideng Liang, Mark Verdecia (CMC – CBER/OTAT/DPPT)**

i. Substantive issues to report:

DPPT CMC reviewers have identified no substantive issues that could prevent approval of this submission. For the remaining issues, stated below, no impact on the review timeline is expected.

1. Potency of Factor VIII (FVIII) used for product labeling is assigned based on chromogenic assay, while one-stage clotting assay is used in clinical analysis of patient plasma samples. However, discrepancies in results between these two assays, depending on analytical set-up, were observed. The results may overestimate or underestimate the FVIII activity up to 60% depending on reagents and kits used. This should be addressed in the PI as described in section 4, Plan for addressing remaining CMC issues. (Mikhail Ovanesov)
2. (a) Some Drug Substance (DS) and Drug Product (DP) specification parameters are not sufficiently justified. Approach to justify specifications is based on using (b) (4), which is not always appropriate. Also, the data from clinical processes are included in the data pool used to establish acceptance criteria, whereas commercial process demonstrates significantly higher consistency for some parameters. For some acceptance criteria (e.g. Reconstitution Time), no data and/or justification are provided.

(b) Acceptance criteria for control of glycosylation are inadequate. Specifically, the analytical procedure results in the (b) (4), but the number and magnitude of (b) (4) are not monitored. Instead, only the (b) (4) is

used as acceptance criterion. Since glycosylation (b) (4), it is recommended to develop the acceptance criteria allowing for a better monitoring of glycosylation consistency and detection of changes in the product glycosylation. (Alexey Khrenov)

3. (a) All updated stability data for DS were received including the primary stability batches, supportive stability batches, and the process performance qualification (PPQ) batches. The updated stability study data for DP have not been received. Novo Nordisk will provide these data in November 2018, as committed previously.

(b) (4)

4. There is no international reference standard for turoctocog alfa pegol; therefore, two standards were established: primary reference material (PRM) and secondary reference material (SRM): PRM is stored at (b) (4) and is given an initial shelf life of (b) (4). Although Novo Nordisk claimed that no trend over time was observed for any tested parameter, potency data show a small (b) (4) after storage for (b) (4). (Mark Verdecia)
5. All information requests from the Mid-Cycle regarding viral clearance studies have been adequately addressed.

ii. Review Update:

1. Review has not been completed to date for select sections of Module 3, sections 3.2.P (Drug Product) and 3.2.P. (Solvent) (Andrey Sarafanov).
2. An information request (IR) was issued on October 12, 2018 regarding justification of specifications. Novo Nordisk committed to provide requested information regarding the DS and DP specifications by November 2, 2018, and requested an extension until that date (original date for response was October 26, 2018). For (b) (4) method validation and procedure, Novo

Nordisk anticipates submission date to be in December 2018. More precise date will be given in response to the October 12 IR, due on November 2 , 2018. (Alexey Khrenov)

iii. Discipline Review Completion:

1. Review completed. (Ze Peng, Alexey Khrenov, Mark Verdecia)
2. Review not completed. (Yiedeng Liang and Andrey Sarafanov)

b. Marie Anderson, Tao Pan, Parmesh Dutt, Karla Garcia, Jing Lin, Charlene Wang (CMC – CBER/OCBQ/DBSQC)

i. Substantive issues to report:

DBSQC CMC has identified no substantial issues that could prevent approval of this submission

ii. Review Update:

1. Routing the CBER Laboratory Quality Product Testing Plan (TP) for review and approval. (Marie Anderson)
2. IRs regarding one-stage and chromogenic assays for the accuracy study, issued September 20, 2018, and October 16, 2018, have not been addressed completely. Applicant has agreed to submit full response by November 26, 2018, or earlier when possible, where they have agreed to include (b) (4) lots of (b) (4) and (b) (4) lots (different than reference standard) of DP, in addition to the reference standard, in both the one-stage and chromogenic assays for the accuracy study. (Parmesh Dutt)
3. A second round of information requests were sent on September 7, regarding the following methods: i) the identity/purity by (b) (4) ; (b) (4)) Methionine by I(b) (4) ; iv) Polysorbate 80 by (b) (4) ; and v) Calcium (b) (4) . Responses have been provided regarding all the other methods except the (b) (4) , the applicant indicated that the requested data would be provided no later than December 19, 2018. (Tao Pan)

iii. Discipline Review Completion:

1. Review memo completed October 30, 2018. (Jing Lin)
2. Review memo will be completed November 7, 2018. (Parmesh Dutt)
3. The PDR review has been completed except the response to the IRs related to the (b) (4) method, where applicant will provide a response in December 2018. (Tao Pan)
4. The primary discipline review has been completed and the draft review memo will be under supervisory review in the next few weeks. (Karla Garcia)

c. Ekaterina Allen, Hector Carrero, Cheryl Hulme (CMC – CBER/OCBQ/DMPQ)

i. Substantive issues to report:

DMPQ CMC has identified no substantial issues that could prevent approval of this submission.

ii. Review Update:

Working on the review memo and the Establishment Inspection Report (EIR).

iii. Discipline Review Completion:

Final draft of review memo will be completed by early December 2018.

d. Gaya Hettiarachi (Animal Pharmacology/Toxicology – CBER/OTAT/DCEPT)

i. Substantive issues to report:

Pharm/Tox has identified no substantial issues that could prevent approval of this submission.

ii. Review Update:

There are no review updates.

iii. Discipline Review Completion:

Review completed on October 28, 2018; revisions to memo will be finalized December 1, 2018.

e. Najat Bouchkouj (Clinical – CBER/OTAT/DCEPT)

i. Substantive issues to report:

No major issues have been identified to date by clinical. 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) (6) 18 yo) developed FVIII inhibitors after 93 exposure days (ED).
- Most frequent adverse reactions (Incidence $\geq 1\%$) included: Upper respiratory tract infection, 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.

Dosing: Q4D for the 25 subjects age 12-17 years (IU/Kg) (SD):

- Mean: 52 (± 1.5)
- Median: 52
- Min-Max: 47-54
- Q1-Q3: 52-53

Dosing for all 161 subjects age >18 years (IU/Kg):

- Mean: 51 (± 4.8)
- Median: 52
- Min-Max: 27-57
- Q1-Q3: 52-53

Extension 1 results:

- Among 46 subjects who were previously on prophylaxis: 32 were on Q7 days regimen at the start of Ext 1 study and 14 were on Q4 dosing. At the end of the Ext 1: 8 out of 32 (25%) switched from Q 7 days to Q 4 days dosing. No one switched from Q4 to Q7 days frequency.
- Among 9 subjects who were previously on on-demand: 6 were on Q7 days dosing regimen at the start of Ext 1, and 3 on Q 4 days. One out of the 6 (17%) subjects who were on Q 7 days at the start of Ext 1 switched to Q4 days at the end of Ext 1 study.
- Therefore, in summary, a total of 55 subjects were randomized 2:1 to 75 IU/kg Q7D (38 subjects) and 50 IU/kg Q4D (17 subjects). Among the 38 subjects who were on the Q7D regimen: 9 (24%) switched to Q4D dosing.

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.

Dosing: BIS (twice weekly) for the 34 subjects age 0-5 years (IU/Kg):

- Mean: 65 (± 5.8)
- Median: 67
- Min-Max: 50-74
- Q1-Q3: 60-69

Dosing: BIS for the 34 subjects age 6-11 years (IU/Kg):

- Mean: 62 (± 4.4)
- Median: 62
- Min-Max: 50-70
- Q1-Q3: 59-65

Trial 3776 (PK trial, 26 subjects, 20-60 years old): Clinical Pharmacology to review.

Trial 4033 (Comparability study for PK and safety, 21 subjects, 25-71 years old): Clinical Pharmacology to review.

Trial 3908 (Previously untreated patients, 32 subjects, <6 years old): Ongoing study. Applicant's results reviewed.

ii. Review Update:

In-depth review of integrated summaries of efficacy and safety not completed to date.

iii. Discipline Review Completion:

December 2018.

f. Iftekhar Mahmood (Clinical Pharmacology – CBER/OTAT/DCEPT)

i. Substantive issues to report:

Clinical Pharmacology has identified no substantial issues that could prevent approval of this submission.

ii. Review Update:

Review is ongoing.

iii. Discipline Review Completion:

Review memo will be completed by December 2018.

g. Lin Huo (Biostatistics – CBER/OBE/DB)

i. Substantive issues to report:

Stats has identified no major issues to date that could prevent approval of this submission. 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 verified.

- 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 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 subjects 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. Review Update:

A couple of exploratory sensitivity analyses have not been completed to-date.

iii. Discipline Review Completion:

Ready for supervisory concurrence in January 2019

h. Ohenewa Ahima (Epidemiology – CBER/OBE/DE)

i. Substantive issues to report:

Epidemiology has identified no substantial issues that could prevent approval of this submission.

ii. Review Update:

No substantive review issues or major deficiencies that would require a PMR or REMS have been identified to date. The applicant has proposed a non-interventional post-authorization safety study (PASS), based on EU regulatory requirement that has been reviewed.

iii. Discipline Review Completion:

Review of safety-related data submitted in support of this BLA and the applicants’s PVP are ongoing.

i. Anthony Hawkins (BIMO – CBER/OCBQ/DIS)

i. Substantive issues to report:

BIMO has identified no substantial issues that could prevent approval of this submission. Bioresearch Monitoring (BIMO) inspections were issued for three foreign and two domestic clinical study sites that participated in the conduct of Protocol NN7088-3859. The inspections did not reveal any issues that impact the data submitted in this original Biologics License Application (BLA).

Study Site#	Site Name	Location	Form FDA 483 Issued	Insepction Final Classification
852	KD Haemophilia Centre & Thrombosis Unit	London, Great Britain	NO	NAI
854	Oxford Haemophilia Center	Oxford, Great Britain	No	NAI
856	Hemophilia Centre	Basingstoke, Great Britain	No	NAI
909	Children's Hospitals and Clinics of Minnesota	Minneapolis, Minnesota	No	NAI
914	Vanderbilt Clinical Trials Center	Nashville, Tennessee	No	NAI

NAI = No action indicated

ii. Review Upate:

Review completed.

iii. Discipline Review Completion:

Review memo completed October 15, 2018.

3. Review of upcoming timeline/deadlines. [Chair,RPM]

Upcoming Meeting or Deadline	Projected Action Due Date
Late-Cycle Meeting Internal	November 2, 2018
Late-Cycle Meeting with Applicant	November 29, 2018
Labeling Weekly Meetings Start	December 07, 2018
Complete Inspection Reports	December 28, 2018
PMC Study Target	January 18, 2019
Contact OCOD	January 15, 2019
Request Compliance Check (Issued by DMPQ), Lot Release Clearance	January 15, 2019
Decipline Review Memo (Concurred at Branch Level)	January 11, 2019
SBRA Draft Completed	January 18, 2019
Labeling Target Completion	January 18, 2019
Officer/Empolyee List Email	January 25, 2019
Letter Draft Circulation	January 25, 2019
Decipline Review Memo (Concurred at Divison Level)	January 25, 2019
SBRA Sign-off by Division	February 01, 2019
SBRA Sign-off by Office	Feburary 12, 2019
OTAT Target Date	February 13, 2019
PDUFA Action Due Date	February 27, 2019

4. Assess status of the review including plans for completing outstanding discipline reviews and any remaining outstanding issues. [Chair]

Overall, there are no substantive issues which could prevent approval of this submission. For the remaining issues, no impact on the review timeline is expected.

Plan for addressing remaining CMC issues

- i. During labeling negotiations, the PI text should be revised to explain the range of FVIII activity assay issues. The recommended text is the following: “*Factor VIII activity levels can be affected by the type of activated partial thromboplastin time (aPTT) reagent used in the assay. Some silica based aPTT reagents can **underestimate the activity of [Tradename] by up to 60%, other reagents may overestimate the activity by 20%.** If an appropriate one-stage clotting or chromogenic assay is not available locally, then use of a reference laboratory is recommended.*” (Mikhail Ovanesov)
- ii. To better control manufacturing consistency, it is recommended that the company recalculates acceptance criteria for several specification parameters, using a tighter statistical approach and excluding the data from clinical processes when commercial process showed improvement. An IR was sent, and the

- company committed to addressing all issues by the end of 2018. (Alexey Khrenov)
- iii. (a) Updated DP stability data can be reviewed if received in November, i.e., within 60 days of action due date (ADD). IR is to be sent regarding the DS batch (b) (4) in the stability study.
- (b) It is recommended to exclude this batch from the stability study as inhomogeneity of the samples yields unreliable data. (Yideng Liang and Andrey Sarafanov)
- iv. The following deficiencies regarding PRM potency increase during storage should be addressed:
- (a) The root cause of the issue should be investigated.
- (b) To improve the PRM stability monitoring, Novo Nordisk should continue to use the (b) (4) WHO International Standard FVIII Concentrate and the frequency of stability testing of all reference materials should be increased.
- (c) Novo Nordisk will be advised to consider decreasing the long-term storage temperature of the PRM and SRM to (b) (4)

The respective requests listed above will be sent to the applicant. (Mark Verdecia)

5. Reach agreement on Late-Cycle Meeting Materials that will be sent to the Applicant.
[Chair, Review Committee Members]

Any outstanding IRs, if any, will be conveyed to the applicant during the late cycle communication.

- a. Applicant communicated on November 1, 2018, that there will be a delay in response to OCBQ/DBSQC IR, issued September 7, 2018, with respect to (b) (4) method validation, (b) (4), because the commercially-obtained (b) (4) reference did not perform as expected and was found to be degraded. This delay will further affect applicant response to the FDA OTAT/DPPT IR issued October 12, 2018, regarding the DS and DP specifications, where applicant anticipates altering the acceptance criteria for DS specification parameter '(b) (4)', assessed by the (b) (4). For these reasons, applicant plans to provide a single submission no later than December 19, 2018, discussing the (b) (4) method validation and procedure, addressing the OCBQ/DBSQC and OTAT/DPPT IRs referenced above.
- b. Two OCB/DBSQC IRs regarding one-stage and chromogenic assays for the accuracy study, issued September 20, 2018, and October 16, 2018, have not been addressed completely. Applicant has agreed to submit full response by

November 26, 2018, or earlier when possible, where they have agreed to include (b) (4) lots of (b) (4) and (b) (4) lots (different than reference standard) of DP, in addition to the reference standard, in both the one-stage and chromogenic assays for the accuracy study.

- c. IR issued on November 1, 2018, by OCBQ/DBSQC, requesting that the applicant provides details of how the data were obtained for the potency of their secondary standard (b) (4) by the chromogenic and one-stage clotting assays, including how many independent sample preparations, analysts, instruments, and laboratories were involved in this study. A response is anticipated by November 15, 2018.
 - d. IR issued November 5, 2018, by OTAT/DCEPT clinical review team regarding applicant proposed dosing, with a projected response due date of Tuesday, November 13, 2018.
6. Come to agreement on the issues to be included on the agenda for the LCM with the Applicant. The timeframes for each agenda item should also be agreed to. **[Chair, Review Committee Members, Management]**
- Please see draft Late Cycle Meeting Agenda to Applicant, as agreed to by the chair, review committee members, and management on pages 14 – 15 of this document.
7. **Concurrence:** RPM, Chair, Division Director of the product office

Late-Cycle Meeting Agenda to Applicant

1. Introductory Comments – 5 minutes (RPM/Chair)

Welcome, Introductions, Ground rules, Objectives of the meeting

2. Discussion of Substantive Review Issues – 2 minutes

To date, there are no pending substantive review issues identified by the review team.

3. Status of Information Requests – 20 minutes

- a. Applicant communicated on November 1, 2018, that there will be a delay in response to OCBQ/DBSQC information request (IR), issued September 7, 2018, with respect to (b) (4) method validation, (b) (4), because the commercially-obtained (b) (4) reference did not perform as expected and was found to be degraded. This delay will further affect applicant's response to the FDA OTAT/DPPT IR issued October 12, 2018, regarding Drug Substance (DS) and Drug Product (DP) specifications, where applicant anticipates altering the acceptance criteria for the DS specification parameter (b) (4) assessed by the (b) (4). For these reasons, applicant plans to provide a single submission no later than December 19, 2018, discussing the (b) (4) method validation and procedure, and addressing the OCBQ/DBSQC and OTAT/DPPT IRs referenced above.
- b. Two OCBQ/DBSQC IRs regarding validation of one-stage and chromogenic assays (the accuracy study), issued September 20, 2018, and October 16, 2018, have not been completely addressed. Applicant has agreed to include (b) (4) lots of DS and (b) (4) lots (different than reference standard) of DP, in addition to the reference standard, in both the one-stage and chromogenic assays for the accuracy study and submit full response by November 26, 2018.
- c. IR issued on November 1, 2018, by OCBQ/DBSQC, requesting that the applicant provides details of how the data were obtained for the potency of secondary standard (b) (4) by the chromogenic and one-stage clotting assays, including how many independent sample preparations, analysts, instruments, and laboratories were involved in this study. A response is anticipated by November 15, 2018.
- d. IR issued November 5, 2018, by OTAT/DCEPT clinical review team regarding applicant proposed dosing, with a projected response due date of Tuesday, November 13, 2018.
- e. Updated stability data for DP is expected to be submitted in November 2018.

- f. An IR regarding the use of the WHO international standard for factor VIII activity in the Primary Reference Standard stability study protocol will be submitted by FDA OTAT/DPPT.
4. Current assessment of risk management activities, e.g, REMS – **2 minutes**

The review team has not identified any issues related to risk management. We do not believe that a risk management action (e.g., REMS) is needed at this time. The applicant has proposed a non-interventional post-authorization safety study (PASS), based on EU regulatory requirement that has been reviewed.
5. Postmarketing Requirements/Postmarketing Commitments – **2 minutes**

Currently, no post marketing commitments or post marketing requirements have been identified. The review for this application is ongoing and development of any post marketing commitments or requirements will be communicated to the applicant by January 25, 2019.
6. Major labeling issues – **2 minutes**
 - a. The labeling review is ongoing, and modifications and recommendations for the text of Prescribing Information and labels for the vial and carton will be communicated to the applicant via IRs in late December 2018 – early January 2019.
 - b. Applicant committed to submit revised labeling to include the proper name, Antihemophilic Factor (Recombinant), glycoPEGylated-exei, and the trade name, ESPEROCT, by November 23, 2018.
7. Review Plans – **5 minutes**

Discipline reviews are ongoing. Pending review of responses to outstanding issued IRs.
8. Applicant Questions – **10 minutes**
9. Wrap-up and Action Items – **12 minutes**