

# Mid Cycle Meeting Summary, March 29, 2013 - Novoeight

## Mid-Cycle Meeting Summary

**Application type and number:** Original BLA STN 125466/0

**Product name:** Antihemophilic Factor (Recombinant), Plasma/Albumin Free [NovoEight]

**Applicant:** Novo Nordisk A/S, Denmark

**Meeting date & time:** Friday, March 29, 2013 10:00-11:30 a.m.

**Committee Chair:** Natalya Ananyeva

**RPM:** Leigh Pracht

### Attendees:

<b>Chairperson, CMC/Product LH Chief</b>	Natalya Ananyeva, PhD, OBRR/DH/LH
<b>CMC/Product</b>	Timothy K. Lee, Ph.D. OBRR/DH/LH Ze Peng, PhD, OBRR/DH/LH (stability and viral safety)
<b>CMC/Product</b>	Andrey Sarafanov, PhD, OBRR/DH/LH (analytical assays and their validation)
<b>CMC/Product</b>	Zuben Sauna, PhD, OBRR/DH/LH (assays for the immunogenicity monitoring)
<b>CMC/Facility, Equipment</b>	Randa Melhem, PhD, OCBQ/DMPQ/BII
<b>Pharmacology/Toxicology</b>	La'Nissa Brown, PhD, OBRR/DH
<b>Clinical Pharmacology</b>	Iftekhar Mahmood, PhD, OBRR/DH
<b>Clinical</b>	Nisha Jain, MD, Chief, OBRR/DH/CRB Lisa Faulcon, MD, OBRR/DH/CRB
<b>Statistical</b>	Judy Li, PhD, OBE/DB/TEB Renee Rees, PhD, OBE/DB/TEB
<b>BIMO</b>	Bhanu Kannan, MS, OCBQ/DIS/BMB
<b>Epidemiology</b>	Wambui Chege, MD, OBE/DE/AEB
<b>APLB</b>	Loan Nguyen, PharmD, OCBQ/DCM/APLB
<b>DBSQC</b>	William McCormick, PhD, OCBQ/DBSQC Karen Campbell, OCBQ/DBSQC
<b>DH</b>	Paul Mintz, MD, Deputy Director, OBRR/DH, and Mahmood Farshid, PhD, Deputy Director, OBRR/DH
<b>OBRR</b>	Betsy Jett, Deputy Associate Director for Regulatory Affairs, OBRR/IOD Iliana Valencia, MS, OBRR/DBA/RPMB and Thomas Maruna, MS, OBRR/DBA/RPMB
<b>ADRM</b>	Chris Joneckis, PhD, OD/RMS

## DISCUSSION SUMMARY

### **Dr. Natalya Ananyeva (Chair, CMC/Product)**

Dr. Ananyeva opened the meeting with an overview of product description, indications, and regulatory history. The original Biologics License Application (BLA) for Antihemophilic Factor (Recombinant), Plasma/Albumin Free (International Nonproprietary Name – turoctocog alfa) from Novo Nordisk A/S, Denmark was received by FDA on October 16th, 2012. The proposed proprietary name is NovoEight. The product was previously reviewed under IND 14059.

NovoEight is a recombinant B-domain-truncated human blood coagulation factor VIII (FVIII) produced in Chinese Hamster Ovary (CHO) cells. NovoEight is a “third generation” Antihemophilic Factor (Recombinant) product manufactured and formulated without animal- or human-derived proteins.

To date, the review was focused on the manufacturing process design for turoctocog alfa Drug Substance, changes during process development, established in-process controls, and process validation studies. Novo Nordisk’s validation strategy appears adequate and consistent with recommendations of ICH Guidelines Q7, Q8 and Q11, with elements of “Quality by Design” approach (Process Design/Evaluation, Process Performance Qualification, and Continuous Process Verification). The validation data support consistency of the manufacturing process to produce Drug Substance that meets pre-determined quality characteristics. Based on the current status of review, no major CMC issues have been identified that could prevent approval of the BLA. Additional information is requested to continue the review.

#### **Items for Mid-Cycle Information Request:**

1. Regarding CHO-derived Anti-FVIII monoclonal antibody (mAb), please provide:
  - a. Information on the specificity of the antibody, the analytical method used to establish its epitope recognition within the FVIII molecule, and the supporting experimental data.
  - b. Information on the affinity of CHO-derived Anti-FVIII mAb for FVIII and the analytical method used to determine the binding constant. Please include this parameter (Kd) in the Release Specifications and in Stability Program for the end-of-study time point.
  - c. Please add process-related impurities, -----(b)(4)-----, as Specification parameters, with established acceptance limits, or justify your decision not to include these parameters in Specification.
  - d. Please submit up-to-date stability data for Anti-FVIII mAb and Anti-FVIII affinity matrix.
2. Regarding the purification process for turoctocog alfa Drug Substance, please submit the validation report for the claimed hold times for the intermediates for Steps -----(b)(4)-----.
3. Please re-submit results of Batch analyses for the PPQ batches (----- (b)(4) ----- Drug product) compared to the *final* specifications. For Drug Product PPQ batches please include Potency values determined by both the chromogenic substrate and one-stage clotting assays.

The review of the manufacturing process for turoctocog alfa Drug Substance will be also continued during the Pre-License Inspection of Novo Nordisk facility in -----(b)(4)----- manufacturing facility) planned for -----(b)(4)-----.

The validation of the manufacturing process for Drug Product, and Specifications-related aspects have not yet been reviewed.

**Dr. Ze Peng (CMC/Product)** reviewed the stability data for NovoEight Drug Substance, Drug Product and the Diluent (0.9% sodium chloride solution). While the submitted stability data are satisfactory, up-to-date stability data will be requested considering that the product formulation changed during process development, and the comparability of the formulation for commercial production needs to be further verified.

Dr. Peng also reviewed the viral safety data for both NovoEight Drug Substance and anti-FVIII mAb. Novo Nordisk used (b)(4) different model viruses, of which --(b)(4)-- is enveloped and (b)(4) other viruses (-----) are non-enveloped. The cumulative reduction factors are satisfactory; however, the resistance of (b)(4) to physico-chemical treatments is categorized as “low” according to ICH Q5A.

Regarding inactivation of enveloped viruses by the manufacturing process, Dr. Ananyeva inquired if it is acceptable to have only one validated enveloped virus with low resistance, or whether additional studies are needed.

Dr. Farshid explained that the principle of current viral validation studies is the use of a panel approach, to maximize the diversity of virus structures and properties that are studied, e.g., RNA viruses, DNA viruses, non-enveloped, enveloped viruses, small versus large viruses, physically resistant versus sensitive viruses. Using a single low resistant enveloped virus (in this case (b)(4)) will not be sufficient to determine the inactivation capacity of a manufacturing process, and its robustness. For these reasons, the panel of viruses used in validation of viral clearance for recombinant products, at the BLA phase, should include at least two (2) enveloped and two (2) non-enveloped viruses. Therefore, Novo Nordisk should validate an additional enveloped virus with a higher resistance to physico-chemical treatments.

**Items for Mid-Cycle Information Request:**

1. Please provide updated data from stability studies No. 717-S507, NovoDOCS: 001288236 and 001118375, and trend analyses of stability-indicating parameters.
2. Please provide updated data from stability study NovoDOCS: 001230802 for 0.9% sodium chloride solution.
3. Please note that viral clearance studies should include at least two enveloped viruses to represent a wide range of physico-chemical properties. Please add pseudorabies virus (PRV) as a model virus for large DNA enveloped viruses with medium resistance in your validation studies for the manufacturing processes of turoctocog alfa and Anti-Factor VIII monoclonal antibody used in the affinity chromatography resin.
4. With reference to 3.2.A.2 Adventitious Agents Safety Evaluation,
  - o In Table 4, please provide the actual clearance data for -----(b)(4)----- by the 20 nm nanofiltration step.
  - o In Table 5, please provide the clearance data for -----(b)(4)----- by step (b)(4) (Anti-FVIII matrix affinity chromatography) after the resins were used (b)(4). Also, please provide Cumulative Reduction Factors (Total clearance) for all viruses with the used resins. If the steps were not evaluated, please provide justification.

The review can be completed only when the results of the new viral clearance study will be submitted by Novo Nordisk.

**Dr. Andrey Sarafanov (CMC/Product)** reviewed analytical methods and found their validation overall adequate, with the following comments:

A number of compendia methods ((b)(4), Particulate Matter and ---(b)(4)---) are stated without supporting validation reports. Drs. Farshid, Lee and Melhem explained that validation of compendia methods is typically not required; Novo Nordisk has to demonstrate the method suitability for the intended use.

The Applicant used in-house standard in FVIII potency determination assays. It is unclear whether this standard was calibrated against any international (WHO) standard, and this will be verified in the Reference Standard section of the BLA.

Novo Nordisk does not include ---(b)(4)--- as process-related impurity in the final Specification. This parameter was controlled during process development, and the values were below the method detection limit. Dr. Sarafanov questioned whether this parameter should be added to Specification, or risk assessment be performed for the worst-case scenario. Dr. Lee commented that as long as Novo Nordisk can reliably demonstrate clearance of ---(b)(4)--- by the manufacturing process, it is acceptable not to have this parameter in the final Specification.

**Items for Mid-Cycle Information Request:**

1. Please provide qualification reports for (b)(4), Particulate Matter and --(b)(4)-- that verify their suitability under actual conditions of use.
2. The provided verification data for Sterility of the final drug product (FDP) only support the system's capability to detect microorganisms. To verify its capability to assess sterility in the FDP, the test organisms should be spiked into the reconstituted FDP prior to the filtration -----(b)(4)-----. Please comment.
3. With reference to the validation of assays for Bacterial Endotoxin for -----(b)(4)- ----- final drug product, please clarify if an Endotoxin standard was spiked into the matrix as a positive control, and used to measure recovery. In addition, please submit the validation protocols for these studies.

The review is on schedule.

**Dr. Zuben E. Sauna (CMC/Product)** reviewed assays that the Applicant used to detect antibody responses in the pre-clinical and clinical samples. Dr. Sauna emphasized that immunogenicity is the central concern in FVIII replacement therapy. Novo Nordisk used assays to detect (1) the presence of neutralizing antibodies against FVIII (referred to as "inhibitors", the -----(b)(4)----- of the Bethesda assay which is a well-established assay that is used in research, clinical studies and during licensure of other FVIII products); (2) -----(b)(4)-----; and (3) anti-murine IgG antibodies because turoctocog alfa is affinity purified using murine anti-FVIII antibodies. The key validation parameters for the three assays included sensitivity, cut point, and variation. At this stage of the review process, Dr. Sauna did not find any significant issues that may prevent approval of the BLA. The assay development and validation are performed adequately, and the assays are suitable to be used in clinical studies to assess the levels of antibodies against the product. Importantly, the results indicate that none of the subjects enrolled in the clinical trials developed inhibitors. As several versions of the Bethesda assay are referenced in the BLA, Dr. Sauna requests respective SOPs for version comparison.

**Item for Mid-Cycle Information Request:**

1. Please provide the following documents (or indicate where they may be located in the original application):
  - a. Validation of the FVIII Bethesda Assay (-----)(b)(4)-----) for the Detection and Quantification of FVIII inhibitors in human plasma, Mar 2009
  - b. LKF WP 0096 (FVIII-Inhibitor (-----)(b)(4)-----), Version 1.00, May 2009; Version 2.00, Nov 2009; Version 3.00, Sep 2010, Version 4.00, Nov 2011.

Dr. Sauna plans to complete his final review on time, with close consultation with the Clinical reviewer.

**Dr. Randa Melhem (CMC/Facility, Equipment)**

Dr. Melhem listed the facilities associated with the manufacturing of NovoEight:

- Novo Nordisk A/S facility in ---(b)(4)---, Denmark: manufacture of Drug Substance (cell culture, capture and purification steps)
- Novo Nordisk A/S facilities in -----(b)(4)-----, Denmark: manufacture of Drug Product (formulation, filling, lyophilization and packaging)
- -----(b)(4)----- (contract manufacturer): manufacture of the 0.9% NaCl sterile diluent

As NovoEight is a recombinant product, the information provided in the BLA submission regarding Facilities and Equipment is general (according to CBER/CDER *Guidance for Industry for the Submission of Chemistry, Manufacturing, and Controls Information for a Therapeutic Recombinant DNA-Derived Product or a Monoclonal Antibody Product for In Vivo use*) and therefore is not sufficient for a comprehensive review. Dr. Melhem plans to get additional information (on the Facilities and Equipment, Sterilization process, Lyophilization process, Container Closure system, and the Filling process) during the Pre-License Inspection of the Novo Nordisk facility in ---(b)(4)--- (Drug Substance manufacturing facility) scheduled for -----(b)(4)-----. The -----(b)(4)----- facilities will not be included in the inspection as they were inspected in 2012. -----(b)(4)----- facility (manufacturer of 0.9% NaCl diluent) will not be inspected as the facility was previously inspected for similar processes that are used in the manufacture of sterile diluents in a syringe presentation. The most recent inspection was -----(b)(4)----- which was classified as NAI (No Action Indicated). Dr. Melhem will prepare inspection waivers for the -----(b)(4)----- facilities. Dr. Melhem will discuss with the management if inspection waiver is needed for the -----(b)(4)----- facility (packaging only).

**Dr. La’Nissa Brown-Baker (Pharmacology/Toxicology)**

Dr. Brown-Baker reviewed the non-clinical program for NovoEight® Antihemophilic Factor (Recombinant) Plasma/Albumin-Free, which consists of the following studies: safety pharmacology (mice and dogs), dose range-finding (mice), acute toxicity (monkeys, with toxicokinetics), repeat-dose toxicity (monkeys with toxicokinetics), and pharmacokinetics (mice and dogs). Animal studies for carcinogenicity, mutagenicity, and fertility were not conducted. These studies are not considered necessary for approval as per the ICH S6(R1) guidance, because NovoEight protein is not expected to directly interact with or damage DNA. Reproductive toxicity or teratogenicity studies are not required for approval in this case, because Hemophilia A affects only male patients.

From the Pharmacology/Toxicology reviewer’s perspective, no deficiencies with non-clinical data and no toxicity concerns (regarding impurities) have been identified that

could prevent approval of the BLA. There are no information requests for additional non-clinical studies at this time; the submitted non-clinical data appear sufficient to continue the review of the BLA for NovoEight®.

There are no special labeling concerns from the nonclinical discipline; recommendations related to Section 13.1 (Carcinogenesis, Mutagenesis, Impairment of Fertility) of the Prescribing Information will be conveyed to the Applicant at a later date.

The primary review is expected to be completed on time or prior to the deadline (tentatively mid-May, 2013).

**Dr. Iftekhar Mahmood (Clinical Pharmacology)**

Dr. Mahmood reviewed the clinical pharmacology section of the BLA submission (four studies) and did not identify any outstanding issues. The study design for pharmacokinetic (PK) studies is adequate and the conclusions drawn by the Applicant based on the PK assessment are acceptable. The clinical pharmacokinetic data indicate bioequivalence of NovoEight and a licensed recombinant full-length FVIII product, Advate, manufactured by Baxter. A single dose PK study indicates that the clearance of turoctocog alfa increases with increasing age that will require dose adjustment in younger and older children as compared to adults. The half-life of turoctocog alfa is comparable between younger and older children but it is about 2 hours longer in adults than children; this difference is of no clinical significance.

There is no information request except that the clinical pharmacology labeling section needs modification, and recommendations will be conveyed to the Applicant at an appropriate time. The review of the submission is finished, and the memorandum will be completed on time.

**Dr. Lisa Faulcon (Clinical)**

Dr. Faulcon provided an overview of the proposed indications and the results from the clinical studies performed to demonstrate safety and hemostatic efficacy of NovoEight Antihemophilic Factor (Recombinant), Plasma/Albumin-Free.

The indications sought are:

- Control and prevention of bleeding episodes in adults, adolescents and children with hemophilia A
- Perioperative management of patients with hemophilia A
- Routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adults, adolescents and children with hemophilia A

The safety and efficacy trials included:

1. NN7008-3543- a pivotal trial done in 150 adolescent and adults
2. NN7008-3545-a pediatric trial in 63 children below age 12
3. NN7008-3568 - ongoing extension trial of 187 children, adolescents, and adults

All trials were designed as multi-center, open-label, uncontrolled trials with a primary endpoint of inhibitor formation. Secondary endpoints included annualized bleeding rate (ABR) during the prophylaxis treatment and hemostatic effect on treatment of bleeds for on-demand and perioperative management using a four-point nominal rating scale of excellent, good, moderate and none. Success was defined as a rating of “excellent” or “good.”

To date, no safety issues have been identified that could prevent approval of the BLA. No confirmed FVIII inhibitors, hypersensitivity/allergic reactions or thromboembolic events were documented for any subject in any of the trials. Hemostatic success was

achieved in > 80% for the treatment of acute bleeds (on-demand therapy) and 100% for perioperative management (during and after surgery). An integrated analysis of pooled data shows that for subjects treated with on-demand regimens prior to trial entry, their annualized bleeding rate (ABR) was reduced by > 50% with a prophylaxis regimen with NovoEight. However, the trial results for inhibitor formation and hemostatic efficacy could not be verified using the submitted data. Dr. Faulcon requested that the datasets be re-submitted in an appropriate SAS format.

**Items for Mid-Cycle Information Request:**

1. We are unable to verify the trial results using the datasets and pdf files that you submitted in the original BLA submission. To evaluate the inhibitor rate, annualized bleeding rate and hemostatic efficacy we will need the relevant data files in SAS format, the corresponding readme files that explains each data file, and the program codes used to generate the study results. Please provide the following data in SAS format for each trial and for pooled trials separately:
  - a. Inhibitor test dates and titer results for each of the pre-specified testing dates
  - b. All bleeding episodes, including cause of bleed, site of bleed, number of infusions required, hemostatic rating
  - c. Relevant baseline characteristics, including subject age, region (country and site), prophylaxis regimen, exposure days, and type of surgical procedure.
2. In Appendix I, Table 23 of the Summary of Clinical Safety, you provide anti-CHO test results for subjects with at least one positive test. However, you have not submitted the titers for each test. Please submit in tabular format a list of all subjects with positive anti-CHO antibodies, their FVIII regimen prior to enrollment, and the titer results at each pre-specified testing dates. FDA needs this information to assess changes in titers after repeated exposure to the product.

At this time, Dr. Faulcon does not think that a Risk Evaluation Mitigation Strategy (REMS) is needed. There may be a potential PMC. Currently, there are no recommendations for the referral of this BLA to the Blood Products Advisory Committee (BPAC). This submission triggers PREA and the Applicant has submitted an assessment of the data gathered to support the safety and efficacy of the product for all appropriate pediatric age groups. Review of these data is ongoing. A PerRC presentation date will be set.

**Dr. Judy Li (Biostatistics)**

The safety dataset consists of three pharmacokinetic studies (3522, 3893, and 3600) and three multicenter, open-label, uncontrolled Phase 3 trials (3543, 3545, and 3568). To verify the trial results, Novo Nordisk is requested to re-submit the relevant data files in the appropriate SAS format (please refer to the Information Request from the Clinical reviewer). Dr. Li defers to the Clinical reviewer to decide whether the efficacy success criteria are adequately specified with regard to the annualized bleeding rate and the hemostatic effect. The Biostatistics primary review is planned to be completed around the end of May or early June.

**Dr. Bhanu Kannan (Bioresearch Monitoring Branch)**

BIMO issued inspection assignments on February 15, 2013 to inspect the clinical investigators conducting investigations at sites #861 and #868 in the U.S. and sites #351 and #352 in Brazil. The inspection of site #861 was completed on March 25, 2013. The inspection is ongoing at this time at site #868. The inspections are pending at sites

#351 and #352 in Brazil. A review will be conducted after the completion of the inspections and the receipt of the inspection reports.

**Dr. Wambui Chege (OBE)** remarked that safety data for pediatric surgical patients appears to be limited. Dr. Jain commented that from the historical aspect for this class of product, the number of 213 patients treated pre-licensure is impressive. With regard to surgical study this number is indeed lower but no safety concerns have been identified within these subjects.

**Dr. Quynh Nhu Nguyen (CDRH Human Factors)**

This is a Human Factors consultative review requested by OBRR for this BLA submission. The submission contains a Human Factors validation test protocol and report on the Turoctocog alfa --(b)(4)-- Delivery System which includes a diluent-containing syringe and eliminates the handling steps for extraction of the diluent from a vial to the syringe. Dr. Nguyen identified some issues that need to be addressed with respect to (i) potential dosing errors and contamination and (ii) potential clinical consequences in order to determine whether additional design/IFU modifications and risk mitigations are necessary.

**Items for Mid-Cycle Information Request:**

1. You reported one count of a hemophilia HCP drawing the full amount of mixed drug instead of the calculated dose, which could lead to dosing errors (underdosing/ overdosing). You also reported one count of an ER nurse while preparing a 3-mL calculated dose, they first emptied 1 mL of solvent from 4 mL prefilled syringe prior to reconstitution, which we were not clear of potential clinical consequence. Both of these counts were observed while the participants were performing the calculated dose scenario. Review of your Instructions for Use revealed that the critical task of drawing draw out a specified volume of the reconstituted drug into the syringe (less than the full contents of the reconstituted solution) does not appear to adequately draw the reader's attention to that task. Please revise your Instructions for Use to address this concern.
2. You reported several counts of performance that could lead to contamination (two counts of an adult participant touching the top of the syringe while removing air bubbles; and four counts of 1 child/adolescent, 2 haemophilia HCPs, and 1 ER nurse of not cleaning the rubber stopper with an alcohol swab). Six counts of ER nurses removing the vial adapter with fingers from protective cap, but did not touch fluid path. We suspect that these actions might also lead to contamination. Review of your Instructions for Use revealed that it does not communicate the negative consequence of contaminating the product while assembling the components, and the importance of cleaning the rubber stopper, not touching the syringe while removing air bubbles, and not using fingers to remove the vial adapter. Please revise your Instructions for Use to address this concern.
3. You reported four counts of ER nurses did not remove the protective cap correctly leading to removal and then remounting of the adapter. The success criteria specified that the participant would not be able to continue if this task fails. Unclear if participants did not remove the protective cap correctly would be considered as task failures. Please provide a clarification.
4. You reported multiple counts of assembling the components not according to the sequence specified in the Instructions for Use. However, you did not discuss

whether any of the techniques applied by these test participants had any potential negative consequences to the patient or the user. Please note that if any of the techniques applied could result in patient harm, the Instructions for Use/labeling should be modified to warn users of those potential consequences. Please provide a clarification.

**Ms. Karen Campbell (Lot Release, DBSQC)**

DBSQC prepared a draft of Laboratory Quality Product Testing Plan which was sent to the Chair, Dr. Ananyeva, on March 29th, 2013 for further development.

Lot Release Protocol may not be needed as NovoEight is a recombinant product, and as such, is exempt from Lot Release requirement post-licensure.

For the BLA review, DBSQC is performing in-support testing of NovoEight samples of the validation batches (as agreed upon at the November 9th, 2012 Meeting). The testing includes:

- Appearance of powder, reconstitution time and appearance of solution
- Potency by APTT-based One-Stage Clotting assay for comparison with the values obtained by the Chromogenic assay that Novo Nordisk uses as label values
- Purity and -----(b)(4)-----
- Content and -----(b)(4)-----
- Water Content by -----(b)(4)-----; review of the validation of the (b)(4) method used by Novo Nordisk
- Endotoxin

There are a few methodological questions related to --(b)(4)-- and Endotoxin tests which possibly can be clarified during the inspection. Historically, recombinant products can be put on surveillance post-approval, to continue in-support testing for a limited period of time, e.g., one year. DBSQC asks the Product Office to determine if surveillance is warranted for NovoEight. Dr. Lee indicated that this decision will be made after the inspection. Dr. Joneckis explained that FDA requires a strong justification if Lot Release testing is requested for a recombinant product post-approval.

**Dr. Loan Nguyen (APLB)** stated that the primary review of the Proprietary Name, NovoEight, has been performed (memo dated November 16th, 2012), and the name is found to be acceptable. APLB will re-review the proprietary name within 90 days of the Action Due Date, to ensure that no new products were approved that could change their current recommendation.

**Ms. Leigh Pracht (RPM)** guided the Review Committee through the Mid-Cycle Check-List:

**MID-CYCLE CHECK LIST**

1. **Major target and milestone dates from RMS/BLA**

**Meeting type Date**

Initial Labeling meeting 16-Apr-13: 11:00-12 p.m.

Mid-Cycle communication with the Applicant 17-Apr-13: 10:00-11 a.m.

Late-Cycle Meeting with the Applicant 28-Jun-13: 01:30-3:00 p.m.

Labeling Target 16-Sep-2013

PMC Study Target 16-Sep-2013

**Action Due Date 16-Oct-13**

Post-Action Debrief Meeting 29-Nov-13

**2. The status of the review for each discipline and a target date for completing the primary reviews, inspections, EIR. Include any consult disciplines.**

All discipline reviewers are on schedule with the review of the BLA. Target date to complete primary reviews is end-of-May to mid-June, 2013.

**3. Determine if any reviews will not meet the deadline, and if not, what date they will be completed.**

As additional virus clearance studies are requested, completion of the CMC review will depend on the time of submission of the study results.

**4. Discuss pending dates of targets and milestones (e.g., Late-Cycle Meeting, Advisory Committee, labeling discussion)**

The Late Cycle Meeting is scheduled for 28 June 2013 from 01:30-3:00 p.m.; the Applicant has inquired whether this can be scheduled earlier in the day as their attendees have international flights later that afternoon. This will depend on Dr. Epstein's and Dr. Michaud's schedules.

**5. Establish a Labeling review plan and agree on future labeling meeting activities**

The initial Labeling meeting is scheduled for 16 April 2013 from 11a.m. to 12 p.m.

**6. If the application will be discussed at an Advisory Committee, potential issues for presentation**

The application will not be presented at the Blood Products Advisory Committee (BPAC). Drs. Ananyeva and Faulcon are preparing the BPAC waiver memo.

**7. Determine whether Postmarketing Commitments (PMCs), Postmarketing Requirements (PMRs) or a Risk Evaluation Mitigation Strategy (REMS) is needed**

At this time, the Clinical reviewer does not think that a Risk Evaluation Mitigation Strategy (REMS) is needed. There may be a potential clinical PMC.

**8. National Drug Code (NDC) assignments to product/packaging**

Ms. Leigh Pracht had inquired as to the Applicant's NDC assignment/strategy and was told, "Our Logistic department has started the process to request the NDC numbers, and we expect to have the NDC numbers for the 6 strengths of the drug product in ~2 months. Therefore it should not be a problem." This inquiry was made as it has been discovered NDC codes have not been created in compliance with the Bar Code Rule within other submissions from Novo Nordisk.

**9. Proper Name convention**

The proper name for NovoEight is Antihemophilic Factor (Recombinant), Plasma/Albumin-Free. Review Committee members discussed the use of descriptor "Plasma/Albumin-Free" in the proper name of the product. Dr. Jain suggested removing this descriptor as it has become obsolete with increasing number of recombinant products manufactured without animal- or human-derived materials. The same recommendation will eventually apply to other relevant products (e.g., Advate and Xyntha). Instead, the specifics of the manufacturing process can be described in section 11 and Highlights of Prescribing Information. The decision will be made during the Labeling meetings.

**10. Status of inspections (GMP, BIMO, GLP) including issues identified that could prevent approval**

Pre-License Inspection of Novo Nordisk manufacturing facilities is scheduled for the period April 3rd through April 12th 2013.

BIMO inspection of the US clinical site #861 was completed on March 25, 2013; the inspection of the U.S. site #868 is ongoing. Foreign inspections of two clinical sites #351 and #352 in Brazil are pending.

#### **Confirm**

11. **Components Information Table** was obtained and notification 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*.

Dr. Ananyeva will request this information during the Pre-License Inspection.

12. **New Facility Information** is included in the application, requiring implementation of regulatory job aid *JA 910.01: Facility Data Entry*. If not done indicate date it will be completed.

Complete to this point.

13. **Status of Decisions regarding Lot Release Requirements**, such as submitting samples and test protocols and the lot release testing plan

The samples for in-support testing were received from Novo Nordisk. Testing is ongoing in DBSQC as specified at the November 9th, 2012 meeting. Decision regarding Lot Release requirement post-licensure will be made after the Pre-License Inspection of Novo Nordisk.

14. **Unique ingredient identifier (UNII) Code** process has been initiated. See regulatory job aid *JA 900.01: Unique Ingredient Identifier (UNII) Code* for additional information.

The UNII Codes have been assigned by CBER SRS and were conveyed to the Applicant on March 21, 2013.

15. **PeRC presentation date**

(Remind the review committee that PeRC forms have to be submitted two weeks in advance of scheduled PeRC meeting, and the clinical reviewer has addressed waiver/deferral/assessment of the PREA decision)

The Clinical reviewer (Dr. Faulcon) will set a PeRC presentation date according to the review schedule.

16. **Reach agreement on information to be included in the Mid-Cycle Communication with the Applicant**

The review committee agreed on the items to be discussed in the Mid-Cycle Communication teleconference with Novo Nordisk A/S under PDUFA V Program. Additional items were included by the Chair following the Pre-License Inspection (----- (b)(4)-----). The final document was concurred by the Chair's supervisor (Timothy Lee, Chief of Laboratory of Hemostasis, OBRR) and CBER upper management (Chris Joneckis, OD/RMS). Mid-Cycle communication (teleconference) was held on April 17th, 2013.

#### **MID-CYCLE COMMUNICATION SUMMARY**

1. No significant issues with the data submitted in the BLA have been identified by the review committee to date.
2. An Information Request will be sent to the Applicant in early April, 2013 with the due date for the responses on May 13th, 2013.

3. Regarding responses to inspectional FDA Form 483 items, Novo Nordisk should submit the resolution plan with the tentative completion dates for each item by May 1st, 2013.
4. Clarification on FDA request to validate the clearance of an additional enveloped virus by the manufacturing process for turoctocog alfa Drug Substance and anti-FVIII monoclonal antibody: Novo Nordisk may proceed with clearance studies using -----(b)(4)----- as proposed in their memorandum dated April 10th, 2013.
5. As discussed during the Pre-License Inspection, please submit the list of raw materials/ ingredients used in the manufacture of turoctocog alfa drug substance/drug product in order of decreasing risk as assessed by Novo Nordisk, and provide information on the suppliers/manufacturers of risk materials. No due date has been specified; please submit as an amendment to the file at the earliest possible date. Any further clarification required pertaining to the list of raw materials will be discussed via email.
6. The review of the clinical data to date did not raise major safety concerns. In item 13 of the April 9th Information Request, FDA requested formatting the datasets to enable verification of the trial results (the inhibitor rate, annualized bleeding rate and demographic data). As agreed upon during the April 15th teleconference, Novo Nordisk will submit the data in the appropriate format as an amendment to the file by COB April 22nd. If the data are available earlier, Novo Nordisk will send them by e-mail.
7. The review committee (currently) does not think that a Risk Evaluation and Mitigation Strategy (REMS) is required.
8. This BLA will not be presented at Blood Products Advisory Committee meeting.
9. As agreed upon between FDA and Novo Nordisk during the Pre-License Inspection, Novo Nordisk will submit the complete stability report for turoctocog alfa Drug Substance, Drug Product and Diluent as a response to the April 9th Information Request (items 4 and 5) by May 13th, 2013. This will also fulfill Novo Nordisk's commitment for updated stability data stated in FDA Meeting Response Memorandum dated June 8th, 2012 (IND 14059; CRMTS #8473, questions 2, 5, and 8).
10. The late-cycle meeting has been scheduled for Friday, June 28, 2013 1:30 - 3 p.m. Over the course of the next two months, it will be decided as to whether the late cycle meeting will be a telecon or a face to face meeting.

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