

Late Cycle Meeting Minutes, July 11, 2013 - Novoeight

DEPARTMENT OF HEALTH & HUMAN
SERVICES

Public Health Service

Food and
Drug Administration

1401 Rockville Pike

Rockville, MD 20852-1448

Our STN: BL 125466/0

LATE CYCLE MEETING MINUTES

Novo Nordisk Inc.
Attention: Mr. Robert B. Clark
P.O. Box 846
Plainsboro, NJ 08536

Dear Mr. Clark:

Please refer to your Biologics License Application (BLA) submitted under section 351 of the Public Health Service Act for Antihemophilic Factor (Recombinant) [NOVOEIGHT].

We also refer to the Late-Cycle Meeting (LCM) between representatives of your firm and the FDA on July 11, 2013.

A copy of the official minutes of the LCM is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Leigh Pracht, Regulatory Project Manager, at (301) 827-6116.

Sincerely yours,

Basil Golding, MD

Director
Division of Hematology
Office of Blood Research and Review
Center for Biologics
Evaluation and Research

Enclosure:
Late Cycle Meeting Minutes

Late Cycle Meeting Summary

Meeting date & time: Thursday, July 11, 2013, 1 p.m. - 2:30 p.m.
Meeting Location: CBER WOC I, Room 200S
Application type and number: Original BLA STN 125466/0
Product name: Antihemophilic Factor (Recombinant)
[NOVOEIGHT]
Applicant: Novo Nordisk A/S, Denmark
Committee Chair: Natalya Ananyeva
RPM: Leigh Pracht

FDA Participants:

Chairperson, CMC/Product	Natalya Ananyeva, PhD, OBRR/DH/LH
LH Acting Chief	Timothy Lee, PhD, OBRR/DH/LH
CMC/Product	Ze Peng, PhD, OBRR/DH/LH
CMC/Facility, Equipment	Mark Schwartz, JD, Acting Deputy Director, OCBQ John Eltermann, PharmD, Director, OCBQ/DMPQ Marion Michaelis, Chief, OCBQ/DMPQ/BII Randa Melhem, PhD, OCBQ/DMPQ/BII
Pharmacology/Toxicology	Anne Pilaro, PhD, Acting Chief, OBRR/DH/TB La'Nissa Brown, PhD, OBRR/DH/TB
Clinical Pharmacology	Iftekhar Mahmood, PhD, OBRR/DH
Clinical	Nisha Jain, MD, Chief, OBRR/DH/CRB Lisa Faulcon, MD, OBRR/DH/CRB
Statistical	Judy Li, PhD, OBE/DB/TEB
BIMO	Bhanu Kannan, MS, OCBQ/DIS/BMB
Epidemiology	Wambui Chege, MD, OBE/DE/PVB
APLB	Loan Nguyen, PharmD, OCBQ/DCM/APLB
DBSQC	Lokesh Bhattacharyya, PhD, Chief, OCBQ/DBSQC/LACBRP Hsiaoling Wang, PhD, OCBQ/DBSQC/LACBRP

	Karen Campbell, OCBQ/DBSQC
DH	Mahmood Farshid, PhD, Deputy Director, OBRR/DH Paul D. Mintz, MD, Deputy Director, OBRR/DH
OBRR	Ginette Michaud, MD, Deputy Director, OBRR/OD Betsy Jett, Deputy Associate Director for Regulatory Affairs, OBRR/OD Iliana Valencia, MS, Chief, OBRR/DBA/RPMB Tracy Tilghman, MS, OBRR/DBA/RPMB
OVRR	Wellington Sun, MD, Director, DVRPA
CBER/ADRM	Chris Joneckis, PhD, Senior Advisor, CMC, OD/RMS
Eastern Research Group	Patrick Zhou
CDER	Kim Taylor, OSP

Novo Nordisk Attendees:

Anne Prener, Senior Vice President Haemophilia R&D Portfolio
 Anja Skands, Senior Drug Product Coordinator, Biopharm Formulation Development
 Anja Suddergaard, Safety Surveillance Advisor, Global Safety
 Andrew Chang, Exec Director, Global Regulatory Affairs
 Bob Clark, Vice President, Regulatory Affairs, US
 Dorthe Kristensen, Area Specialist, Analytical Coordinator, Biopharm QC Support
 Henrik Kim Nielsen, Corporate Vice President, RA Haemophilia
 Frank Bringstrup, Senior Regulatory Project Manager, RA Haemophilia
 Hanne Stampe Jensen, Principal Scientist, DP Manufacturing
 Jens Peder Pedersen, Project Vice President
 Knud Vad, Project Vice President
 Karin Knobe, Vice President, Medical & Science Haemophilia
 Lewis Pollack, Sr. Director, Regulatory Affairs, US
 Niels Kristian Klausen, CMC Project Manager, CMC Haemophilia Portfolio
 Patty Wilson, Sr. Manager, Regulatory Affairs, US
 Per Rexen, Project Director, API Manufacturing
 Sergey Zaets, Director Hemostasis, US
 Sanne Slot Valentin, Vice President, CMC Haemophilia Portfolio
 Stephanie Seremetis, CVP and Chief Medical Officer, Hemophilia R&D Portfolio

BACKGROUND

BLA 125466/0 was submitted on October 15, 2012, for Antihemophilic Factor (Recombinant) [NOVOEIGHT].

Based on the results described above, FDA concluded that the method, as proposed in the BLA, is unsuitable for its intended use. FDA recommended that Novo Nordisk optimize the method to specify the -----(b)(4)----- required for the assay to meet the criteria for both -----(b)(4)-----, and demonstrate that this can be achieved reproducibly through appropriate validation

studies. Alternatively, another method may be developed for the determination of content and (b)(4) in this product.

With reference to the provided slides, Novo Nordisk explained that the (b)(4) method had been validated in accordance to ICH Q2(R1) for the quantitative content of rFVIII -----(b)(4)----- drug product (DP). Novo Nordisk recognized that this method requires -----(b)(4)----- and a well trained technician. Novo Nordisk also stated that -----(b)(4)-----; a standard approach is essential in order to maintain consistency, and noted that the method is under control in their hands. Referring to the March 27, 2013 information request, however, Novo Nordisk had not been able to find a suitable QC method yet, and would follow up with testing ----(b)(4)---- to overcome the problems encountered by the FDA. Novo Nordisk proposed providing a laboratory technician and /or fully translated operating manuals to CBER.

FDA staff have used the same ---(b)(4)--- and have followed the same standard operating procedures (SOPs), but found that the method did not work. FDA would appreciate detailed SOPs and a visit from Novo Nordisk technicians to FDA's [Division of Biological Standards and Quality Control (DBSQC)] laboratory upon concurrence from management. Furthermore, DBSQC had identified a -----(b)(4)----- which could be stably -----(b)(4)----- by a ----(b)(4)---- and met all assay validation criteria stated in the BLA. In addition, DBSQC tested three product lots that met the proposed specifications. DBSQC agreed to share the information on -----(b)(4)-----, and the preliminary data with Novo Nordisk.

b. Discussion on the assignment of potency by one-stage clotting assay.

FDA acknowledged that Novo Nordisk's data demonstrated good agreement between the chromogenic substrate (CS) and one-stage clotting (OC) assays for NOVOEIGHT. FDA's preference is to define the potency of NOVOEIGHT by the OC assay based on the following reasons:

1. The OC assay has historically been used in clinical laboratories world-wide for testing patient plasma samples, and it remains the most commonly used method for FVIII potency.
2. In a series of collaborative studies and assay validation procedures, CS and OC assays showed similar intra- and inter-laboratory variability.

Novo Nordisk understood FDA's preference and agreed to include the OC assay in the specification. However, Novo Nordisk proposed the use of the CS assay globally. to label the potency of the vials.

FDA noted that the potency values derived from the CS assay tend to be higher (b)(4) than those from the OC assay when a plasma standard is used. Depending on the reagents and reference standards, the OC assay values could be expected to be lower than the labeled potency.

Novo Nordisk added that for all recombinant products, they too noticed higher potency values in clinical samples when measured with the CS assay. However, for potency assignment of NOVOEIGHT, because the values derived from both assays are the same, the clinical consequences will be the same.

FDA noted that the EU may be leaving this topic open because the ISTH recommendations cover both assays. FDA reiterated that potency should be determined using methods commonly used in clinical laboratories. FDA indicated that this will be a point of negotiation as the review moves toward the goal date.

c. Overview of pending Information Requests (June 18 & 24, 2013), any clarifications (if needed), and current status of responses (whether any delay of responses is anticipated).

An Information Request regarding specification parameters and stability data was sent on June 24, 2013. Per the July 10, 2013 amendment on DS and DP specifications, Novo Nordisk was working on tightening the acceptance ranges. FDA will comment after all the information has been reviewed.

As illustrated in their slides, Novo Nordisk agreed to combine ----- (b)(4)----- to establish a new parameter: total (b)(4) with a proposed limit of ----(b)(4)----. The specifications for DP release, shelf-life, and in-use stability were set at -----(b)(4)-----, respectively. Novo Nordisk also showed that the specifications for ----(b)(4)---- and endotoxins had been tightened, and specific activity had been added as a parameter following FDA recommendation.

Novo Nordisk also discussed FDA's request to measure excipients in DP, and explained their control strategy based on the validation of the manufacturing process. Novo Nordisk reasoned that measurement of two excipients, ----- (b)(4)----, should provide sufficient control to ensure DP quality. Novo Nordisk also proposed to tighten the --(b)(4)-- specification to (b)(4) to enhance control.

FDA noted that --(b)(4)--- is not an adequate indicator of excipient concentrations because ---(b)(4)-- does not provide information on the amount of individual excipients. Similarly, (b)(4) does not show the exact amount of histidine in DP. Novo Nordisk stated that the process is validated and controls are in place, therefore it is not necessary to measure all the excipients. Novo Nordisk added that doing so would require significant effort and time, which may not be accomplished by the goal date of October 16, 2013.

FDA will review Novo Nordisk's complete responses to the information requests, and reserves further discussion until then.

d. FDA may have comments on Novo Nordisk's responses to Information Requests (Amendments # 17, 18, 21, 22, 23).

At this time, FDA did not have additional comments to Novo Nordisk's responses to Information Requests (Amendments #17, 18, 21-23)

e. FDA may have comments on Novo Nordisk's responses to Form FDA 483 (received on June 21, 2013).

Responses to inspectional 483 items were received on June 21, 2013. Based on a cursory FDA review, additional clarifications will be needed to assess if the corrective actions are adequate. An Information Request related to Observation numbers 1 and 4 was sent on July 4, 2013. An Information Request related to Observation numbers 2 and 3 will be sent in the near future.

3. Current Assessment of the need for Risk Evaluation and Mitigation Strategy (REMS) or other risk management actions:

FDA stated that no issues were identified that would require a REMS or a Postmarketing Requirement study. FDA considers two of the protocols that were submitted in the pharmacovigilance plan, specifically the Previously Untreated Patients study and the Long-Term Treatment Post-authorization study as Postmarketing Commitment (PMC) studies. FDA requested Novo Nordisk to submit specific goal dates for trial completion and final report submissions for both studies.

4. Major Labeling Issues:

FDA advised that the review of the label is ongoing, and therefore specific recommendations for revisions would not be discussed at this time. FDA noted two issues:

- a. The use of tallman lettering is not acceptable. The proprietary name should be written in either all capital letters or with only the initial letter capitalized. FDA advised that a new request for proprietary name review be submitted.
- b. FDA will no longer allow the term "plasma/album free" to be used in the product name. For consistency, whenever the opportunity arises, FDA will work with manufacturers to revise the labels of licensed products that currently use this or similar terms.

5. Postmarketing Requirements/Postmarketing Commitments

A milestone scheduled for the two planned PMC studies (trials NN7008-3553 and NN7008-3809) listed in the pharmacovigilance plan (PVP) should be submitted.

Novo Nordisk replied that their commitments will be included in the July 29, 2013 response.

6. Questions from Novo Nordisk:

Novo Nordisk appreciated FDA's clarification on the critical points that were discussed. The Applicant had one concern regarding the inspection of the ---(b)(4)--- facility, and inquired if FDA could comment on their responses to the 483 observations. Novo Nordisk stated that its executive management is committed to resolve all the issues, and its staff has completed 22 of 37 actions. FDA explained that the Division of Case Management is currently reviewing the inspectional findings and Novo Nordisk's responses to the 483 observations. The status of the review was not available for this meeting.

7. Wrap up and Action Items

1. Novo Nordisk will send fully translated manuals so that FDA may better reproduce the ---(b)(4)--- assay.
2. Novo Nordisk will send a technical expert(s) to assist with performing the assay.
3. DBSQC will provide Novo Nordisk their ---(b)(4)--- method that appears to show better performance than the Novo Nordisk method, and will also provide preliminary data obtained using this method.
4. Novo Nordisk will submit complete responses to the June 24, 2013 Information Request (Specification and Stability) by July 29, 2013. Also, the two clinical PMCs will be included in this response.
5. FDA will send an Information Request related to Novo Nordisk's responses to Form FDA 483 observations within one week.
6. FDA will send an Information Request with recommendations for labeling revisions.
7. Discussion on potency assignment for NOVOEIGHT will continue. Novo Nordisk will submit their justifications to use the chromogenic substrate assay in their responses to the June 24, 2013 Information Request, or as soon as available, as an amendment to the BLA file.
8. Discussion on measurement of excipients will continue. FDA will provide comments after reviewing Novo Nordisk's responses.

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