



Late-Cycle Meeting Summary

Application type and number: STN BL 125555/0
Product name: Antihemophilic Factor (Recombinant),
Applicant: Octapharma Pharmazeutika Produktionsges.m.b.H.
Meeting category: Late Cycle Meeting (LCM)
Meeting date & time: May 4, 2015, 12:20 p.m. to 1: 20 p.m.
Meeting format: Teleconference
Meeting Chair/Leader: Basil Golding, MD
Meeting Recorder: Jiahua Qian PhD

LCM package sent: April 28, 2015

FDA Attendees:

Victor Baum, MD, Clinical Review Branch, Division of Hematology Clinical Review, OBRR
Lokesh Bhattacharyya, PhD, Chief, Laboratory of Analytical Chemistry and Blood Related Products, Division of Biological Standards and Quality Control, OCBQ
La'Nissa Brown-Baker, PhD, Pharmacologist, Division of Hematology Clinical Review, OBRR
Karen Campbell, Biologist, Division of Biological Standards and Quality Control, OCBQ
Wambui Chege, MD, Medical Officer, Division of Epidemiology, OBE
John Eltermann, RPh, MS, Director, Division of Manufacturing and Product Quality, OCBQ
Jay Epstein, MD, Director, Office of Blood Research and Review
Mahmood Farshid, PhD, Deputy Director, Division of Hematology Research and Review, OBRR
Basil Golding, MD, Director, Division of Hematology Research and Review, OBRR
Ellen Huang, Consumer Safety Officer, Division of Manufacturing and Product Quality, OCBQ
Colonious King, Consumer Safety Officer, Division of Inspections and Surveillance, OCBQ
Timothy Lee, PhD, Acting Chief, Laboratory of Hemostasis, Division of Hematology Research and Review, OBRR
Min Li, PhD, Mathematical Statistician, Division of Biostatistics, OBE
William McCormick PhD, Director, Division of Biological Standards and Quality Control, OCBQ
Erin McDowell, Consumer Safety Officer, Division of Inspections and Surveillance, OCBQ
Marion Michaelis, Chief, Review Branch II, Division of Manufacturing and Product Quality, OCBQ
Paul D. Mintz, MD, Director, Division of Hematology Clinical Review, OBRR
Loan Nguyen, PharmD, Consumer Safety Officer, Division of Case Management, OCBQ
Michael Ovanosov PhD, Senior Staff Fellow, Division of Hematology Research and Review, OBRR
Ze Peng, PhD, Biologist, Division of Hematology Research and Review, OBRR
Jiahua Qian, PhD, Regulatory Project Manager Staff, OBRR

Renee Rees, PhD, Lead Mathematical Statistician, Division of Biostatistics, OBE
Andrey Sarafanov, PhD, Chemist, Division of Hematology Research and Review, OBRR
Michael Vardon, Consumer Safety Officer, Division of Manufacturing and Product Quality,
OCBQ

Mark Weinstein, PhD, Associate Deputy Director, OBRR
Boguang Zhen PhD, Chief, Therapeutics Evaluation Branch, OBE

Contractor Participant:

(b) (4)

Octapharma Attendees:

Josef Weinberger, Corporate Quality and Compliance Officer
Peter Stenlund, Analytical Specialist QC
Johanna Persson, Analytical Specialist QC
Ann-Christine Eskekärr-Head of QC Laboratory
Parivash Gunnerfält, Head of Quality Unit
Christina Leo, Head of Production Unit
Annika Dahl, Validation Engineer
Martin Zarazua Mujo-Validation Administrator
Shahla Eskandari, Validation Engineer
Ulf Höglund, Head of Validation
Irena Knappik, Project Manager
Olaf Walter, Board Member International Business Unit
Larisa Belyanskaya, VP Head of International Business Unit Haematology
Sigurd Knaub, Vice President Clinical R&D
Johann Bichler, Senior Clinical Project Manager
Ulrich Thibaut, Board Member R&D
Maya Tiemeyer, Scientific Head Octapharma Biopharmaceuticals
Jürgen Römisch, Senior Vice President R&D
David Holliday, Vice President of Commercial Development
Tor-Einar Svae, Senior VP Scientific & Medical Affairs
Stanley Ammons, Senior Director Compliance & Government Policy
Marianne Hollaus, Int. Drug Regulatory Affairs Manager
Melanie Six, Int. Drug Regulatory Affairs Manager
Barbara Rangetiner, Director Int. Drug Regulatory Affairs

Background and Objectives:

Octapharma requested postponement of the late cycle meeting that was originally scheduled for February 18, 2015. The meeting was rescheduled for May 4, 2015. The purpose of the meeting is to share information, to discuss substantive review issues, and to communicate our objectives for the review cycle of STN BL 125555/0 for Antihemophilic Factor (Recombinant),

FDA conveyed the Late-Cycle Meeting package to Octapharma on April 28, 2015, and received five information amendments since then. Some questions have been resolved and the remaining issues are to be addressed at this meeting.

Discussion:

FDA Questions 1-5 in LCM package:

These questions are related to a number of ambiguities/deficiencies found in the data for validation of the (b) (4) Assay used for (b) (4) analysis.

Additional discussion:

FDA stated that in response to our previous IR, Octapharma indicated in Amendment # 37 that they observed (b) (4) when the (b) (4). Octapharma reported that their investigation showed that there was (b) (4)

However, FDA pointed out that the conclusion was not consistent with the results provided in Amendment #27, which shows that (b) (4)

are necessary. In addition, analyses by a (b) (4) method in the DBSQC laboratory showed that the results depend upon the method (b) (4).

When (b) (4) was used (same (b) (4) method as Octapharma), the (b) (4) and (b) (4) respectively for three lots that were analyzed. However, when

monitored by (b) (4) these (b) (4) for both (b) (4)

This is presumably because (b) (4)

Octapharma should develop an appropriate (b) (4) method, validate the method, and reanalyze the retains of clinical and validation lots to reevaluate the specifications.

This may take some time and could be done after approval. Octapharma was advised to develop a (b) (4) method during inspection of the facility in Stockholm on October 24, 2014, and also on a teleconference in December 17, 2014. Octapharma informed that they attempted to develop an alternate (b) (4) method but was unable to provide a reasonable method.

Based on the discussion with Octapharma, FDA requested two PMCs to resolve the issue – one short term and the other longer term, in relation to the (b) (4) analysis of the recombinant Antihemophilic Factor (FVIII), as discussed below.

1. Octapharma will validate their current (b) (4) method, as described in their SOP # 130SOP735/09. Octapharma will reanalyze all retains from the clinical and validation lots of the product using the method after it is successfully validated. Octapharma will reevaluate their specifications for (b) (4) based on the results and submit their results to FDA for review. Octapharma will provide a plan and time-line for completing the proposed PMC for review and approval by FDA within one week of receiving the written request.
2. Octapharma will receive via technology transfer from FDA an (b) (4) method, which involves (b) (4), for analysis of the (b) (4) of Nuwiq (STN BL 125555). Octapharma will commit resources to work with FDA to evaluate the method within 3 months after receiving the procedure. It will develop a plan and timeline to validate the method and reanalyze all retains from the clinical and validation lots of the product using the method after it is

successfully validated, and submit the results for approval by FDA. Octapharma will reevaluate the specifications for (b) (4) of Nuwiq based on the results and submit a new assay, validation, and product specifications to FDA for review as a Prior Approval Supplement (PAS).

FDA Question 6 in LCM package:

You have provided us information on prophylactic use. Please indicate if an indication for prophylaxis is desired.

Additional Discussion

FDA was uncertain from Octapharma's package insert, dated April 29, 2015, whether Octapharma's use of the word "prevent" meant that they wished to obtain an indication for routine prophylaxis. Octapharma stated that they are seeking an indication for routine prophylaxis, and that they thought they had provided enough information about dosing and prophylaxis trial results in the package insert for this purpose. FDA, however, did not find the submitted material sufficient. Octapharma did not provide analysis-ready data sets in its original application to enable FDA to compare the prophylaxis data to the on-demand data to show a 50% reduction in ABR. FDA will need to review these data, and use analysis-ready data sets/programs to verify Octapharma's reported results to support the prophylaxis indication.

FDA requested Octapharma submit the analysis-ready data to support the prophylaxis indication in SAS transport format by Tuesday, May 5, 2015. FDA informed Octapharma that the review of these data and results may not be completed prior to the action due date because of the substantial change in the indication.

FDA asked Octapharma either to provide analysis-ready data to support the prophylaxis indication, which will be considered as a major amendment and extend the review clock for 3 months, or to submit a supplement for the prophylaxis indication.

END

Concurrence Page

Application Number: STN 125555/0

Letter Type: Late Cycle Meeting Summary (LCMS)

Cc: EDR

History: Drafted/Revised Jiahua Qian/ May 5, 2015
 Reviewed/Revised Victor Baum /May 7 & 25, 2015
 Reviewed/Revised Min Lin / May 13 & 25, 2015
 Reviewed/Revised Lokesh Bhattacharyya / May 13 & 27, 2015
 Reviewed/Revised Andrey Sarafanov /May 13, 2015
 Reviewed/Revised Mark Weinstein/ May 15, 2015
 Reviewed/Revised Nannette Cagungun/ May 27, 2015
 Reviewed/Revised Trevor Pendley/ May 27, 2015

Minutes verified:

(for attendees)	_____ Andrey Sarafanov	_____ Lokesh Bhattacharyya
	_____ Lin Min	_____ Renee Rees
	_____ Victor Baum	_____ William McCormick
	_____ Paul D. Mintz	_____ Mark Weinstein

Concurrence box

Office	Name/Signature
OBRR	Jiahua Qian
OBRR	Trevor Pendley
OBRR	Basil Golding