Mid-Cycle Meeting Summary

Application type and number: BLA, STN BL 125612/0

Product name: Fibrinogen (Human)

Proposed Indication: For the treatment of acute bleeding episodes (b) (4) in adult and pediatric patients with congenital fibrinogen deficiency, including afibrinogenemia and hyperfibrinogenemia

Applicant: Octapharma Pharmazeutika Produktionsges.m.b.H.

Meeting date & time: November 17, 2016, 2:30 pm to 3:30 pm, EST

Committee Chair: Ze Peng

RPM: Lorraine Wood

Attendees:

Discipline	Name [with credentials (not title)]	Attended meeting?
Regulatory Project Manager (RPM)	Lorraine Wood, MS, MLS(ASCP)CM	Y
Chair & Product Reviewer	Ze Peng, PhD	Y
Clinical Reviewer	Victor Baum, MD	Y
Clinical Pharmacology Reviewer	Iftekhar Mahmood, PhD	Y
Non- clinical Pharmacology & Toxicology Reviewer	Yolanda Branch, PhD	Y
OCBQ/DMPQ Reviewer	Randa Melhem, PhD	Y
OCBQ/DMPQ/PRB Reviewer	Jacqueline Glen	N
Statistical Reviewer of non-clinical data and clinical data	Shuya (Joshua) Lu, PhD	Y
Post-marketing Safety Epidemiological / Pharmacovigilance Reviewer	Faith Barash, MD, MPH	Y
OCBQ/APLB Reviewer	Alpita Popat, PharmD	Y
OCBQ/BIMO Reviewer	Anthony Hawkins, MS	Y
OCBQ/DBSQC Regulatory Coordinator	Varsha Garnepudi	Y
Consult Reviewer	Sapana Patel, PharmD, CDRH	Y
Consult Reviewer	Rakhi M. Dalal, PhD, CDRH	N
OCBQ/DBSQC Reviewer	Tao Pan, PhD	Y
OCBQ/DBSQC Reviewer	Grainne Tobin	Y
OCBQ/DBSQC Reviewer	Obinna Echeozo	Y

Discipline	Name [with credentials (not title)]	Attended meeting?
Other Attendees		
OTAT/IOD, Director	Wilson Bryan, MD	Y
OTAT/IOD, Deputy Director	Stephanie Simek, PhD	Y
OTAT/DRPM/RPMBII, Branch Chief	Patrick Riggins, PhD	Y
OTAT/DCEPT/PTBI, Branch Chief	Mercedes Serabian, PhD	Y
OTAT/ DCEPT/PTBI, Team Leader	Becky Robinson, PhD	Y
OTAT/DPPT/HB, Acting Branch Chief	Tim Lee, PhD	Y
OTAT/DPPT, Deputy Director	Mahmood Farshid, PhD	Y
OBRR/IOD, Associate Deputy Director for Science	Mark Weinstein, PhD	Y
OTAT/DCEPT/CHB, Branch Chief	Bindu George, MD	Y
OTAT/DCEPT/GMBI, Team Leader	Mitchell Frost, MD	Y
OBE/DB, Team Leader	Renee Rees, PhD	Y
OCBQ/DMPQ/MRBII	Ellen Huang	Y

Discussion Summary:

Report and Discuss:

1. Reviewers' Reports

   CMC (Ze Peng) - There are no substantive review issues that will prevent approval or impact the review timeline of this application. However, IRs will be conveyed to Octapharma on the release specifications of the drug product, and the physical segregation of the unit operations before and after the nanofiltration step by the end of December 2016.

   Primary discipline review will be completed by January 30, 2017.

   Clinical (Victor Baum) - A Pediatric Study Plan (PSP) was not submitted in the application. In response to a telecon held on November 10, 2016 among Victor Baum, Lorraine Wood and Octapharma, a pediatric study plan will be submitted to the application within the next two weeks. This may be based on the original pediatric protocol submission and may require revisions based on prior input from FDA to allow approval of an Agreed iPSP. In addition, the original submission of the pivotal trial was at approximately the time of FDASIA cutoff. We are exploring exact date that would exclude from PREA (date of protocol submission vs. date of initiation). Primary discipline review will be completed by December 30, 2016. The current label requests indication for adult and pediatric patients. Given that there are no pediatric data for age <12, this will need to be revised during the labeling review.

CMC Facilities (Randa Melhem) - The primary discipline review is anticipated for completion by January 10, 2017. Please refer to item # 11 regarding inspections.

Bioresearch Monitoring (Anthony Hawkins) - There are no substantive review issues that will prevent approval at this time. The primary discipline review is anticipated to be completed within 30 days after CBER receipt and review of each of the four completed inspection reports (EIR packages).

Quality Control Testing Plan (Varsha Garnepudi) - No substantive review issues identified at this time. The lot release testing plan is being drafted.

CMC-Fibrinogen (b) (4) (Granine Tobin) - Completion of primary discipline review is anticipated by January 30, 2017. There are no substantive review issues that will affect approval of the application.

CMC (Obinna Echeozo) - The applicant submitted the sterility validation information without some pertinent information. An IR was sent to the applicant and its response was received. No further issues at this time.

Quality Control (Tao Pan) - Primary discipline review anticipated completion upon review of responses from the applicant to IR.

Pharmacovigilance/Epidemiology (Faith Barash) - No substantive review issues that will affect the approval of this application. A summary of the safety concerns is listed below:

Summary of safety concerns	
Important Identified Risks	- Hypersensitivity reactions, including anaphylactic reactions - Thromboembolic events
Important Potential Risks	- Suspected transmission of infectious agents
Missing Information	- Safety in elderly patients - Safety in pregnant or breast feeding women - Safety in patients with hepatic impairment

Clinical Pharmacology (Iftekhar Mahmood) - There are no substantial issues at this time. Primary discipline review is anticipated to be completed by December 15, 2016.

Statistics (Shuya (Joshua) Lu) - No substantive review issues that will affect the approval of the application identified at this time. Primary discipline review is anticipated to be completed by December 9, 2016. One clinical study, FORMA-02, was submitted to this BLA and is considered the pivotal study according to the applicant. FORMA-02 was a prospective, open-label, uncontrolled, phase III study. The primary

outcome was the number of subjects with "success" which was defined as a rating of 'excellent' or 'good' in the overall clinical assessment of the first documented bleeding episode of each patient. The success rate was pre-specified as 70%. It is an interim analysis (IA) report for this submission. The applicant plans to enroll 24 subjects; 11 subjects are included in this IA. Of these 11 subjects, the rate of success for the treatment of the first BEs is 100% and the 2-sided Blyth-Still-Casella confidence 90% CI is (80, 100).

Pharmacology/Toxicology (Yolanda Branch) - No substantive review issues that will affect the approval of this application are identified at this time. Primary discipline review is anticipated to be completed by January 13, 2017.

2. The review committee confirmed that no Discipline Review Letters will be issued for this application.

3. The current thinking of the review committee is that this BLA will not be presented at the meeting with the Blood Products Advisory Committee.

4. The review committee identified no need for Post-marketing Commitments, Post-marketing Requirements or a Risk Evaluation and Mitigation Strategy (REMS) at this time.

5. National Drug Code (NDC) assignments are currently under review.

6. Proper naming convention is under review.

7. DMPQ and product office agreed to waive the GMP pre-license inspection, and the inspection waiver memo has been uploaded in the EDR.

   The status of BIMO inspections is summarized as follows:

Protocol / Study Site for BIMO Inspection	**Status of Inspection**
FORMA-01 / Study Site # 11 - Bangalore, India	Inspection Pending - ORA scheduled inspection dates 11/07 -11/11/2016
FORMA-01 / Study Site # 51 - London, UK	Inspection Pending - ORA scheduled inspection dates 11/21 - -11/26/2016
FORMA-02 / Study Site # 91 - Bangalore, India	Inspection Pending - ORA scheduled inspection dates 11/14 - 11/18/2016
FORMA-02 / Study Site # 10 - London, UK	Inspection Pending - ORA scheduled inspection dates 11/28 - 12/02/2016

8. Major target and milestone dates from RMS/BLA. Discussed pending dates of targets and milestones.

Mid-Cycle Communication Telecon	December 12, 2016
Late-Cycle Meeting	February 22, 2017
Labeling Target	May 10, 2017
PMC/PMR Study Target if FDA has	May 10, 2017
First Action Due	June 9, 2017

9. Labeling review will begin after the Late-Cycle Meeting.

10. Components Information Table was obtained and notification will be sent to the Data Abstraction Team (DAT) if discrepancies are found per *SOPP 8401.5: Processing Animal, Biological, Chemical Component Information Submitted in Marketing Applications and Supplements.* It should be completed by the end of December 2016.

11. New facility information is included in the application, requiring implementation of regulatory job aid *JA 910.01: Facility Data Entry.* If not complete, indicate date it will be completed. There is no new facility information in this application. The inspection was waived for the OPG Vienna facility (manufacturing packaging and labeling) (b) (4) facility (packaging and labeling). The inspection waiver memos are in the EDR.

    Please note that there were no data in the initial BLA submission to support packaging/ labeling of Fibrinogen (Human) at the (b) (4) facility, and Octapharma was informed that they need to submit supportive data or withdraw this facility from STN BL 125612/0. Octapharma responded in amendment STN BL 125612/0.15 (received 10 November 2016) that "*data to demonstrate validation of visual inspection, packaging and labeling of Fibrinogen at the* (b) (4) *are currently not available. Therefore, we hereby withdraw the submission of* (b) (4) *as VI, labelling and packaging site. Section 2.2 Introduction, 2.3.P Drug Product, 2.3.A Appendices, 3.2.S.2.2 Description of Manufacturing Process and Process Controls and 3.2.P.3.1 Manufacturers have been updated accordingly. Section 3.2.A.1 Facilities and Equipment (manufacturer: Octapharma* (b) (4) *) has been deleted*".

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

    The review committee considered that lot release by CBER is needed for the licensure of this class of products. Additionally, as part of the review of the BLA, conformance lots of this product will be assessed by DBSQC.

13. Unique ingredient identifier (UNII) code process has been initiated. Review in progress.

14. PeRC presentation was originally scheduled for December 7, 2016. PeRC presentation is withdrawn and will be requested again in the future after the pediatric plan is submitted to the application.