



Our Reference: BL 125555/0

**LATE CYCLE MEETING
BACKGROUND PACKAGE**

Octapharma Pharmazeutika Produktionsges.m.b.H.
Attention: Mr. Stanley Ammons
Octapharma USA, Inc.
121 River Street, Suite 1201
Hoboken, NJ 07030

Dear Mr. Ammons:

Please refer to your biologics license application (BLA), submitted under section 351(a) of the Public Health Service Act, for Antihemophilic Factor (Recombinant), rAHF .

We also refer to the Late Cycle meeting (LCM) scheduled for May 4, 2015. Attached is our background package, to include a review status update and an agenda for the meeting.

If you have any questions, please contact Jiahua Qian at (240) 402-8432.

Sincerely,

A handwritten signature in cursive script, appearing to read "B. Golding", is written above the typed name.

for Basil Golding, MD
Director
Division of Hematology Research and Review
Office of Blood Research and Review
Center for Biologics
Evaluation and Research

ENCLOSURE:
Late Cycle Meeting Background Package

LATE CYCLE MEETING BACKGROUND PACKAGE

Meeting Date and Time: Tuesday, May 4 2015; 1:00 p.m. - 2:00 p.m. EDT

Meeting Location: Face to face or Teleconference

Application Number: STN 125555/0

Product Name: Antihemophilic Factor (Recombinant)

Indication: Indicated for the control and prevention of bleeding episodes (also during and after surgery) in adults and children with Hemophilia A.

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

INTRODUCTION

The purpose of this Late Cycle meeting (LCM) is to share information, to discuss substantive review issues identified to date, and to communicate our objectives for the remainder of the review cycle. The application has not yet been fully reviewed by the signatory authority, division director or chairperson; therefore, the meeting will not address the final regulatory decision for the application. We are sharing this information to promote collaborative and successful discussion.

Please be advised that any new information submitted before the LCM that had not been requested by the Agency will not be addressed during the meeting. Furthermore, during the meeting, we may request the submission of additional information, as necessary, to address identified issues. Our planned review timelines for any requested additional information will be communicated to you during the meeting.

SUBSTANTIVE ISSUES TO BE DISCUSSED AT THE LATE CYCLE MEETING:

CHEMISTRY, MANUFACTURING AND CONTROLS

For (b) (4) Analysis:

1. The method you originally validated did not (b) (4) step. (b) (4) has a substantial impact on assay results; therefore introduction of this step constitutes a substantial change in the assay method. Please revalidate the revised method based on (b) (4) and submit relevant data for review.
2. Please analyze retains of lots used in clinical trials by the revised method after it is revalidated to see if there are significant differences in assay results, and submit data for review.
3. The procedure you used to identify (b) (4) is not acceptable. (b) (4) in Amendment 35 shows that the (b) (4) for three of the batches, (b) (4). It was obvious that the results for these three lots would have failed to meet acceptance criterion for the (b) (4) Section 6.1 of your SOP (130SOP735/08) permits (b) (4) of (b) (4). We have concerns about the (b) (4) because of the information we discussed above and also because, in general, employing a (b) (4) has the potential to introduce personal bias. Please revise your SOP, before the method is revalidated, to delete the (b) (4) option and indicate that (b) (4) method of your (b) (4).
4. Please reanalyze all validation lots of the drug product following the revised and validated procedure using the (b) (4) method described above, including the batches (b) (4) and submit the results.
5. Your (b) (4) in Amendment 35 (b) (4). However, you have not considered (b) (4). Please provide appropriate data to (b) (4). Unless your data show otherwise, please include (b) (4) and submit the results to show that they still meet your proposed acceptance criteria.

NON-CLINICAL PHARMACOLOGY / TOXICOLOGY

There are no substantive review issues at this time.

CLINICAL PHARMACOLOGY

There are no substantive review issues at this time.

CLINICAL

6. You have provided us information on prophylactic use. Please indicate if an indication for prophylaxis is desired.
7. You have indicated a higher dose range in pediatric subjects. Please provide us with information to substantiate that rounding up accounted for the higher dosing in children and not pharmacokinetic differences between pediatric and adult subjects.

BIORESEARCH MONITORING

There are no substantive review issues at this time.

PHARMACOVIGILANCE

There are no substantive review issues at this time.

LABELING

FDA revised PI was sent to the OCTAPHARMA on April 22nd

ADVISORY COMMITTEE MEETING

Presentation of the BLA at the Blood Products Advisory Committee meeting is not planned.

REMS OR OTHER RISK MANAGEMENT ACTIONS

No issues were identified that would require a Risk Evaluation and Mitigation Strategy (REMS).

DMPQ

The following issues need additional clarification:

8. Shipping validation data for summer and winter for the 8mL product vial and the 3 mL diluent syringe, including overseas transportation.
9. Please explain how the limit of detection for a critical leak is less than or equal to (b) (4) for the 3 mL diluent syringe. Also please provide data demonstrating that the operators can (b) (4) that approaches a critical leak.

10. The (b) (4) criteria for the cleaning of filling equipment should reflect the WFI specification of (b) (4). You state that your acceptance criterion for (b) (4) cannot be tightened due to the influence of (b) (4) in the surrounding rooms impacting sampling. Please clarify where the (b) (4) are coming from and what you are doing to mitigate the impact of the (b) (4) on the filling equipment. Furthermore, please explain how you can assess if the high (b) (4) results are actually from the (b) (4) or residues on the equipment.

OUTSTANDING INFORMATION REQUESTS

DMPQ	IRs dated April 23 and 24, 2015; Requested response date April 29, 2015.
DBSQC	IR dated April 22, 2015; Requested response date April 29, 2015.
	IR April 27, 2015; Requested response date May 4, 2015
	Labeling IR dated April 23, 2015; Requested response date April 29, 2015.

POSTMARKETING STUDIES NOT SUBJECT TO REPORTING REQUIREMENTS OF 21 CFR 601.70

None up to date

END

LCM AGENDA

1. Introductory Comments – 5 minutes (RPM/Chair)
Welcome, Introductions, Ground rules, Objectives of the Meeting
2. Discussion of Substantive Review Issues – 40 minutes
 - a. Other noted issues
 - b. Outstanding information requests
3. Post-marketing commitments and risk management – 5 minutes
4. Questions from OCTPHARMA – 5 minutes
5. Wrap up and Action Items – 5 minutes