

# Summary of Bioresearch Monitoring Inspections Memo - XYNTHA

## MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
Public Health Service  
Food and Drug Administration  
Center for Biologics Evaluation and Research

DATE  
January 4, 2008

FROM  
Bhanu Kannan, Bioresearch Monitoring Branch, HFM-664  
Division of Inspections and Surveillance  
Office of Compliance and Biologics Quality

THROUGH  
Patricia Holobaugh, Chief, Bioresearch Monitoring Branch, HFM-664

TO  
Timothy Lee, HFM-392  
Chair, BLA Licensing Committee

SUBJECT  
**Summary of Bioresearch Monitoring Inspections**  
SPONSOR: Wyeth Pharmaceuticals  
PRODUCT: Moroctocog alfa (AF-CC)  
BLA: STN 125264/0

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## Summary

The bioresearch monitoring inspections of three clinical investigators did not reveal significant problems that impact the data submitted in the Biologics Licensing Application (BLA). The problems found during the inspections at one clinical site are noted in this memorandum.

## Background

Inspections of three clinical sites were requested in support of the BLA and were conducted in accordance with FDA's Compliance Program Guidance Manual (CPGM) 7348.811, Inspection Program for Clinical Investigators. The inspection assignment included specific questions on the following study protocol entitled *A Randomized, Two-way Blinded Crossover-Design Study to Establish the Bioequivalence of B-Domain Deleted Recombinant Factor VIII (BDDrFVIII, Moroctocog Alfa [AF-CC]) with a Full-Length Recombinant factor VIII Preparation (FLrFVIII, Advate), Followed by an open-Label Trial Safety and Efficacy of Moroctocog Alfa (AF-CC) in Previously Treated Patients with Hemophilia A (Protocol 3082B2-310-WW).*

The inspections were conducted at three clinical sites and represented 15% of the total subjects enrolled in the study submitted in the BLA. The data audit portion of the inspection focused on the verification of the study data on safety and efficacy endpoints submitted by the sponsor in the BLA for all the enrollees at the inspected site. The following table identifies the inspection results.

### Inspection of clinical sites and outcome

Clinical investigator	Study site / Site #	Location	Number of subjects enrolled/PK subjects	Form FDA 483 issued	Final classification
Michael Recht, M.D., Ph.D.	Phoenix Children's Hospital /001	Phoenix , AZ	6/4	No	NAI
M. Elaine Eyster, M.D	Milton Hershey Medical Center/005	Hershey , PA	4/2	No	NAI
Marilyn Manco-Johnson, M.D.	University of Colorado Health Sciences Center /031	Aurora , CO	4/0	Yes	VAI

VAI-Voluntary Action Indicated NAI-No Action Indicated

### Inspectional findings

1. Failure to prepare and maintain adequate records of drug disposition. [21 CFR § 312.62(a) ]. For subject -----, the investigator did not maintain adequate records of drug disposition and use of eight vials by the subject:
  - o The pharmacy Dispensing and Inventory Master Records indicate the return of 32 used study drug vials on 6/21/06. We note that the pharmacy dispensed 26 vials on 5/19/06. Of the 32 vials returned, 8 were from the total vials dispensed on 4/26/06 and 24 were from the total vials dispensed on 5/19/06. However, the

subject diaries and drug infusion records account for the use of 30 vials between 5/19/06 and 6/21/06, a discrepancy of 2 vials. The investigator agreed that another two vials were not accounted for.

- The pharmacy Dispensing and Inventory Master Records indicate the return of 20 used drug vials on 10/6/06. 17 of the 20 study drug vials used were from the total vials dispensed on 9/15/06 and 3 vials were from the study drug dispensed on 9/13/06 when the subject made an unscheduled visit to the pharmacy. However, subject diaries and the infusion log indicate the use of 16 vials between 9/18/06 and 10/2/06 and did not account for 4 vials that were used and returned.

Without adequate documentation we cannot determine if the subject used the vials and whether they were used for routine prophylaxis or on-demand bleeding episodes.

2. Failure to prepare and maintain adequate and accurate case histories. [ 21 CFR § 312.62(b) ]. The investigator maintained multiple copies of case report forms (CRFs) that were discrepant, had out-of-order entries, or had corrections without any rationale as shown in the examples:

For subject ----- the following document deficiencies were noted for the routine prophylaxis infusions:

- The CRF for visit-8 contained out-of-order entries, and an infusion on 8/3/06 was crossed out without explanation and in apparent contradiction to the subject diary.
- The CRF for visit-6 contained out-of-order entries for the dates of infusion.
- The CRF entry for the time of infusion on 6/15/06 for visit-6 conflicts with the source data in the subject diary for routine prophylaxis. Further, the study coordinator added then crossed out the infusion on 5/19/06 without a rationale.
- The CRF entry for visit-5 for the infusion on 5/9/06 was not adequately supported by the corresponding source data, subject's diary for routine prophylaxis infusions, as the dates are inconsistent in subject's diary. Further, it appears that the study coordinator crossed out the infusion on 5/19/06.

For subject -----, the CRF (Book 93 page 48) entry for the non-scheduled infusion on 5/8/06 conflicted with the subject diary data as the subject's diary has an illegible date and an infusion time that does not match with the transcribed CRF entry.

3. Failure to include all basic elements of the informed consent. [ 21 CFR § 50.25(a)(5) ]. Dr. Manco-Johnson failed to include one of the basic elements in the informed consent obtained from subjects. The consent/assent forms approved by the ----- Institutional Review Board ----- and signed by subjects or the

subject's legally authorized representative do not indicate the possibility that FDA may inspect the records.

**Sponsor issues:**

***Document discrepancies: Site 031 (Dr. Manco-Johnson)***

4. Documents were discrepant for subject randomization dates for 3 of 4 subjects enrolled at the site as illustrated:

Subject #	Source document	BLA table 16.1.7
----	4/27/06	4/3/06
----	5/9/06	4/3/06
----	5/12/06	5/9/06

5. Documents are deficient or discrepant for the number of days subject ----- participated in the study. The sponsor reported that subject ----- was discontinued from the study after 47 exposure days (110 days on routine prophylaxis) due to non-elective surgery. However, study records document that this subject exited the study on 8/14/06 after receiving an infusion of 3 vials at the clinic and that no vials were distributed after 8/14/06. Further, the visit on 8/14/06 was an unscheduled visit and the subject was scheduled to have surgery on 8/22/06. Study documents indicate that the conclusion visit was on 8/22/06. Due to the discrepancy in the randomization date as described in item 4 above we could not determine the accurate number of days subject ----- participated in the study.

**BIMO actions**

We will issue letters to Drs. Eyster, Manco-Johnson, and Recht. Should you have any questions or comments about this memo or any aspect of Bioresearch Monitoring, please contact me at 301-827-6188.

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Bhanu Kannan