

Recommendation to Waive Pre-Approval Inspection - XYNTHA

Food and Drug Administration

Center for Biologics Evaluation and Research

Division of Manufacturing and Product Quality

Recommendation to Waive Pre-Approval Inspection

Date: September 27, 2007, 2007

From: Daniel Kearns, HFM-675, CMC/Facility Reviewer

To: BLA File - STN 125264/0

Subject: Recommendation to waive the pre-approval inspection for ReFacto® to produce Antihemophilic Factor (Recombinant), Plasma/Albumin-free (also referred to as Moroctocog Alfa (AF-CC) and B-Domain Deleted Recombinant Factor VII (BDDrFVIII, ReFacto AF)

Sponsor: Wyeth Pharmaceuticals, Inc.

Product: Antihemophilic Factor (Recombinant), Plasma/Albumin-free

Through: Carolyn Renshaw, Branch Chief, HFM-675

PDUFA February 23, 2008

ACTION

DUE DATE:

Concurrent Clearance Routing

John A. Eltermann, Jr., R.Ph.,

M.S.

Date

Concur

Do Not Concur

Director, Division of Manufacturing and

Product Quality, HFM-670

Office of Compliance and Biologics Quality

Center for Biologics Evaluation and Research

Basil Golding,

M.D.

Date

Concur

Do Not

Concur

Director, Division of Hematology, HFM- 330

Office of Blood Research and Review

Center for Biologics Evaluation and Research

Summary:

This memorandum recommends that a pre-approval inspection be waived for Wyeth Pharmaceuticals, Inc.'s (Wyeth) biologic license application STN 125264/0 for the manufacture of ReFacto® to produce Antihemophilic Factor (Recombinant), Plasma/Albumin-free (also referred to as Moroctocog Alfa (AF-CC) and B-Domain Deleted Recombinant Factor VII (BDDrFVIII, ReFacto AF). Concurrence for this recommendation is requested.

History:

Wyeth is a licensed biologics manufacturer. The applicant's product consists of ReFacto® Antihemophilic Factor, Recombinant and is a B-Domain Deleted recombinant antihemophilic FVIII [BDDrFVIII] (STN 103779) and was submitted to the FDA on February 2, 1998 and received approval on March 6, 2000. Wyeth Pharmaceuticals, Inc. has submitted a BLA (125264/0) for Antihemophilic Factor (Recombinant), Plasma/Albumin-free. This Antihemophilic Factor (Recombinant), Plasma/Albumin-free represents a modified drug substance manufacturing process from the currently approved product ReFacto® Antihemophilic Factor (Recombinant) STN 103779 (formerly BLA 98-0137).

Wyeth states that it has developed an improved manufacturing process for the drug substance that eliminates the need for all human- or animal-derived proteins from the manufacturing process and in addition incorporates virus-retaining filtration. The significant changes contained in this application include:

- -----
- Elimination of human serum albumin in the cell culture media
- Replacement of the monoclonal antibody Sepharose resin with a chemically-synthesized affinity ligand resin (TN 8.2)
- Introduction of a virus-retaining filtration step -----

One page determined

not to be releasable

Basis for the Waiver:

This waiver is based on criteria outlined in CBER SOPP 8410 "Determining When Pre-

Licensing/Pre-Approval Inspections (PLI/PAI) are Necessary." As stated in the aforementioned SOPP, it is CBER's policy that a pre-license or pre-approval inspection will generally be necessary for a pre-approval supplement if any of the following criteria in bold are met:

- **The facility does not hold an active US license.**
Wyeth holds US license 3
- **The facility has not been inspected in the last two years by the FDA.**
The ----- facility was inspected within the last two years; the last inspection occurred ----- (Dr. T. Lee was one of the inspectors) and was classified VAI. ----- was inspected from ----- and was classified VAI. ----- was inspected ----- and was classified as NAI. A compliance check of all remaining ----- reveals no compliance actions related to any of the sites.
- **The establishment is performing significant manufacturing step(s) in new (unlicensed) areas using different equipment (representing a process change). This would include areas that are currently dedicated areas that have not been approved as multi-product facilities/buildings/areas**
The manufacturer is performing significant manufacturing, ----- . However, the equipment, facilities, and processes have been inspected. There are no novel manufacturing issues associated with this submission. The only manufacturing process unique to this application is the use of albumin/plasma free cell culture, and the virus filtration step, the reason for the submission.
- **The previous inspection revealed significant GMP deficiencies in areas related to the processes in the application/supplement (similar processes) or systemic problems, such as QC/QA oversight.**
The most recent inspections associated with facilities involved in manufacture this product have been classified VAI or NAI.
- **The manufacturing process is sufficiently different (new production methods), specialized equipment or facilities) from that of other approved products produced by the establishment.**

As noted, the supplement is for a process that no longer uses cells grown in plasma/albumin containing media. As such, the manufacturing process, facilities, and controls do not represent any novel or significant manufacturing issues.

A -----, resulting from the -----
---- is used for production. This
---- was described in a supplement 103779/----, and approved on July 6, 2007.

Waiver Recommendation:

This submission is a BLA (biologics license application). Therefore, Center SOPP 8410 requires an inspection or documentation that an inspection is not necessary. However, the Wyeth site(s) for this application have been subject to previous inspections for processes that comprise the new product.

Based on the information provided in the Biologics License Application, the previous inspection history, and the overall compliance status of the license holder, I recommend waiving the pre-approval inspection for the Wyeth facilities associated with this submission.

Timothy Lee, Ph.D., Committee Chair	Date
Division of Hemostasis, HFM-392	

Daniel Kearns, Reviewer	Date
Division of Manufacturing and Product Quality, HFM-675	