

DMPQ Final Memo - XYNTHA

DATE of MEMORANDUM:

August 21, 2007; revised December 11, 2007

FROM:

Daniel Kearns, HFM-675

TO:

STN 125264/0 file (Dr. T. Lee, Chair, and P. Cottrell, RPM)

THROUGH:

Carolyn Renshaw, Branch Chief, HFM-675

SUBJECT: Wyeth Pharmaceuticals, Inc. PAS 125264/0 for the modified manufacturing process 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) without human- or animal-derived proteins.

CONCLUSION: The applicant appears to have submitted all information in accord with the *Guidance For Industry For The Submission Of Chemistry, Manufacturing, And Controls Information For A Therapeutic Recombinant Dna-Derived Product Or A Monoclonal Antibody Product For In Vivo Use*, August 1996 and *Guidance for Industry M4Q: CTD - Quality*, August, 2001.

The methods, procedures, data, and validation documentation provided in this submission, under DMPQ review purview, appear satisfactory to conclude that the applicant is capable of consistently manufacturing a product that meets its predetermined quality attributes. Therefore, I find the submission acceptable for approval as submitted.

PDUFA SUMMARY: This PAS (pre-approval application) submission was received at CBER on April 25, 2007 and was assigned to myself on June 4, 2007. It had been initially assigned to Robert Stevenson, but to due to workload constraints was reassigned to me on June 4, 2007. The PDUFA Action Due date is February 23, 2008. A pre-approval inspection will not be necessary for this application, as all manufacturing sites have been inspected within the last 12 months.

NOTEWORTHY ASPECTS:

On 09 October 2006, Wyeth submitted the moroctocog alfa (AF-CC) Pre-BLA Briefing Book that contained a list of questions for discussion (BB IND -----, SN 0119). FDA provided a written response to the questions and additional comments (FDA Letter CRMTS# 5925, dated 09 November 2006). In lieu of having a face-to-face meeting, Wyeth and FDA agreed to a teleconference on 14 November 2006, to discuss questions 1, 3a, 8 and 12.

Below are the pertinent portions of the meeting minutes and discussions as they relate to manufacturing (DMPQ). In this meeting, DMPQ gave advice about the temperature

range during mapping of the lyophilization cycle that was permissible, i.e., $\pm 1^{\circ}\text{C}$. ***I do not believe that meeting a 1°C or less temperature variation during mapping of the lyophilization ----- is necessary for critical quality attributes of the product.*** I believe the procedures, validation studies, and product specifications submitted demonstrate ----- and that the outcome of the lyophilization process is satisfactory without the more stringent lyophilization temperature mapping range of $\pm 1^{\circ}\text{C}$.

Question 12

Drug Product Master Validation Plan

a. Does the Agency concur with the number of lots, batch sizes, and lyophilizer ----- strategy planned to support the manufacture of moroctocog alfa drug product (AF-CC) at the Wyeth -----, -----?

FDA Response:

*The ----- approach may be acceptable; however this cannot be fully assessed given the information in this pre-read. You have provided no information regarding the lyophilizer cycle itself -----
----- You have also provided no information regarding temperature mapping, moisture mapping, sampling plan, -----, etc. for us to evaluate your proposed plan regarding the validation lots. Validation of the ----- lyophilizers should demonstrate ----- performance ----- Product produced and lyophilized in the ----- facility, should be -----
-. **Temperature mapping should show consistency within 1°C .***

Please provide the sampling plan for the seeded lots and the process validation lots. Please provide additional information on the container closure size and fill volume for all dosage strengths.

Will the same lyophilizer cycle be used for all dosage strength? Please explain how the thermal characteristics of the placebo are similar to product.

Wyeth Response:

Wyeth appreciates the Agency's comments on the drug process validation plan, and would like to provide additional clarification. See Attachment 1 for additional information needed to answer the original question from Wyeth. b. Does the Agency concur with Wyeth's proposal to ----- the BLA with the remaining ----- post-approval? File with --
----seeded stability evaluations and ---- process qualifications. Follow-up with -----
----- as a post-approval commitment.

FDA Response:

Please see comments above.

Wyeth Response:

Wyeth intends to provide data in the BLA to demonstrate that the --- lyophilizers (--- ----) operate -----, as discussed in Attachment 1. Additionally, Wyeth will provide process

data in the BLA demonstrating that the ReFacto and morcotocog alfa (AF-CC) drug product processes are ----- . Is the number of lots proposed for the submission acceptable to gain approval of the morcotocog alfa drug product (AF-CC) process run in --- lyophilizers at the Wyeth ----- facility?

The final report documenting the morcotocog alfa drug product (AF-CC) process validation lots will be available -----.

ATTACHMENT 1 - ADDITIONAL INFORMATION TO ANSWER QUESTION 12A

Wyeth appreciates the Agency's comments on the drug process validation plan, and would like to provide additional clarification. Regarding the Agency's request for additional information regarding the lyophilizer cycle itself and its -----
----- . In the BLA covering the Albumin-Free Cell Culture (AF-CC) process for manufacture of ReFacto, **Wyeth will provide the lyophilization cycle for moroctocog alfa drug product for -----**
----- . The lyophilization cycle is -----
----- . It is also ----- to the -----, which is ----- . Table Q12-1 details the recently approved and proposed submissions to the FDA for drug product from the Wyeth ----- facility.

For lyophilization cycle ----- lyophilizers, -----
----- . For temperature, the cycle acceptance limits are -----
----- . Regarding proposed validation for temperature mapping, moisture mapping, sampling, -----, etc., Wyeth's project plan includes the availability of all of the information that was mentioned in the Agency response. Table Q12-2 summarizes the availability of the information.

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BACKGROUND

The product for which this application is submitted is designated as an Orphan Drug. ReFacto® Antihemophilic Factor, Recombinant 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. The International Nonproprietary Name (INN) of the active pharmaceutical ingredient is ***moroctocog alfa***. 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. BDDrFVIII manufactured using this albumin free cell culture process is referred to as moroctocog alfa (AF-CC).

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).

To distinguish references to the current licensed ReFacto (STN 103779), from B Domain Deleted Recombinant Factor VIII (BDDrFVIII, ReFacto AF) conducted under BB-IND -----, Wyeth will refer to the former as ReFacto or ReFacto (current) and the later as moroctocog alfa (AF-CC). In some instances, the term ReFacto AF has been used, however this is synonymous with moroctocog alfa (AF-CC).

As for the approved product ReFacto, the proposed indications for this Antihemophilic Factor (Recombinant), Plasma/Albumin-free include:

- Control and prevention of hemorrhagic episodes in patients with hemophilia A (congenital factor VIII deficiency or classic hemophilia)
 - Surgical Prophylaxis in Patients with Hemophilia A
- -----

According to Wyeth, moroctocog alfa (AF-CC) BB IND -----was submitted to the Office of Blood Research and Review on 21 September 2001, effective 21 November 2001, to support the development program for moroctocog alfa (AF-CC). Wyeth states that communications with the Agency were conducted to address key aspects of the clinical development program to meet FDA requirements for approval of moroctocog alfa (AF-

CC). A summary of these communications are included in module 1.6.3
Correspondence regarding Meetings.

Wyeth states Moroctocog alfa (AF-CC) is a formulated as a *sterile, non-pyrogenic, lyophilized* powder preparation for intravenous (IV) injection. It is provided in single-use vials containing the labeled amount of FVIII activity (International Units [IU]). Each vial contains nominally 250, 500, 1000, or 2000 IU per vial. Upon reconstitution with the supplied diluent (0.9% Sodium Chloride solution), the product is a clear to slightly opalescent, colorless solution that contains sodium chloride, sucrose, L-histidine, calcium chloride and polysorbate 80.

Module 3 of this application includes data from a full complement of **commercial-scale drug substance process validation studies performed at the -- facility -----**, -----
----- Validation studies at the ----- facility include -----

----- The module also includes all other chemistry and manufacturing information required per CTD guidance to demonstrate consistent processing of the drug substance and drug product.

Wyeth states that the commercial manufacturing site for drug product is the Wyeth ----- facility located in -----.

Wyeth states that comparability has been demonstrated between moroctocog alfa produced by the current process to that produced by albumin-free cell culture process. The components of the comparability program include an -----

----- The analytical methods and assessment criteria ensure that moroctocog alfa (AF-CC) drug substance and moroctocog alfa (current) drug substance have comparable identity, purity, potency, and quality. In addition, the moroctocog alfa (AF-CC) used in the non-clinical studies was found to be comparable to moroctocog alfa (current) and representative of the moroctocog alfa (AF-CC) used in clinical studies.

Wyeth states that changes from the current manufacturing process for ReFacto with respect to the ----- are delineated in module 2.2 Introduction to Summaries, section 2.1.1 Changes From the Current Process. Wyeth claims that there were **no major changes to the manufacturing process used to make ReFacto Drug product** (i.e., between ReFacto and AF-CC). The manufacturing process for drug product manufactured using drug substance from the AF-CC process -----
-----.

Wyeth states that to minimize potential product impact -----

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26 USP <1116> Microbiological Evaluation of Clean Rooms and Other Controlled Environments

26 USP <1231> Water for Pharmaceutical Purposes

26 USP <381> Elastomeric Closures for Injection

26 USP <1207> Sterile Product Packaging--Integrity Evaluation

26 USP <71> Sterility tests

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