



MEMORANDUM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

To: File of STN 125398/0 & Jiahua Qian

From: Zuben Sauna
Chair of Review Committee & CMC/Product Reviewer

Through: Timothy Lee
Acting Chief, Laboratory of Hemostasis/DH/OBRR

Subject: Addendum 2 to the review of CMC information in the Biologics License Application by Novo Nordisk Inc. for Coagulation Factor XIII A-Subunit (Recombinant) [TRETEN] expressed in *Saccharomyces cerevisiae*

This biologics license application (BLA) for Coagulation Factor XIII A-Subunit (Recombinant) was reviewed by a committee that included the following CBER reviewers:

Dr. Harold Boxenbaum (Clinical Pharmacology), Mr. Michael Brony (Advertising and Labeling), Dr. La'Nissa Brown-Baker (Pharmacology/Toxicology), Ms. Karen Campbell (Lot Release/Analytical Methods), Deborah Cordaro (Administrative/Regulatory), Dr. Al Del-Grosso (CMC/Analytical Methods), Ms. Grace Deneke (CMC/Facility), Dr. Roman Drews (Former Chair of Review Committee and CMC/Product), Mr. Anthony Hawkins (Bioresearch monitoring), Dr. Nisha Jain (Clinical), Ms. Carla Jordan (Bioresearch monitoring), Dr. Charles Maplethorpe (Clinical), Dr. Alan Ou (Epidemiology), Dr. Zuben E. Sauna (Current Chair of Review Committee and CMC/Immunogenicity methods), Mr. Destry Sullivan (CMC/ Facility), and Dr. Jean Wang (Biostatistics).

Pre-approval inspections were conducted at the following manufacturing facilities: Novo Nordisk A/S for the up-stream production of drug substance (Bagsvaerd, Denmark), and Novo Nordisk A/S for the down-stream production of drug substance and final drug product (b) (4).

Several CMC (Product and Facility) and Clinical deficiencies in addition to outstanding issues resulting from the pre-approval inspections were not resolved during the first review cycle of this BLA. Thus, based on the recommendation of

the review committee, a Complete Response (CR) letter dated December 23rd 2011, listing all the deficiencies in the BLA, was issued to Novo Nordisk.

At the request of Novo Nordisk, FDA participated in two type C meetings to discuss the CMC and clinical deficiencies in the CR letter on March 14th and 15th, 2012, respectively.

Novo Nordisk responded to the CR letter on December 27th 2012. The resubmission included responses to the CMC and Clinical deficiencies and to the observations during pre-approval inspections.

Novo Nordisk's responses to the product-related deficiencies identified in the CR letter were determined to be adequate from the perspective of the product reviewer. Although there were no unresolved product-related issues, the submission could not be approved pending the review of a GMP inspection of Novo Nordisk's (b) (4) facility conducted by TeamBio inspectors from (b) (4). In addition, Mr. Sullivan still found deficiencies in the validation of the visual inspection program, which he included in the second CR letter issued on 27 June 2013.

In this review cycle, the reviewers conclude that all the deficiencies listed above have been adequately addressed. In addition, research by APLB and consultation with CDER indicated that the proposed proprietary name Novothirteen[®] had the potential for prescribing and dispensing errors, and an alternative proprietary name, TRETEN, was provided by the applicant and found acceptable by the FDA.

Conclusions and Recommendations

Outstanding issues from previous review cycles have all been resolved, and all reviewers unanimously recommend approval of Novo Nordisk's BLA under STN 125398/0 for Coagulation Factor XIII A-Subunit (Recombinant) [TRETEN] expressed in *Saccharomyces cerevisiae*.