



MEMORANDUM

Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation Research
Office of Blood Research and Review

To: STN BL 125555/0, Andrey Sarafanov, PhD, Committee Chair and Jiahua Qian, PhD, RPM

From: Nancy Kirschbaum, PhD, Product Reviewer

Applicant: Octapharma Pharmazeutika GmbH

Product: Antihemophilic Factor (Recombinant), Nuwiq™

Subject: Chemistry, Manufacturing and Controls Product Review

Through: Tim Lee, PhD, Acting Chief, OBRR/DHRR/LH
Basil Golding, MD, Director, OBRR/DHRR

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Review Scope

Review of [CTD section 3.2.S.2](#): Drug Substance Manufacture is documented in this memo.

Introduction

Octapharma Pharmazeutika GmbH (Octapharma) has submitted an original biologics license application (BLA) to seek US licensure for Antihemophilic Factor (Recombinant). The commercial product is a lyophilized powder in a single-dose vial, available in nominal potencies of 250, 500, 1000, or 2000 international units (IU). The product is reconstituted with sterile water for injection provided in a pre-filled syringe. The proprietary name of the US marketed product is Nuwiq™. Nuwiq™ is indicated in adults and children with Hemophilia A (congenital Factor VIII deficiency) for: (1) control and prevention of bleeding episodes, (2) perioperative management, and (3) routine prophylaxis to prevent or reduce the frequency of bleeding episodes. Nuwiq™ is not indicated for the treatment of von Willebrand Disease. Clinical trials that provided substantial evidence of safety and efficacy were conducted under IND 13722.

Hemophilia A is a rare, hereditary, hematologic disorder caused by deficiency or dysfunction of Coagulation Factor VIII (historically referred to as Antihemophilic Factor), resulting in bleeding

secondary to abnormal clot formation. Because the Factor VIII gene is located on the X-chromosome, Hemophilia A has an X-linked, recessive inheritance pattern, affecting 1 in 5,000 male births with rare occurrence in females. There is no available cure for Hemophilia A. To promote clotting, patients are treated to replace the deficient Factor VIII by intravenous administration of a purified Coagulation Factor VIII (Antihemophilic Factor) concentrate. Both plasma derived and recombinant DNA derived Antihemophilic Factor concentrates are commercially available. The majority of commercially available recombinant Antihemophilic Factor concentrates are produced using rodent cell lines, which presents a theoretical, increased risk for patient immunogenic response to both the recombinant FVIII (rFVIII) molecule and host cell protein impurities. Nuwiiq™ was developed in a human cell line in order to decrease the potential immunogenic risk. The active ingredient in Nuwiiq™, B-domain deleted recombinant Factor VIII (BDD-rFVIII), retains the majority of the human amino acid sequence but deletes the B-domain, and is produced in a human embryonic kidney cell line (HEK 293F).

Nuwiiq™ is currently approved in the European Union and Canada.

Regulatory Process

STN BL 125555/0 was reviewed under the PDUFA V program (standard 12 month review); regulatory milestones are listed in Table I-1.

Table I-1: Regulatory Milestones

| Task | Date |
|-------------------------|-----------------------|
| Received | June 5, 2014 |
| First committee meeting | June 26, 2014 |
| Filing meeting | July 24, 2014 |
| Filing date | August 4, 2014 |
| Mid-cycle meeting | November 19, 2014 |
| Pre-license inspection | October 21 – 28, 2014 |
| Action Due | June 5, 2015 |

Drug Substance

Process – Method of Manufacture and Packaging and Process Controls

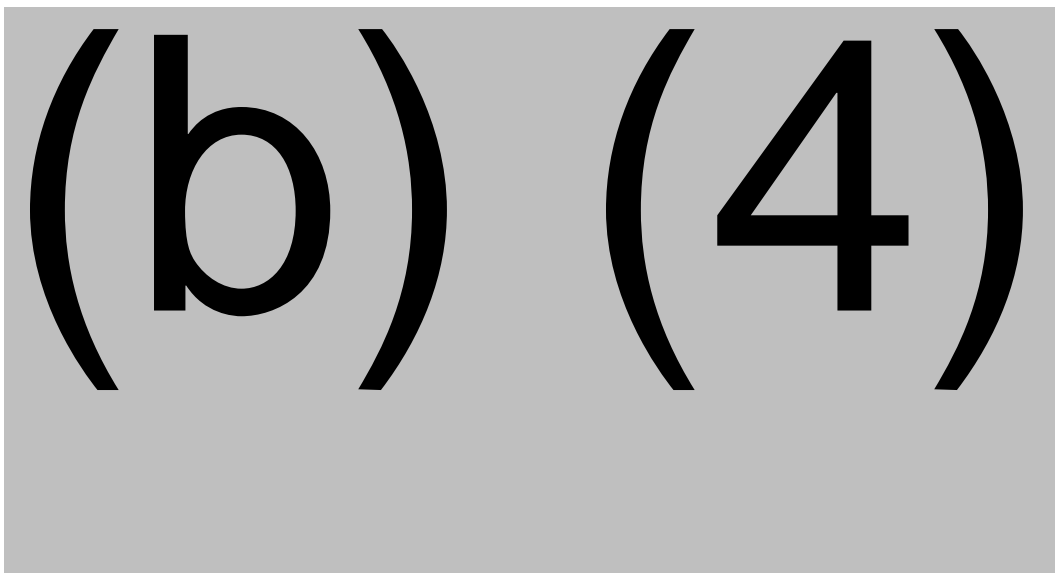
Description of the Product, Manufacturing Process and Process Controls

Product Description

The active moiety in the drug substance is B-domain deleted recombinant Factor VIII (BDD-rFVIII) produced by stably transfected, human cell line HEK293F (b) (4). The BDD-rFVIII molecule is a glycoprotein, ~170 kDa in molecular mass possessing the A1-A2 heavy chain and A3-C1-C2 light chain domain structures described in the literature for the naturally occurring plasma protein. In contrast to the native protein, which comprises 2332 amino acids, including a B-domain between the heavy and light chains, the BDD-rFVIII construct in (b) (4) codes for (b) (4)

Production in a human cell line was designed to achieve molecular post-translational modifications in conformity with the native plasma protein. Of note, (b) (4) BDD-rFVIII directs complete sulfation of tyrosine at amino acid 1680¹, critical for binding plasma von Willebrand Factor to promote *in vivo* stability. Figure S2-1 illustrates the molecular structure of (b) (4) BDD-rFVIII.

Figure S2-1: Molecular Structure of (b) (4) BDD-rFVIII



Summary of the Manufacturing Process and Process Controls

The manufacturing process and production controls are documented in quality document, “*Method of Preparation 160MOP137/03/US.*”

Manufacturers and Testing Facilities – [section 3.2.S.2.1](#)

| <u>Site</u> | <u>FEI</u> | <u>Function</u> |
|--|------------|---|
| Octapharma AB Elersvägen 40 112 75 Stockholm, Sweden | 300555915 | Drug substance manufacture, QC testing and release of drug substance and drug product |

¹ Numbering according to native protein amino acid sequence

(b) (4)

Information Requests and Amendments

Table IR-1 lists information requests and amendment responses within the scope of this review.

Table IR1: Product Information Requests and Amendment Responses

| IR | Subject | Amendment Response |
|---------------------------------|--|---|
| FDA Form 483, Observation #1 | Process validation to support (b) (4) | <ul style="list-style-type: none">0/.10; 11/18/14: Commitment to provide summary of EU and US validation to support (b) (4)0/.19; 1/30/15: Report OC14-05180/.23; 2/27/15: Report OC15-0064 |
| February 9, 2015 | <ul style="list-style-type: none">Revision of 160MOP137/02/USInformation to support sourcing, manufacture and control (quality, performance, safety) of (b) (4) | <p>0/.22; 2/20/15:</p> <ul style="list-style-type: none">Revised 160MOP137/03/US with: (b) (4); (b) S/D treatment time specified as (b) (4), (c) chromatography step yields and operating pressures providedRegulatory support files from (b) (4) and flow chart for QA approved notification system in case of a manufacturing change |

Conclusion

The information contained in [section 3.2.S.2](#) adequately supports the intended drug substance commercial manufacturing process.