



MEMORANDUM

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

To: BLA STN 12555/0 & Jiahua Qian, Regulatory Project Manager, OBRR/IOD/RPM Staff
From: Andrey Sarafanov, PhD, OBRR/DHRR/LH
Applicant: Octapharma Pharmazeutika Produktionsges.m.b.H.
Product: Antihemophilic Factor (Recombinant) [Nuwiq]
Indication Control and prevention of bleeding episodes in adults and children with Hemophilia A
Subject: Chemistry, Manufacturing and Controls Review
Through: Mark Weinstein, PhD, OBRR/IOD
Basil Golding, MD, DHRR
CC: Tim Lee, PhD, DHRR/LH

EXECUTIVE SUMMARY

This memorandum summarizes the review of product-related information in an original Biologics License Application (BLA) under STN 125555 submitted by Octapharma Pharmazeutika Produktionsges.m.b.H. (Octapharma) for Antihemophilic Factor (Recombinant) [Nuwiq]. I reviewed the following sections of the Module 3 (Quality): 3.2.S.1 and 3.2.S.3 (Drug Substance) and 3.2.P.1-3.2.P.3 (Drug Product). During review of these data, the Applicant provided additional information. Upon review of all data, I found them to be acceptable, and thus recommend approval.

BACKGROUND

Nuwiq is the first product based on the use of human factor VIII (FVIII) expressed in human cells (rhFVIII) to potentially avoid the formation of some immunogenic epitopes on the molecule, which may occur when proteins are expressed in non-human cells. The cell line that was used, HEK 293F, is adapted to grow in a medium free of animal-derived compounds. During production, the media with expressed rhFVIII is concentrated, and rhFVIII is purified in a process involving chromatography, solvent/detergent treatment and nanofiltration. The resulting drug product (DP) is supplied as a lyophilized powder in single-dose vials containing 250 IU, 500 IU, 1000 IU or 2000 IU of rhFVIII. For reconstitution, the DP is supplemented with sterile water for injection (WFI), presented in a single-dose pre-filled syringe. Nuwiq is indicated for control and prevention of bleeding in patients with FVIII deficiency (Hemophilia A).

REVIEW SUMMARY

Drug Substance: Characterization (Sections 3.2.S.1 and 3.2.S.3)

3.2.S.1 GENERAL INFORMATION (DS)

3.2.S.1.1 Nomenclature

European Pharmacopoeia

Human Coagulation Factor VIII (rDNA)

3.2.S.1.2 Structure

The amino acid sequence of rhFVIII corresponds to that of native FVIII, but with replacement of the B-domain with a (b) (4)

Thus, rhFVIII is a heterodimer composed of a heavy chain of ~90 kDa (A1-A2 domains with the C-terminal linker), and a light chain of ~80 kDa (A3-C1-C2 domains). (b) (4)

3.2.S.1.3 General Properties

The Drug Substance (DS) contains RhFVIII, a protein of ~170 kDa with properties corresponding to those of plasma-derived FVIII. (b) (4)

3.2.S.2 MANUFACTURE

This section was reviewed by Dr. Nancy Kirschbaum, who found the information to be acceptable.

(b) (4)

(b) (4)

- (b) (4)

Physico-Chemical Characterization

(b) (4)

- (b) (4)

Drug Product: Description, Composition, Pharmaceutical Development and Manufacture (Sections 3.2.P.1-3.2.P.3)

Drug Product - Powder

3.2.P.1 DESCRIPTION AND COMPOSITION

The lyophilized DP (powder) is supplied in single-dose vials containing 250 IU, 500 IU, 1000 IU and 2000 IU of rhFVIII per vial. These vials are manufactured from glass of (b) (4) glass, closed with (b) (4) stoppers (b) (4) and sealed with aluminum flip-off caps. The package of the final DP also contains a syringe filled with 2.5 mL of water for injections (WFI) used for the powder reconstitution and injection of the solution into a patient. The reconstituted DP contains 100 IU, 200 IU, 400 IU and 800 IU of FVIII/mL (respectively the dosage of lyophilized DP), and the same concentration of each excipient (Table 1).

Table 1. **Composition of reconstituted DP** (per vial).

Name of Active Ingredient	Quantity per ml of reconstituted solution (± 20%)				Function	Quality	
Human-cl rhFVIII	100 (b) (4) FVIII:C	200 (b) (4) FVIII:C	400 (b) (4) FVIII:C	800 (b) (4) FVIII:C	Active Ingredient	Internal	
Name of Excipients							
Sodium chloride	(b) (4)				(b) (4)	(b) (4)	
Sucrose	(b) (4)				(b) (4)	(b) (4)	
L-arginine hydrochloride							
Calcium chloride dihydrate							
Poloxamer 188							
Sodium citrate dihydrate							
Solvent	Quantity [ml]					(b) (4)	
Sterilised water for injections	2.5						
					Solvent		

3.2.P.2 PHARMACEUTICAL DEVELOPMENT

The objective for the manufacture process design was to obtain a robust process that gives a stable product throughout the defined shelf life, 24 months at +2 to 8 °C. The critical quality attributes were defined to be (b) (4)

The DP formulation was developed during preclinical and clinical phases (Table 2) that included three steps.

1. Formulation A: (b) (4) .
2. Formulation B: Lyophilized DP (preclinical), developed in 2007.
3. Formulation C: Lyophilized DP (clinical and intended commercial), developed in 2008.

Table 2. **Formulations A, B and C** (quantities per mL of (b) (4) DP solution).

Excipient	Function	Pre-clinical Formulation A (Frozen, thawed)	Pre-clinical Formulation B (Freeze-dried, reconstituted)	Clinical and intended Commercial Formulation C (Freeze-dried, reconstituted)
Sodium chloride	(b) (4)	(b) (4)	(b) (4)	18 mg
Glycine	(b) (4)	(b) (4)	(b) (4)	-
L-Lysine hydrochloride	(b) (4)	(b) (4)	(b) (4)	-
Trehalose dihydrate	(b) (4)	(b) (4)	(b) (4)	-
Sucrose	(b) (4)	(b) (4)	(b) (4)	5.4 mg
L-Arginine hydrochloride	(b) (4)	(b) (4)	(b) (4)	5.4 mg
Calcium chloride dihydrate	(b) (4)	(b) (4)	(b) (4)	0.3 mg
Poloxamer 188	(b) (4)	(b) (4)	(b) (4)	1.2 mg
L-Histidine	(b) (4)	(b) (4)	(b) (4)	-
Sodium citrate dihydrate	(b) (4)	(b) (4)	(b) (4)	1.2 mg

During the process development, a number of other parameters and conditions were optimized. In particular, these were (b) (4), conditions of its sterile filtration and freeze-drying. It was found that (b) (4) of the DP reconstituted solution is (b) (4) when it is relatively stable up to (b) (4) when stored at 25 °C. (b) (4)

Different vials and stoppers for DP container were evaluated with final selection of glass vials of (b) (4) and (b) (4) stoppers (b) (4)

Compatibility of DP with container and injections device was tested by comparing the FVIII activities in the samples taken after passing through the injection set and those taken immediately after reconstitution. The results demonstrated compatibility of the DP with the contact materials.

Development of the product specification started in the preclinical phase and was finalized during the manufacturing process for DP clinical lots. These changes were (b) (4)

Based on testing of DP clinical lots produced in 2008-2012, acceptance criteria were set for Water Content, (b) (4), Sodium, Calcium, Amount of Total Protein and (b) (4).

3.2.P.3 MANUFACTURE

3.2.P.3.1 Manufacturer

Manufacturer: Octapharma – Stockholm (OAB)

- Octapharma AB, Elersvägen 40, 112 75 Stockholm, Sweden.

Additional Testing (sucrose testing in final DP)

- Octapharma – (b) (4)

Visual inspection

- Octapharma – Stockholm (OAB): Octapharma AB Elersvägen 40, SE-112 75 Stockholm, Sweden.
- Octapharma – (b) (4)

Labeling and Secondary Packaging

- Octapharma – (b) (4)

3.2.P.3.2 Batch formula

One lot of DP is defined as (b) (4) vials (number of vials in freeze-dryer) containing 250, 500, 1000 or 2000 IU rhFVIII per vial. The typical lot size of DP is (b) (4) vials, originating from up to (b) (4) different DS batches. (b) (4)

Table 3. **Batch Formula** (a batch size of (b) (4) vials).

Ingredient		Quantity per batch of (b) (4) vials	Quality
Human-cl rhFVIII Drug Substance	250 IU/vial	(b) (4)	Internal
	500 IU/vial		
	1000 IU/vial		
	2000 IU/vial		
Sodium chloride		(b) (4)	(b) (4)
Sucrose			
L-arginine hydrochloride			
Calcium chloride dihydrate			
Poloxamer 188			
Sodium citrate dihydrate			
Water for injections			

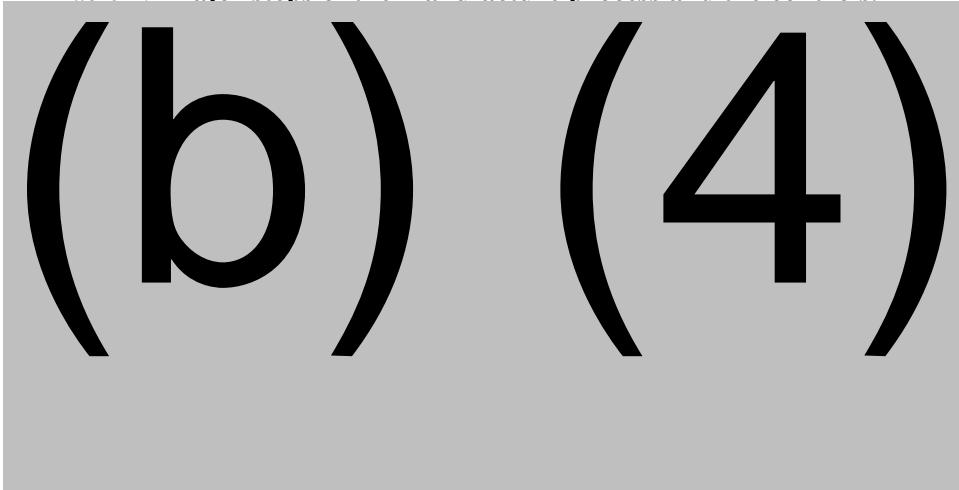
The respective (six) specifications for excipients are provided; information for WFI is provided in section 3.2.P Solvent. For each excipient received, Octapharma performs a test for the identity.

3.2.P.3.3 Description of Manufacturing Process and Process Controls

(b) (4)

- (b) (4)

Table 4. Major steps of the manufacture process and the controls.



3.2.P.3.4 Controls of Critical Steps and Intermediates

(b) (4)

- (b) (4)

3.2.P.3.5 Process Validation and/or Evaluation

The process validation included manufacture of (b) (4) DP lots produced in 2013 covering all product strengths (250, 500, 1000, and 2000 IU/vial), and minimum and maximum lot sizes. The validation also included testing of (b) (4) filling lines / freeze-dryers. Also, the process was evaluated using other (b) (4) DP lots manufactured in 2008-2012. Data of analysis of all these lots are provided section 3.2.P.5.4 (Batch Analyses). The results were within the specifications (Report 30-1684-R02).

Risk Assessment:

The data resulted in determination of critical quality attributes and critical process parameters for the manufacturing process (Report OC14-0184). The critical quality attributes were defined to be (b) (4)

and were included in the specifications. The critical process parameters were defined to be (b) (4)

These parameters were used for the design of the process validation study (Report OC14-0184).

Homogeneity during filling

This study was performed to demonstrate that the DS solution is homogeneous during the filling and that the process is consistent and reproducible. The solution is filled on using (b) (4) filling lines, the (b) (4). Homogeneity was demonstrated by analysis of (b) (4) in vials filled in the beginning, middle and end of the filling process (Report 30-1684-R03).

Validation of freeze dryers

This study was performed to demonstrate that the freeze-drying process is consistent and reproducible. The DP samples taken during freeze-drying were analyzed for (b) (4)

The samples were taken from all loaded shelves at evenly distributed positions to cover all areas of the shelves. (b) (4) freeze-dryers (b) (4) were tested. For each unit, to validate the maximum batch size, placebo (buffer) vials were added to three of the product batches to reach the maximum batch size. The product temperature mapping of each lyophilizer confirmed that the process results in producing of homogenous DP in its either minimum or maximum load (Report OC14-

0097). The freeze-drying of the DP validation batches was performed without deviations, and the process parameters (b) (4) were within the specified ranges for all batches. The (b) (4) parameters demonstrated consistency within and between batches. All acceptance criteria were met (Report 30-1684-R04).

Mediafill Reports

This study was performed to demonstrate that the process preserves sterility of the formulated DS during (b) (4)

A number of consecutive media (b) (4) fills with was tested for each fill line. All acceptance criteria for sterility were met, and each line was validated for the fill size of (b) (4) (Reports OC14-0063, OC14-0145 and OC14-0144).

Transport Validation

This study included validation of the temperature control (2-8°C) during transportation of the DP from OAB Stockholm Sweden to Octapharma (b) (4). The study was performed for summer and winter weather condition, and all acceptance criteria were met (Reports OC13-0363 and 080RPQ12019.000)

Reviewer's Comment

According to SOPP 8401.4, the review of this section (3.2.P.3.5) is supplemental to the review of Division of Manufacture and Product Quality (DMPQ).

Drug Product – Solvent

3.2.P.1 DESCRIPTION AND COMPOSITION

The solvent (2.5 mL) is sterile Water for Injection (b) (4) (2.5 mL) marketed in pre-filled syringe, composed of (b) (4) glass barrel, (b) (4) plunger and closure system (3.2.P.7).

3.2.P.2 PHARMACEUTICAL DEVELOPMENT

The manufacturing process for the WFI pre-filled syringes was defined on the basis of prior experience by the manufacturer (b) (4). During the process validation study, (b) (4) lots of WFI pre-filled syringes (b) (4) approach) were produced. A number of parameters were tested: (b) (4)

The results matched the acceptance criteria.

3.2.P.3 MANUFACTURE

Manufacturers

(b) (4)

Batch Formula

Typical batch size per filling day for the WFI pre-filled syringes (3.0 mL format) is (b) (4).

Description of Manufacturing Process

The production of the WFI pre-filled syringes consists of the following steps:

- (b) (4)

(b) (4)

3.2.P.3.5 Process Validation and/or Evaluation

Process validation was performed on consecutive batches of WFI pre-filled syringes to demonstrate the consistency of the manufacturing process. (b) (4) batches of WFI (b) (4) filled into the syringes were produced; and the following critical steps were controlled.

- (b) (4)

During this study, the parameters of container closure integrity and terminal sterilization were validated. The results met the acceptance criteria and predefined release specification (Reports 5020619, 5021878, 5023068, 5021235, 5018083 and 5021634). The manufacturing process was concluded to be consistent.

Reviewer's Comment

According to SOPP 8401.4, the review of this section is supplemental to the review of Division of Manufacture and Product Quality (DMPQ).

Communication for Additional Information

On December 3, 2014, the following informational request (IR) was sent to Octapharma.

1. In section 3.2.S.3.2 (Impurities) you stated that (b) (4) was analyzed using "a commercially available (b) (4)" (P. 30). Please provide details of this methodology, and data to support the suitability of this assay for the intended purpose.

Response (December 19, 2014, Amendment 14)

Octapharma explained that for determination of (b) (4), they use a commercial assay kit (b) (4) and that this assay was optimized by the manufacturer (b) (4). As a reference, Octapharma uses (b) (4) standard. The company also presented a summary of data for the method suitability assessment.

Reviewer's Comment

The response is acceptable.

2. In section 3.2.S.3.2, in the (b) (4) of the anti-HCP (b) (4) (Fig. 8, named within the text as Fig. 9, P. 34), there is no positive standard, (b) (4). A positive standard is needed for FDA to evaluate the data. Please provide data from such an analysis using the positive standard (HCP); also, please mark where the (b) (4).

Response (December 19, 2014, Amendment 14)

Octapharma explained that as the anti-HCP antibody was generated by immunization with (b) (4), the latter was used as a positive standard (b) (4). The company performed all the corrections in the updated eCTD file.

Reviewer's Comment

The response is acceptable.

3. In the eCTD file of the submission, an evaluation of Leachables and Extractables is not presented. At a recent FDA inspection of the facility in Stockholm (October 20-28, 2014), we noted that in the Extractables Study (Report #2390013), no data were provided to support the validity of methodology that was used to detect potential contaminants. Please provide an evaluation of in-process Leachables and Extractables to support approval of the BLA; and validate the respective analytical methodology that was used. Therefore, please address the following, and update the eCTD file accordingly.

- a) In regard to Extractables, as advised on October 28, 2014 during the FDA inspection, please perform an experiment that includes spiking the extraction solution with a selection of standards that cover the major types of the expected extractables. This will enable you to do an assessment of their recovery and a retrospective evaluation of extractables from previous studies. In case you redo the whole study, please consider testing the fully assembled container/closure system rather than its individual components (b) (4)
- b) Please perform an evaluation of potential leachables throughout the entire manufacturing process of the Drug Product. Most likely, this can be done by a “mock” process run from step (b) (4). The potential of leachables arising from the (b) (4) at the preceding step should also be evaluated. Chemical identification of the detected compounds is not necessary, unless a specific concern arises.

Response (February 27, 2015, Amendment 24)

- a. Octapharma performed a study, in which three standards, represented extractable compounds found in typical plastic materials, were spiked into the extraction solution at respective concentrations and analytical recovery of these standards were evaluated by (b) (4). The recovery of the standards was found to be (b) (4) indicating that the initial evaluation of leachables was meaningful.
- b. Octapharma performed a study, in which all plastic components used for DP manufacture were assessed for leachables using the same methodology as in the previous study. For identified and quantified compounds, a toxicological risk assessment was performed. This resulted in a conclusion that the use of all plastic materials (i. e. filters, bags, bottles and tubing) in the production of DP is unlikely to cause any toxic effect in patients.

Reviewer's Comment

The response is acceptable.

4. Your statement that rhFVIII has a higher affinity for vWF does not appear to be well grounded because use of the 1:1 (Langmuir) model is questionable, and the derived K_D values for all variants of FVIII are very close and do not contain RSD values. In this regard, the fact that rhFVIII gives higher binding signals than those of the comparators may be a result of higher avidity, not affinity. To support your claim about higher affinity from the Binding to von Willebrand factor assay (Section 3.2.S.3.1), please provide information about conditions used for (b) (4); explain the relevance of using 1:1 model for fitting the binding curves; provide RSD values for K_D s determined; and comment on the statistical significance of the statement that the affinity of rhFVIII for vWF is higher than those of the comparators.

Response (January 29, 2015, Amendment 18)

Octapharma provided data supporting the use of the Langmuir fitting model. In particular, they showed global fits of the families of the binding curves recorded for Nuwiq and three other FVIII products (Refacto, Advate and Kogenate). The company provided the buffer composition used for (b) (4) with immobilized vWF regeneration that was (b) (4) and data confirming that upon the (b) (4), the surface performance was not affected. For Nuwiq and its comparators, Octapharma provided the RSD values for the calculated K_D s and the respective statistical significance. The data demonstrate that even with

the errors (RSD), the calculated K_D values do not overlap. This information indeed supports the statement that the affinity of rhFVIII for vWF is higher than those of the comparators.

Reviewer's Comment

The response is acceptable.

5. There are no hyperlinks to the referenced reports “5. Characterization of Impurities of Human Cell Line Recombinant Human Factor VIII (Human-cl rhFVIII). 230CIM140/00 (OC08-0058)” and “12. Development of an (b) (4) for determination of host cell proteins (HCP) from HEK293F cells (R7038). OC12-0386.” (3.2.S.3.1 Elucidation of Structure and Other Characteristics, P.19). Please provide these materials and update the eCTD file accordingly.

Response (January 29, 2015, Amendment 18)

Octapharma provided the documentation and respective hyperlinks in the updated eCTD file.

Reviewer's Comment

The response is acceptable.

6. With reference to your stability study reports (OC14-0210, OC14-0187, OC14-0211, OC14-0209, D15-13R033-01 and FDA 266), the results for (b) (4) method (analytical method R7026-02-01) are missing at multiple time-points. Problems with the performance of this method were noted during the pre-license inspection of the manufacturing facility in Stockholm, Sweden. The inability to measure this parameter of stability may impede review of the BLA and affect the determination of the shelf-life of the product. To address this issue, please provide the following.

- a) Please demonstrate that the analytical method you use for evaluation of the (b) (4) parameter is properly validated. In your validation study, please also use an (b) (4) method(s) to confirm and complement the results of the measurement of the parameter.
- b) Using the validated method(s) to evaluate the (b) (4) of the product in stability study samples, please demonstrate that the product is stable throughout the duration of the stability study and the proposed shelf-life.
- c) Please note that the naming of the method you use for analysis of the (b) (4) parameter should be relevant to the common practice and not misleading. The conventional naming of your method is relevant to (b) (4) but not to its present designation as (b) (4). In contrast to your (b) (4) Please make sure that the correct naming of the method is maintained through the whole eCTD file including the drug product specifications. (My part for review)
- d) Please be advised that submission of the requested information later than May 5, 2015 may not allow us to have adequate time for review.

In addition, on December 11, 2014, FDA had a teleconference with Octapharma to discuss a number of concerns. Regarding this question (#6), the discussion was as follows.

6a. FDA asked Octapharma to specify what type of the new equipment they are going to test. Octapharma explained that instead of their current (b) (4) instrumentation, they were going to use

instrumentation based on a (b) (4) with the same type of (b) (4) that they currently use. FDA recognized that the new equipment will be of essentially the same type as the one currently in use (b) (4). FDA reminded Octapharma that during the recent inspection of the facilities in Stockholm (October 20-28, 2014), the Agency advised Octapharma to: i) use (b) (4) . In parallel to this method, Octapharma agreed to set-up and validate a method based on (b) (4)

6b. Not discussed.

6c. Octapharma noted that it is difficult to update the whole eCTD file with the requested change of the term (b) (4) as the submission contains 18 original study reports with the term (b) (4). FDA suggested each of these reports be marked with a footnote stating that (b) (4) should be read as (b) (4), while within the rest of eCTD, the terminology should be corrected.

6d. FDA noted that if the data are submitted too close to the BLA action due date, the Agency could have insufficient time for the review, resulting in the extension of the due date. From this perspective, FDA recommended to send the data as soon as possible. Octapharma responded that they will submit the data (re-validation of the (b) (4) ” parameter and characterization of the Drug Product stability lots for this parameter) by the end of February, 2015. At the same time, Octapharma will be testing/validating a true (b) (4)-based method for the parameter.

Response (February 27, 2015, Amendment 24).

In the response to question 6c, the company corrected the name of the method into (b) (4) through the submission. The responses for questions 6a and 6b were reviewed by Dr. Lokesh Bhattacharyya and Dr. Yideng Liang, respectively.

Reviewer's Comment

The response for question 6c is acceptable. The responses for questions 6a and 6b were found to be acceptable by Dr. Lokesh Bhattacharyya and Dr. Yideng Liang, respectively.

CONCLUSION

Upon review of all information, I have not identified issues that prevent approval. Thus, from my perspective, STN 125555 can be approved.