



FOOD AND DRUG ADMINISTRATION
CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

MEMORANDUM

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Subject: *Final Review of OCTAPHARMA's Container Closure System and Stability Studies in the Biologics License Application for a recombinant analog of human coagulation factor VIII (rFVIII), Nuwiq*

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1. Executive Summary

OCTAPHARMA submitted an original biologics license application (BLA) for Antihemophilic Factor (Recombinant) [Nuwiq] on 5 June 2014. Nuwiq is a recombinant analog of human coagulation factor VIII (rFVIII) expressed in a human cell line. The proposed indications are for 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. Nuwiq final drug product (FDP) is a lyophilized powder in single-dose vials, available in nominal potencies of 250, 500, 1000, or 2000 international units (IU). The product is reconstituted with sterile Water for Injection (sWFI) in a pre-filled syringe prior to intravenous administration.

I reviewed the stability data for the bulk drug substance (BDS), FDP and sWFI provided in the original BLA and amendment 24 dated 27 February 2015. I also reviewed information on the container closure system.

The results and information on stability and container closure system support the proposed shelf-life and dating periods for Nuwiq BDS, FDP and sWFI as follows:

- For Nuwiq BDS – (b) (4) .
- For Nuwiq FDP – 24 months at 2-8°C when protected from light. The product can also be stored at room temperature (25°C) for up to 3 months within the shelf-life.
- For sWFI pre-filled syringes – 60 months at 2°C to 30°C.

From the perspective of product stability and container closure system, I recommend approval of this BLA.

Stability studies:

Stability data on (b) (4) batches of FDP, (b) (4) batches of BDS and (b) (4) batches of sWFI in pre-filled syringes were available for review. All FDP and BDS batches were manufactured at the (b) (4) plant at Octapharma AB (OAB), Stockholm, Sweden; and the sWFI pre-filled syringes were manufactured at (b) (4) .

The following storage conditions were investigated:

- (b) (4)
- FDP: 2-8°C (proposed real-time storage condition) for 24 months, 25°C /60% relative humidity (b) (4) (accelerated storage conditions) (b) (4) and reconstitution study (b) (4)
- BDS: (b) (4)
- FDP: The test parameters are appearance (a white cake, possibly a small amount of white powder), visual inspection of solution (clear, colorless solution, practically free from visible particles), solubility (b) (4) FVIII:C (250 IU dose: (b) (4) , 500 IU: (b) (4) 1000 IU: (b) (4) , and 2000 IU: (b) (4) total protein, specific FVIII:C activity (b) (4) retention times and

(b) (4)
water content (b) (4) integrity testing (b) (4)
, sterility, endotoxin (b) (4)
and concentrations of citrate,
sucrose, poloxamer 188, sodium, calcium, chloride and arginine.

Two issues were identified and successfully resolved during the review cycle. Preliminary stability reports included multiple Out-Of-Specification (OOS) results for the (b) (4). These OOS results were not confirmed by subsequent studies. As requested by FDA, Octapharma identified the root-causes for the OOS results as poor robustness of the (b) (4) method and (b) (4) in sample aliquots during the pre-testing period. The (b) (4) method was revalidated, and all stability results were found to be in specification at subsequent stability time points. The validity of the revalidated method and quality of stability samples were confirmed by similar results obtained with an (b) (4) method, (b) (4).

. The second objectionable stability finding was related to the incorrect use of European specifications based on nominal potency of filled FDP vials during stability studies. Octapharma re-evaluated the stability data using US stability specifications of (b) (4) of the labeled potency and found no substantial adverse trends in potency.

Conclusions:

My review of the container closure system and stability studies confirmed that the manufacturing process is sufficiently established to manufacture the Nuwiq product of consistent quality. I conclude that the stability data for BDS, FDP and sWFI support the proposed shelf-life and storage conditions:

- BDS for (b) (4).
- FDP for 24 months at 2 - 8°C when protected from light. The product can be kept at room temperature (up to 25°C) for a single period not exceeding 3 months within shelf-life. After storage at room temperature, the product must be used or discarded, and must not be put back to refrigerator.
- The reconstituted FDP must be used immediately or within 3 hours after reconstitution.
- The shelf-life of sWFI pre-filled syringes is 60 months at 2°C to 30°C.


Under these storage conditions, there is no impact of storage on the purity, strength and quality of Nuwiq BDS and FDP, and sWFI within the proposed shelf-life.

Conclusion: I recommend the approval of this submission.


2. Container Closure System

i. Container Closure System for BDS


(b) (4)




(b) (4)




(b) (4)




(b) (4)




(b) (4)




(b) (4)




(b) (4)




(b) (4)



(b) (4)



(b) (4)



- (b) (4)

- (b) (4)

(b) (4)

(b) (4)

ii. Container Closure System for FDP

The container closure system for Nuwiq FDP consists of vials corresponding to (b) (4) glass closed with (b) (4) lyophilisation stoppers corresponding to (b) (4). The vials are sealed with aluminium flip off caps, which have no direct contact with the protein product.

Table 1. An overview of the container closure system of FDP is listing below.

Container Closure System	Supplier
Injection vial: 8 mL (b) (4) (b) (4).	(b) (4)
Lyophilisation stopper: (b) (4).	(b) (4)
Flip-off Cap: Lower part aluminium, upper part polypropylene 20 mm.	(b) (4)

(b) (4) **Test:**

- 1) Integrity test: The integrity tests for the container/closure system were performed at the time of manufacture on the primary package consisting of an 8-mL vial, lyophilisation stopper and flip-off cap. The test goal was to study the seal and integrity at the time of manufacture. The initial integrity test of the container/closure system was performed on (b) (4) of each batch, by using a (b) (4). The test made use of (b) (4)
- 2) Table 2. Results of the integrity test

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

Reviewer's comments:

The results indicate that the integrity of the primary package consisting of the vial, rubber stopper and cap is well maintained. There is no significant difference between before (b) (4) in the (b) (4). Therefore the primary package system can be approved for use.

iii. Container Closure System for sWFI

Sterile Water for Injection 2.5 mL in syringe, stored at (b) (4)

<u>General Requirements:</u>	
Container Closure System (see drawing att.1)	
Syringe:	(b) (4)
Rubber Stopper:	
V-OVS 10.6:	

3. Stability Study for Bulk Drug Substance

(b) (4)

(b) (4)

(b) (4)

4. Stability Study for Final Drug Product

FDP for the US market

a) Materials

(b) (4) FDP batches were included in the US market stability study, manufactured according to the intended commercial manufacturing process (b) (4) at Octapharma AB, Stockholm, Sweden.

b) Specifications for FDP:

Table 5. FDP Parameters and Specifications

Analysis	Testing Method	Acceptance Criteria
<u>Each time point</u>		
Appearance	(b) (4)	A white cake. Possibly a small amount of white powder
Visual inspection of solution ¹⁾		Clear, colorless solution, practically free from visible particles
Solubility at 20-25°C, m		(b) (4)
(b) (4)		
FVIII:C, IU/vial ¹⁾		(b) (4) 250 IU 500 IU (1000 IU) (b) (4) (2000 IU)
Confidence limit (P=0.9)		Within (b) (4) of the estimated potency
Total protein, mg/vial		(b) (4) 250 IU 500 IU 1000 IU 2000 IU
Specific FVIII:C activity, IU/mg protein	Ratio FVIII:C/	(b) (4)
(b) (4)	(b) (4)	(b) (4)
(b) (4)		
<u>0, 12 and 24 months</u>		
Container Closure Integrity Testing (CCIT) ²⁾		Approved
<u>0 and 24 months</u>		
Sterility		Approved
Endotoxin, EU/100 IU		(b) (4)
(b) (4)		
Citrate, mg/mL		
Sucrose, mg/mL		
Poloxamer 188, mg/mL		
Sodium, mg/mL		
Calcium, µg/mL		
Chloride, mg/mL		
Arginine, mg/mL		

1) Tests are performed for the reconstitution studies at 0 h, 3 h and (b) (4) after reconstitution, at room temperature.

2) Tests are performed for the reconstitution studies at 0 h and (b) (4) after reconstitution, at room temperature.

3) The limits of the (b) (4) were changed during the stability study according to Change Control TW#29574.

4) Test included in addition to the specification 913FPS139/04/US. Only samples stored at 5°C long-term are included at 12 months. Only samples stored at 5°C long-term and from excursion studies 1 and 2 are tested at 24 months.

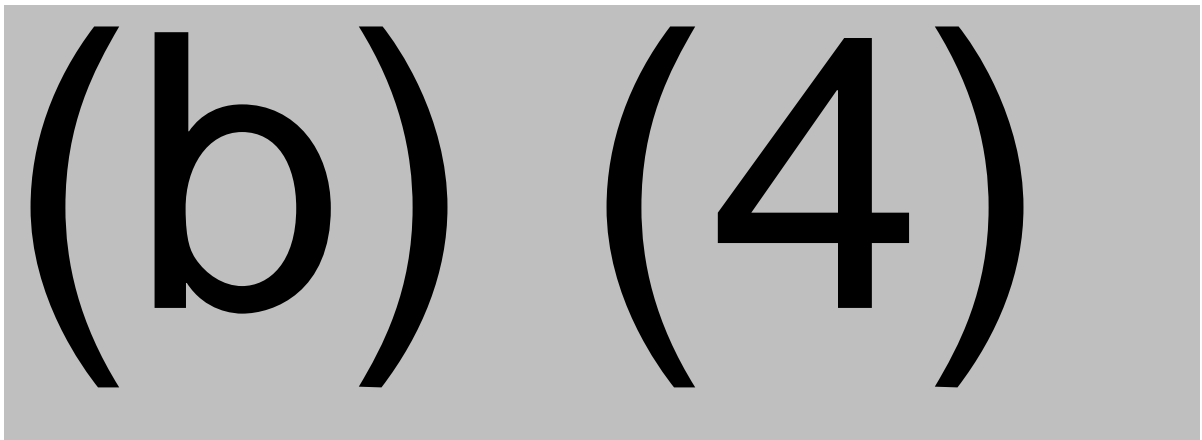
c) FDP Storage Conditions

- Long-Term Condition: 5°C /amb. RH, dark
- Accelerated Condition: 25°C/(b) (4)
- Accelerated Condition: (b) (4)
- Accelerated Condition: (b) (4)
- (b) (4)
- (b) (4)
- Reconstitution, room temperature ^{(U) (4)} -25°C)

d) Stability Study Results:

Long-Term Studies 5°C

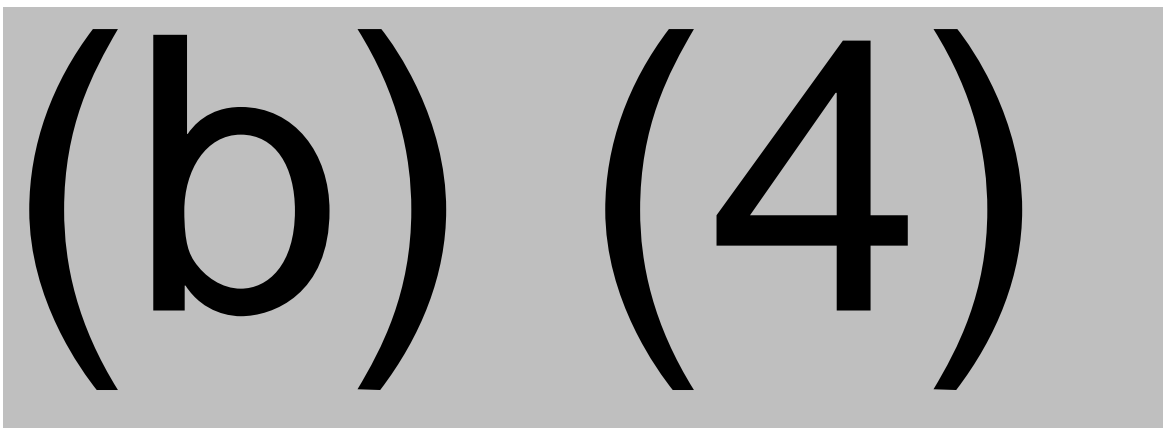
Fig. 6. FVIII:C (Chromogenic and One-Stage Clotting) in a 5 °C stability study, US market



Results for long-term storage at 5°C (up to 12 months) were provided for three batches, see Figure 6. All results were within the acceptance criteria, except for (b) (4), which will be discussed below.

Accelerated Studies 25°C

Fig. 7. FVIII:C (Chromogenic and One-Stage Clotting) in a 25 °C stability study, US market



All FVIII:C (one-stage clotting method) results were within the acceptance criteria after storage for up to (b) (4) . Several data after (b) (4) of storage indicating that FVIII:C were below the acceptance criteria. The amounts of (b) (4) were also out of specification.

Reviewer's comments:

All Factor VIII:C results were within the specification limits for all dosage strengths for up to (b) (4) for both the one-stage and chromogenic assays, except for one of the 250 IU batches, which was just below the limit after (b) (4) of storage. However, the activities of FVIII:C showing negative trend in both the one-stage and chromogenic assays, for the lowest dosage strength, 250 IU, the activity approaches the lower specification limit after (b) (4) of storage. For the highest strength, 2000 IU, the activity is well above the lower limit up to (b) (4) of storage. Therefore, the company's claim that the FDP can be stored at room temperature (up to 25°C) for up to 3 months within the shelf-life is reasonable.

Accelerated Studies (b) (4)

(b) (4)

(b) (4)

(b) (4)

Accelerated Studies (b) (4)

(b) (4)

(b) (4)

(b) (4)

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Reconstitution Studies (b) (4) -25 °C)

The product was dissolved in 2.5 ml sterilized water and stored at room temperature until analysis is performed.

Fig. 10. FVIII:C (Chromogenic and One-Stage Clotting) data in Reconstitution Studies, US market

(b) (4)

Reconstitution studies have been performed with samples after (b) (4) of storage, and the analyses were performed at 0, 3 (b) (4) hours after reconstitution.

All results were within the acceptance criteria after storage for up to (b) (4) except for the level of (b) (4). Also, results for (b) (4) are missing for many time-points, which will be discussed below.

Reviewer's comments:

For long-term stability study at 5°C, all results were within the acceptance criteria, except for (b) (4), which were not confirmed after the revalidation of the analytical method (see discussion below). Negative trends were observed in all the accelerated studies. At the 25 °C (b) (4) accelerated study, all FVIII:C (one-stage clotting and chromogenic methods) results were within the acceptance criteria after storage for up to (b) (4). Therefore, the company claims that FDP can be stored at room temperature (up to 25°C) for up to (b) (4) within the shelf-life is acceptable; At (b) (4) accelerated conditions, all results were within the specification limits after storage for (b) (4).

The reconstitution study of FDP, after storage for up to (b) (4), all results were within the acceptance criteria at room temperature up to (b) (4).

Stability data from FDP batches meant for the EU market

e) Materials

(b) (4) batches of FDP produced according the intended commercial manufacturing process (b) (4) at Octapharma AB, Stockholm, Sweden.

f) Specifications for FDP

Same as those used in the study for FDP batches distributed in the US market

g) FDP Storage Conditions

- Long-Term Condition: 5°C /amb. RH, dark,
- Accelerated Condition: 25°C (b) (4)
- Accelerated Condition: (b) (4)

- (b) (4)
- (b) (4)
- Reconstitution study, room temperature (b) (4) -25°C)

h) Stability Study Results:

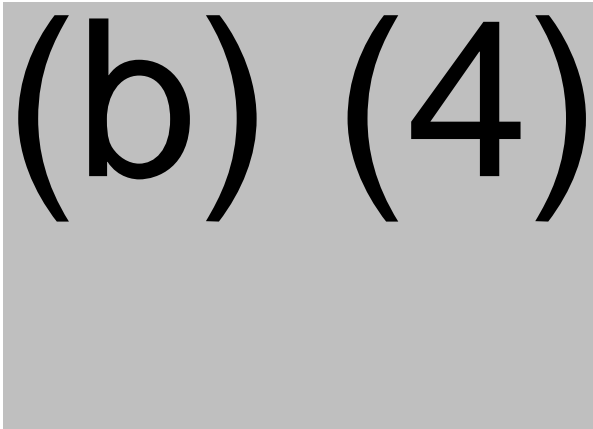
Long-Term Studies at 5°C/Amb RH, dark

Fig. 11, FVIII:C (Chromogenic) in a 5 °C stability study, EU market



Accelerated Condition: 25°C/(b) (4)

Fig.12, FVIII:C (Chromogenic) in a 25 °C stability study, EU market



Reviewer comments:

For long-term storage at 5°C, all results were within the acceptance criteria up to 24 months, except for (b) (4), which will be discussed below. In the 25°C (b) (4) accelerated studies, all FVIII:C results were within the acceptance criteria after storage for up to (b) (4) although a negative trend was observed. In the FDP reconstitution study using samples that were stored for up to (b) (4), all results were within the acceptance criteria except some batches were above the upper limit for FVIII:C when stored at room temperature (b) (4) after reconstitution, indicating that the FDP should be used within 3 hours after reconstitution.

Review of multiple Out-Of-Specification results for (b) (4)

In the ongoing stability studies, the data available for (b) (4) of the storage of BDS and FDP, (b) (4) results were missing at many time-points. Therefore, FDA

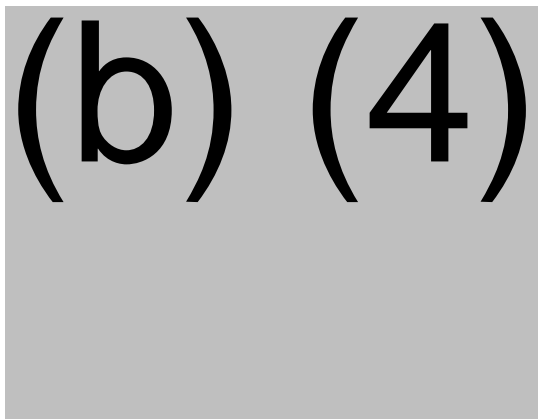
sent an information request on 3 December 2014 to request these results. Below is my review summary of the firm's response received on 27 February 2015 (Amendment 24).

- a) Please demonstrate that the analytical method you used for the 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.

Summary of Octapharma's Response: The updated validation report demonstrates that the method is considered properly validated with a successfully proven specificity, accuracy, precision, linearity and robustness, including

- 1) Variation of (b) (4) due to the stability of the control sample: The result after (b) (4) of standing time shows a higher amount of (b) (4) compared to the immediately (b) (4) analyzed control sample. Therefore, it was concluded that the samples were not stable for (b) (4)
- 2) Comparison of old and new (b) (4) instruments in regard to stability studies: the new (b) (4) instruments (b) (4) have been qualified and used. A comparison between the results obtained on the old and new equipment was performed. The results indicated there is no significant difference between the (b) (4) instruments in comparison data (b) (4) using FDP and BDS. See Figure 13.

Fig. 13. Comparison of the new (b) (4) instruments with the old (b) (4) system



- 3) Good correlation was observed between results derived from the (b) (4) method and those from the (b) (4), which detects and determines (b) (4) in the range from (b) (4). Octapharma provided data for statistical evaluation of the (b) (4). The data indicated that there is no statistical difference between the (b) (4) within a confidence interval of (b) (4)
- 4) Complementary study for (b) (4): due to the low precision of the (b) (4), it was not possible to compare (b) (4)

(b) (4), so samples with about (b) (4) were spiked with induced (b) (4) to increase the (b) (4) which has previously been assessed to be accurate with the (b) (4). The spikes of (b) (4) to the untreated sample from (b) (4) respectively, showed a linear relationship with a correlation coefficient (b) (4) or better.

- 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.

Summary of Octapharma's Response: The supportive EU studies for FDP and BDS indicated that the BDS and FDP are stable throughout the duration of the stability study under real-time storage conditions. Results from the ongoing stability studies for US BDS and FDP batches for up to (b) (4) are available, the results so far support the proposed shelf-life.

Reviewer's comments: Octapharma experienced issues with the (b) (4) resulting in multiple OOS results in stability studies. The method was improved and revalidated. The levels of (b) (4) in Nuwig were within the specification, (b) (4) are very low and consistent over time. Therefore, all stability batches were successfully retested confirming that they remain in specification, and the available test results are satisfactory and within specification after the improvement of the assay.

5. Stability Study for sterile Water for Injection

The stability studies were conducted on (b) (4) batches of sWFI pre-filled syringes manufactured at (b) (4). Stability data over a period of 60 months were obtained.

Stability storage conditions:

- Long-term 2°C to 8°C / ambient relative humidity (RH)
- Long-term (b) (4)
- Accelerated (b) (4)
- Long-term 2°C to 8°C / ambient relative humidity (RH)

Stability Assays and Specifications

Table 6. Stability Assays and Specifications for sWFI syringe

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

6. Post Approval Stability Study

Octapharma plans to add (b) (4) of FDP, manufactured at Octapharma AB in Stockholm, Sweden, in the stability study. Since several dosage strengths (250, 500, 1000 and 2000 IU/vial) will be presented to the market, the dosage strength for the (b) (4) batch will alternate (b) (4). Samples will be stored upright at $+5^{\circ}\text{C} \pm 3^{\circ}\text{C}$ /ambient RH, sealed in the dark.

7. Conclusion & Recommendation

I recommend approval of this BLA because the data from the container and closure system and the stability studies for BDS, FDP and sWFI are acceptable and support the proposed shelf-life as follows:

- For Nuwig BDS – (b) (4) t.
- For Nuwig FDP – 24 months at 2-8°C when protected from light. The product can also be stored at room temperature (up to 25°C) for up to 3 months within the shelf-life.
- For sWFI pre-filled syringes – 60 months at 2°C to 30°C.
 - The container and closure system for BDS, including (b) (4) were investigated and evaluated by using (b) (4) assessment. The results indicated that no toxic effects are to be expected from these compounds.
 - The container and closure system for FDP, including injection vial, Lyophilisation stopper and Flip-off Cap, were investigated. The results indicated that the integrity of package was well maintained. Therefore the packaging can be considering suitable for use.
 - Overall, the stability data demonstrate consistency of the manufacturing process. The specific activity of Nuwig (b) (4) FDP batches is consistently within their respective ranges of (b) (4) indicating that there is no significant variability in Nuwig purity in different batches. The data also show that the (b) (4) in Nuwig were consistently within specification with very low levels of (b) (4) over time.
 - sWFI pre-filled syringes were studied under different storage conditions, the data demonstrate consistent quality, and support its shelf-life.