



FOOD AND DRUG ADMINISTRATION
CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

MEMORANDUM

Final Review

To: File (BLA STN 125555/0), Andrey Sarafanov & Jiahua Qian

From: Mikhail V. Ovanesov, PhD, Senior Staff Fellow, Laboratory of Hemostasis (LH), Division of Hematology Research and Review (DHRR)/OBRR

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

Sponsor: Octapharma Pharmazeutika Produktionsges; m.b.h.

Product: Antihemophilic Factor (Recombinant)

Subject: Final review of controls of drug substance and drug product, reference materials and excipients in BLA under STN 125555/0

Contents

| | |
|--|----|
| 1. Executive summary..... | 1 |
| 2. Release specifications | 2 |
| 3. Method validation | 4 |
| 4. Batch analyses..... | 8 |
| 5. Reference standards | 10 |
| 6. Excipients..... | 10 |
| 7. Review of responses to information requests | 10 |
| 8. Conclusions and recommendation | 11 |

1. Executive summary

Background

This memorandum summarizes the review of the release specifications and methods for the bulk drug substance (BDS) and final drug product (FDP), reference materials and excipients in an original Biologics License Application (BLA) under STN 125555/0 submitted by Octapharma Pharmazeutika Produktionsges.m.b.H (Octapharma) for a recombinant analog of human factor VIII (FVIII) expressed in a human cell line. The proposed proprietary name of this product is NUWIQ.

Conclusion & Recommendation

The BDS and FDP specifications and release method validations are acceptable and can ensure the safety, quality and consistency of the product. All specifications are in agreement with the analyses data for batches used in the clinical trials and process validation data. Batch analyses demonstrate good consistency of the manufacturing process and good compliance with release specifications. Therefore, from this perspective, I recommend the approval of this BLA.

2. Release specifications

The BDS and FDP release specifications are shown in Tables 1 and 2, respectively. The proposed methods and acceptance limits are sufficiently informative and meet regulatory expectations for recombinant FVIII products. For example, the proposed release specifications are consistent with the approved specifications for the two recently licensed recombinant FVIII products, NovoEight (Novo Nordisk A/S) and Eloctate (Biogen Idec).

The potency of NUWIK FDP is assigned with a validated one-stage clotting assay for FVIII activity using a product specific-standard calibrated in units of the current WHO 8th International Standard for FVIII. This is consistent with the FDA recommendation provided in the IND advice letter dated August 05, 2008. Therefore, the NUWIK potency assignment is consistent with the current practices in clinical laboratories which almost exclusively use the one-stage clotting assay for the evaluation of FVIII activity in patient samples. Please note that the BDS is released (b) (4)

The limits for the FDP potency are based on the available manufacturing experience. Originally, Octapharma cited (b) (4) but later provided data to justify the specifications with the batch analysis data.

Pharmacopeial tests (e.g., (b) (4) *appearance, bioburden and bacterial endotoxins*) are validated and the limits are in compliance with the (b) (4). The limits for the remaining quantitative tests were developed and verified using batch analyses data (e.g., potency specification). The specifications for qualitative tests without numerical limits (b) (4) are based on existing scientific evidence on the identity and purity of NUWIK product.

All specifications are in agreement with the analyses data for batches used in the clinical trials and process validation data.

In conclusion, the specifications were established appropriately and are able to ensure the safety, quality and consistency of the product.

(b) (4)

(b) (4)

Table 2: FDP Release Specifications

| Description | Method | Specification |
|--------------------------------|----------|---|
| <u>Characters</u> | | |
| Appearance: | (b) (4). | A white cake. Possibly a small amount of white powder |
| <u>Identification</u> | | |
| (b) (4) : | (b) (4) | (b) (4) |
| (b) (4) | (b) (4) | (b) (4) |
| <u>Tests</u> | | |
| Solubility at 20-25°C, time: | (b) (4) | (b) (4) |
| Visual inspection of solution: | (b) (4) | Clear, colorless solution, practically free from visible particles |
| (b) (4) | (b) (4) | (b) (4) |
| (b) (4) | (b) (4) | (b) (4) |

| | | | |
|--|--|----------------|--|
| Water: | (b) (4) | > | (b) (4) |
| (b) (4) | (b) (4) |) | (b) (4) |
| Total protein: | (b) (4) | (b) (4) | (b) (4) (250 IU) (500 IU) (1000 IU) (2000 IU) |
| Specific FVIII:C activity: | Ratio FVIII:C/Total protein | (b) (4) | (b) (4) |
| (b) (4) | (b) (4) | (b) (4) | (b) (4) |
| Sterility: | (b) (4) | approved | |
| Endotoxin: | (b) (4) | (b) (4) | |
| Assay | | | |
| FVIII:C | One-Stage (clotting) | (b) (4) | (250 IU) (b) (4) (500 IU) (b) (4) (1000 IU) (b) (4) (2000 IU) Factor VIII potency should be within (b) (4) of the labeled value throughout the product shelf-life under the licensed storage conditions. |
| Confidence limit: | (b) (4). | Within (b) (4) | of the estimated potency |
| Additional tests | | | |
| Citrate: | (b) (4) | (b) (4) | |
| Sucrose: | (b) (4) | (b) (4) | |
| Poloxamer 188: | (b) (4) | (b) (4) | |
| Sodium: | (b) (4) | (b) (4) | |
| Calcium: | (b) (4) | (b) (4) | |
| Chloride: | (b) (4) | (b) (4) | |
| Arginine: | (b) (4) | (b) (4) | |
| Storage and Expiry Date | | | |
| Period of validity from the date of manufacturing: | Expected shelf-life is 24 months at 2 –8°C (35.6 – 46.4°F) and protected from light from the date of manufacture. During the shelf-life, the product may be kept at room temperature [up to 25°C (77°F)] for a single period not exceeding 3 months. After storage at room temperature, the product must be used or discarded, and must not be put back to the refrigerator. | | |

3. Method validation

Review summary for the validated BDS and FDP methods are presented in Tables 3 and 4, respectively. All tests including Pharmacopeial and commercially available test systems were validated to demonstrate their ability to control NUWIQ BDS and FDP quality. Please note that review of FDP release methods was the responsibility of OCBQ/DBSQC, therefore I only conducted cursory analysis of these methods in relation to the validity of FDP release specifications.

Table 4: Validated FDP release methods.

| Validated Method | Reviewer comments |
|---|--|
| • Appearance | (b) (4) |
| • Arginine | (b) (4) method validated for multiple products |
| • Bioburden (membrane filtration) | (b) (4) method validated for multiple products |
| • Calcium | Validated commercial method |
| • Chloride | Method validated for multiple products |
| • Citrate | Method validated for multiple products |
| • (b) (4) | (b) (4) |
| • Endotoxin (b) (4) | (b) (4) method validated for multiple products |
| • FVIII:C determination (chromogenic assay) | (b) (4) |
| • FVIII:C determination (one-stage clotting assay) | Method validated for multiple products |
| (b) (4) | (b) (4) |
| (b) (4) | (b) (4) method validated for multiple products |
| (b) (4) | (b) (4) method validated for multiple products |
| (b) (4) | (b) (4) |
| • Poloxamer 188 | Method validated for multiple products |
| • Sodium | Method validated for multiple products |
| • Solubility | Method validated for multiple products |
| • Sterility | (b) (4) method validated for multiple products |
| • Sucrose | (b) (4) method validated for multiple products |
| • Total Protein | (b) (4) |
| • Visual Inspection | (b) (4) |
| • Water | (b) (4) method validated for multiple products |

Although NUWIK is the first Octapharma's recombinant product on the US market, this firm has extensive expertise in the development of methods for characterization of plasma-derived and recombinant coagulation factor products. In addition, for many years, Octapharma served as a contract manufacturer for the first generation of Wyeth's recombinant Factor VIII product ReFacto®.

Some release methods are currently validated for other Octapharma products, e.g., (b) (4). For all multi-product methods, the respective methods were re-validated using representative NUWIK samples.

A number of test methods (e.g., (b) (4)) were developed specifically for the NUWIK process. The majority of these new tests was introduced as early as 2006 but was subsequently modified and improved to address performance issues and changes in instrumentation.

Two methods, *in vitro adventitious virus* and *Mycoplasma*, are performed and validated by a contract firm (b) (4). These methods are typically performed by contract laboratories because special expertise and instrumentation are required.

Minor robustness and precision issues were reported for several method validation packages including (b) (4).

(b) (4), *Determination of Coagulation Factor VIII by Chromogenic Assay*, and *Determination of host cell proteins* by (b) (4). Octapharma conducted additional studies and provided evidence that the observed problems with the methods' performance are unlikely to have an impact on product potency and quality. I agree with these conclusions.

With the exception of the (b) (4) method discussed below, the currently available versions of the methods demonstrate good robustness as evidenced from the batch analyses and stability studies.

Deficiencies of (b) (4) method validation

Starting in the middle of 2013, Octapharma experienced recurrent robustness problems with the (b) (4) as manifested, for example, in multiple consecutive Out-of-Specification (OOS) results for (b) (4)s (specification (b) (4)) in the on-going stability studies. Detailed analysis of the technical issues with this method can be found in the review memorandums of Dr. Lokesh Bhattacharyya and Dr. Andrey Sarafanov. Dr. Bhattacharyya's laboratory reviewed method validation and conducted in-support testing for representative NUWIQ batches. Dr. Sarafanov reviewed validation and performance data for this test during pre-approval inspection in October 2013.

I reviewed the most current method validation data and Octapharma responses to numerous Information Requests from FDA reviewers concerning this method. **I found that the recently revalidated version of (b) (4) demonstrates acceptable performance and that the previous deficiencies of the method have no adverse impact on the quality and potency of release products.** These conclusions are supported by the following evidence:

1. As requested by FDA, Octapharma identified the root causes for the OOS results as poor robustness of the (b) (4) method due to non (b) (4). Both issues were addressed in the revalidated version of the (b) (4) method. The (b) (4) issue was addressed with the new validated (b) (4) step and more stringent (b) (4) criteria. The stability of the tested samples is now assured through stringent validated pre-test storage conditions.
2. Acceptable performance of the new (b) (4) method was demonstrated in stability studies where all previous OOS results were invalidated. All stability samples were found in specification at subsequent stability time-points.
3. Since the previous robustness issues were partly caused by under-reporting of (b) (4) due to increased (b) (4), the existing specifications potentially represent more stringent limits compared to those found in the clinical batches of NUWIQ.

5. Reference standards

Octapharma developed and maintains appropriate standards or reference materials for all methods including methods for (b) (4)

(b) (4) *Total protein*, (b) (4), *Endotoxin*, *Citrate* and *Potency*.

Specifically, (b) (4), the internal reference standard for the determination of FVIII activity is made using the commercial NUWIQ process. Two potencies (b) (4) by chromogenic assay and (b) (4) by clotting assay) are assigned to the internal reference standard. The potency assay was standardized against the 8th International Standard for Blood Coagulation Factor VIII:C concentrate (8th IS), code 07/350. The standard was obtained from the National Institute for Biological Standards and Control (NIBSC) and replaced the 7th International Standard for Blood Coagulation Factor VIII:C (7th IS, NIBSC, code 99/678) in October 2009. The validation report for the internal reference standard is included in Section 3.2.P.5.3 of the BLA.

In addition, the (b) (4) standard was prepared from in-process intermediate (b) (4), batch no. (b) (4) and characterized using (b) (4)

6. Excipients

All chemical raw materials used in the manufacture of NUWIQ comply with the (b) (4) criteria. The respective manufacturers guarantee quality control and compliance. In addition, quality control tests as prescribed in (b) (4) are performed regularly by Octapharma. Octapharma always performs a test for identity on each batch of excipient received. Octapharma's approach is consistent with the commonly accepted industry practices.

7. Review of responses to information requests

My requests for additional information were submitted as part of a combined CMC Information Request on December 03, 2014. Below is the review of Octapharma's responses provided in several amendments between December 19, 2014 and February 28, 2015.

FDA question 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) by the (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)

- 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.*

Response:

FDA question 7. In accordance with your statement in Section 11 Description of the Full Prescribing Information “Each vial of Nuwiiq® is labeled with the actual FVIII potency expressed in IU.” please add the word “Range” to the potency identifiers on the carton and container labels, e.g., “250 IU Range”, etc.

Response:

Octapharma introduced requested changes.

FDA question 8. *Regarding the FDP release specifications, please*

- a. *Establish the FDP potency specification for each dosage strength as an acceptance range based on your manufacturing experience. For example, the specification for the 250 IU range dosage strength is (b) (4) IU per vial.*

Response:

In order to establish the FDP potency specification for each dosage strength as an acceptance range based on the manufacturing experience, (b) (4) batches produced from July 2013 until November 2014 were statistically evaluated. The specification limits of (b) (4) of the target for each dosage strength were found to meet or exceed limits derived from the FDP batch analyses.

- b. *Add the following requirement to the FDP potency specification: “Factor VIII potency should be within (b) (4) of the labeled value throughout the product shelf-life under the licensed storage conditions.”*

Response:

Octapharma introduced requested changes.

8. Conclusions and recommendation

I conclude that the BDS and FDP specifications and release method validations are acceptable and can ensure the safety, quality and consistency of the product. Therefore, from this perspective, this BLA may be approved.