



MEMORANDUM

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

To: File (STN 125555/0)
Jiahua Qian, PhD, Regulatory Project Manager, OBRR/IOD/RPM Staff

From: Ze Peng, PhD, OBRR/DHRR/LH

Through: Mark Weinstein, PhD, Assoc. Dep. Dir. for Science, OBRR/IOD
Basil Golding, MD, Division Director, OBRR/DHRR

Subject: Final review of Adventitious Agents Safety Information in Octapharma's original BLA for Antihemophilic Factor VIII (Recombinant) plasma/albumin free

Cc: Andrey Sarafanov, PhD, Committee Chair, OBRR/DHRR/LH

Executive Summary

This memorandum summarizes the review of Adventitious Agents Safety Information in an original Biologics License Application (BLA) under STN 125555/0 submitted by Octapharma for Antihemophilic Factor VIII (Recombinant) plasma/albumin free. The proposed proprietary name of this product is *Nuwiq*. As described below, the measures taken by Octapharma to control adventitious agents in the manufacture of *Nuwiq* drug product are acceptable; therefore, I recommend approval of the BLA under STN 125555/0.

Evaluation of safety regarding adventitious agents

For the non-viral adventitious agents including bacteria, fungi, and mycoplasma, the potential of contamination of these agents is well controlled through the use of: (1) validated cleaning/sanitization procedures; (2) in-process controls, e.g., (b) (4) and (3) filtration steps including (b) (4) sterile filtration. The potential of *Nuwiq* to be contaminated with non-viral adventitious agents is further reduced by testing the final product for (b) (4), endotoxin, and sterility. Octapharma manufactures *Nuwiq* according to GMP criteria.

The potential risk of contaminating adventitious viruses or transmissible spongiform encephalopathy (TSE) agents is minimized because there are no raw materials or

ingredients of human or animal origin used in the manufacturing process or in the formulation of the *Nuwiq* drug product.

The potential of contamination of cell culture by infectious viruses is well controlled in the manufacture of *Nuwiq*, which is produced in a genetically modified human embryonic kidney (HEK) 293F cell line. Octapharma performed viral tests on the Master Cell Bank (MCB) for *Nuwiq* that are consistent with the International Conference on Harmonisation (ICH) Q5A(R1) guideline. All results of viral tests were negative. Moreover, all viral tests were negative at the limit of the established cell age used for production (b) (4). Octapharma routinely tests cell cultures used in the manufacturing process for *in vitro* adventitious viruses to ensure that viruses are below their detectable levels.

Additionally, the potential risk of viral contamination of *Nuwiq* is further mitigated through two dedicated viral clearance steps: Solvent/Detergent (S/D) treatment (b) (4) and (b) (4) 20N nanofiltration (mean pore size, (b) (4)). Octapharma has evaluated these steps in down-scale studies. The enveloped viruses selected in the studies include (b) (4)

The non-enveloped viruses selected in the studies include (b) (4) and (b) (4) model virus for (b) (4). The wide range of physico-chemical properties of these viruses demonstrates the ability of the manufacturing process to reduce potential viral contamination of *Nuwiq*. Down-scale studies on the relevant steps resulted in the following overall log reduction factors, in parenthesis, for these viruses: (b) (4). We find these results support the proposal that viral clearance is effective in the manufacture of *Nuwiq*.

Background

The active ingredient in *Nuwiq* is recombinant human coagulation factor VIII (rhFVIII) with a deleted B domain, which is produced in a HEK 293F cell line. The molecular mass of this product is 170 kDa. *Nuwiq* is formulated as a sterile lyophilized powder for intravenous injection only. When reconstituted with its diluent, sterile Water for Injection, each container of *Nuwiq* contains nominally 250, 500, 1000, or 2000 IU of rhFVIII.

The manufacturing process of *Nuwiq* includes two dedicated viral clearance steps: S/D treatment (b) (4), a viral inactivation step; and (b) (4) 20N nanofiltration, a viral removal step. Additionally, no raw materials or ingredients of human or animal origin are used in the manufacturing process, which further mitigates the potential of viral contamination.

Summary of Review

Flow chart of the manufacturing process for Nuwiq

The flow chart of the manufacturing process for *Nuwiq* includes the following steps:

Nuwiq drug substance



Nuwiq drug product

16. (b) (4)
17. Formulation
 18. Sterile filtration
 19. Aseptic filling
 20. Freeze-drying
 21. Capping
 22. Visual inspection
 23. Labeling and packaging

Product reviewer's comment: Bolded in the above flow chart are the two dedicated viral inactivation/removal steps. The validation reports for these two clearance steps were reviewed, and the results demonstrate that these steps are capable of either inactivating or removing viruses, thus lowering the potential of viral contamination.

Evaluation of safety of adventitious agents (Section 3.2.A.2)

1. Control of non-viral adventitious agents

For the non-viral adventitious agents including bacteria, fungi, and mycoplasma, the potential of contamination of these agents is well controlled through the use of

(1) validated cleaning/sanitization procedures; (2) in-process controls, e.g., (b) (4); and (3) filtration steps including (b) (4) sterile filtration. The potential of *Nuwiq* to be contaminated with non-viral adventitious agents is further reduced by testing the final product for (b) (4) endotoxins, and sterility. Octapharma manufactures *Nuwiq* according to GMP regulations.

2. Testing of all mammalian cell banks for the absence of infectious viruses

MCB used for the production of *Nuwiq* is well controlled regarding the potential of viral contamination. The MCB named (b) (4) has been tested for viruses according to ICH Q5A(R1). All the tests were found negative for the presence of viruses. This MCB is also found to be absent of mycoplasma, bacteria, and fungi. Furthermore, cells at the limit of *in vitro* cell age used for production (b) (4) were tested, and found negative for mycoplasma, bacteria, fungi, and adventitious viruses. The data are summarized as follows:

(b) (4)

(b) (4)

Octapharma routinely tests cell cultures used in the manufacturing process for *in vitro* adventitious viruses to ensure that viruses are below their detectable levels.

Product reviewer's comment: The tests performed on the MCB are consistent with ICH Q5A(R1) guidance. All test results for endogenous and adventitious viruses were negative. Moreover, there are two dedicated virus inactivation/removal steps in the manufacturing process. These steps are used to reduce the potential of the DP to be contaminated with endogenous or adventitious viruses.

According to the ICH guidance Q5A, the full tests for viral safety are not required to be performed on the WCB if the tests are performed on the MCB; viral safety should be evaluated at least once on the cells at the limit of *in vitro* cell age used for production. The data shown above provided further assurance that the manufacturing process is not prone to be contaminated by potential adventitious viruses. Therefore, these data are considered to be sufficient to support both MCB and WCB used for the manufacture of *Nuwiq*.

3. Control of materials used in the manufacturing process

The potential risk of adventitious virus or TSE agent contamination is minimized in the manufacturing process of *Nuwiq*. There are only (b) (4) materials of biological origin used in the manufacture of *Nuwiq*, and none of them is of human or animal origin. (b) (4)

Thus, these raw materials are unlikely to pose a virus or TSE safety risk to *Nuwiq*.

Additionally, no raw materials or ingredients of human or animal origin are used in the formulation of *Nuwiq* final product.

4. Testing the capacity of the *Nuwiq* purification process to clear viruses

Regarding viral clearance, two dedicated steps are included in the manufacturing process of *Nuwiq*, which are S/D treatment (b) (4) at (b) (4) and (b) (4) 20N nanofiltration. The enveloped viruses selected in these studies include (b) (4)

The non-enveloped viruses selected in the studies include (b) (4)

(b) (4) These viruses resemble viruses which may contaminate the *Nuwiq* product, and represent a wide range of physico-chemical properties that tests the ability of the manufacturing process to eliminate viruses.

1) Solvent/Detergent treatment

To evaluate the capacity of S/D treatment to clear viruses, Octapharma validated the down-scale system (*final study report No. OC12-0146*). The equivalence of the down-scale system and the full-scale was demonstrated by determination of a broad set of process parameters and by comparing the values obtained with the respective ranges specified for manufacturing. Comparison of the (b) (4) in the relevant intermediates further demonstrated that the S/D treatment did not have significant impact on the rhFVIII molecule with regard to (b) (4). The data support the qualification of the system scaled down for up to (b) (4). Thus, the viral clearance data derived from the down-scale system appear to be appropriate to be used for evaluating the viral clearance capacity of S/D treatment at the full-scale.

The samples used for the virus clearance study were obtained from the full-scale, and all samples are tested for toxicity and interference with (b) (4) assays. The down-scale viral clearance data on the S/D treatment are summarized below:

(b) (4)

(b) (4)

As shown above, (b) (4) of S/D treatment achieved at least a virus reduction factor of (b) (4). No infectivity was detected after (b) (4) of S/D treatment for both (b) (4) viruses. Similar results were generated in the relevant robustness studies, in which the concentrations of S/D treatment are (b) (4) of the targeted values, and the incubation temperature with S/D is (b) (4) at the full-scale. For (b) (4), infectivity was still detected after (b) (4) of S/D treatment when using the (b) (4) assay although no infectivity was detected after (b) (4) of S/D treatment when using (b) (4).

Product reviewer's comment: In the viral validation Study No. SP1396, residual (b) (4) still remained after (b) (4) of incubation in the presence of S/D when the test was performed using (b) (4). The incomplete inactivation of (b) (4) indicates that the incubation time for the S/D treatment step is not sufficient to completely inactivate (b) (4) and potentially other similar large enveloped viruses, and thus reduces the margin of viral safety of the product. For this, I consulted with Dr. Mahmood Farshid. We all agreed to ask Octapharma to re-evaluate and re-validate the S/D treatment step using a longer incubation time to achieve complete inactivation of enveloped viruses in general, and (b) (4) in particular.

This comment was sent to Octapharma on 3 December 2014, and they responded in an amendment on 9 February 2015. Their response is summarized as follows:

Octapharma's response: A new virus validation study on (b) (4) (Study No. 2/14/12/132/3/71) was initiated to investigate a prolonged S/D incubation time (Up to (b) (4)). The limit of detection was already reached within (b) (4) of S/D treatment using (b) (4).

Because the samples taken during the S/D treatment were (b) (4) prior to testing to avoid cytotoxicity/interference effects originating from the starting material, samples incubated with the S/D treatment for (b) (4) were more extensively investigated using a (b) (4) assay. The respective viral titer was (b) (4) and (b) (4) at the time-point of (b) (4) after the S/D treatment. These results are comparable to that generated at the (b) (4) time-point of S/D treatment (b) (4).

To demonstrate the consistency of product quality, Octapharma compared the test results of quality attributes for batches undergoing (b) (4) of S/D treatment (batches (b) (4)) to those of batches (batches (b) (4)) undergoing (b) (4) of S/D treatment at the full-scale. The results are comparable for the batches treated with S/D under the referenced incubation times. Also, as discussed in the mid-cycle teleconference, Octapharma will revise the

incubation time limit of the S/D treatment from (b) (4). This change will be reflected in the relevant *batch record* (b) (4) beginning at 27 February 2015.

Product reviewer's comment: The new information provided in this amendment support the consistency of the product quality regardless of S/D treatment incubation time within (b) (4). Regarding the viral clearance capacity of S/D treatment, after consulting with Dr. Farshid, we consider Octapharma's response to be acceptable based on the following information:

- The data from Study No. 2/14/12/132/3/71 confirmed that the limit of detection was reached within (b) (4) of S/D treatment using (b) (4)
- The virus reduction factor can reach at least (b) (4) when the incubation time of S/D treatment is extended to (b) (4), although residual (b) (4) virus is still detectable using (b) (4)
- Octapharma agreed to revise the S/D incubation time to (b) (4) in the commercial manufacturing process in which case a total virus reduction factor for (b) (4) of at least (b) (4) can be achieved

2) (b) (4) 20N Nanofiltration:

The nanofiltration step is executed through a (b) (4)

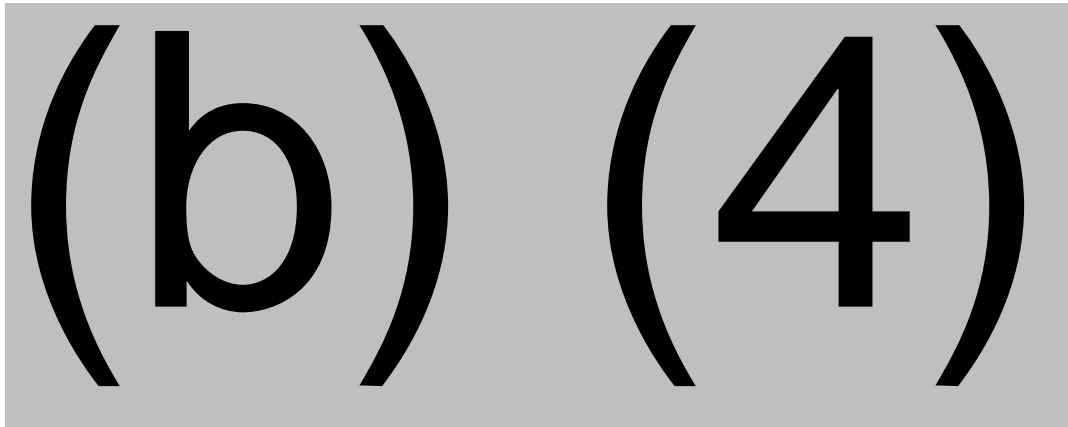
To evaluate the capacity of nanofiltration to clear viruses, Octapharma validated the down-scale system (final study report No. OC12-0149). In this study, the acceptance criteria for critical parameters such as (b) (4) are identical between the down-scale and the full-scale. As shown in the table below, (b) (4) were found to be comparable between the down-scale and the full-scale.

(b) (4)

These data support the qualification of this system scaled down to (b) (4). Thus, the viral clearance data derived from the down-scale system can be used to evaluate the viral clearance capacity of nanofiltration at the full-scale.

To demonstrate the robustness of the down-scale system, Octapharma increased the rhFVIII load to nanofilter area (kg/m^2) up to (b) (4) times of that used at the full-scale. The recovery of the product was (b) (4) and met the acceptance criterion. Additionally, no visible signs of product degeneration were detected using (b) (4).

The samples used in the virus clearance studies were obtained from the full-scale. All samples were tested for (b) (4) assays. (b) (4) independent runs were used for each virus in the study. Viruses selected include (b) (4) enveloped viruses (b) (4) and (b) (4) non-enveloped viruses, (b) (4). These studies indicated that no residual viruses were detected in each (b) (4) after nanofiltration. As the data show in the following table, nanofiltration can remove both enveloped and non-enveloped viruses by at least (b) (4).



Product reviewer's comment: Octapharma provided the data on the removal of (b) (4) 20N nanofiltration under standard (*Study SP1384*) and robust (*Study SP13101*) conditions. In these studies, Octapharma stated that negative matrix effects on the assay system are overcome by a (b) (4) of the matrix in (b) (4). However, the data from the hold control show that the matrix itself contributed (b) (4) clearance by the nanofiltration step. We will ask Octapharma to re-validate the assay for (b) (4) to verify that the log reduction factor of the nanofiltration step is not confounded by the matrix.

This comment was sent to Octapharma on 3 December 2014, and they responded in an amendment on 19 December 2014. The response is summarized as follows:

Octapharma's response: To investigate the impact of the matrix on the (b) (4) assay, a cytotoxicity and interference study *SP1373* was performed and reported as a prerequisite for the main spiking studies. The cytotoxicity investigation revealed that the (b) (4) without viruses was not cytotoxic towards the indicator cell line following a (b) (4) dilution with the cell culture medium. (b) (4) spiked with a low titer of virus (b) (4) did not interference with viral infection, replication or detection after (b) (4) dilution with the cell culture medium.

In the subsequent viral clearance studies (*SP1384* and *SP13101*), the samples were diluted to an even higher, (b) (4) dilution with the cell culture medium. Such a dilution further minimized the matrix-related impact on the assay system itself. Thus, in comparison to the spiked starting material, the titer reduction of the hold control (b) (4) was considered to be the result of a partial inactivation of (b) (4) over the duration of the process in the matrix, and not the result of any interference effect on the assay system.

Product reviewer's comment: The data from the validation study *SP1373* in this amendment indicated that test samples diluted with cell culture medium at a ratio of (b) (4) can mitigate the impact of the matrix on the measurement of cytotoxicity and interference caused by the assay system. The titer reduction of the hold control in comparison to the spiked starting material in the viral clearance studies *SP1384* and *SP13101* appears to be process-related, and not caused by interference from the assay system. Dr. Farshid agreed with this conclusion. Additionally, a (b) (4). These steps may contribute to the viral clearance capacity, although Octapharma has not validated them. The viral clearance data on nanofiltration are sufficient, and this response is acceptable.

3) Virus reduction factors

The viral clearance data from the above mentioned down-scale studies are summarized as follows:

(b) (4)

Product reviewer's Comment: Virus selection in the down-scale studies is consistent with the FDA recommendation regarding biological drug products derived from cell lines of human or animal origin. The qualification of the down-scale systems used for viral clearance is acceptable, and the viral clearance data derived from these down-scale systems are sufficient to support the effectiveness of viral clearance in the commercial manufacturing process.

Recommendation

The process assuring the safety from non-viral adventitious agents including bacteria, fungi, and mycoplasma is well controlled through the use of validated cleaning/sanitization procedures, in-process controls, filtration steps including (b) (4) sterile filtration, and release tests for sterility, endotoxins, and (b) (4) in the final product. The safety of the product from contamination with adventitious viruses is enhanced through complete viral tests of the MCB and cells at the limit of the *in vitro* cell age used for production. Furthermore, no raw materials or ingredients of human or animal origin are used in the manufacturing process. Additionally, viral safety is further enhanced by two dedicated viral clearance steps: (b) (4) minutes, and (b) (4) 20N nanofiltration. The measures taken by Octapharma to control adventitious agents in the manufacture of *Nuwiq* are acceptable. Therefore, I recommend approval of the BLA under STN 125555/0.