

Final Review CMC, October 2013 - Novoeight

To: File (STN 125466/0)
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Through: Tim Lee, PhD, Acting Chief, LH/DH/OBRR

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Subject: Final Review of Stability and Adventitious Agents Safety information in Novo Nordisk's original BLA for Antihemophilic Factor (Recombinant)
Cc: Natalya Ananyeva, PhD, Committee Chair, LH/DH/OBRR

Executive Summary

This memorandum summarizes the review of Stability and Adventitious Agents Safety information in an original Biologics License Application (BLA) under STN 125466/0 submitted by Novo Nordisk (Novo) for Antihemophilic Factor (Recombinant). The proposed proprietary name of this product is Novoeight. As described below, in general, the product stability and the measures taken by Novo to control adventitious agents in the manufacture of Novoeight are acceptable; therefore, I recommend approval of the BLA under STN 125466/0.

Stability studies

The stability data indicate that no critical trends are detected during the observed long-term storage period. The data support the shelf-life of Novoeight proposed by Novo, which is 24 months when stored at 2 – 8°C (36 – 48°F). Within this period, this product may be stored at room temperature ($\leq 30^{\circ}\text{C}$ or 96°F) for a single period of up to 6 months not to exceed the expiration date. Thus, the Novoeight label states “Do not use beyond the expiration date (2-8°C for 24 months) or 6 months at room temperature up to 30°C, whichever is earlier”.

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 and sanitization procedures, e.g., for cell culture equipment: ---(b)(4)-
------(b)(4)-----; and for purification equipment: ---
(b)(4)--; (2) in-process controls, e.g., sterility testing, bioburden, and freedom from mycoplasma in -----(b)(4)-----; and (3) filtration steps including 0.2 mm sterile filtration. The potential of Novoeight to be contaminated with non-viral adventitious agents is further reduced by testing the final product for sterility, endotoxins, and particulate matter. Novo manufactures Novoeight according to GMP regulations.

The potential risk of adventitious viruses or transmissible spongiform encephalopathy agents is minimized because there are no raw materials or ingredients of human or animal origin used in the manufacturing process.

The potential of contamination by infectious viruses in cell culture is well controlled for up to (b)(4). Novoeight is produced by a Chinese Hamster Ovary (CHO) cell line. Novo performed viral tests on the Master Cell Bank (MCB) for Novoeight that are consistent with International Conference on Harmonisation (ICH) Q5A(R1) guideline. All results of viral tests were negative except for the presence of retrovirus-like particle (RVLP) found in (b)(4). RVLPs are considered to be nonpathogenic. Moreover, all viral tests were negative except for RVLPs by (b)(4) on cells that were at the limit of the *in vitro* cell age used for production (b)(4) in cell culture). In addition, Novo routinely tests cell cultures used in the manufacturing process for adventitious viruses to ensure that viruses are below their detectable levels.

Additionally, the potential risk of viral contamination of Novoeight is further mitigated through two dedicated viral clearance steps – a capture step by the mixed mode chromatography that includes a (b)(4), and a nanofiltration step on a 20-nm filter. In addition, the anti-Factor (F) VIII matrix affinity chromatography (b)(4) chromatography steps in the manufacturing process also contribute to virus removal. Novo has evaluated these viral clearance steps in relevant down-scale studies using model viruses. The viruses selected for the studies include

(b)(4)

(b)(4). The wide range of physico-chemical properties of these model viruses demonstrates the ability of the manufacturing process to reduce potential viral contamination from Novoeight. 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 to be acceptable to support the proposal that viral clearance is effective in the manufacture of Novoeight.

Background

Novoeight is a recombinant analogue of human coagulation factor VIII (rFVIII) with a truncated B domain of 21 amino acid residues, which is produced in a CHO cell line CHO-(b)(4). The molecular mass of this product is 166 kDa. Novoeight is formulated as a sterile, non-pyrogenic, white or slightly yellow lyophilized powder for intravenous injection only. When reconstituted with its diluent, 0.9% Sodium Chloride, Novoeight contains 250, 500, 1000, 1500, 2000 or 3000 IU of rFVIII per vial. The manufacturing process of Novoeight includes two dedicated viral clearance steps: (b)(4), and 20-nm nanofiltration. In addition, the anti-FVIII matrix affinity chromatography (b)(4) chromatography steps in the manufacturing process also contribute to virus removal. Furthermore, 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 of Novoeight

The flow chart of the manufacturing process of Novoeight includes the following steps:

Novoeight drug substance

- 1. -----(b)(4)-----
- 2. -----(b)(4)-----
- 3. -----(b)(4)-----
- 4. -----(b)(4)-----
- 5. -----(b)(4)-----
- 6. -----(b)(4)-----
- 7. -----(b)(4)-----
- 8. -----(b)(4)-----
- 9. -----(b)(4)-----

Novoeight drug product

- 10. Formulation
- 11. Sterile filtration
- 12. Filling, lyophilization, and capping
- 13. Labeling and packaging

Product reviewer’s comment: Bolded in the above flow chart are the two dedicated viral inactivation/removal steps. There are (b)(4) additional steps including anti-FVIII matrix affinity chromatography -----(b)(4)----- chromatography, which also contribute to viral clearance. The validation reports for these 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.

3 pages redacted (b)(4)

 -----(b)(4)-----

 -----(b)(4)-----

- 1. Drug product
- Novoeight DP is supplied as nominally 250 IU, 500 IU, 1000 IU, 1500 IU, 2000 IU, and 3000 IU per vial. The composition of the Novoeight DP is the same among these six product presentations except for the content of the active ingredient. Therefore, Novo introduced a bracketing design in the stability studies in accordance with ICH guidance Q1D.

1) Stability study (novoDOCS: 001118375) for the Novoeight DP manufactured using Formulation (b)(4) Novoeight DS

Three batches of 250 IU and three batches of 3000 IU Novoeight DP were used in the stability study. All of them were manufactured using the Formulation (b)(4) Novoeight DS. The container closure system used in the stability study is identical to the commercial one. Since Formulation (b)(4) is considered comparable to the commercial one (Formulation (b)(4)), these six batches are qualified to support the following proposed shelf life of Novoeight DP:

The Novoeight DP can be stored at 2 – 8°C for 24 months. Within this period, the product may be stored at room temperature (≤ 30°C) for a single period up to 6 months.

These batches were investigated under the long-term storage conditions (5 ± 3°C for (b)(4) months; 5 ± 3°C for (b)(4) months followed by 30 ± 2°C----- (b)(4)----- months) and stressed condition ----- (b)(4)----- . Novo also performed a stability study on the batches stored at 30 ± 2°C/---- (b)(4)---- months. The parameters used in this study included Appearance of powder, Reconstitution time/solubility, Water content, Appearance of solution/clarity, (b)(4), Potency (chromogenic assay), Purity, ----- (b)(4)-----, Content, --- (b)(4)---, Particulate matter, Endotoxin, Sterility. The acceptance criteria are the same as those from the release specification except for the slightly modified ones for the following parameters: Water content, Potency, Purity, ----- (b)(4)----- (with reference to the amendment dated 29 July 2013).

For the long-term storage of 5 ± 3°C, all test results from the six batches are within the acceptance criteria for up to 24 months. The potency results are listed as follows:

Batch No.	Strength	Storage time (months)						
		0	3	6	9	12	18	24
---(b)(4)--	250 IU	100% (246 IU)	96%	107%	98%	106%	104%	103%
---(b)(4)--		100% (221 IU)	107%	110%	113%	109%	116%	114%
---(b)(4)--		100% (219 IU)	109%	113%	107%	110%	115%	115%
---(b)(4)--	3000 IU	100% (2830 IU)	92%	91%	99%	110%	104%	107%
---(b)(4)--		100% (2497 IU)	108%	109%	114%	115%	119%	122%
---(b)(4)--		100% (2409 IU)	113%	125%	117%	112%	123%	120%

The test results for the same batches stored at 5 ± 3°C for 18 months and followed by 6 months at 30°C/-(b)(4)- are also within the acceptance criteria. For ----- (b)(4)----- and water content, there are upward trends detected during storage at long-term (5 ± 3°C) and accelerated (30°C/--- (b)(4)--- conditions. However, all results are within the pre-defined acceptance criteria. An upward trend for ----- (b)(4)----- Water content is detected under the stressed condition (b)(4), and a downward trend for Purity is observed. However, all results met the acceptance criteria.

Product reviewer’s comment: As previously discussed, Formulation (b)(4) is comparable to Formulation (b)(4), the commercial one. The six Novoeight DP batches were manufactured using Novoeight DS formulated in Formulation (b)(4). Thus, the 24-

month long-term stability data generated from these DP batches is considered to fully support the proposed shelf-life of Novoeight final product.

2) Stability study (novoDOCS: 001288236) for commercial Novoeight DP manufactured using Formulation (b)(4) Novoeight DS

Novo also included the following three conformance batches in the stability study to support the proposed shelf-life of Novoeight final product. These batches were investigated under the long-term storage conditions ($5 \pm 3^{\circ}\text{C}$ for (b)(4) months; $5 \pm 3^{\circ}\text{C}$ - (b)(4)- months --- (b)(4)--- $30 \pm 2^{\circ}\text{C}$ /----- (b)(4)----- months) and accelerated condition ----- (b)(4)----- . These batches were manufactured using the Formulation (b)(4) Novoeight DS. The container closure system used in the stability is identical to the commercial ones. Therefore, the stability data from these lots are qualified to support the shelf-life of Novoeight DP.

Long-term stability: The 12-month stability data for long-term storage ($2-8^{\circ}\text{C}$) are available. All results are within the acceptance criteria. There is no significant trend detected. The potency data for these batches are listed as follows:

Batch No.	Strength	Storage time (months)				
		0	3	6	9	12
---(b)(4)---	250 IU	100% (271 IU)	103%	99%	106%	97%
---(b)(4)---	2000 IU	100% (2147 IU)	97%	99%	103%	95%
---(b)(4)---	3000 IU	100% (3069 IU)	100%	103%	113%	106%

Stressed condition: An upward trend for ----- (b)(4) ----- Water content, and a downward trend for Purity are observed under the stressed condition ----- (b)(4) ----- . However, the test results are still within the acceptance criteria during the 6-month storage period. The potency data for these batches are listed as follows:

Batch No.	Strength	Storage time (months)			
		0	1	3	6
---(b)(4)---	250 IU	100% (271 IU)	96%	97%	89%
---(b)(4)---	2000 IU	100% (2147 IU)	95%	97%	87%
---(b)(4)---	3000 IU	100% (3069 IU)	100%	101%	99%

Product reviewer's comment: Although the long-term stability data for these commercial batches are available for only 12 months, there are no significant trends found for each parameter, and all the stability data are within the acceptance criteria. Together with the 24-month long-term stability data from the batches manufactured using Formulation (b)(4) DS, they support the proposed shelf-life of Novoeight DP. The stability data provided in this BLA indicated that the level of endotoxin in Novoeight DP is < 1 EU/mL for all tested dosage strengths, whereas the acceptance criteria for endotoxin used in the stability protocol are relatively wide (----- (b)(4) ----- for 250 IU per vial; and ----- (b)(4) ----- for 3000 IU per vial). Novo was requested to tighten these limits based on updated manufacturing experiences. The same is true for Purity in Novoeight DP. Novo was requested to tighten the acceptance criterion for Purity in Novoeight DP.

These comments, *in italics*, were sent to Novo on 24 June 2013. We received the response from Novo on 29 July 2013. Their response is summarized as follows:

- *The 18-month long-term stability data provided in this submission indicated that the level of endotoxin in the Novoeight final product was < 0.43 EU/mL for all tested strengths, whereas the acceptance limits for bacterial endotoxin are set relatively high in all the stability protocols (e.g., ----(b)(4)---- for 250 IU per vial; and -----(b)(4)----- for 3000 IU per vial). To better control product safety and represent manufacturing capability, please tighten the limits of bacterial endotoxin in all dosage strengths of Novoeight in the stability protocols.*

Novo's response: Novo agreed to change the acceptance criterion of Endotoxin as ----(b)(4)---- for all 6 dosage strengths.

Product reviewer's comment: The modification of the acceptance criteria on Endotoxin represents the current manufacturing capability, and product safety is further enhanced. Therefore, this response is acceptable.

- *The acceptance criterion of Purity is set to be (b)(4) in all stability protocols, whereas all stability data provided in the submission indicated that the test results for Purity were > 90.0%. To better control product quality and represent manufacturing capability, please revise the acceptance criterion of Purity.*

Novo's response: Novo re-calculated the acceptance criterion of Purity based on the release and stability data on both Novoeight (b)(4) and DP batches manufactured since 2010.

The specification of purity in Novoeight (b)(4) is re-calculated to be ----(b)(4)--. Accommodation for the manufacture (b)(4) and handling (b)(4) is subtracted from the Novoeight (b)(4) specification, and the Novoeight DP release specification is set to be --(b)(4)--. A significant change over time is observed for Purity (mainly due to the increase in -----(b)(4)-----) contributing to (b)(4); therefore the shelf-life limit of Novoeight DP is set to be (b)(4). These modifications are to enhance the control of product quality and represent the current manufacturing capability.

Acceptance criterion of Purity	----(b)(4)----	Novoeight DP	Shelf-life of Novoeight DP
Former proposed	(b)(4)	(b)(4)	(b)(4)
New proposed	(b)(4)	(b)(4)	(b)(4)

Product reviewer's comment: The acceptance criterion on Purity is tightened based on the manufacturing experiences, and this response is acceptable.

3) In-use stability (novoDOCS: 001118426)

The Novoeight DP batches in the stability study novoDOCS: 001118375 (manufactured using Formulation (b)(4) DS) were also used for in-use stability study (novoDOCS: 001118426). These batches are investigated at three time points:

- Time 0
- 3 months at 5°C followed by ---(b)(4)--- at 30°C
- The end of shelf-life

After reconstitution, these batches are tested at 0, (b)(4), and (b)(4) hours when stored at (b)(4); and 0, 4, (b)(4), and (b)(4) hours when stored at 30°C.

The parameters used in this study include Appearance, (b)(4), Purity, ----(b)(4)-----, FVIII Potency (chromogenic assay), Content, ---(b)(4)---, Particulate matter, and Anti-oxidant (L-Methionine).

At the time points, 0 month and storage at 5°C for 3 months followed at 30°C for ---(b)(4)---, the test results for the abovementioned parameters met the acceptance criteria except for -(b)(4)-. Although there was an upward trend for -(b)(4)- during the storage of 30°C after reconstitution, the (b)(4) results were within acceptance criterion for all the Novoeight DP batches except for batch --(b)(4)-- (3000 IU). For batch --(b)(4)--, the --(b)(4)-- result -(b)(4)- was out of specification -(b)(4)- at the 4-hour time-point during storage at 30°C after reconstitution. We requested Novo to provide additional stability data to support the in-use stability of Novoeight DP: 4 hours at 30°C after reconstitution. This comment, *in italics*, was sent to Novo on 24 June 2013, and we received their response on 29 July 2013. This response is summarized as follows:

Regarding batch ---(b)(4)--- in the in-use stability study (novoDOCS: 001118426), the test result of -----(b)(4)----- was out of the specification of (b)(4) at the 4-hour time-point during storage at 30°C after reconstitution. Please provide data to support the proposed in-use stability of the reconstituted final product for 4 hours at 30°C.

Novo's response: Based on the available results of (b)(4) from batches manufactured since 2010, Novo performed an evaluation on the level of -(b)(4)- during storage for 4 hours at 30°C after reconstitution. There is a -----(b)(4)----- level. When (b)(4) is added to the proposed limit of (b)(4), the limit of (b)(4) is expected to be (b)(4) for in-use stability. Thus, the test result of (b)(4) for batch ----(b)(4)----- would still be within the acceptance criterion according to the adjusted limit.

Product reviewer's comment: Because the safety of the (b)(4) level in Novoeight DP is supported by the results of the clinical studies (with reference to page 7 of 76 in the document id 001513340, Novo's amendment dated 29 July 2013), the adjustment of (b)(4) limit for its in-use stability is acceptable.

4) Stability protocol and commitment for the stability studies on drug product

In general, the stability protocol for DP is acceptable except for the removal of bacterial endotoxin from the stability protocol for long-term storage. With reference to Table 3 in the file named novoDOCS:001161268, Novo is planning to keep sterility test but remove the bacterial endotoxin parameter from the proposed on-going stability protocol. We do not agree with this revision because sterility test has its scientific and practical limitations. To better follow the stability of the DP, we requested Novo to keep endotoxin testing in the protocol or establish a validated test for container closure integrity to be included in the stability program.

This comment, *in italics*, was sent to Novo on 24 June 2013, and we received their response on 29 July 2013. This response is summarized as follows:

- *With reference to Table 3 in the file named novoDOCS:001161268, Novo is planning to keep sterility testing but remove the parameter bacterial endotoxin from the proposed on-going stability protocol. Considering that sterility testing has its scientific and practical limitations, please also keep the parameter bacterial endotoxin in this protocol through its shelf-life.*

Novo's response: The parameter bacterial endotoxin has been included at the end of shelf-life in the on-going stability study (novoDOCS: 001518265).

Product reviewer's comment: This response is acceptable.

With reference to the amendment dated 29 July 2013, we agree with Novo to have a Post Marketing Commitment in which it will enroll at least one commercial batch, each of 500 IU, 1000 IU, and 1500 IU dosage strengths in the stability program, and these batches should be monitored under the referenced storage conditions as described on page 4 of 11 of the document novoDOCS: 001161237. The interim stability data from these batches should be submitted as annual updates (PMC Submission – Status Update) through the dating period, and a final report should be submitted within 3 months of completion (PMC Submission – Final Study Report).

2. Stability for the diluent, 0.9% sodium chloride solution

There are three consecutive conformance batches in the stability studies. These batches are investigated under the long-term storage conditions ($5 \pm 3^{\circ}\text{C}$ for ---(b)(4)---; $30 \pm 2^{\circ}\text{C}$ /------(b)(4)----- and accelerated condition -----(b)(4)----- -----. The container closure system of batches used in the stability study is identical to that used in commercial batches. The parameters used in long-term stability study include Appearance, -----(b)(4)-----, Assay sodium chloride, Particulate matter, Bacterial endotoxins, and sterility.

The stability data support the proposed shelf-life of the diluent (0.9 % sodium chloride solution in prefilled syringe) of ---(b)(4)--- when stored at $5 - 30^{\circ}\text{C}$. The supportive data include results from 24-month long-term stability studies, and -----(b)(4)-- accelerated stability studies. There are no significant changes detected for all the test parameters, and all the test results are within the acceptance criteria under both storage conditions.

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 and sanitization procedures, e.g., for cell culture equipment: -----(b)(4)-----; and for purification equipment: ---(b)(4)---; (2) in-process controls, e.g., sterility testing, bioburden, and freedom from mycoplasma in -----(b)(4)-----; and (3) filtration steps including 0.2 mm sterile filtration. The potential of Novoeight to be contaminated with non-viral adventitious agents is further reduced by testing the final product for sterility, endotoxins, and particulate matter. Novo manufactures Novoeight according to GMP regulations.

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

Master cell bank used for the production of Novoeight is also 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 except for the expected presence of non-infectious endogenous RVLP. 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 adventitious viruses, mycoplasma, bacteria, and fungi.

The data are summarized as follows:

------(b)(4)-----

---(b)(4)---

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 except for the presence of non-infectious endogenous RVLPS that were found through (b)(4). RVLPS are considered to be non-pathogenic. 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 these 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 Novoeight.

3. Selection of raw materials that are non-animal derived

1) No animal-derived raw materials have been used during the establishment of the cell banks for Novoeight.

2) An anti-FVIII mAb was used in the purification process. This antibody is also expressed in CHO cells, produced without any animal-derived raw materials. The virus tests for the MCB and cells at the limit of *in vitro* cell age used for production are performed in accordance with current ICH guideline. No viruses were found except for the expected presence of nonpathogenic RVLPS in (b)(4). The concentration of RVLPS in the -----(b)(4)----- is approximately -----(b)(4)-----.

There are two dedicated steps for viral clearance in the manufacturing process, which are -----(b)(4)----- and 20-nm nanofiltration. There is at least one additional step to contribute to viral clearance, which is -----(b)(4)----- . All these steps have been evaluated in down-scale studies. The comparison of key parameters for the -----(b)(4)-----, nanofiltration, and -----(b)(4)----- steps at full-scale and down-scale is listed as follows:

----- (b)(4) -----

As the table shown, the acceptance criteria set for the down-scale study are either representing the worst-case scenario or identical to the ones at full-scale. The viruses selected in the down-scale studies include an -----(b)(4)----- . Total viral clearance factors for these model viruses are listed as follows:

----- (b)(4) -----

Product reviewer's comment: FDA recommends at least two enveloped viruses and two non-enveloped viruses in the viral clearance studies for the manufacture of recombinant biological product. The viral clearance data on non-enveloped viruses are complete and sufficient. However, there is only one enveloped virus used in virus clearance studies, an additional model enveloped virus such as pseudorabies virus (PRV) is needed for these viral clearance studies to fully validate the viral clearance capacity for enveloped viruses.

This comment, *in italics*, was sent to Novo on 9 April 2013, and we received the response from Novo on 13 May 2013. Their response is summarized as follows:

- *Please note that viral clearance studies should include at least two enveloped viruses to represent a wide range of physico-chemical properties. Please add pseudorabies virus (PRV) as a model virus for large DNA enveloped viruses with medium resistance in your validation studies for the manufacturing processes of Anti-Factor VIII monoclonal antibody used in the affinity chromatography resin.*

Novo's response: Novo proposes to use -----(b)(4)-----
- but not PRV for this viral clearance study, because the Danish regulation authority does not allow Novo to work with PRV since this type of virus is being eradicated from Denmark. They are planning to perform a viral validation study on (b)(4) at the referenced two steps (i.e., -----(b)(4)----- and nanofiltration), and expecting to submit these data to FDA by 24 July 2013.

Product reviewer's comment: (b)(4) and PRV belong to the same subfamily, and the same genus, and both types of viruses have common genetic and biological properties. After consulting with Dr. Mahmood Farshid, we agree with Novo to use (b)(4) instead of PRV in the planned viral clearance study. We will have further comments based on the data they provided on (b)(4).

Novo provided the viral clearance validation study data on (b)(4) on 25 June 2013. Their response is summarized as follows:

Novo's response: Novo provided the viral clearance data on enveloped virus (b)(4) for the manufacturing process of anti-FVIII antibody. In this down-scale study, the data showed that the overall clearance for (b)(4) is -----(b)(4)----- from the step of -(b)(4)-, and --(b)(4)-- from the step of 20-nm nanofiltration).

Product reviewer's comment: The study design of the viral clearance for (b)(4) is similar to the one used for (b)(4). The yield and chromatography profile at down-scale and full-scale are comparable. Therefore, the viral clearance data generated at down-scale can be used to evaluate the viral clearance capacity of the Anti-FVIII mAb manufacturing process. The viral clearance data on (b)(4) are considered to be complete and sufficient. Therefore, this response is acceptable.

4. Testing the capacity of the Novoeight purification process to clear viruses

There are two dedicated steps for viral clearance in the manufacturing process of Novoeight, which are 20-nm nanofiltration, and capture by mixed-mode chromatography including -----(b)(4)----- . There are two additional steps that contribute to viral removal, which are anti-FVIII affinity chromatography, and -----
--(b)(4)----- . The viruses selected in these down-scale studies include -----
----- (b)(4) ----- .

1) Down-scale studies

(b)(4)-----

----- (b)(4)-----

----- .

However, Novo proposed to use (b)(4) but not PRV for this viral clearance study because the Danish regulatory authority does not allow Novo to work with PRV since this type of virus is being eradicated from Denmark. They are planning to do a viral validation study on (b)(4) at the referenced two steps (i.e., -----(b)(4)-----, and nanofiltration), and expecting to submit these data to FDA by 24 June 2013.

Product reviewer's Comment: (b)(4) and PRV belong to the same subfamily, and same genus, and both types of viruses have common genetic and biological properties. After consulting with Dr. Mahmood Farshid, we agree with Novo to use (b)(4) instead of PRV in the planned viral clearance study.

Novo provided the viral clearance validation study data on (b)(4) on 25 June 2013. Their response is summarized as follows:

Novo's response: Novo provided the viral clearance data on enveloped virus (b)(4) for the manufacturing process of Novoeight. In this down-scale study, the concentration of --(b)(4)---- during the wash step was kept at (b)(4) of the standard concentration at full-scale to represent the worst-case scenario. This study showed that the overall clearance for (b)(4) is -----(b)(4)----- from the step of -----(b)(4)----- and ---(b)(4)--- from the step of 20-nm nanofiltration).

Product reviewer's comment: The study design of the viral clearance for (b)(4) is similar to the one used for (b)(4). The yield and chromatography profile at down-scale and full-scale are comparable. Therefore, the viral clearance data derived from this study support the viral clearance capacity of the manufacturing process. The viral clearance data on (b)(4) are considered to be complete and sufficient. Therefore, this response is acceptable.

3) Viral clearance validation for re-used resins

The 20-nm filters used in the nanofiltration step are one-time use, so Novo only provided the viral clearance data for the resins introduced in the referenced chromatography steps. As the table shown below, these viral clearance data support the qualification of these re-used resins:

----(b)(4)----

Product reviewer's comment: Regarding the anti-FVIII matrix affinity chromatography, the resins have been used --(b)(4)-- so far. The viral clearance data on non-enveloped viruses are comparable between the new resins and the resins used for --(b)(4)--.

However, Novo did not perform the viral clearance validation on (b)(4) after the resins used for -(b)(4)-. To support the proposed shelf life of resins at Anti-FVIII matrix affinity chromatography step, Novo needs to provide the (b)(4) clearance data experimentally. This comment was sent to Novo on 9 April 2013, and we received the response from Novo on 13 May 2013. Their response is summarized as follows:

Novo's response: Novo did not perform viral clearance study on -(b)(4)- in the used resins in anti-FVIII matrix affinity chromatography. However, the cumulative "used resin" clearance is ---(b)(4)--- for (b)(4), which was contributed by the -----(b)(4)-----, and nanofiltration steps. Thus, even without viral clearance data on used

resin in the anti-FVIII matrix affinity chromatography step, the sufficiency of viral clearance of the manufacturing process is demonstrated.

Product reviewer's comment: The potential risk of viral contamination in the manufacture of Novoeight appears to be minimal. I agree with Novo that the total LRV for ----(b)(4)---- is quite acceptable even in the absence of contribution from the anti-FVIII matrix affinity chromatography step. Also, Novo has planned to perform viral clearance study on (b)(4) with used affinity resins. Therefore, this response is acceptable.

Recommendation

The measures taken by Novo to control adventitious agents in the manufacture of Novoeight are acceptable. The safety for 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 0.2 µm sterile filtration, and release tests of sterility and endotoxins in 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 *in vitro* cell age used for production. No raw materials or ingredients of human or animal origin are used in the manufacturing process or in the formulation of the product. Additionally, viral safety is further enhanced by two dedicated viral clearance steps: -----(b)(4)-----, and 20-nm nanofiltration.

Novo introduced a bracketing design in the stability studies in accordance with ICH guideline Q1D, and the stability data provided in this submission support the proposed shelf life of Novoeight DP. To further confirm product stability of three dosage strengths (500 IU, 1000 IU, and 1500 IU per vial), which are between 250 IU and 3000 IU, I recommend approval of the BLA under STN 12546/0 with the following PMC from Novo made on 29 July 2013:

Novo Nordisk commits to include at least one commercial batch each of 500 IU, 1000 IU, and 1500 IU strengths in their stability study, and these batches should be monitored under the referenced storage conditions as described on page 4 of 11 of the document novoDOCS: 001161237. The interim stability data from these batches should be submitted as annual updates (PMC Submission – Status Update) through the dating period, and a final report should be submitted within 3 months of completion (PMC Submission – Final Study Report).

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