



Chemistry, Manufacturing and Controls (CMC) Review Memorandum

To: File of STN 125776/0

Eden Chane, Regulatory Officer, Review Management Support Branch 1/Division of Review Management & Regulatory Review 1/Office of Review Management & Regulatory Review/Office of Therapeutic Products (OTP)

From: Ze Peng, PhD, Hemostasis Branch 1 (HB1)/Division of Hemostasis (DH)/ Office of Plasma Protein Therapeutics CMC (OPPT)/OTP

Through: Alexey Khrenov, PhD, Chief, HB1/DH/OPPT/OTP

Zuben Sauna, PhD, Director, DH/OPPT/OTP

Subject: Final review of CMC information in Octapharma's BLA for prothrombin complex concentrate, human-lans [*BALFAXAR*]

Executive Summary

This memorandum summarizes the review of CMC information in an original Biologics License Application (BLA) under STN 125776/0 submitted by Octapharma Pharmazeutika Produktionsges. M.b.H. (Octapharma) for prothrombin complex concentrate, human-lans. The proprietary name of the product is *BALFAXAR*. The product is indicated for the urgent reversal of acquired coagulation factor deficiency induced by Vitamin K antagonist (VKA, e.g., warfarin) therapy in adult patients with need for an urgent surgery/invasive procedure.

BALFAXAR is a human plasma-derived, purified, virus inactivated, and nanofiltered non-activated prothrombin complex concentrate (PCC) containing the pro-coagulation factors II (FII), VII (FVII), IX (FIX), and X (FX), as well as anti-coagulation proteins, Protein C and Protein S. It is manufactured at Octapharma's facility in Vienna, Austria. The manufacturing steps including visual inspection, labeling, and secondary packaging may also be performed at Octapharma's facility in (b) (4)

BALFAXAR is supplied as a lyophilized powder for reconstitution with sterile Water for Injection (sWFI) and is administered intravenously. *BALFAXAR* is offered in two nominal dosage strengths, 500 IU (International Unit) or 1000 IU of FIX activity per vial. FIX activity is used for the product potency and dosing.

BALFAXAR is a co-packaged combination product consisting of three different parts: a lyophilized powder of *BALFAXAR* in the product container, sWFI in a separated container, and a transfer device (Nextaro).

The manufacturing process including in-process controls, and the specifications used to control the quality of *BALFAXAR* are adequately validated and sufficiently justified to ensure the consistent manufacture of a product that will meet acceptance criteria for all relevant quality attributes. The safety with regards to viral transmission is well established in the manufacturing process of *BALFAXAR* by the control of potential virus load in the starting plasma (b) (4) and by demonstrated capability of the two dedicated virus clearance steps, Solvent/Detergent (S/D) treatment and 20-nm nanofiltration (Planova 20N or Pegasus SV4). The measures taken by Octapharma to control other adventitious agents in the manufacture of *BALFAXAR* are also acceptable. As described in detail below, we found the CMC information provided in the original BLA and Octapharma's responses to our information requests (IRs) to be sufficient to support identity, quality, purity, safety, and potency of the product when used for the proposed indication; therefore, we recommend approval of this BLA.

History of the Product

BALFAXAR has been marketed in Germany since 2003 under the trade name *Octaplex*, and subsequently licensed in 87 other countries. Currently, there is another PCC product licensed in the U.S. (*Kcentra*®) for the urgent reversal of acquired coagulation factor deficiency induced by Vitamin K antagonist (VKA, e.g., warfarin) therapy in adult patients with need for an urgent surgery/invasive procedure, which is manufactured by CSL Behring. *BALFAXAR* will be the second member of this product class in the U.S. for this indication.

(b) (4)

Summary of Review

MANUFACTURERS

The manufacture of *BALFAXAR* starting from U.S. human (b) (4) Plasma to the final drug product (FDP) is performed at the following address:

Octapharma Pharmazeutika Produktionsges.m.b.H.
Oberlaaer Strasse 235
A-1100 Vienna
Austria

The manufacturing steps including visual inspection, labeling, and secondary packaging can also be performed at the following address:

Octapharma (b) (4)
(b) (4)

DRUG SUBSTANCE

1. *Manufacturing process steps*

(b) (4)

(b) (4)

11 pages have been determined to be not releasable: (b)(4)

(b) (4)

DRUG PRODUCT

1. Description and Composition of the BALFAXAR drug product

BALFAXAR is a human plasma-derived, purified, virus inactivated and nanofiltered non-activated PCC, supplied as a lyophilized powder for reconstitution for intravenous injection. The active ingredients of BALFAXAR include the vitamin K dependent pro-coagulation factors, FII, FVII, FIX, FX and anti-coagulation proteins, Protein C and Protein S. The other ingredients include the excipients heparin (b) (4) and sodium citrate.

BALFAXAR is supplied in a package with a single-dose glass container of powder and its diluent (sWFI), together with a transfer device Nextaro that is used to allow for the transfer of the diluent into the BALFAXAR container for reconstitution. BALFAXAR is offered in two nominal dosage strengths, 500 IU or 1000 IU per vial, which is defined by the FIX potency. When reconstituted with its diluent (20 mL for 500 IU and 40 mL for 1000 IU), the final solution contains the following ingredients in targeted amounts per container (see Table 6) based on the information provided in the amendment dated 16 May 2023:

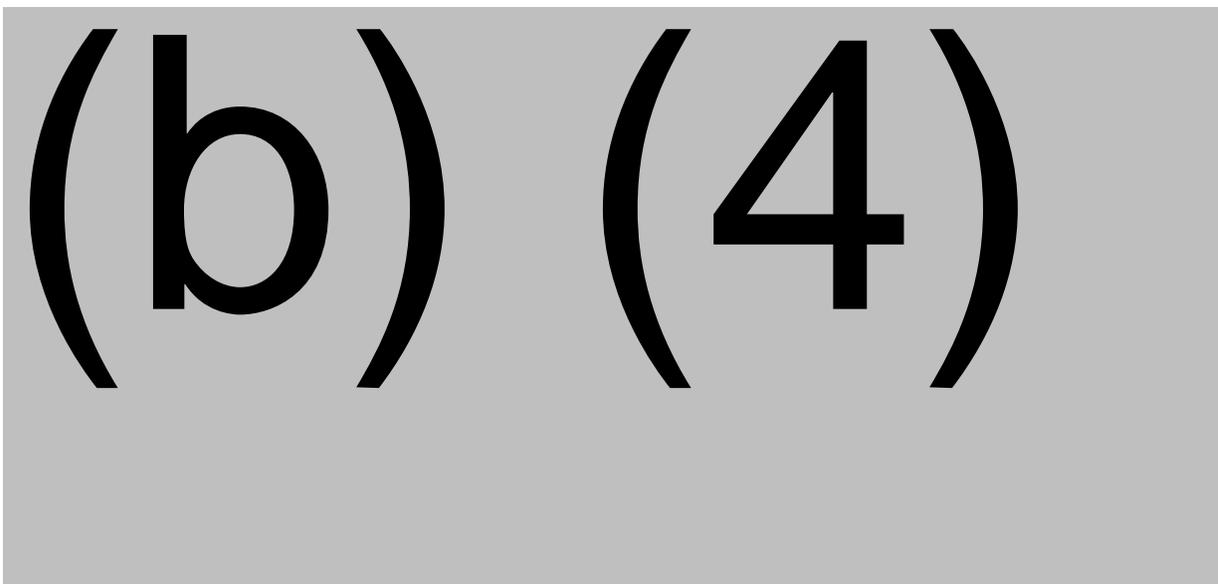
Table 6. Composition

Ingredient	Amount	Function
(b) (4)	(b) (4)	N/A
FII activity	17 – 25 IU/mL	Active ingredient
FVII activity	12 – 20 IU/mL	
FIX activity	20 – 32 IU/mL	
FX activity	15 – 27 IU/mL	
Protein C	16 – 28 IU/mL	
Protein S	12 – 30 IU/mL	
Heparin (b) (4)	(b) (4)	Excipient/stabilizer
Sodium citrate	16.8 – 23.4 mmol/L	Excipient/buffer substance
sWFI	20 mL for 500 IU 40 mL for 1000 IU	Solvent

N/A: not applicable

2. A brief description of the drug product manufacturing process

(b) (4)



3. *In-process control*

See the information listed for IPCs above in the DS section of this memo.

4. *Process validation and/or evaluation*

The information regarding container closure system, lyophilization, media fill, and shipping validation was reviewed by DMPQ reviewers.

To demonstrate the consistency of the filling process and homogeneity of product solution during filling, Octapharma evaluated ^{(b) (4)} conformance DP batches of *BALFAXAR* by sampling ^{(b) (4)} containers at (b) (4)

^{(b) (4)} respectively (with reference to Process performance qualification report No. 089PQR21497.102/01). The filled containers were tested for FIX and (b) (4) and filling (b) (4) was also evaluated. The test results from these batches met the pre-defined acceptance criteria, and these data demonstrated the homogeneity of sterile filtered (b) (4) and a consistent filling process when using the filling line (b) (4). The steps of Sterilizing filtration and Aseptic filling were also supported by the following process validation reports:

- *Sterile filter validation for filter (b) (4) for Octaplex 500 IU, 1000 IU (Report No. 150VRE1534/01)*
- *Performance qualification report for Octaplex 500 IU and 1000 IU: Filling process on filling line-(b) (4) using (b) (4) set (b) (4) (Report No. 089PQR21389.102/01)*
- *Performance qualification report for Octaplex 500 IU and 1000 IU: Filling process on filling line-(b) (4) and (b) (4) container (Report No. 089PQR22032.102_US/00)*

Moreover, product quality attributes in the manufacture of *BALFAXAR* DP were further evaluated at full-scale with (b) (4) conformance batches (with reference to Process performance qualification report No. 089PPQR21495.102/01).

Product reviewer’s comment: Octapharma performed the requisite validation studies for the manufacturing process of the *BALFAXAR* DP. Process and quality control results for the conformance batches complied with prospectively defined acceptance criteria, demonstrating successful process validation. Moreover, these data indicate that carrying out the process at minimum and maximum process times for the steps including aseptic filling and freeze-drying have no significant impact on product quality.

5. *Control of excipients*

Heparin (b) (4) and sodium citrate serve as excipients of *BALFAXAR*. Heparin (b) (4) is manufactured from (b) (4). The information for the description of the heparin (b) (4) manufacturing process was found to be very limited upon review of the original submission. To verify if heparin (b) (4) used in the manufacture of *BALFAXAR* is qualified in accordance with the (b) (4) (b) (4) we communicated an IR dated 9 January 2023 to Octapharma seeking detailed information on the manufacturing process for heparin (b) (4). Octapharma responded in an amendment dated 23 January 2023, in which a description of the whole manufacturing process of heparin (b) (4) was provided. We agree with Octapharma’s assessment that there are at least (b) (4) manufacturing steps (b) (4) (b) (4) which contribute to (b) (4) in the production of heparin (b) (4). The release tests of heparin (b) (4) are performed in accordance with the current (b) (4) (b) (4) especially to control for the potential contamination with (b) (4) (b) (4). Therefore, heparin (b) (4) is qualified to be used in the manufacture of *BALFAXAR*. Sodium citrate used in the manufacture of *BALFAXAR* also complies with the requirements of the current (b) (4) (b) (4). Moreover, in addition to verifying the information in the manufacturer-supplied Certificate of Analysis (CoA), Octapharma performs an identity test for each excipient in-house. The identity tests performed by Octapharma are in accordance with the requirements of (b) (4) which we consider to be acceptable.

6. *Control of drug product*

1) Specification of the *BALFAXAR* final drug product

The release specifications of *BALFAXAR* DP provided in the original submission are listed in the following table.

Table 7. Release specifications of *BALFAXAR* drug product from the original submission

Product quality attributes	Specifications	Test methods
Appearance	A white to ice-blue powder or friable mass, very hygroscopic	(b) (4)

(b) (4)	(b) (4)	(b) (4)
Solubility	The preparation dissolves completely in 20 mL (500 IU) or 40 mL (1000 IU) of water for injection by gentle swirling within (b) (4) minutes at 20 – 25°C, giving a clear solution that may be colored	(b) (4)
(b) (4)	(b) (4)	(b) (4)
Water	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
FII	IU/mL	(b) (4)
FVII	IU/mL	(b) (4)
FIX	IU/mL	(b) (4)
FX	IU/mL	(b) (4)
Protein C	IU/mL	(b) (4)
Protein S	IU/mL	(b) (4)
Specific activity	(b) (4)	
(b) (4)	(b) (4)	
Confidence limits	FII: within (b) (4) of the estimated potency	
	FVII: within (b) (4) of the estimated potency	
	FIX: within (b) (4) of the estimated potency	
	FX: within (b) (4) of the estimated potency	
(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
Heparin	(b) (4)	(b) (4)
Citrate	(b) (4) mmol/L	(b) (4)
(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
Sterility	Sterile	(b) (4)
Endotoxin	(b) (4)	(b) (4)

Product reviewer’s comment: European Pharmacopeia is not a legally recognized compendium in the US. For the compendial methods listed in the release specifications, we asked Octapharma to provide references to *USP* monograph (if harmonized *USP/Ph. Eur.* monograph exist) or reference validated in-house analytical procedures.

Additionally, the acceptance criteria for DS and DP specifications are not adequately justified. We asked Octapharma to provide the revised Justification of Specifications for *BALFAXAR* DS and DP, including the complete data sets used to establish acceptance criteria and description of statistical approaches used. The acceptance criteria need to be statistically justified to allow control manufacturing consistency of final

commercial manufacturing process, as well as to allow control of product safety and efficacy.

These IRs were communicated to Octapharma on 13 and 14 March 2023, and they responded in amendments dated 22 and 24 March 2023, respectively. In the amendment dated 22 March 2023, Octapharma updated the release specifications of *BALFAXAR* DP to include references to USP monograph or reference validated in-house analytical procedures. The response on the IR item related to the justification of the release specifications of *BALFAXAR* DS and DP is summarized as follows:

Octapharma's response: (b) (4) Octaplex (i.e., *BALFAXAR*) batches manufactured from US plasma from (b) (4) were included in the evaluation of acceptance criteria for DP. The specification limits of the final container parameters were calculated using the formula with a process capability index. To get the upper and lower specification limits, a process capability index of (b) (4) was applied in the formula.

For the DS, (b) (4) Octaplex bulk ($n = (b) (4)$) and (b) (4) Octaplex bulks ($n = (b) (4)$) manufactured from (b) (4) were used for statistical evaluation of the specification limits as listed in the acceptance criteria of DS.

The calculation of mean ± 3 standard deviations (SD) for each parameter from actual batches reflect well the limits once defined. The variance of parameters is lower for (b) (4) bulks in comparison to (b) (4) Octaplex bulk.

Product reviewer's comment: The acceptance criteria of the parameters for *BALFAXAR* DS were established based on a statistical analysis of the (b) (4) Octaplex bulk batches produced in the last (b) (4) years, which is acceptable. However, the updated acceptance criteria of *BALFAXAR* DP were inadequate. Specifically, a process capability index of (b) (4) was used in the referenced statistical approach. Using this approach, the specification ranges are translated as mean ± 4 SD of the actual data distributions. We considered that this approach and acceptance criteria based on this approach were not sufficiently stringent to control manufacturing consistency of *BALFAXAR* DP. Additionally, some of acceptance criteria established using this approach were significantly outside of the manufacturing or clinical experience. Therefore, we asked Octapharma to establish the acceptance criteria using more conservative statistical approach.

These comments were communicated to Octapharma on 14 April 2023, and they responded in an amendment dated 25 April 2023. In the amendment, Octapharma used a more stringent approach to re-calculate the acceptance criteria of *BALFAXAR* DP, and these acceptance criteria were updated in the amendment dated 16 May 2023 (see the table below). Additionally, the information on *Justification of Specification of Drug Product* was updated in the same amendment. This response is acceptable.

Table 8. Release specifications of *BALFAXAR* drug product from the amendment dated 16 May 2023

Product quality attributes	Specifications	Test methods
Appearance	A white to ice-blue powder or friable mass, very hygroscopic	Visual inspection
(b) (4)	(b) (4)	(b) (4)
Solubility	The preparation dissolves completely in 20 mL (500 IU) or 40 mL (1000 IU) of water for injection by gentle swirling within 5 minutes at 20 – 25°C, giving a clear solution that may be colored	Visual inspection
(b) (4)	(b) (4)	(b) (4)
Water	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
FII	17 – 25 IU/mL	(b) (4)
FVII	12 – 20 IU/mL	(b) (4)
FIX	20 – 32 IU/mL	(b) (4)
FX	15 – 27 IU/mL	(b) (4)
Protein C	16 – 28 IU/mL	(b) (4)
Protein S	12 – 30 IU/mL	(b) (4)
Specific activity	(b) (4)	
(b) (4)	(b) (4)	
Confidence limits	FII: within (b) (4) of the estimated potency	
	FVII: within (b) (4) of the estimated potency	
	FIX: within (b) (4) of the estimated potency	
	FX: within (b) (4) of the estimated potency	
(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
Heparin	(b) (4)	(b) (4)
Citrate	16.8 – 23.4 mmol/L	(b) (4)
(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
Sterility	Sterile	(b) (4)
Endotoxin	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)

2) Analytical procedures for *BALFAXAR* final drug product

- Appearance and Solubility (Method No. 130SOP006): Visual inspection
- (b) (4) (130SOP028): Determination in accordance with (b) (4)
- (b) (4) (130SOP008): Determined by the (b) (4)

- Water (130SOP086): Determination of water in lyophilized products by (b) (4) method
- Water (130SOP130/06): Determination of water in lyophilized products by (b) (4) (b) (4)
- (b) (4) (130SOP191/00): Determination of (b) (4) in Octaplex samples by the (b) (4) method
- FII activity (130SOP139): Determination of Coagulation factor II by (b) (4) (b) (4) assay using (b) (4)
- FVII activity (130SOP140): Determination of Coagulation factor VII by (b) (4) (b) (4) assay using (b) (4)
- FIX activity (130SOP203): Determination of Coagulation factor IX by (b) (4) (b) (4) assay using (b) (4)
- FX activity (130SOP141): Determination of Coagulation factor X in (b) (4) samples by (b) (4) assay using (b) (4)
- Protein C (130SOP142): Determination of Protein C by (b) (4) assay using (b) (4)
- Protein S (130SOP150): Determination of Protein S in Octaplex samples by (b) (4) (b) (4) assay
- Heparin (130SOP244/04): Determination of heparin using (b) (4) by (b) (4) (b) (4) assay using (b) (4)
- Citrate (130SOP032): Citrate determined using (b) (4)
- (b) (4) (130SOP048/03): Determination of (b) (4) in accordance with (b) (4)
- (b) (4) (130SOP164): Determination of (b) (4) in Octaplex final product samples using (b) (4)
- (b) (4) (130SOP049): Determination of (b) (4) by (b) (4)
- (b) (4) (130SOP153/06): Determination of (b) (4) by (b) (4)
- Endotoxin (130SOP162): (b) (4) assay in accordance with (b) (4)
- Sterility (131SOP120): (b) (4) method in accordance with (b) (4)

All the aforementioned test methods have been validated as shown in the relevant validation reports. Please also refer to the review memos from our DBSQC colleagues, who determined that the data are sufficient. Therefore, these test methods are acceptable for the use in the release testing of the *BALFAXAR* DP.

3) Batch analysis

CoAs for (b) (4) conformance batches of *BALFAXAR* manufactured at full-scale are included in the BLA. The release test results of these batches are listed in Table 9:

Table 9. Release test results of the conformance DP batches from the process validation report No. 089PPOR21495.102/01

(b) (4)

(b) (4)

As depicted in Table 9, the results of the conformance batches met the current release specifications of *BALFAXAR* FDP that was updated in Document No. *CORP-FPS-01156*

version 3.0 per the amendment dated 16 May 2023. Thus, these data support the validation of the proposed commercial manufacturing process of *BALFAXAR* for the U.S. market.

4) Impurities

The impurity profile of *BALFAXAR* FDP is described in Report No. 020STD26x_28x.713/00. The product-related impurities include (b) (4)

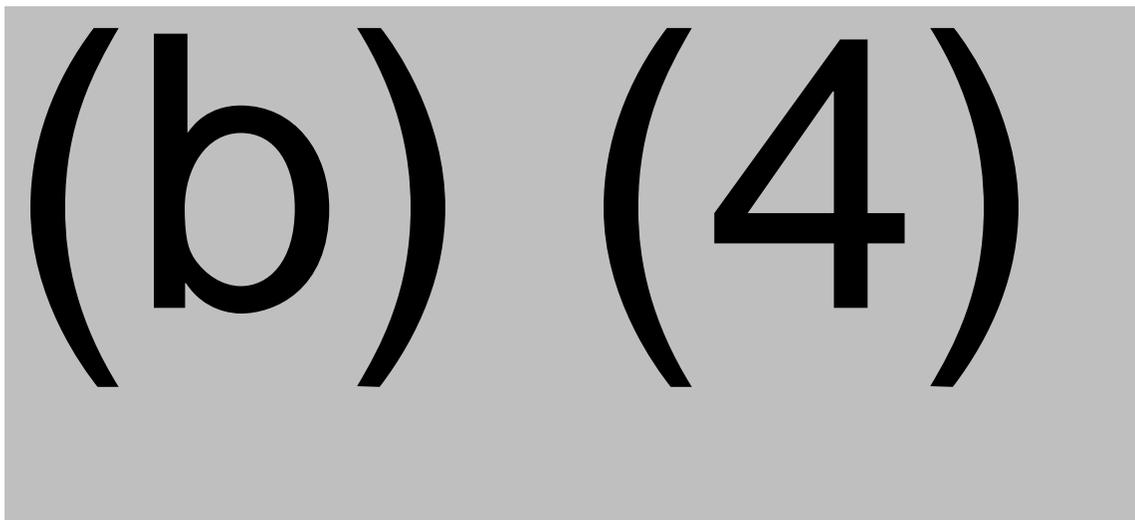
(b) (4) These impurities in the *BALFAXAR* FDP were found below the detection limits of the assays. The process-related impurities include (b) (4) potential leachables from the (b) (4) materials used for the processing of *BALFAXAR*. The process-related impurities were found either in detectable but small amounts or below the detection limits of the assays.

Product reviewer’s comment: The product- and process-related impurities are well controlled in the manufacture of *BALFAXAR* based on the study. However, heparin is described as a process-related impurity in the Section 3.2.P.5.5 *Characterization of Impurities* whereas heparin was also considered as an excipient in the manufacturing of *BALFAXAR* DP and described as such in Section 3.2.P.4 *Control of Excipients*. To be consistent, we asked Octapharma to delete the information related to heparin in Section 3.2.P.5.5 *Characterization of Impurities*.

This IR was sent to Octapharma on 14 March 2023, and they responded in an amendment dated 24 March 2023. In the amendment, the information related to heparin in Section 3.2.P.5.5 was deleted, and the relevant report No. 020STD26x_28x.713 was updated. This response is acceptable.

7. Reference standards

The reference standards for testing of FII, FVII, FIX, FX, Protein C, and Protein S are listed as follows:



(b) (4)

Product reviewer's comment: The reference standard used for the quantification of FIX activity in the product samples can be either Human Coagulation Factor IX Concentrate (b) (4) (b) (4) Standard for Blood Coagulation Factor IX Concentrate. To ensure the consistency of the testing of FIX activity, we asked Octapharma to provide the CoA of the reference standard used for the determination of FIX by the (b) (4) assay.

This IR was sent to Octapharma on 9 January 2023, and they responded in the amendment dated 23 January 2023. Per the CoA of Human Coagulation Factor IX Concentrate (b) (4) it is the same material used for the establishment of the (b) (4) (b) (4) for Blood Coagulation Factor IX, concentrate. The testing of FIX activity is confirmed to be calibrated against the relevant (b) (4) standard. The practice of calibrating each reference standard against the relevant (b) (4) standard is acceptable and was followed here.

8. Container closure system

The container closure system for *BALFAXAR* DP consists of a single-dose (b) (4) glass container (b) (4) and a rubber stopper (b) (4) sealed with an aluminum flip off cap. The single-dose glass container with a nominal size of either 30 mL for 500 IU or 50 mL for 1000 IU meets the requirements of (b) (4). The glass container is closed with bromobutyl rubber stopper (20 mm), which complies with (b) (4) requirements of (b) (4) and is not made with natural rubber latex. The stopper is sealed with an aluminum flip off cap.

- Container closure integrity:

The stability data from the studies No. 17P044 and 17P050 demonstrated that the container closure integrity, as tested by (b) (4) test, can be maintained under the proposed storage conditions.

- Extractables:

For the glass containers from (b) (4) (30 mL) and (b) (4) (30 mL or 50 mL), Octapharma performed an extractables study (Report No. 089STD21462.102/00) to detect any extractables identified under exaggerated conditions. In the study, the test materials were extracted with (b) (4). The extraction was completed after (b) (4) was used for screening of inorganic elements. (b) (4) (b) (4) (b) (4) was measured as well.

For the rubber stopper from (b) (4) Octapharma performed an extractables study (Report No. 089STD21462.102/00) to detect any extractables identified under exaggerated conditions. In the study, the test materials were extracted with (b) (4) organic

substances, and with (b) (4) The extraction was completed after (b) (4)
(b) (4) Volatile, semi-volatile, and non-volatile extractables were determined
using (b) (4) respectively. (b) (4)
(b) (4) was used to test (b) (4) Moreover,
(b) (4) was used for screening of inorganic elements.

In the abovementioned studies, none of the extractables showed the estimated human daily exposure level to be above the respective tolerable intake values.

Product reviewer's comment: We deferred the general assessment of container closure to DMPQ reviewers. The extractables study showed that no significant levels of hazardous materials were detected in container closure for *BALFAXAR* DP. These data support the use of the referenced container closure for the storage of *BALFAXAR* DP.

9. CMC Comparability Assessment

Although Octapharma provided the batch numbers of *BALFAXAR* DP used in the clinical studies in the BLA, it was unclear whether the manufacturing process of these batches is comparable to the proposed commercial process. Consequently, we asked Octapharma to provide the information on the DP batches used in the referenced clinical studies to demonstrate that the batches used in these clinical studies are comparable to the proposed commercial process.

This request was sent to Octapharma on 9 January 2023, and they responded in an amendment dated 23 January 2023. In the amendment, Octapharma confirmed that *BALFAXAR* DP used in the pivotal clinical study LEX-209 was manufactured using the proposed commercial process. LEX-209 is the major study to support the proposed indication of this product. Therefore, no CMC comparability assessment between clinical and commercial product is needed for this BLA.

10. Combination product

BALFAXAR is a co-packaged combination product consisting of three different constitute parts: a lyophilized powder of *BALFAXAR* in a product container, sWFI in a separated container, and a transfer device (Nextaro). For this reason, CBER consulted with Dr. David Wolloscheck from CDRH for evaluation of Nextaro device used in this combination product, and Dr. Ebony Whaley from CDER for evaluation of the human factors (HF) study. The information used to support device use for the reconstitution of *BALFAXAR* are summarized as follows:

- Nextaro, which contains integrated 15 µm filters on both the solvent and the active ingredient sides and is used for the reconstitution of *BALFAXAR* product, has been cleared under 510(k) No. K183187.
- Octapharma provided a compatibility study (Report No. 270STD26x_28x001_01) for Nextaro used in the combination product, but the manufacturing dates of the *BALFAXAR*

product batches were missing. To qualify the *BALFAXAR* batches in this study, the manufacturing date information was provided in the amendment on 22 March 2023 upon our request. This information supported the use of these batches in this study, which showed that the active ingredients (FII, FVII, FIX, FX, Protein C, and Protein S) were within the specified limits when *BALFAXAR* FDP was reconstituted with Nextaro.

- To support use of the device with this biologic, Octapharma submitted a use-related risk assessment, a risk management report, the instructions for use (IFU) of the device, a threshold analysis, and a design traceability matrix. Our CDRH colleague concluded that the data from these assessments/studies support that the use of this reconstitution device does not have a significantly adverse impact on the quality of *BALFAXAR* FDP.
- Our CDER colleagues reviewed the information related to device used for the reconstitution of *BALFAXAR* product in terms of the HF study under IND 13323/116. Based on the evaluation, they agreed with the revisions to IFU made by the sponsor and recommended that submission of additional HF data is not required.

11. Stability

1) Batches tested

The (b) (4) conformance batches of *BALFAXAR* DP from the validation report No. 089PPQR21495.102/01 are included in stability studies No. 17P044 and 17P050. The batch information is listed in Table 10.

Table 10. Batch information for those in stability studies No. 17P044 and 17P050

(b) (4)

2) Stability protocol

Table 11. Storage at 25°C (b) (4) RH

Parameter	Specification	Storage time (months)							
		0	3	6	9	12	18	24	36
Appearance	A white to ice-blue powder or friable solid, very hygroscopic	X	X	X	X	X	X	X	X
Solubility	The preparation dissolves completely in 20 mL (500 IU) or 40 mL (1000 IU) of sWFI by gentle swirling within (b) (4) minutes at 20 – 25 C, giving a clear solution that may be colored	X	X	X	X	X	X	X	X
(b) (4)	(b) (4)	X	X	X	X	X	X	X	X
Water	(b) (4)	X	NT	X	NT	X	NT	X	X
(b) (4)	(b) (4)	X	NT	X	NT	X	NT	X	X

FII	(b) (4)	IU/mL	X	X	X	X	X	X	X	X
FVII	(b) (4)	IU/mL	X	X	X	X	X	X	X	X
FIX	(b) (4)	IU/mL	X	X	X	X	X	X	X	X
FX	(b) (4)	IU/mL	X	X	X	X	X	X	X	X
Protein C	(b) (4)	IU/mL	X	X	X	X	X	X	X	X
Protein S	(b) (4)	IU/mL	X	X	X	X	X	X	X	X
(b) (4)	(b) (4)	(b) (4)	X	X	X	X	X	X	X	X
Specific activity	(b) (4)	(b) (4)	X	NT	X	NT	X	NT	X	X
(b) (4)	(b) (4)	(b) (4)	X	X	X	X	X	X	X	X
(b) (4)	(b) (4)	(b) (4)	X	X	X	X	X	X	X	X
Heparin	(b) (4)	(b) (4)	X	NT	X	NT	X	NT	X	X
(b) (4)	(b) (4)	(b) (4)	X	NT	NT	NT	X	NT	X	X
(b) (4)	(b) (4)	(b) (4)	X	NT	NT	NT	X	NT	X	X
Sterile	(b) (4)	Sterile	X	NT	NT	NT	NT	NT	X	X
Endotoxin	(b) (4)	(b) (4)	X	NT	NT	NT	NT	NT	X	X

RH: Relative humidity; X: Tested; NT: Not tested

Table 12. Storage at 5°C ± 3°C or (b) (4) RH

Parameter	Specification	Storage time (months)					
		0	6	12	18*	24	36
Appearance	A white to ice-blue powder or friable solid, very hygroscopic	X	X	X	X	X	X
Solubility	The preparation dissolves completely in 20 mL (500 IU) or 40 mL (1000 IU) of sWFI by gentle swirling within ^{(b) (4)} minutes at 20 – 25 C, giving a clear solution that may be colored	X	X	X	X	X	X
(b) (4)	(b) (4)	X	X	X	X	X	X
Water	(b) (4)	X	X	X	NT	X	X
(b) (4)	(b) (4) (b) (4)	X	X	X	NT	X	X
FII	(b) (4) IU/mL	X	X	X	X	X	X
FVII	(b) (4) IU/mL	X	X	X	X	X	X
FIX	(b) (4) IU/mL	X	X	X	X	X	X
FX	(b) (4) IU/mL	X	X	X	X	X	X
Protein C	(b) (4) IU/mL	X	X	X	X	X	X
Protein S	(b) (4) IU/mL	X	X	X	X	X	X
(b) (4)	(b) (4)	X	X	X	X	X	X
Specific activity	(b) (4)	X	X	X	NT	X	X
(b) (4)	(b) (4)	X	X	X	X	X	X
(b) (4)	(b) (4)	X	X	X	X	X	X
Heparin	(b) (4)	X	X	X	NT	X	X
(b) (4)	(b) (4)	X	NT	X	NT	X	X
(b) (4)	(b) (4)	X	NT	X	NT	X	X
Sterile	(b) (4) Sterile	X	NT	NT	NT	X	X
Endotoxin	(b) (4)	X	NT	NT	NT	X	X

*: Tested only for the samples from batches stored at 5 C ± 3 C; X: Tested; NT: Not tested

Table 13. Storage at (b) (4) RH



(b) (4)

Table 14. Stability after reconstitution (Storage at 25°C (b) (4) RH or (b) (4) RH for up to 36 months)

Parameter	Specification	Previous storage at 25°C (b) (4) RH or (b) (4) RH		
		0 month	24 months [#]	36 months
		Storage period (hours) at 25°C		
		0, 4, and 8	0, 4, and 8	0, 4, and 8
Appearance	A clear solution that may be colored	X	X	X
FIX	(b) (4) IU/mL	X	X	X
(b) (4)	(b) (4)	X	X	X

[#]: Tested only for the samples stored at (b) (4) RH; X: Tested; NT: Not tested

Product reviewer’s comment: The parameters selected in the stability studies were sufficient, and the acceptance criteria are slightly different from the updated release specification of *BALFAXAR* DP. To be consistent, the acceptance criteria in the stability protocols and ongoing stability studies will be revised accordingly as stated in the amendment dated 28 June 2023 upon our request. Considering that the test results of these conformance batches met the updated release specifications of *BALFAXAR* DP, it is acceptable for Octapharma to use these parameters to monitor *BALFAXAR* stability over time.

3) Currently available results from the stability studies for *BALFAXAR* drug product

- Stability study No. 17P044

(b) (4) 500 IU (b) (4) and (b) (4) 1000 IU (b) (4) (b) (4) conformance batches manufactured using the Pegasus SV4 nanofilters and (b) (4) were investigated in the stability study No. 17P044. The test results for long-term storage at 2°C – 8°C, 25°C/(b) (4) RH, and (b) (4) RH are available for up to 36 months. All results met the specifications. Under accelerated conditions of (b) (4) RH, all results from these batches met the specifications for up to (b) (4). The in-use stability of *BALFAXAR* DP was tested for up to 8 hours after reconstitution at the starting time-point (0 month), 24 months ((b) (4) RH), and 36 months (25°C/(b) (4) RH) of the long-term storage conditions. All results were within the specifications.

- Stability study No. 17P050

(b) (4) 500 IU (b) (4) and (b) (4) 1000 IU (b) (4) conformance batches manufactured after the introduction of a backup for the (b) (4) were investigated in the stability study No. 17P050. The test results for long-term storage at 2°C – 8°C, 25°C/(b) (4) RH, and (b) (4) RH are available for up to 36 months. All results met the specifications. Under accelerated conditions of (b) (4) RH, all results from these batches met the specifications for up to (b) (4). The in-use stability of *BALFAXAR* FDP was tested for up to 8 hours after reconstitution at the starting time-point (0 month), 24 months (b) (4) RH, and 36 months (25°C/(b) (4) RH or (b) (4) RH) of the long-term storage conditions. All results were within the specifications.

- Stability study No. 05PN15

Additionally, Octapharma performed a stability study No. 05PN15 on (b) (4) 500 IU *BALFAXAR* DP (b) (4) which was manufactured after the introduction of the (b) (4). This batch was manufactured on (b) (4) and the stability studies only include the long-term storage conditions (25°C/(b) (4) RH, and (b) (4) RH). The stability testing protocols, which do not include the test parameters Specific activity, (b) (4) and heparin, were slightly different from those for the conformance batches. All the test results from this batch were within the acceptance criteria for up to (b) (4).

Product reviewers' comment: The available stability data for the conformance batches (Studies No. 17P044 and 17P050) indicate that there are no significant trends detectable under both the long-term (25°C) and accelerated storage conditions. However, we noticed that none of the conformance batches (b) (4) (b) (4) from the process validation study Report No. 089PPQR20618.102_US/01 was put in stability for the introduction of an alternative (b) (4) (b) (4). To justify the absence of the stability data from the referenced conformance batches, we checked whether the stability data of batch (b) (4) from the stability study No. 05PN15 can be leveraged to support the CMC change introduced in the study report No. 089PPQR20618.102_US/01. For this, we requested the manufacturing date information on the conformance batches (b) (4) (b) (4). These conformance batches were manufactured on (b) (4) (b) (4) respectively, per the amendment dated 22 March 2023. As mentioned above, batch (b) (4) from the stability study No. 05PN15 was manufactured on (b) (4) after the implementation of alternative (b) (4) (b) (4). Based on the update of the manufacturing date information, the data from batch (b) (4) can be used to support the introduction of an alternative (b) (4) (b) (4) as well. As the stability study No. 05PN15 showed, all the available data of batch (b) (4) met the acceptance criteria for up to 6 months under the long-term storage condition, and there are no significant trends detected so far. Taken together, these data support the proposed 36 months shelf-life of *BALFAXAR* DP under the storage of 2°C – 25°C/(b) (4) RH.

Additionally, the stability data from the abovementioned conformance batches support the proposed holding time after reconstitution, i.e., stored at 25°C for up to 8 hours after reconstitution. However, *BALFAXAR* does not contain any preservative, and the 4-hour storage period after reconstitution is not only related to the stability of the product, but also to the safe level of bacterial load in the event of contamination of the product during reconstitution. Therefore, in our first prescribing information revision communicated to Octapharma on 22 May 2023, we suggested that the storage period after reconstitution to be limited to 4 hours. Octapharma responded in an amendment on 30 May 2023, proposing to add “*provided sterility is maintained*” to the in-use stability section of the PI as follows:

As BALFAXAR contains no preservatives, the solution should be administered immediately after reconstitution, or within 8 hours, provided sterility is maintained. The reconstituted solution can be stored for up to 8 hours at room temperature (20°C to 25°C; 68°F to 77°F).

Moreover, in the amendment dated 7 June 2023, Octapharma provided the following information to support this statement:

- When aseptic technique is used to reconstitute *BALFAXAR*, the risk of bacterial contamination is minimized. Since 2003, approximately (b) (4) (b) (4) patients have been exposed to (b) (4) (b) (4) IUs of Octaplex (i.e., *BALFAXAR*) worldwide. Octaplex has been used in other countries with the 8-hour post-reconstitution stability stated in their respective product monographs over 10 years with no signals of concern.
- The longer (8 hours vs. 4 hours) post-reconstitution stability provides healthcare professionals the flexibility. Physicians have requested longer post-reconstitution hold times.

I consulted with Drs. Alexey Khrenov, Zuben Sauna, and Mahmood Farshid on this issue, and we all agree that the justification from Octapharma is reasonable, and the 8-hour storage period after reconstitution is acceptable.

4) Stability of the diluent, sterile Water for Injection

sWFI is manufactured by (b) (4) located at (b) (4). This product has two filling sizes, 20 mL and 40 mL, which are supplied in (b) (4) colorless glass vials (20 mL and 50 mL vial sizes) closed with bromobutyl rubber stoppers and sealed with aluminum flip-off caps. The glass vials and stoppers used in container closure meet the requirements of (b) (4).

(b) (4) 20 mL (b) (4) and (b) (4) 40 mL (b) (4) (b) (4) sWFI DP batches are included in the stability studies. These batches are being investigated under the long-term storage conditions (2°C – 8°C for (b) (4) months; 25°C/(b) (4) RH for (b) (4) months) and the accelerated condition ((b) (4) RH for (b) (4) months). The container closure system used in the stability study is identical to the one used

commercially. The parameters used in the long-term stability study include Visual inspection, (b) (4)

Bacterial endotoxins, and Sterility.

(b) (4) months of long-term stability and (b) (4) months of accelerated stability data are available. The test results were within the acceptance criteria for the samples stored under the long-term conditions, and no significant changes were detected. The test results for the samples stored at (b) (4) RH for up to (b) (4) months met the acceptance criteria as well.

Product reviewer's comment: The stability studies on these conformance batches are complete, and the data from these studies are sufficient to support Octapharma's proposed shelf-life of the diluent to be (b) (4) months under the storage condition of 2°C – 25°C.

12. Virus safety

The following three-principle complementary approaches are applied to control viral safety in *BALFAXAR* DP:

- 1) Selecting and testing the US (b) (4) human plasma for the absence of detectable viruses

Only human plasma collected in centers and community blood banks licensed by the FDA can be used for the manufacture of *BALFAXAR* for the U.S. market. Each donation is tested for the absence of HBsAg, antibodies against HCV and HIV-1/2. Thus, donor selection is performed in accordance with the requirements of the 21 CFR and the respective FDA guidelines.

- 2) Testing the plasma (b) (4) for fractionation for the absence of contaminating infectious viruses

Octapharma did not provide complete information on the viral tests performed on the plasma (b) (4) for fractionation. To further evaluate the viral safety profile related to the manufacturing of *BALFAXAR*, we asked Octapharma to summarize all the viral tests performed on donors, (b) (4), and manufacturing plasma pools in an IR dated 9 January 2023. Their response was submitted in an amendment on 23 January 2023 and is summarized as follows:

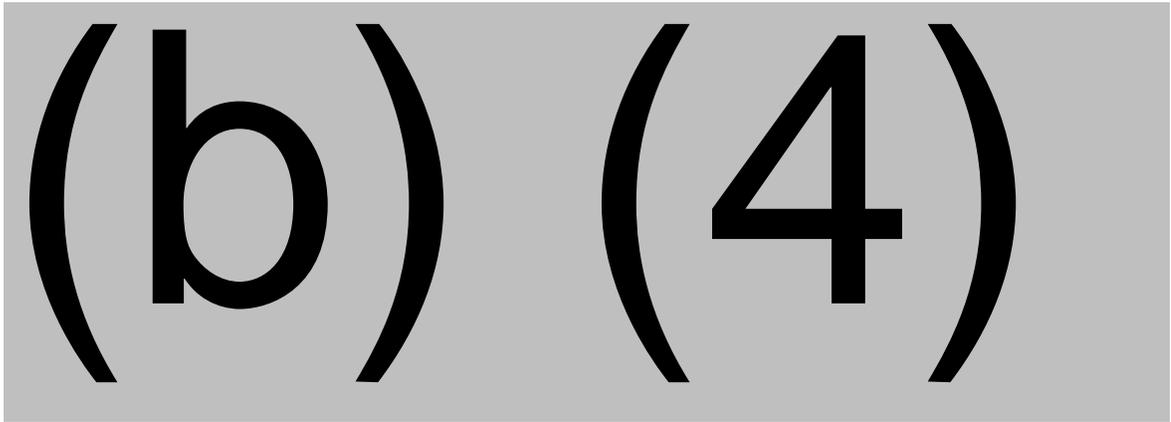
Octapharma's response: The tests performed on the donors are the same as those provided in the original BLA. (b) (4) using the respective nucleic acid amplification technique (NAT) assay. The acceptance criterion for (b) (4) is (b) (4) and negative for the other viruses. For the manufacturing pools, they will be tested for the absence of (b) (4) (b) (4) Additionally, the manufacturing pools have to be non-reactive for (b) (4)

(b) (4) The acceptance criterion for B19V is $< 10^4$ IU/mL.

Product reviewer's comment: The viral tests performed in the plasma (b) (4) (b) (4) manufacturing pools, appear to be sufficient according to the requirements of the relevant FDA guidance. Therefore, this response is acceptable.

- 3) Selected steps in the *BALFAXAR* manufacturing process were validated for the capacity to inactivate and/or remove viruses

Viral clearance studies:



S/D treatment

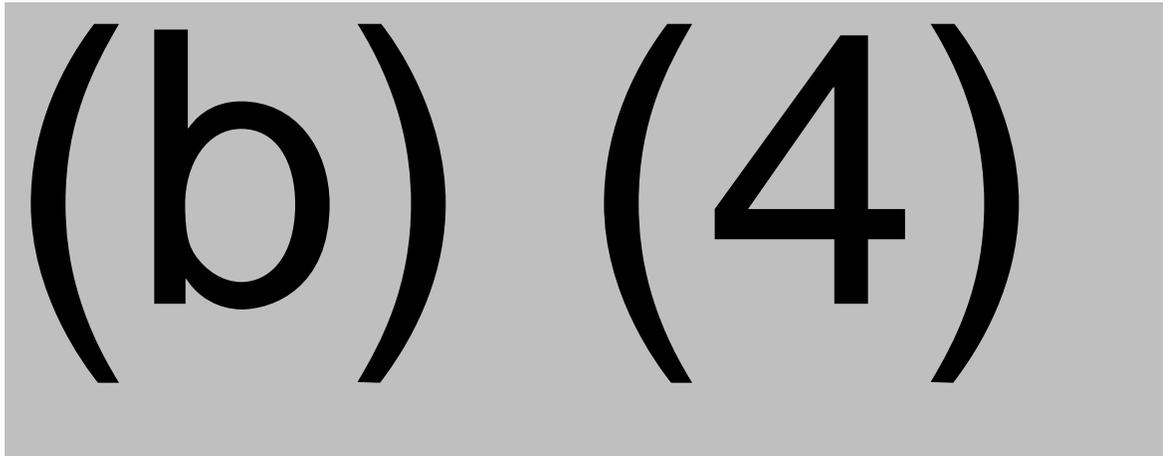


Table 15. The kinetics of HIV-1, PRV, and BVDV inactivated by the S/D treatment at the (b) (4)-scale

(b) (4)

Product reviewer's comment: Octapharma performed extensive viral clearance studies on the S/D treatment process, which included those under various conditions, e.g., (b) (4) These data support that the S/D treatment process is a robust step for the inactivation of the referenced enveloped viruses in the manufacturing process of *BALFAXAR*.

20 nm viral filtration

(b) (4)

2 pages have been determined to be not releasable: (b)(4)

Virus reduction claimed

Based on the above data, Octapharma listed log reduction factors of the different manufacturing steps for the relevant and model viruses in the following table.

Table 20. Overall virus reduction factors (log₁₀) for inactivation/removal of various viruses achieved by the BALFAXAR manufacturing process

Manufacturing steps	Virus reduction factors (log ₁₀)				
	Enveloped viruses			Non-enveloped viruses	
	HIV-1	PRV	BVDV	HAV	PPV
S/D treatment	≥ 4.35	≥ 5.77	≥ 5.96	Not applicable	Not applicable
Planova 20N nanofiltration	≥ 4.58	≥ 6.01	≥ 5.95	≥ 5.36	5.79
Overall log reduction factors	≥ 8.93	≥ 11.78	≥ 11.91	≥ 5.36	5.79
S/D treatment	≥ 4.35	≥ 5.77	≥ 5.96	Not applicable	Not applicable
Pegasus SV4 nanofiltration	≥ 4.82	≥ 6.13	≥ 5.01	≥ 5.24	3.98
Overall log reduction factors	≥ 9.17	≥ 11.90	≥ 10.97	≥ 5.24	3.98

Product reviewers' comment: As described above, product safety related to the potential viral contamination in the manufacturing processes is mainly demonstrated through these viral clearance studies other than the control of the potential viral load in plasma pools. These results are sufficient to support the effectiveness of viral clearance in the proposed commercial manufacturing process of *BALFAXAR*.

LABELING

For the drafted Prescribing Information (PI), we asked Octapharma to make the following revisions in the first PI draft sent on 22 May 2023:

- Multiple edits were made regarding Section “*Warnings and Precautions*” in Highlights of PI, Section 2.1 “*Dosage*”, Section 5.3 “*Transmissible Infectious Agents*”, and Section 11 “*Description*”.
- Regarding Section 2.2 “*Preparation and Reconstitution*” and Section 16 “*How supplied/storage and handling*”, please reduce the holding time after reconstitution from “up to 8 hours” to “up to 4 hours”.

Octapharma responded in an amendment on 30 May 2023, in which they fully agreed with our requests except for the holding time after reconstitution. As discussed under the section *Stability* of this memo, after consulting with management we agreed with Octapharma to revise the relevant statement in the PI as follows:

As BALFAXAR contains no preservatives, the solution should be administered immediately after reconstitution, or within 8 hours, provided sterility is maintained. The reconstituted solution can be stored for up to 8 hours at room temperature (20°C to 25°C; 68°F to 77°F).

Additionally, Octapharma agreed to make the following revisions:

- To include the manufacturer address on the carton and container label other than the distribution address (reference to the amendment dated 1 June 2023)
- To use “500 IU Range” or “1000 IU Range” across the labeling of *BALFAXAR* (PI, container and carton labels) to avoid the potential administration use error (reference to the amendment dated 7 June 2023)
- To revise the product information in the PI based on the updated product release specifications provided in the amendment dated 16 May 2023 (reference to the amendment dated 7 June 2023)

All these requested labeling changes were reflected in the amendment dated 15 June 2023. Therefore, their responses are acceptable.

Recommendation

The manufacturing process, its in-process controls, and the specifications used to control the quality of *BALFAXAR* DS and DP are adequately validated and sufficiently justified to ensure consistent manufacture of the product that meets the acceptance criteria of all quality attributes. The safety of adventitious agents is well demonstrated through the controls of the manufacturing process of *BALFAXAR*, including the control of the starting material, potential virus load in the manufacturing plasma pool, and capability of the two dedicated virus clearance steps, S/D treatment and 20-nm nanofiltration (Planova 20N or Pegasus SV4). The measures taken by Octapharma to control other adventitious agents in the manufacture of *BALFAXAR* are also acceptable. Therefore, we found the CMC information to be supportive of product quality, identity, purity, potency, and safety, and recommend approval of this BLA.