

CBER DMPQ CMC/Facility BLA Review Memorandum

BLA 125776/0

Prothrombin Complex Concentrate (Human), Balfaxar

**Obinna Echeozo, Reviewer, DMPQ/MRB2
Zhongren Wu, Reviewer, DMPQ/MRB2**

1. **BLA#:** STN 125776/0

2. **APPLICANT NAME AND LICENSE NUMBER:** OCTAPHARMA Pharmazeutika Produktionsges.m.b.H., U.S. License number 1646

3. **PRODUCT NAME/PRODUCT TYPE**

Prothrombin Complex Concentrate (Human), Balfaxar

4. **GENERAL DESCRIPTION OF THE FINAL PRODUCT**

a. **Pharmacological category**

Prothrombin Complex Concentrate (PCC)

b. **Dosage form**

Powder and solvent for intravenous use

c. **Strength/Potency**

500 IU / 1000 IU

d. **Route of administration**

Intravenous

e. **Indication(s)**

Urgent reversal of acquired coagulation factor deficiency induced by Vitamin K antagonist (VKA, e.g., warfarin) therapy in adult patients with a need for an urgent surgery/invasive procedure.

5. **MAJOR MILESTONES**

Received: July 28, 2022

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PDUFA Action Due Date: July 28, 2023

6. **DMPQ CMC/FACILITY REVIEW TEAM**

Reviewer/Affiliation	Section/Subject Matter
Obinna Echeozo, DMPQ Reviewer, OCBQ/DMPQ/MRB2	<ul style="list-style-type: none">• 3.2.S Drug Substance [PCC Human]• 3.2.P Drug Product [Octaplex]• 3.2.P Drug Product [WFI]• 3.2.A.1 Facilities and Equipment [Octapharma Vienna]• 3.2.A.1 Facilities and Equipment [Octapharma (b) (4)]
Zhongren Wu, DMPQ Reviewer, OCBQ/DMPQ/MRB2	<ul style="list-style-type: none">• 3.2.A.1 Facilities and Equipment (b) (4)

7. SUBMISSION(S) REVIEWED

Date Received	Submission	Comments/ Status
July 28, 2022	STN 125776/0	Original application/ Reviewed
June 27, 2023	Amendment STN 125776/0.45 (response to information request (IR) sent June 26, 2023)	Diluent container closure integrity testing facility information / Reviewed
July 03, 2023	Amendment STN 125776/0.48 (response to information request (IR) sent June 28, 2023)	Diluent shipping process and shipping validation / Reviewed

8. REVIEWER SUMMARY AND RECOMMENDATION**A. EXECUTIVE SUMMARY**

Octapharma Pharmazeutika Produktionsges.m.b.H (Octapharma) submitted this Biologics License Application (BLA), STN 125776/0, for Prothrombin Complex Concentrate (Human), Balfaxar, indicated for the urgent reversal of acquired coagulation factor deficiency induced by Vitamin K antagonist (VKA, e.g., warfarin) therapy in adult patients with (b) (4) need for an urgent surgery/invasive procedure.

Balfaxar is a co-packaged combination product consisting of 1) the lyophilized Balfaxar drug product (DP), 2) sterile water for injection (WFI) diluent, and 3) a 510(k) cleared transfer device, Nextaro (FDA 510(k) No. K183187).

The Balfaxar DP contains the coagulation factors II, VII, IX, and X and antithrombotic Proteins C and S. It is available as a white to ice-blue lyophilized powder for reconstitution for intravenous use in a single-dose 30 mL glass vial, provided in a nominal strength of 500 Factor IX units in 20 mL reconstitution volume and 1000 Factor IX units in 40 mL reconstitution volume contained in a 50 mL glass vial. The diluent is supplied in 20 mL and 50 mL glass vials containing 20 mL and 40 mL WFI, respectively.

The Balfaxar drug substance (DS) and DP are manufactured at the Octapharma, Vienna Austria site (OPG). The diluent is manufactured by (b) (4) (b) (4) a contract manufacturing organization, CMO, located in (b) (4). As an alternate site for OPG, visual inspection, labeling, and packaging of the final DP are conducted by (b) (4) located in (b) (4).

Facility inspections were waived for the OPG, (b) (4). The inspection waivers were based on the evaluations of the facilities' inspection compliance histories. The inspection waivers are documented in a separate inspection waiver memo dated (b) (4).

This review memo covers the Chemistry, Manufacturing, and Controls (CMC), with a focus on the microbial controls, facility, major equipment, cleaning, environmental monitoring (EM), and cross-contamination controls.

Based on the information submitted to BLA 125776/0, the manufacturing process, facilities, equipment, and quality controls appear acceptable for the manufacture of Balfaxar, and approval is recommended.

B. RECOMMENDATION

I. APPROVAL

Based on the information provided in this application and its amendments, DMPQ recommends the approval of Balfaxar, which is manufactured at Octapharma Pharmazeutika Produktionsges.m.b.H. at Oberlaaer Strasse 235, A-1100, Vienna, Austria and (b) (4)

The sterile WFI diluent used to reconstitute the Balfaxar DP is manufactured at (b) (4)

Approval is recommended with the inspectional recommendation below:

Octapharma Pharmazeutika Produktionsges.m.b.H., (OPG); FEI: 3002809097

- (b) (5), (b) (7)(E)

CBER understands the inspectional recommendations may or may not be taken (based on risk and available resources) and is not requesting documentation to be submitted as evidence of completion.

II. SIGNATURE BLOCK

Reviewer/Title/Affiliation	Concurrence	Signature and Date
Obinna Echeozo, Microbiologist, OCBQ/DMPQ/MRB2	Concur	
Zhongren Wu, Consumer Safety Officer, OCBQ/DMPQ/MRB2	Concur	
Anthony Lorenzo, Branch Chief, OCBQ/DMPQ/MRB2	Concur	
Carolyn Renshaw, Director, OCBQ/DMPQ	Concur	

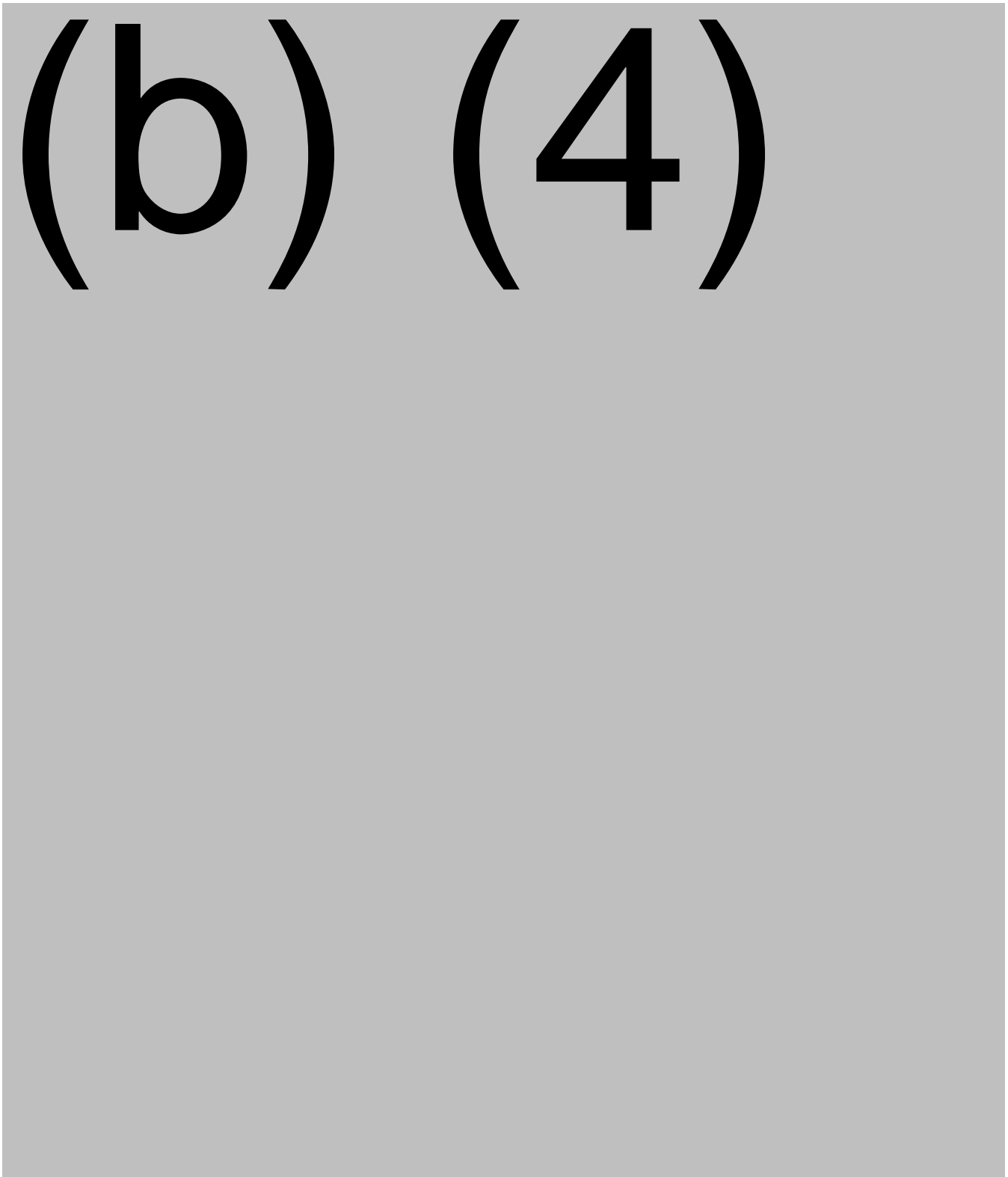
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Module 3

3.2.S DRUG SUBSTANCE

(b) (4)



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

(b) (4)

3.2.P DRUG PRODUCT

3.2.P.1 Description and Composition of the Drug Product

Balfaxar DP is a sterile lyophilized powder, which is reconstituted with diluent (WFI) prior to administration via intravenous injection. It is available with a nominal strength of 500 IU (factor IX) in 20 mL reconstitution volume and 1000 IU (factor IX) in 40 mL reconstitution volume per vial. Balfaxar DP composition is shown in the Table below:

Table: Composition of Balfaxar DP

Names of ingredients	Quantity per mL reconstituted solution	Function	Standard
Factor IX	(b) (4) IU/mL	Active ingredient	(b) (4)
Factor II	(b) (4) IU/mL	Active ingredient	(b) (4)
Factor VII	(b) (4) U/mL	Active ingredient	(b) (4)
Factor X	(b) (4) IU/mL	Active ingredient	(b) (4)
Protein C	(b) (4) IU/mL	Active ingredient	internal

Names of ingredients	Quantity per mL reconstituted solution	Function	Standard
Protein S	(b) (4) IU/mL	Active ingredient	internal
(b) (4)	(b) (4)	N/A	internal
Heparin	(b) (4)	Stabilizer	(b) (4)
Sodium citrate	(b) (4)	Buffering Substance	(b) (4)

The lyophilized Balfaxar DP is supplied in labeled 30 mL (500 IU) or 50 mL (1000 IU) (b) (4) glass vials, which are closed with 20 mm (b) (4) bromobutyl rubber stoppers and sealed with a 20 mm aluminum flip off cap. One vial of the DP is reconstituted with 20 mL (500 IU) or 40 mL (1000 IU) WFI (b) (4) prior to administration via intravenous injection. The final package contains a single-dose vial of the lyophilized DP co-packaged with the diluent (i.e., WFI contained in 20 mL or 50 mL (b) (4) colorless glass vials) and an FDA cleared single-use transfer device.

3.2.P.2.5 Microbiological Attributes

Balfaxar DP and WFI diluent are manufactured via aseptic processing; and the diluent (WFI) is (b) (4) sterilized. The development of the aseptic process is based on the general prothrombin complex products manufacture [note, OPG currently manufactures multiple FDA approved human plasma-derived products, example Octagam (STN 125062), Cutaquig (STN 125668), Wilate (STN 125251)]. The bioburden load of the product (b) (4) is controlled throughout the manufacturing process (i.e., from (b) (4) (b) (4)

An in-process bioburden test sample is collected (b) (4) (acceptance criteria: (b) (4) Release testing for sterility and endotoxin of the final DP and solvent are conducted per (b) (4) and (b) (4) respectively.

To qualify the DP CCS, container closure integrity testing (CCIT) was performed for the DP using (b) (4) (b) (4). CCIT for the diluent CCS was conducted using (b) (4) (b) (4) and (b) (4) methods.

Additionally, the co-packaged transfer device is supplied single packed, sterile, and endotoxin free, and is intended for single-use only.

Reviewer's comment: As noted in the description, Balfaxar DP is a single-dose product, and no antimicrobial preservatives were reported. The in-process bioburden testing, microbial quality attributes (sterility and endotoxin), and analytical procedure (i.e., CCIT) for the sterile DP and diluent appear appropriate.

3.2.P.3 Manufacture

3.2.P.3.1 Manufacturer(s)

The Balfaxar DP and solvent manufacturing, testing and warehouse facilities are summarized in the Table below.

Site	Responsibility
Octapharma Pharmazeutika Produktionsges.m.b.H. Oberlaaer Strasse 235, A-1100 Vienna, Austria (OPG) FEI: 3002809097	Production from plasma to final container, visual inspection, labeling and secondary packaging, batch release testing
Octapharma (b) (4) (b) (4) (b) (4) (b) (4)	Visual inspection, labeling and secondary packaging
(b) (4) (b) (4)	Storage of final product
(b) (4)	Storage of final product
(b) (4)	Production of WFI (diluent)
(b) (4) (b) (4)	WFI sterility testing

* CGMP operating system identical to OPG

** CGMP operating system: Good Distribution Practice of medicinal products for human use according to EU Guidelines 2013/C 343/01, meeting the requirements in 21 CFR 211.142 (Warehousing procedures).

3.2.P.3.3 Description of Manufacturing Process

Description of the Balfaxar DP Manufacturing Process

Sterile filtration: (b) (4)

1 page has been determined to be not releasable: (b)(4)

(b) (4)

Visual inspection, labeling, and packaging: Visual inspection, labeling, and packaging processes at OPG and (b) (4) are identical. Prior to visual inspection, all vials are tested for adequate (b) (4) (i.e., DP vial integrity) using a (b) (4) or by (b) (4) method. 100% visual inspection is performed for DP vials at both OPG and (b) (4) using a semi-automatic visual inspection machine. Visual inspection of DP vials is performed to evaluate conformance of lyophilized product cake and to identify defective bottles and/or flip-off caps and faulty stoppering.

Passing final container vials are labeled and packaged. The lyophilized DP vial is co-packaged with the diluent vial (WFI) and the transfer device (Nextaro) within a single carton and stored at 2°C to 25°C pending quality control (QC) release.

Reviewer's comment: *The firm indicated that the Balfaxar manufacturing process has no distinct definition of DS and DP. However, for ease of review, description of DP manufacture started from the (b) (4) step. The firm provided validation reports for the various manufacturing process steps described above. See the respective sections below for details.*

Description of the Diluent Manufacturing Process

WFI manufactured at (b) (4) is used as the diluent for Balfaxar DP. The WFI manufacturing process is as follows:

Batch preparation: (b) (4)

(b) (4)

Filling: (b) (4)

(b) (4)

(b) (4)

Visual inspection: Filled vials are 100% automatically visually inspected for (b) (4) (b) (4) defects. Rejected vials are discarded. After visual inspection, the caps are marked with the lot number. The accepted final containers are packed into a shipping carton, which is marked with a shipping carton label stating product name, fill size, and batch number. They are transported back into the storage area and kept at (b) (4) pending QC release.

Reviewer's comment: *Validation of these processes are reviewed in their respective sections below.*

3.2.P.3.4 Controls of Critical Steps and Intermediates

Control of Critical Steps for DP manufacture

(b) (4)

Reviewer's comment: *The DP microbial control strategy appears acceptable. See equipment sections below for equipment related microbial control. Detailed review of this section is deferred to the OTP reviewer.*

Control of Critical Steps for diluent manufacture

(b) (4)

3.2.P.3.5 Process Validation and/or Evaluation

Process validation was performed to qualify the DP and diluent manufacturing processes at OPG (alternative (b) (4) Visual inspection, labelling and secondary packaging) and (b) (4) facilities, respectively. The PPQ batches were manufactured using routine manufacturing steps. The PPQ data are reviewed in the sections below.

Process validation at OPG

PPQ

The PPQ strategy for DP manufacturing is (b) (4) to the DS PPQ (*as covered under this review memo*). An initial PPQ was conducted to qualify the Balfaxar manufacturing process at OPG. A second PPQ was performed to qualify the DP batches manufactured from an alternative (b) (4)

The PPQ reports are reviewed below.

(b) (4)

12 pages has been determined to be not releasable: (b)(4)

(b) (4)

3.2.P.5 Control of Drug Product

3.2.P.5.1 and 3.2.P.5.6 Specification(s) and Justification of Specification(s)

Reviewer's comment: *The Balfaxar DP specifications are provided in Sections 3.2.P.3.5 Process Validation and/or Evaluation and 3.2.P.5.4 Batch analyses of the memo and the justification with respect to microbial attributes are provided in Section 3.2.P.2.5 Microbiological Attributes in the memo.*

The (b) (4) sterilized WFI diluent specifications are provided in Sections 3.2.P.3.5 Process Validation and/or Evaluation and 3.2.P.5.4 Batch analyses of the memo and are established based on (b) (4) requirements for WFI.

3.2.P.5.2 and 3.2.P.5.3 Analytical Procedures and Validation of Analytical Procedures

Reviewer's comment: *The Balfaxar DP release sterility and endotoxin testing are performed according to (b) (4) and (b) (4) (b) (4) The (b) (4) sterilized WFI diluent tests are performed according to (b) (4) methods. The method validations are deferred to the Division of Biological Standards and Quality Control (DBSQC) reviewer.*

3.2.P.5.4 Batch Analyses

In Table 1 of Section 3.2.P.5.4 *Batch analyses* [Balfaxar DP], and Table 1 of Section 3.2.P.5.4 *Batch analyses* [WFI], the release testing results for the DP under DMPQ

purview (i.e., appearance, sterility, and endotoxin) met acceptance criteria (white to ice-blue powder or friable solid very hygroscopic, sterile, and (b) (4) respectively). The release testing results for WFI under DMPQ purview (i.e., appearance, (b) (4) endotoxin, and sterility) met acceptance criteria (clear colorless liquid free from particles, (b) (4) and sterile, respectively).

Review's comment: The release testing results for Balfaxar DP and WFI under DMPQ purview appear acceptable. DMPQ defers the review of release testing results for all other parameters to the OTP reviewer. There were no deviations related to microbial contamination during the manufacture of Balfaxar DP PPQ batches.

3.2.P.7 Container Closure System

The 500 IU and 1000 IU presentations of the lyophilized Balfaxar DP are each filled into 30 mL and 50 mL (b) (4) glass vials (supplied by (b) (4) respectively, and stoppered with sterilized gray 20 mm (b) (4) bromobutyl rubber stoppers coated with (b) (4) coating (supplied by (b) (4)). The stoppered product vial is sealed with a 20 mm aluminum seal with a blue plastic flip-off cap manufactured by (b) (4).

The WFI diluent is supplied in 20 mL and 50 mL (b) (4) glass vials (supplied by (b) (4) (b) (4) for the reconstitution of the lyophilized 500 IU and 1000 IU Balfaxar DP presentations, respectively. The WFI vials are stoppered with 20 mm gray (b) (4) bromobutyl rubber stoppers supplied by (b) (4) and sealed with aluminum flip off caps manufactured by (b) (4).

A single-use needleless transfer device (Nextaro) with an integrated 15 µm (nominal) filter is co-packaged with the lyophilized DP and WFI vials. This device is cleared under FDA 510(k) No. K183187 and is used to transfer the WFI diluent into the DP vial for reconstitution.

- **CCIT for Balfaxar DP**

The CCIT study was reported in 000SSR26x 28x.17P044.17P050.00/CCIT. The CCIT was initially carried out using the (b) (4) method at time zero of stability studies (i.e., batch release testing), where 100% of the batches are vial integrity tested per the routine manufacturing procedure. (b) (4) batches each of Balfaxar 500 IU (b) (4) filled into 30 mL glass vials, and Balfaxar 1000 IU (b) (4) filled into 50 mL glass vials, were evaluated. (b) (4) was filled on filling line (b) (4) (b) (4).

Following the initial CCIT at time zero, the batches were placed on stability study under long-term conditions at +5°C, +25°C (b) (4) RH (relative humidity), and (b) (4) RH, and samples were collected and tested for CCIT after 36 months storage using the (b) (4) measurement. Octapharma states that due to the limited number of reserve samples, the test was performed on a

(b) (4)

(b) (4)

(b) (4)

At the completion of CCIT, no deviations were observed, all results confirmed CCI of the CCS for Balfaxar 500 IU and 1000 IU, manufactured at OPG and filled at filling (b) (4)

Reviewer's comment: *Octapharma's CCIT methods appear acceptable for the product/vial combination. CCIT is performed at release and expiry. A summary of the process description was not submitted; however, the firm indicated that CCIT was conducted according to their facility procedures. Note, the firm has experience manufacturing lyophilized plasma derived products and has received FDA approval for multiple drug products. Therefore, the data submitted appears acceptable.*

- **CCIT for WFI**

The CCIT was performed by (b) (4) different contract firms. (b) (4) performed the CCIT of the WFI vials, using the (b) (4) method (a (b) (4) (b) (4) method). A second CCIT was conducted by (b) (4) using the (b) (4) method. The (b) (4) CCIT methods were performed at the expiration of the WFI shelf-life (i.e., (b) (4) months at 2 - 25°C).

- (b) (4) CCIT method: (b) (4)

(b) (4)

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(b) (4)

The firm's response and CCIT results for the WFI vials appear to have met acceptance criteria for the individual test methods implemented and are acceptable.

3.2.P.8 Stability

3.2.P.8.1 Stability Summary and Conclusion and 3.2.P.8.3 Stability Data

Balfaxar DS Stability Studies

Balfaxar DP may be stored for up to 36 months at +2°C to +25°C (protected from light) from the date of manufacture. The firm stated that the lyophilized DP must be reconstituted directly prior to injection and used immediately. However, if it is not administered immediately, the reconstituted solution can be stored for up to 8 hours at +20°C to +25°C.

Long-term stability studies (at +5°C, +25°C^{(b) (4)} RH, and (b) (4) RH) and accelerated studies (at (b) (4) RH) were conducted to demonstrate stability of the following 500 IU and 1000 IU Balfaxar DP batches:

- Initial PPQ batches manufactured at OPG (using the Pegasus SV4 nanofilter and (b) (4) : batches (b) (4) (b) (4) 36 months stability data was provided.
- Initial PPQ batches manufactured at OPG (using the Planova 20N nanofilter and (b) (4) batches (b) (4) 36 months stability data was provided.
- Process validation batch manufactured in 2021 at OPG following implementation of an alternative (b) (4) : batch (b) (4) Six-month stability data was provided.

The stability batches were stored, (b) (4) position. Following batch release testing (i.e., timepoint zero, considered part of stability study), the stability batches were tested at the following timepoints and temperature conditions:

Table: Stability study timepoints and storage conditions

Storage Conditions	3 months	6 months	9 months	12 months	18 months	24 months	36 months
+5°C ± 3°C	N/A	x	N/A	x	x	x	x
+25°C/(b) (4) RH ¹	x	x	x	x	x	x	x
(b) (4) C/(b) (4) RH ¹	N/A	x	N/A	x	N/A	x	x
(b) (4) C/(b) (4) RH ¹	x	x	N/A	N/A	N/A	N/A	N/A

¹) Tolerances: temperature (b) (4) C, relative humidity (b) (4) % RH

The stability of Balfaxar DP was evaluated at +25°C/(b) (4) RH and (b) (4) RH following reconstitution.

At the conclusion of stability studies, all batches met acceptance criteria for sterility (sterile) and endotoxin (b) (4). Both parameters were tested at timepoints zero, 24 months, and 36 months.

Reviewer's comment: The submitted stability results under DMPQ purview (i.e., sterility and endotoxin) were reviewed and met acceptance criteria. DMPQ defers the detailed review of stability studies and results of all other test parameters to OTP.

3.2.A APPENDICES

3.2.A.1 Facility and Equipment

OCTAPHARMA VIENNA, AUSTRIA (OPG) FACILITY OVERVIEW

Balfaxar DS and DP are manufactured at the OPG manufacturing facility. The facility is approximately (b) (4). The OPG facility is an existing, multi-product facility for the manufacture of aseptically filled large and small volume parenterals, clinical, and investigational products. No toxic or hazardous substances (e.g., penicillin, cephalosporins, or cytotoxic substances) are processed or produced at this site. Furthermore, no veterinary products are manufactured at OPG.

OPG currently manufactures numerous FDA-approved products including Albumin (STN 125154), Wilate (STN 125251), Octagam 5 % and 10 (STN 125062), Cutaquig (STN 125668), Panzyga (STN 125587), and Fibryga (STN 125612).

Manufacturing Areas

Floors in the manufacturing areas are covered with either (b) (4) on the base of (b) (4) or other (b) (4) on the base of (b) (4). Aseptic areas are covered with (b) (4) floors. All inside walls are (b) (4) or (b) (4). The ceilings are (b) (4) (b) (4) ceilings.

QC laboratories are in buildings (b) (4) while the stability rooms are in building (b) (4) and (b) (4). The manufacturing areas for Balfaxar are divided into the pre-viral inactivation (pre-V.I.) area, post-viral inactivation (post-V.I.) area, pharmaceutical production, and packaging and storage areas.

(b) (4)

- **Packaging and storage areas:** The packaging areas are in building (b) (4) and (b) (4) and include visual inspection (room (b) (4)) and labeling and packaging (rooms (b) (4)). Plasma storage rooms are in building (b) (4). Buildings (b) (4) and (b) (4) house the storage areas for raw materials and final container DP.

Reviewer's comment: The multi-product facility appears suitably sized and appears to have the segregation needed to manufacture Balfaxar DS and DP. OPG has a known compliance history with FDA. ORA/OBPO (Office of Regulatory Affairs/ Office of Biological Products Operations) conducted a recent inspection of OPG in December 2022, covering areas listed above, and the inspection was classified VAI (Voluntary Action Indicated).

Manufacturing Flow

The flow of materials, equipment, waste, and personnel at OPG for the purposes of controlling contamination and preventing cross-contamination are in accordance with the firm's procedures. The manufacturing flows include:

(b) (4)

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(b) (4)

Reviewer's comment: *The submitted facility flow diagrams were reviewed and found acceptable. All manufacturing areas are access controlled. (b) (4) of personnel appears to be implemented in Grade (b) (4) (and above) areas. Flow patterns do not appear to present unnecessary challenges that could potentially introduce contaminants during manufacturing. The manufacturing flows described in the submission appear acceptable.*

Contamination/cross-contamination control

OPG operates as a multi-product facility. Access to the manufacturing areas is controlled by a card key system and is limited to authorized personnel. The cleanrooms are designed to provide controlled manufacturing. Room pressurization, airlocks, and gown rooms facilitate product/process separation and containment. The surface finishes in the manufacturing areas are consistent with the intended function of the area and were designed for durability and ease of cleaning.

(b) (4) manufactured in respective rooms. The different product groups are processed in their respective production lines, thus cross-contamination with other product groups is prevented. Furthermore, processing is performed in closed containers/systems.

The pre-V.I. and post-V.I. areas are physically segregated for each manufacturing line by means of separate rooms, equipment, HVAC (heating, ventilation, and air conditioning) systems, and pressure cascade. Transfer of product from the pre-V.I. area to the post-V.I. area is performed using (b) (4). After transfer is completed, (b) (4) of in the pre-V.I. area. Therefore, cross-contamination from the pre-V.I. area to the post-V.I. area is prevented. Specific measures implemented include:

- **Cleaning:**

Facility cleaning: After completion of each batch, line clearance is performed, and the equipment are cleaned/sanitized/sterilized (where applicable) according to written procedures prior to processing the next batch. Cleaning of each production room is performed and documented according to written procedures, and cleaning of the different surfaces in the respective production areas is performed according to a defined schedule. Cleaning/disinfection agents (b) (4) (b) (4) disinfectant) to be used in the respective production areas are defined in written procedures. The (b) (4) disinfectant used is rotated (b) (4). The effectiveness of the disinfectant used has been proven during validation studies.

The sterile filtration room is cleaned (b) (4)



Reviewer's comment: Access control into manufacturing spaces is in place. The frequency of cleaning appears acceptable for the degree of manufacturing performed. The cleaning schedule for filling line (b) (4) appears acceptable since filling is performed (b) (4)

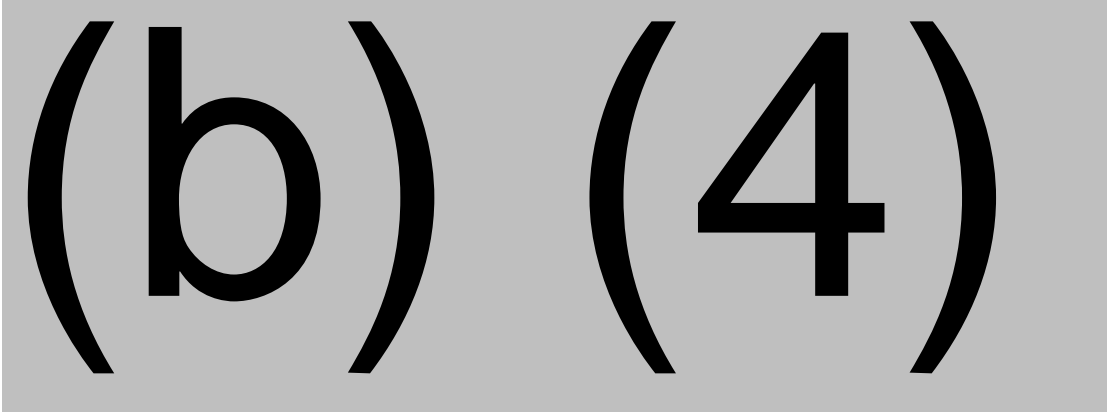
(b) (4) The facility and filling lines are existing and disinfectant effectiveness studies have been previously conducted and reviewed for other approved products, including those in the same product family as Balfaxar. The facility cleaning measures implemented appear acceptable. Equipment cleaning is reviewed under the equipment section of this memo.

- **Area Classifications/HVAC:**

Air supply to the various manufacturing and administrative areas is provided by individual air handling units (AHUs) equipped with pre-filters and terminal HEPA-filters. The plasma donation control area, packaging area, and the storage areas are furnished with (b) (4)

(b) (4) A positive cascading pressure is maintained from the cleanest to dirtiest areas, e.g., (b) (4) air flow from cleanrooms (where manufacturing processes are conducted in closed systems) to airlocks then to corridors.

The air pressure difference between critical manufacturing areas are as follows:



(b) (4)

The air pressure differential between the cleanroom and surrounding areas is monitored by air pressure differential gauges. Fresh air intake is provided through (b) (4)

Regulation of temperature and humidity of air supply to the rooms is performed by monitoring temperature and humidity recorded in the exhaust air ducts.

A summary of the AHUs, amount of air recirculation, and area classifications for Balfaxar DP manufacturing activities are tabulated below:

Table: AHUs and critical manufacturing areas serviced

(b) (4)

The HVAC system is qualified. Written procedures are available for preventive maintenance of HVAC systems. The HVAC system has been qualified. Pre-filters are changed at least (b) (4) a year. The integrity of HEPA filters is tested (b) (4) a year, laminar flow filters are tested (b) (4) a year.

Reviewer's comment: *Pre-V. I. and post-V.I. areas appear to be adequately segregated. Physical, equipment, HVAC, and pressure cascade measures appear to have been implemented. A differential pressure cascade is maintained. In addition, the air recirculation rates provided for the critical manufacturing rooms (as indicated in the Table above) appear suitable for activities conducted in the respective rooms. While details of the HVAC system and the AHU qualifications and the environmental monitoring performance qualification (EMPQ) were not provided in the submission, this appears acceptable as the facility is multi-product and the HVAC system that supports the filling lines and freeze dryers used in the manufacture of Balfaxar DP has been previously reviewed to support the manufacture of other FDA approved products. Additionally, the firm did not identify any changes to the HVAC system as a result of introducing Balfaxar DP.*

It is noted that the integrity of HEPA filters is tested (b) (4) a year. For critical manufacturing areas, including Grade (b) (4) areas where aseptic processing is performed, HEPA filters are typically integrity tested (b) (4) a year. (b) (5), (b) (7)(E)

(b) (4)

In the AHU/critical areas table above, it is noted that Octapharma states the Grade (b) (4) filling line (b) (4) rooms are supplied by (b) (4) air. However, this appears to be a typographical error as filling line is used to manufacture other FDA approved products such as Wilate under STN 125251 and that submission states there is (b) (4) air supplied to those Grade (b) (4) filling line (b) (4) rooms. Furthermore, filling line (b) (4) has been assessed during the December 2022 ORA/OBPO surveillance inspection and no objectionable issues identified were associated with filling line (b) (4)

- **Environmental monitoring program:**

The environmental monitoring program is divided into (1) in-operation monitoring performed in cleanroom Grades (b) (4) through (b) (4) as well as (2) environmental batchwise and campaign monitoring performed on aseptic filling lines. To prove that all operations are performed within the acceptable limits of the respective cleanroom classified areas, the in-operation monitoring is performed during routine operations on a (b) (4) basis according to associated procedures. The number, location of sampling points, and frequency of sampling are determined based on risk depending on the activity and proximity

to the product. The monitoring frequency for the critical Grade (b) (4) areas during dynamic conditions is summarized below.

- Total particulate (b) (4)
- Settling plates (b) (4)
- Viable air (b) (4)
- Contact plating of critical surfaces and (b) (4) gloves (b) (4)
- Microbial counts, gowning, and fingerprint operators [during manufacture of (b) (4) batch (b) (4) additionally for (b) (4)]

(b) (4)

Reviewer's comment: *The submitted environmental monitoring program information was reviewed and appears acceptable.*

- **Gowning:**

The gowning procedures and requirements are in place at OPG. Entry into the respective manufacturing areas is via personnel locks, where personnel change over to the gowning type of the respective room classified area. Each area has its defined gowning requirements per approved procedures. Use of dedicated cleanroom gowns for different cleanroom classifications is implemented. Examples of personal protective equipment used in the cleanroom areas are single-use caps and overalls with integrated hood, beard cover, face mask, gloves, safety goggles, cleanroom socks, and cleanroom shoes.

Reviewer's comment: *The firm has procedures for gowning covering requirements per room classifications. The facility gowning measures were reviewed, and they appear acceptable.*

Utilities

Critical utilities associated with the manufacture of the Balfaxar DP at OPG include HVAC (reviewed in the section above), WFI, (b) (4) water, clean steam, and computer systems.

Water Systems: Portable water supplied by the city provides water to the various water preparation plants on the OPG site. WFI and (b) (4) water is manufactured from the

water preparation plants. The major (b) (4) water plants consist of filters, softeners, (b) (4) and (b) (4) control. The WFI system mainly consists of stills, cWFI (cold WFI) preparation plants, storage tanks, and distribution loops. Hot WFI is circulated in loops at a temperature of (b) (4). Temperature and pressure are monitored in the (b) (4). Clean steam is also generated from WFI. All components of the water system at OPG (i.e., (b) (4) WFI, and clean steam) have been qualified.

To assure consistent water quality from each plant, a routine monitoring program is in place for portable water, (b) (4) WFI, and clean steam. Intervals of monitoring are defined based on the quality and criticality of the water system involved. The parameters and monitoring intervals for WFI are summarized in the table below.

Table: Parameters and monitoring intervals for WFI

(b) (4)

*The same parameters and action limits are implemented for clean steam; however, clean steam monitoring is performed (b) (4)

Written procedures defining actions to be taken when limits are exceeded during routine monitoring are also in place and the evaluation of monitoring data is performed (b) (4)

Reviewer's comment: The use and routine monitoring for the water systems at OPG were reviewed and appear acceptable. While details of water system qualification was not provided in the submission, this appears acceptable as the facility is multi-product and the water system supports the critical manufacturing area and equipment such as filling lines and freeze dryers used in the manufacture of Balfaxar DP has previously reviewed to support the manufacture of other FDA approved products. Additionally, the firm did not identify any changes to the water system as a result of introducing Balfaxar DP.

Computer Systems

The computerized systems are divided into automated systems used in manufacture and administrative information technology (IT) systems. The automated systems used in manufacturing can be divided into three categories: remote control systems (RCS), sequence control systems (SCS), and package unit systems (PUS).

- The RCS are based on programmable logic controls (PLC) with a user interface such as a control panel or a computer. Mechanical functions (e.g., control valves or dosage ports) are visualized on the user interface allowing the operator to direct actions on components or operations. E.g., opening and closing valves, setting temperatures, etc.

- The SCS systems are based on PLCs with a user interface (e.g., control panel, PC) that allow a functional sequence of several steps under programmed control, including the transition between steps. Examples of these system include CIP (clean-in-place) and SIP.
- The PUS systems are standalone computer systems controlling equipment like (b) (4) etc.

The administrative systems include Manufacturing Execution System (MES) and a Laboratory Information Management System (LIMS). These systems control tracking of plasma donations as well as material identification and labeling, stock administration, and warehouse management of plasma, auxiliary material, primary and secondary packaging, intermediates, and final products is supported by a computerized Manufacturing Execution System (MES).

Computer systems at OPG are validated based on the GAMP guidelines (Good Automated Manufacturing Practice). In general, computer validation is performed as part of the equipment qualification where the software and automation hardware are integral components.

Reviewer's comment: *A general description of the computer systems controlling the manufacturing processes was provided and reviewed. The computer systems are validated and appear acceptable.*

Equipment

Equipment with product contacting surfaces ((b) (4)) vessels and filling needles for filling line^{(b) (4)} use only (b) (4)

All surfaces and materials involved in the manufacturing process were selected to withstand defined processing parameters as well as cleaning and sanitization/sterilization (as applicable) during the manufacture of Balfaxar. Single-use, disposable equipment or auxiliary material is used, where possible.

New equipment implemented for the manufacture of Balfaxar include the (b) (4) (b) (4) (used in the virus inactivation, (b) (4) (b) (4) steps). All other major equipment used in the manufacture of Balfaxar DP at OPG have been previously qualified and used in the manufacture of other FDA approved products as submitted in section 3.2.A.1.3, *Annex I*. The major equipment is summarized below.

Table: Maior equipment used in the manufacture of Balfaxar

(b) (4)

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

(b) (4)

Reviewer's comment for equipment summary: *The major equipment described above are qualified and have been approved or reviewed during review of previously approved FDA products, including those in the same product family as Balfaxar. The most recent revalidations/requalifications were provided as these activities are performed according to an established frequency to demonstrate the equipment continues to function as intended. The requalification/revalidations were conducted using worst-case conditions (e.g., shorter cycles for sterilization, worst-locations, worst-case soiling agents), as applicable, and all studies met the acceptance criteria. Product-contact equipment (b) (4) [REDACTED] were noted. Equipment cleaning and sterilization are described in the sections below.*

Equipment Cleaning: Multi-use equipment is cleaned (b) (4) (b) (4) per Octapharma's procedures. The reusable product contact equipment includes (b) (4) (mobile and stationary), (b) (4) and (b) (4). All other product contact equipment is single-use disposable.

- **Routine cleaning:** Prior to using equipment for processing, equipment checks are conducted (by checking the attached label or equipment logbooks), to determine the equipment's cleaned/sanitized or sterilized status. Unlabeled equipment or equipment with unknown cleaning/sanitization/sterilization status is regarded as used and is removed for cleaning. After the completion of each

batch manufacturing process, used mobile equipment is removed during line clearance from the respective production area.

Equipment used in manufacture is either cleaned automatically (using (b) (4) system or equipment (b) (4)) or manually. (b) (4) is used to clean stainless steel surfaces and inactivate adventitious agents. (b) (4) rinse (b) (4) samples (final rinse performed with (b) (4) from equipment undergoing (b) (4) are monitored for the presence of residual contaminants as measured by (b) (4) Swab samples are collected from product-contact surfaces and tested for (b) (4) [specifically (b) (4) (b) (4)].

An (b) (4) detergent solution (e.g., (b) (4)) is used as the cleaning agent for all manual cleaning procedures. Manual cleaning is conducted per Octapharma's approved procedures.

- **Cleaning validation:** Besides the listed (b) (4) vessels listed in the section above, cleaning validation have been previously conducted for all the major equipment used in the Balfaxar DS and DP manufacturing process at OPG. The cleaning validation strategy implemented for automated cleaning and manual cleaning are summarized below.

(b) (4)

(b) (4)

Reviewer's comment: *The equipment cleaning procedures and cleaning validation for major equipment, many of which are shared equipment, have been previously reviewed and approved for other FDA products as noted in the major equipment summary section of this review memo. The automated cleaning validation utilizes worst-case soil, evaluates spray pattern, provided types of assays evaluated, and qualified clean and dirty hold times. The submitted cleaning re-validation results for filling needles used on filling line (b) (4) was reviewed and appears acceptable. Note, (b) (4) needles are used for filling line (b) (4). Also, note that the cleaning validation for the new (b) (4) were reviewed in the major equipment summary section of this review memo. The cleaning validation approach implemented at the firm appears acceptable.*

Equipment Sterilization:

(b) (4)

(b) (4)

Reviewer's comment: *The equipment sterilization cycle parameters used have been previously validated. See the major equipment summary section of this review memo for details of the most recent sterilization revalidations/requalifications.*

OCTAPHARMA (b) (4) FACILITY OVERVIEW

The (b) (4) site comprises an area of (b) (4) of which the commercially used effective surface is (b) (4) for Building (b) (4) and (b) (4) for Building (b) (4). Visual inspection, packaging, and labeling activities are performed in Building (b) (4).

Floors in the manufacturing and warehousing areas of (b) (4) Building (b) (4) are made of (b) (4) and the area is environmentally controlled. Access to the buildings and manufacturing and warehousing areas are subject to access control using electronic key cards. Manufacturing areas are equipped with airlocks through which personnel enter. An additional, contract warehouse space is available for use in the storage of packed and released finished products.

(b) (4) currently conducts labeling and packaging activities for other FDA approved products including Albumin (STN 125154), Wilate (STN 125251), Octagam 5 % and 10 (STN 125062), Cutaquig (STN 125668), and Panzyga (STN 125587).

Other products that could be labeled and packed in the same area are investigation plasma derived products, WFI, and solvent for reconstitution.

Reviewer's comment: *The site already performs labeling and packaging activities on approved FDA DPs, which appears to provide assurance of manufacturing capabilities. Other products packed in the manufacturing area do not appear to pose a risk to the Balfaxar DP. Additionally, the facility size appears adequate for the manufacturing activity performed. (b) (4) was last inspected by ORA in (b) (4) and the inspection was classified VAI.*

Manufacturing Flow

Products are delivered from other Octapharma manufacturing sites by truck to (b) (4). The transport is performed in compliance with the temperature requirement of the products. The products are subjected to incoming goods control in room (b) (4) and transported to the warehouse according to the temperature requirements (rooms (b) (4) for temperature 2°C to 25°C, room (b) (4) for 2°C to 8°C).

The received product is transported to room (b) (4) where integrity testing and 100% visual inspection are conducted. The product vials are manually inspected for transport damages during placement of the vials onto the packaging lines (room (b) (4)).

Labeling of the vials is performed using automated labeling machines and are manually packed into folding cartons in room (b) (4). The folding cartons can be printed with the batch data and serialized in advance or after the vials and other components have been packed.

After labeling, samples are taken for QC testing (*note, Balfaxar DP release testing is performed at OPG*). After packaging, finished products are transferred through the material lock to the warehouse for storage and subsequently transferred to room (b) (4) for shipment.

Gowning

The manufacturing areas (visual inspection, labeling, and packaging) at (b) (4) are unclassified. Personnel outdoor clothing is changed to industrial garments, single-use head cover and shoes (production or single-use) in changing rooms (b) (4). (b) (4)

Reviewer's comment: *As the manufacturing areas are unclassified, the gowning level implemented appears acceptable.*

Contamination/cross-contamination control

Cleaning of manufacturing rooms and equipment and the frequency of cleaning are guided by existing facility procedures. Contamination/cross-contamination prevention measures are in place at (b) (4). These are summarized as follows:

(b) (4)

Reviewer's comment: *These measures appear acceptable for the product and manufacturing activities performed at the site.*

Utilities

- **Computer Systems:** The computer systems are divided into administrative IT systems and PLCs.

PLCs: In general, the packaging process is manually monitored, but certain packaging steps are supported by computerized systems. The OQ of the computerized system is performed in (b) (4)

The packaging machines controlled by the computer system PLC are the (b) (4)
(b) (4)

Furthermore, the computer systems control serialization, tracking, and tracing using the (b) (4)

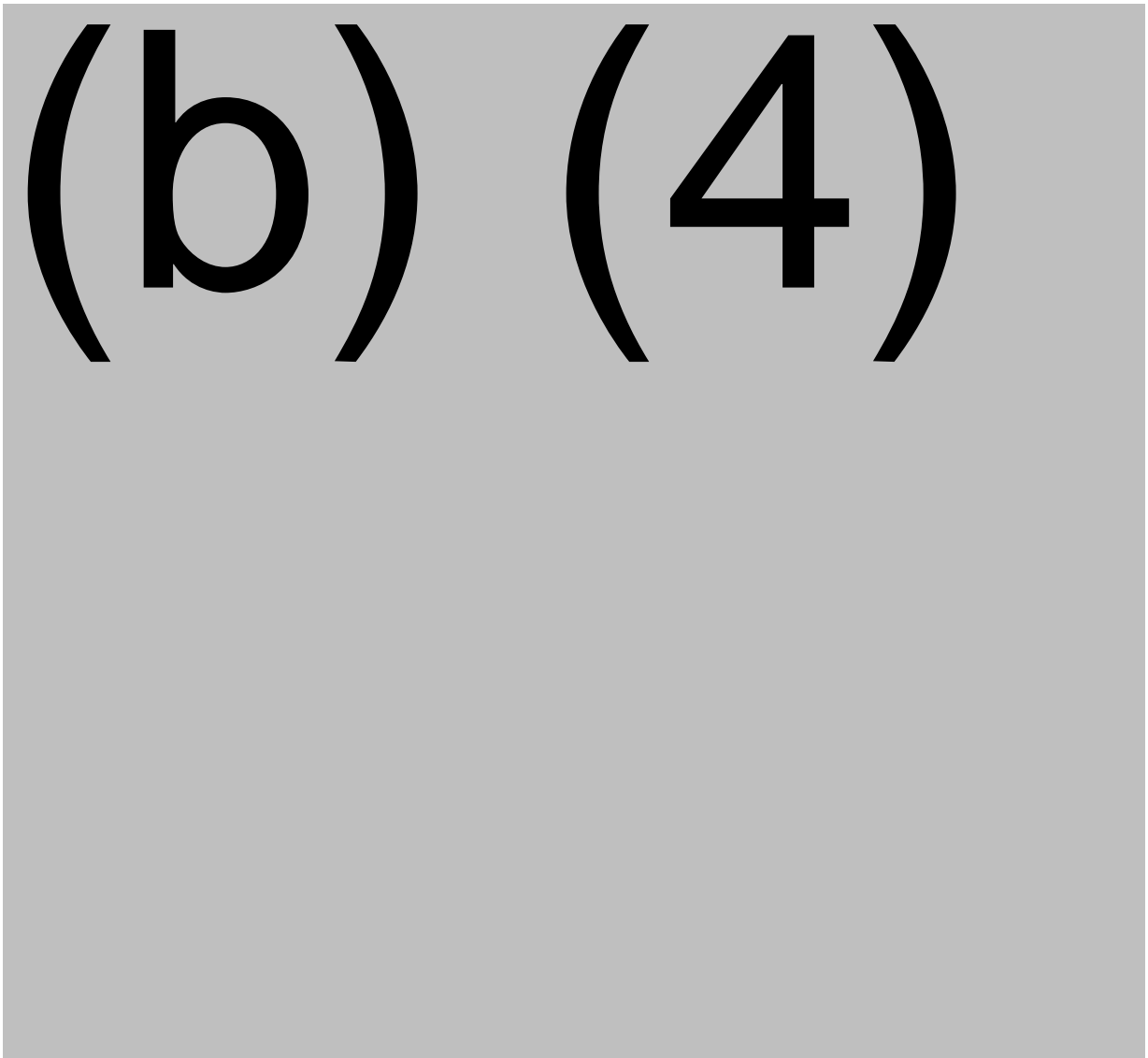
Administrative IT: The (b) (4) in Data Processing) system is used as the administrative IT. The system oversees packaging orders, warehousing, tracking, inventory control, and quality management at (b) (4) The (b) (4) system allows the administration of material quantity and status (in stock / released / blocked). Any retrieval of packaging materials, medical devices, semi-finished bulk products, and finished products for packaging is also controlled by the (b) (4)

- **Validation:** Computer validation is performed as part of the equipment qualification where the software and automation hardware are integral components. The computer system functions were validated with the mechanical functions of the respective equipment.

Reviewer's comment: *The firm only submitted information regarding computer systems to the utility section of the submission. This is acceptable as the activities conducted at (b) (4) for the subject BLA appear relevant to just the computer systems utility. The computer system is validated and appears acceptable.*

Equipment

The major equipment used for integrity testing, visual inspection, labeling, and packaging and their qualification status are described in the section below.



(b) (4)

Reviewer's comment: *The firm stated that all equipment used in manufacturing at (b) (4) have been qualified and are currently in use for the manufacture of other FDA approved products. The implemented list of equipment appears acceptable.*

(b) (4) **FACILITY OVERVIEW**
The WFI diluent is filled into glass vials at a volume of 20 mL or 40 mL into (b) (4) colorless glass vials 20 mL or 50 mL, respectively, and (b) (4) sterilized. (b) (4) (b) (4) is dedicated to the manufacture of parenteral products, with (b) (4) (b) (4) production area for sterile manufacturing and packaging.

(b) (4)

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

3.2.R REGIONAL INFORMATION

Combination Product

Reviewer's comment: *While Octapharma did not provide details regarding the purchasing controls and Corrective and Preventive Action (CAPA) for their combination product, this is acceptable as the manufacturing facilities have acceptable compliance histories with the FDA. The scope of the previous FDA inspections of the facilities have included the materials system, which include purchasing controls (e.g., supplier evaluation process, type/extent of control over suppliers, record maintenance of suppliers) and CAPAs. The design controls, including the risk analysis, is deferred to OTP.*