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

Chemistry, Manufacturing and Controls (CMC) Review Memorandum

To: File of STN 125612/0
Thomas Maruna, Regulatory Officer, RPMB II/DRPM/OTAT

From: Ze Peng, PhD, HB/DPPT/OTAT

Through: Tim Lee, PhD, Acting Chief, HB/DPPT/OTAT

Basil Golding, MD, Director, DPPT/OTAT

Subject: Final review of CMC information in Octapharma's BLA for Fibrinogen (Human)

Executive Summary

This memorandum summarizes the review of CMC information in an original Biologics License Application (BLA) under STN 125612/0 submitted by Octapharma for Fibrinogen (Human). Its proprietary name is Fibryna. The proposed indication of this product is for the treatment of acute bleeding episodes in adults and adolescents with congenital fibrinogen deficiency, including afibrinogenemia and hyperfibrinogenemia.

The manufacturing process, its in-process controls, and the specifications used to control the quality of Fibryna are adequately validated and sufficiently justified to ensure the consistency of the manufacture of a product that will meet the standards of all quality attributes. The safety of adventitious agents is well demonstrated through the controls of the manufacturing process of Fibryna, 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). Enveloped viruses are inactivated by S/D treatment and then removed by the 20-nm nanofilter, whereas non-enveloped viruses are removed by the 20-nm nanofilter. The measures taken by Octapharma to control other adventitious agents in the manufacture of Fibryna are also acceptable. As described in detail below, we found the CMC information provided in the BLA and Octapharma's responses to our information requests (IRs) sufficient to support the identity, quality, purity, safety, and potency of the product for the proposed indication; therefore, we recommend approval of the BLA.

Background

Fibrinogen (Human) is manufactured in Octapharma's facility in Vienna, Austria. It is a sterile, purified, virus inactivated, and nanofiltered fibrinogen concentrate made from pooled U.S.

human (b) (4) Plasma. The proposed proprietary name, Fibryna, is found acceptable based on the review by Dr. Oluchi Elewachi in the Advertising and Promotional Labeling Branch. Fibryna is supplied as a lyophilized powder for reconstitution with sterile Water for Injection (sWFI), and is administered intravenously. Fibryna is offered only in one dosage strength, i.e., approximately 1 g per glass container.

Fibryna has not been approved in any country so far. Currently, there is another human fibrinogen product licensed in the U.S. for the treatment of congenital fibrinogen deficiency – RiaSTAP® manufactured by CSL Behring. Fibryna will be the second member in this product class in the U.S. for adults and adolescents with congenital fibrinogen deficiency, including afibrinogenemia and hypofibrinogenemia.

Summary of Review

The manufacture of Fibryna starting from U.S. human Source 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

DRUG SUBSTANCE

1. Flow chart of the manufacturing process

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(b) (4)

(b) (4)

(b) (4)

DRUG PRODUCT

1. *Description and Composition of the Fibryna drug product*

   Fibryna is a human plasma-derived, sterile, purified, virus inactivated and nanofiltered fibrinogen concentrate, supplied as a lyophilized powder for reconstitution for intravenous injection. The reconstituted product contains the following excipients and stabilizers: sodium chloride, sodium citrate dihydrate, glycine, and L-arginine hydrochloride.

   Fibryna is supplied in a package with a single-dose glass container of powder together with a transfer device Octajet and a particle filter, which are used to allow for the transfer of the diluent into the Fibryna container for reconstitution. (b) (4) When reconstituted with 50 mL sWFI (not provided in the

kit), the final solution contains the following excipients and/or stabilizers in targeted amounts per container:

Composition

Ingredient	Amount	Function	Standard
Human fibrinogen	20 mg/mL	(b) (4)	
Sodium chloride	6 mg/mL	(b) (4)	(b) (4)
Sodium citrate dihydrate	1.5 mg/mL	(b) (4)	(b) (4)
Glycine	10 mg/mL	(b) (4)	(b) (4)
L-arginine hydrochloride	10 mg/mL	(b) (4)	(b) (4)

2. *A brief description of the manufacturing process*

1) Aseptic filling
2) Freeze-drying
3) Visual inspection
4) Labeling and packaging
5) Drug product

Prior to filling, (b) (4) , and then filled into (b) (4) , sterilized (b) (4) glass containers on (b) (4) . The nominal filled volume is 50 mL per container. After the containers are filled and partially stoppered, the product is lyophilized using (b) (4) , and the containers are sealed in the lyophilizer by (b) (4) . The caps are crimped onto the sealed containers, which are tested the presence of (b) (4), and subjected to visual inspection, labeled, and boxed.

3. *In-process control*

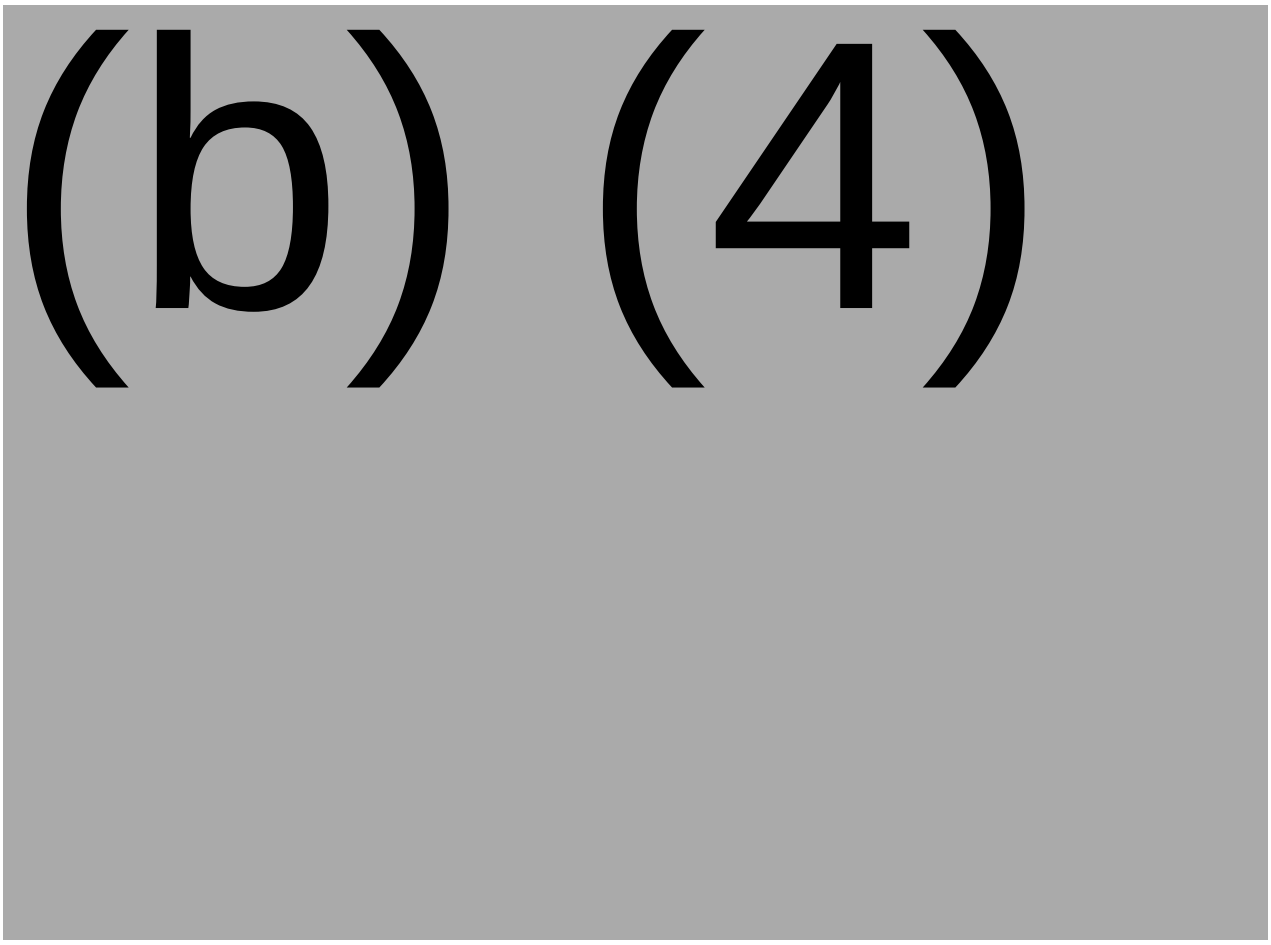
(b) (4)

4. *Process validation and/or evaluation*

We defer the comments on the container closure system, lyophilization, media fill, and shipping validation to our DMPQ colleagues.

To demonstrate the consistency of the filling process (b) (4)

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



Product reviewer's comment: In general, Octapharma conducted various validation studies regarding the manufacturing process of the Fibryna FDP. Process and quality controls for conformance batch manufacture complied with prospectively defined acceptance criteria for successful process validation except for the OOS result of fibrinogen for the DP batch (b) (4) at the step of (b) (4) (see the result highlighted in red on the above table). Although Octapharma conducted an investigation (Deviation report No. 34913), they still cannot identify the root cause for this OOS result. Considering that the result of the parameter for this batch met the acceptance criterion in the final container, we agree with Octapharma that this deviation has no significant impact on the product quality.

Again, these data indicate that the minimum and maximum process times for the steps including aseptic filling and freeze-drying do not have a significant impact on the product quality.

5. *Control of excipients*

Sodium chloride, sodium citrate dehydrate, glycine, and L-Arginine hydrochloride serve as excipients in Fibryna. The excipients in the manufacture of Fibryna comply with the requirements of current (b) (4) . Octapharma performs an identity test for each excipient other than the tests performed by the respective manufacturer. 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 Fibryna final drug product

Product quality attribute	Specification	Justification
Characters	A white or pale yellow, hygroscopic powder or friable solid	(b) (4).
(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
Solubility	The preparation dissolved within (b) (4) minutes at 20 – 25°C; the reconstituted solution is almost colorless and slightly opalescent	(b) (4)
Stability of solution	(b) (4)	(b) (4)
Water	(b) (4)	(b) (4)
Sterility	No growth or no growth detected	(b) (4)
Endotoxin	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	
Fibrinogen	(b) (4)	(b) (4)
Glycine	(b) (4)	(b) (4)
Citrate	(b) (4)	(b) (4)
Chloride	(b) (4)	(b) (4)
L-Arginine HCl	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)

Product reviewer's comment: General safety test was included in the release specifications of Fibryna FDP when Octapharma submitted this BLA on 9 June 2016. However, they decided to remove this test from the release specification of Fibryna FDP as mentioned in the amendment dated 16 January 2017. Considering that general safety test is no longer required according to the FDA regulation (21 CFR Parts 601, 610, and 680) published on 2 July 2015, we agree with Octapharma to remove this test from the release specification of Fibryna FDP.

We asked Octapharma to revise the limit of Water in the release specification of final drug product from (b) (4). They agreed with us for this modification in the amendment dated 24 November 2016, and this change was reflected in the amendment dated 16 January 2017.

To control the (b) (4) purity of Fibryna FDP, we asked Octapharma to include (b) (4) in the release specifications of Fibryna FDP. Also, we asked them to include the testing of (b) (4), a process-related impurity, and its acceptance criterion in the release specifications.

These IR items were sent to Octapharma on 15 December 2016, and they responded in an amendment on 3 January 2017. Their responses are summarized as follows:

Octapharma's response: (b) (4)

(b) (4)

(b) (4) are only qualitative test methods, and to establish a limit for these two methods for release is not possible. Additionally, there is no international Fibrinogen standard for quantitation of the (b) (4) available.

The monograph (b) (4) requests (b) (4) and stability of solution as (b) (4) parameters instead of (b) (4). Stability of solution performed according to this monograph showed that there was (b) (4) are present. Furthermore, (b) (4) is tested as release parameter to demonstrate purity (b) (4) of the final product. Stability after reconstitution and (b) (4) are therefore deemed more suitable to prove (b) (4) purity of Fibryna FDP.

Product reviewer's comment: This response is acceptable.

Octapharma's response: (b) (4)

(b) (4)

Product reviewer's comment: The level of (b) (4) in Fibryna final container is much lower in comparison to that in the licensed product of (b) (4). The volume of (b) (4) used can be similar to that of Fibryna. Together with the clinical experience for the use of (b) (4), this response is acceptable.

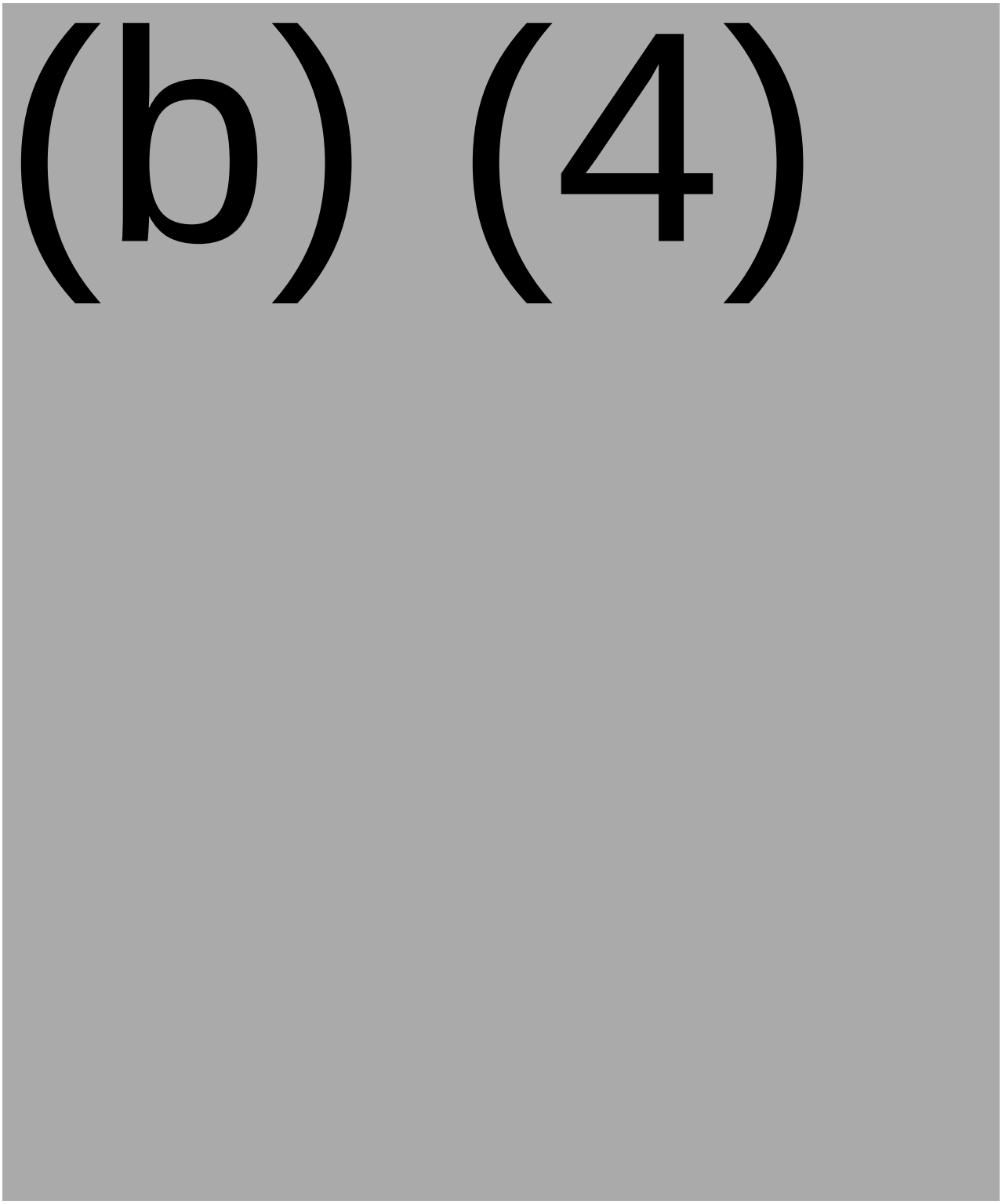
2) Analytical procedures for Fibryna final drug product

- Practicability and organoleptic properties (130SOP006/07): Appearance (Characters) and Dissolution time (Solubility)
- (b) (4)
- (b) (4) : Determined by (b) (4)
- Water (b) (4)
- Sterility (131SOP120/04): (b) (4) method in accordance with (b) (4)
- Endotoxin (130SOP162/03): (b) (4) assay in accordance with (b) (4)
- (b) (4)
- (b) (4)
- Fibrinogen (130SOP111/07): (b) (4) assay)
- Glycine (130SOP161/03): Determination of glycine using a (b) (4)
- L-Arginine (130SOP160/03): Determination of L-Arginine using a (b) (4)
- Citrate (130SOP032/05): Citrate determined using (b) (4)
- Chloride (130SOP131/07): Determination of chloride by (b) (4)
- (b) (4)
- (b) (4)

All the aforementioned test methods have been validated as shown in the relevant validation reports. Please refer to the review memos from our DBSQC colleagues, who considered the data are sufficient, e.g., the method validation data on (b) (4) in the following table are complete and sufficient. Therefore, these test methods are acceptable for the use in the release testing of the Fibryna final drug product.

Method validation on the determination of (b) (4) in Fibryna final drug product

Parameters	Acceptance criteria	Results	Evaluation



3) Batch analysis

Certificates of analysis for (b) (4) conformance batches manufactured at full-scale are included in the BLA. The release test results of these batches are listed as follows:

Process control parameter	Acceptance criteria	Conformance DP batches
Character	A white or pale yellow, hygroscopic powder or friable solid	(b) (4)
(b) (4)	(b) (4)	
Solubility	The preparation dissolves within (b) (4) mins at 20 – 25 C. The reconstituted solution is almost colorless or slightly opalescent	
Stability of solution (20 – 25 C)	(b) (4)	
Water	(b) (4)	
Sterile	Sterile	
Endotoxin	(b) (4)	
General safety	Complies	
(b) (4)	(b) (4)	
(b) (4)	(b) (4)	
(b) (4)	(b) (4)	
Fibrinogen	(b) (4)	
Glycine	(b) (4)	
Citrate	(b) (4)	
Chloride	(b) (4)	
L-Arginine HCl	(b) (4)	
(b) (4)	(b) (4)	
(b) (4)	(b) (4)	

As the table shown above, the results of these conformance batches met the current release specifications of Fibryna FDP (Specification No. 013FPS347/04/US). Thus, these data support the validation of the commercial manufacturing process of Fibryna for the proposed U.S. market.

4) Impurity

The impurity profile of Fibryna FDP is described in Report No. *020STD34x.312/00*. The product-related impurities include accompanying plasma proteins, (b) (4)

These impurities were found either in detectable but

small amounts or below the detection limits of the assays in the final drug product. The process-related impurities include (b) (4) Again, these impurities were found either in detectable but small amounts or below the detection limits of the assays in the Fibryna FDP.

Product reviewer's comment: In general, the product-related and process-related impurities are well controlled in the manufacture of Fibryna based on this study. However, we needed Octapharma to clarify the following discrepancy:

On Table 4 in this report, the levels of (b) (4) in either the clinical batches or the conformance batches of Fibryna FDP were (b) (4), whereas on Page 14 of the same report, Octapharma stated that the test results of (b) (4) in these batches were (b) (4).

This IR was sent to Octapharma on 10 November 2016, and they responded in an amendment on 24 November 2016. Their response is summarized as follows:

Octapharma's response: µg/mL used in the acceptance criterion for (b) (4) on Table 4 is typographical error. The correct unit used for the quantification of this impurity in Fibryna FDP is µg/L.

Product reviewer's comment: This response is acceptable.

7. *Reference standards*

The reference standard for testing of Fibrinogen using (b) (4) assay is calibrated against the (b) (4) for fibrinogen in plasma, human ((b) (4)). Therefore, it is acceptable. For (b) (4), no reference standard is required, which is consistent with the procedure described in (b) (4). It is acceptable.

8. *Container closure system*

The container closure system for Fibryna consists of a single-dose glass container, and a rubber stopper sealed with an aluminum flip off cap. The single-dose glass container with a nominal size of 100 mL meets the requirements for (b) (4) glass in accordance with the (b) (4). The glass container is closed with (b) (4) rubber stopper (32 mm) and this type of stopper 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.

The available data from the stability studies (No. 14P012 and 14P013) demonstrated the container closure integrity through (b) (4) test. These two reports are ongoing.

Product reviewer's comment: We defer the comments on the container closure system to Dr. Randa Melhem from DMPQ, and the review of the extractables and leachables data on the container closure system to Dr. Ying Huang from DCEPT.

9. Combination product

One container of lyophilized human fibrinogen is packaged with a reconstitution device set (i.e., Octajet, a reconstitution device, and a particle filter ((b) (4))) in each carton box. Therefore, we consider Fibryna a combination product, co-packaged after we confirmed with CBER management, Dr. Sherry Lard and Dr. Patricia Love.

Octapharma provided two compatibility studies for the devices used in the combination product. The compatibility study for Octajet with human fibrinogen indicates that no absorbance of the active ingredient was detected when Octajet was used. The compatibility study also indicates that the data for the (b) (4) particle filter (with human fibrinogen are comparable to those for the (b) (4) . Therefore, the data from the compatibility studies demonstrated that the use of this reconstitution device set does not have significantly adverse impact on the quality of Fibryna.

The (b) (4) particle filter is manufactured by (b) (4) , and is cleared under 510(k) No. (b) (4) . Octajet, a single-use disposable transfer device is manufactured by (b) (4) . Per the advice from CBER management, we consulted with Drs. Sapana Patel and Rakhi M. Dalal from CDRH for the evaluation of the device components of this combination product, including human factors studies. Please refer to the review memos from Drs. Sapana Patel and Rakhi Dalal for their reviews of data to support the use of the reconstitution device set in this combination product.

10. Stability

1) Batches tested

The (b) (4) conformance DP batches manufactured for process validation are included in stability studies No. 14P012 and 14P013.

Batch No.	Dosage form/filling size	Manufacturing date	Batch size
(b) (4)			

2) Stability protocol

Storage at 5 ± 3°C or 25 ± 2°C/(b) (4)

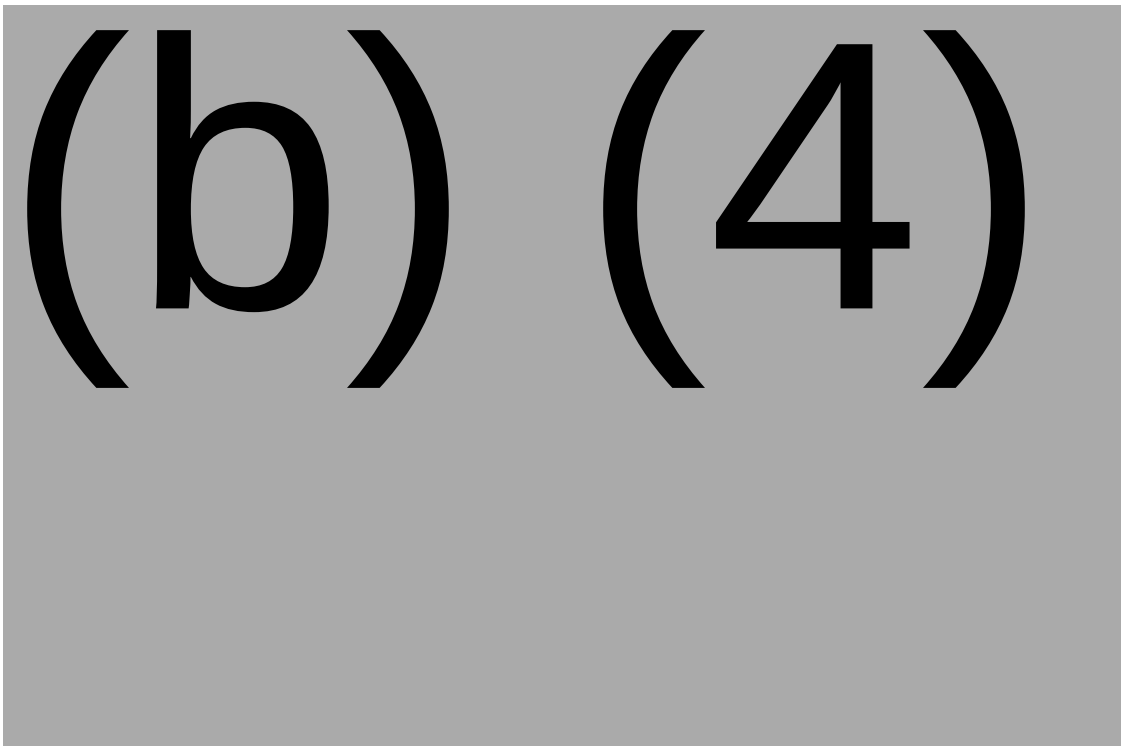
Parameter	Specification	Storage time (months)							
		0	3	6	9	12	18	24	(b) (4)

Characters	A white or pale yellow, hygroscopic powder or friable solid	X	X	X	X	X	X	X	(b) (4)
Solubility	The preparation dissolves within (b) (4) mins at 20 – 25 C. The reconstituted solution is almost colorless or slightly opalescent	X	X	X	X	X	X	X	
Stability of solution (20 – 25 C)	(b) (4)	X	X	X	X	X	X	X	
Water	(b) (4)	X	NT	X	NT	X	X	X	
(b) (4)	(b) (4)	X	X	X	X	X	X	X	
(b) (4)	(b) (4)	X	NT	NT	NT	X	NT	X	
(b) (4)	(b) (4)	X	X	X	X	X	X	X	
Fibrinogen	(b) (4)	X	X	X	X	X	X	X	
(b) (4)	(b) (4)	X	NT	NT	NT	X	NT	X	
(b) (4)	(b) (4)	X	NT	NT	NT	X	NT	X	
Glycine	(b) (4)	X	NT	NT	NT	X	NT	X	
Citrate	(b) (4)	X	NT	NT	NT	X	NT	X	
Chloride	(b) (4)	X	NT	NT	NT	X	NT	X	
L-Arginine hydrochloride	(b) (4)	X	NT	NT	NT	X	NT	X	
Sterile	Sterile	X	NT	NT	NT	NT	NT	X	
Endotoxin	(b) (4)	X	NT	NT	NT	NT	NT	X	
General safety	Complies	X	NT	NT	NT	NT	NT	X	
Pyrogens	Pyrogen free	X	NT	NT	NT	NT	NT	X	
(b) (4)	For information	X	X	X	X	X	X	X	
Particulate contamination (b) (4)	(b) (4)	X	NT	NT	NT	X	NT	X	

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

(b) (4)

(b) (4)



Stability after reconstitution (Storage at 25°C/(b) (4) for up to (b) (4) months)

Parameter	Specification	Previous storage at 25°C (b) (4)		
		0 month	24 months	(b) (4) months
		Storage period (hours) at 25°C		
		0, 4, (b) (4)	0, 4, (b) (4)	0, 4, (b) (4)
Visual	The solution is almost colorless and slightly opalescent	X	X	X
Fibrinogen	(b) (4)	X	X	X
(b) (4)	No remarkable changes	X	X	X

X: Tested

Product reviewer's comment: The parameters selected in the stability protocol are sufficient, and the acceptance criteria are consistent with those from the release specification of Fibryna DP for the proposed U.S. market. Therefore, it is acceptable for Octapharma to use these parameters to monitor Fibryna stability over time.

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

- Stability study No. 14P012

  The (b) (4) conformance batches manufactured using the Planova 20N nanofilter are investigated in the stability study No. 14P-012. The test results for long-term storage at 2 – 8°C, 25°C/(b) (4), and (b) (4) are available for up to (b) (4). All results met the specifications to date. Under accelerated conditions of (b) (4), all results from these (b) (4) batches met the specifications for up to (b) (4). The stability of Fibryna FDP was tested for up to (b) (4) hours after reconstitution at the

starting time-point (0 month) of the long-term storage condition (25°C/(b) (4)). All results are within the specifications.

- Stability study No. 14P013

  The (b) (4) conformance batches manufactured using the Pegasus SV4 nanofilter are investigated in the stability study No. 14P-013. The test results for long-term storage at 2 – 8°C, 25°C/(b) (4), and (b) (4) are available for up to (b) (4). All results met the specifications to date. Under accelerated condition of (b) (4), all results from these (b) (4) batches met the specifications for up to (b) (4). The stability of Fibryna DP was tested for up to (b) (4) hours after reconstitution at the starting time-point (0 month) of the long-term storage condition ((b) (4)). All results are within the specifications.

- Stability study No. 11P023

  Additionally, Octapharma performed a stability study (study No. 11P023) on (b) (4) clinical DP batches. Regarding these batches, the (b) (4) was produced in the same facility as those for the conformance batches, but the DP was manufactured at Octapharma's (b) (4). The stability protocols used are the same as those for the conformance batches. All the test results from the (b) (4) batches (batches (b) (4)) were within the acceptance criteria for up to (b) (4) months under long-term storage conditions. The test results of these batches also met the acceptance criteria when stored at (b) (4).

Product reviewers' comment: The available stability data for the conformance batches (Studies No. 14P012 and 14P013) indicate that no critical trends are detected during the observed long-term storage period. Although the data from the stability study No. 11P023 are available for up to (b) (4) months, the facility where the DP batches was manufactured is different from that for the proposed commercial process. To support the proposed shelf-life of 24 months at 2°C ~ 25°C/(b) (4), we needed to request additional stability data from the ongoing stability studies No. 14P012 and 14P013.

This comment was sent to Octapharma on 10 November 2016. They responded in an amendment on 24 November 2016, in which they provided long-term stability data for up to 18 months for all (b) (4) conformance batches (2 – 8°C and 25°C/(b) (4)). All the results from these batches met the acceptance criteria for up to 18 months at 25°C/(b) (4). Again, as shown below, there are no significant trends detectable under both the long-term (25°C) and accelerated storage conditions:

Long-term storage condition at 2 – 8°C

Conformance DP batches	Storage time (months)					
	0	3	6	9	12	18
	(b) (4)					
Batches produced using Planova 20N nanofilters	(b) (4)					

Batches produced using Pegasus SV4 nanofilters	(b) (4)					

Long-term storage condition at 25°C/(b) (4)

Conformance batches	Storage time (months)					
	0	3	6	9	12	18
	(b) (4)					
Batches produced using Planova 20N nanofilters	(b) (4)					
Batches produced using Pegasus SV4 nanofilters	(b) (4)					

Accelerated storage condition at (b) (4)

(b) (4)

Based on the results of these stability studies, Octapharma proposed a shelf-life of 24 months for Fibryna FDP when stored at 2 – 25°C. (b) (4) .

Product reviewer's comment: The shelf-life of the Fibryna FDP is mainly dependent on the stability data generated from the conformance DP batches, which are available for up to 18 months under the long-term conditions. Considering that the manufacturing processes between the referenced clinical batches and the conformance batches are similar, the stability data derived from the referenced clinical batches can be used to support the shelf-life of Fibryna FDP. Taken together, these data support the proposed 24 months shelf-life when stored at 2°C ~ 25°C/(b) (4) for Fibryna. However, in the negotiation of labeling in the package insert, Octapharma requested a shelf-life of (b) (4) months. Based on the ICH Guideline, we considered a compromise of 30 months to be reasonable, which was accepted by Octapharma in their amendment dated 6 June 2017.

Fibryna does not contain any preservative. 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. Thus, we suggest the storage period after reconstitution be limited to 4 hours, not (b) (4) hours in our IR dated 26 May 2017. Octapharma agreed with us in the amendment dated 31 May 2017. Therefore, their response related to the storage period after reconstitution is acceptable.

11. Virus safety

The following three principle complementary approaches are applied to control viral safety in Fibryna 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 Fibryna for the U.S. market. Each donation is tested for the absence of HBsAg, antibodies against Hepatitis C Virus (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 pool for fractionation for the absence of contaminating infectious viruses*

   Octapharma did not provide complete information on the viral tests performed on the plasma pools for fractionation. To further evaluate the viral safety profile related to the manufacturing of Fibryna, we asked Octapharma to summarize all the viral tests performed on donors, mini-pools, and manufacturing plasma pools in an IR dated 10 November 2016. They submitted their response in an amendment dated 24 November 2016. Their response is summarized as follows:

   Octapharma's response: The tests performed on the donors are the same as those provided in the original BLA. In addition, in accordance with revisions in 21 CFR 610.40 in April 2016, the Syphilis test has also been included. Each mini-pool ((b) (4) donors) will be tested for Hepatitis A Virus (HAV) RNA, Hepatitis B Virus (HBV) DNA, HCV RNA, HIV-1 RNA, and human parvovirus B19 (B19V) DNA using the respective nucleic acid amplification technique (NAT) assay. The acceptance criterion for B19V is $\leq 10^3$ IU/mL; and negative for the other viruses. For the manufacturing pools, (b) (4) .

   Product reviewer's comment: The viral tests performed in the plasma pools, including the mini-pools and the 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 Fibryna manufacturing process were validated for the capacity to inactivate and/or remove viruses*

   Viral clearance studies:

   Regarding viral clearance, two dedicated steps are included in the manufacturing process of Fibryna, which are S/D treatment ((b) (4)), and 20-nm nanofiltration using either Planova 20N or Pegasus SV4. The enveloped viruses selected in these studies include relevant virus HIV-1; Pseudorabies

Virus (PRV, model for enveloped DNA viruses including HBV); and Bovine Viral Diarrhea Virus (BVDV, model virus for enveloped RNA viruses). The non-enveloped viruses selected in the studies include relevant virus HAV; and Porcine Parvovirus (PPV, model virus for B19V). These viruses resemble viruses which may contaminate the Fibryna DP, and represent a wide range of physico-chemical properties that tests the ability of the manufacturing process to clear viruses. Virus inactivation and/or removal by the respective step(s) were tested at least twice.

S/D treatment

To evaluate the capacity of S/D treatment to clear viruses, Octapharma validated the down-scale system (*Study No. 020STD34x_.062/00*). The relevance of the down-scale study to the full-scale process was demonstrated by the determination of a broad set of process parameters. The data support the qualification of the system scaled down to (b) (4) . Thus, the viral clearance data derived from the down-scale system appear to be appropriate to be used for evaluating the viral clearance capacity of the S/D treatment conditions at full scale.

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

(b) (4)

(b) (4)

Product reviewer's comment: These results indicate an incomplete inactivation of (b) (4) under the referenced robustness conditions. Considering the viral clearance capacity of nanofiltration as described below, all enveloped viruses are still well controlled in the manufacture of Fibryna.

20 nm viral filtration

The Planova 20N nanofiltration step is executed through a (b) (4)

The Pegasus SV4 nanofiltration step is executed through a (b) (4) test, which Octapharma had confirmed in the amendment dated 24 November 2016.

To evaluate the capacity of nanofiltration to clear viruses, Octapharma validated each down-scale system used for the two types of nanofiltration step. The Planova 20N viral filtration step was validated at down-scale ((b) (4)) in a validation study (Study No. *020STD346.212/00*). The parameters used at both full scale and down scale are listed as follows:

(b) (4)

The Pegasus SV4 viral filtration step was validated at down-scale ((b) (4)) in a validation study (Study No. *020STD346.211/00*). The parameters used at both full scale and down scale are listed as follows:

(b) (4)

(b) (4)

(b) (4)

Planova 20N nanofiltration

(b) (4)

Pegasus SV4 nanofiltration

(b) (4)

(b) (4)

Product reviewer's comment: These data showed that no infectivity was detected after nanofiltration for HIV-1, PRV, BVDV, and HAV viruses. Nanofiltration could achieve at least 4.53 $\log_{10}$ of PPV reduction although Octapharma did not use an (b) (4) assay in the viral clearance studies on PPV. Octapharma also performed robustness studies on BVDV and PPV, the most challenging enveloped and non-enveloped viruses in the tested viruses. They tested the viral clearance capacity of nanofiltration under a variety of conditions: (b) (4) These studies indicate that there are no substantial differences for the level of removal of all the tested viruses. Thus, nanofiltration (either using Planova 20N or Pegasus SV4) can be considered to be an effective step for the removal of these enveloped and non-enveloped viruses.

Virus reduction claimed

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

Overall virus reduction factors ($\log_{10}$) for inactivation/removal of various viruses achieved by the Fibryna manufacturing process

Manufacturing step	Virus reduction factor ($\log_{10}$)				
	Enveloped viruses			Non-enveloped viruses	
	HIV-1	PRV	BVDV	HAV	PPV
S/D treatment ((b) (4)) at (b) (4)	≥ 5.15	≥ 6.57	≥ 5.80	n.d.	n.d.
Planova 20N nanofiltration	≥ 4.19	≥ 6.64	≥ 4.85	≥ 5.21	5.25
Overall log reduction factors	≥ 9.34	≥ 13.21	≥ 10.65	≥ 5.21	5.25
S/D treatment ((b) (4)) at (b) (4)	≥ 5.15	≥ 6.57	≥ 5.80	n.d.	n.d.
Pegasus SV4 nanofiltration	≥ 3.89	≥ 6.34	≥ 4.97	≥ 5.21	4.53
Total log reduction factors	≥ 9.04	≥ 12.91	≥ 10.77	≥ 5.21	4.53

n.d.: Not determined

Product reviewers' comment: As described above, S/D treatment proves effective in inactivating these enveloped viruses. The data also confirmed that 20 nm nanofiltration

is a critical step for the removal of both enveloped and non-enveloped viruses. Additionally, (b) (4) steps may contribute to clearance of both enveloped and non-enveloped viruses although Octapharma did not validate these steps. The viral safety in the manufacturing process is mainly validated through these two dedicated viral clearance steps in addition to the control of the potential virus loading in the manufacturing plasma pool.

12. Transmissible spongiform encephalopathy agent safety

To minimize the risk of transmissible spongiform encephalopathy (TSE) agent (i.e., prion) transmission, donors who are potentially at risk are excluded from plasma donation as specified in the current FDA guidance regarding donations collected in the U.S. Additionally, Octapharma performed TSE agent validation studies regarding the following Fibryna manufacturing steps at down scale:

- (b) (4)
- Nanofiltration (Planova 20N and Pegasus SV4)

Octapharma assessed the capacities of TSE agent removal at the referenced manufacturing steps using (b) (4) in down-scale studies. However, I consider these TSE agent clearance studies inadequate because of the following two reasons:

- Octapharma did not provide data generated from animal infectivity assays, which is the gold standard for the determination of prion infectivity.
- The sensitivity of (b) (4) used is considered to be relatively low.

Considering that Octapharma does not claim TSE agent clearance in the label and there is no requirement for TSE clearance for this class of products, it is not a review issue at this time.

LABELING

For the drafted Prescribing Information (PI), we asked Octapharma to make the following revisions in our IR dated 26 May 2017:

a. Multiple edits were made regarding Section 2.2 "*Preparation and Handling*", Section 5.3 "Transmissible Infectious Agents", and Section 11 "*Description*".

b. Regarding Section 16 "*How supplied/storage and handling*", please add "<u>How Supplied</u>" above Fibryna is supplied in a single-use container; please replace the content under the subtitle "Shelf life" with the following description:

   <u>Storage and Handling</u>

   - Store Fibryna for up to 24 months at 2°C to 25°C (36°F to 77°F) from the date of manufacture.
   - Do not use Fibryna beyond the expiration date on the carton or contain label.

- Do not freeze. Store in the original container to protect from light.
- After reconstitution, do not refrigerate or freeze the Fibryna solution. Use the reconstituted solution immediately or within 4 hours after reconstitution.
- Dispose of any unused product or waste material in accordance with local requirements.

c. Accordingly, please also revise the carton and vial labels to include the associated label changes recommended by the FDA. The actual potency of fibrinogen in mg is stated on each Fibryna carton and container.

They submitted their responses on 31 May 2017, in which they fully agreed with our requests except for the shelf-life of 24 months for the drug product. In this amendment, Octapharma requested a shelf-life of (b) (4) months. Based on the ICH Guideline, we considered an extrapolation of the available data to a shelf-life of 30 months to be reasonable. Octapharma accepted a shelf-life of 30 months for the drug product in the amendment dated 6 June 2017. Additionally, the relevant PI, carton, and vial labels were updated accordingly. Therefore, their responses are acceptable.

Recommendation

The manufacturing process, its in-process controls, and the specifications used to control the quality of Fibryna are adequately validated and sufficiently justified to ensure consistency of the manufacture of the product that will meet the standards of all quality attributes. The safety of adventitious agents is well demonstrated through the controls of the manufacturing process of Fibryna, 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). Enveloped viruses are inactivated by S/D treatment and then removed by the 20-nm nanofilter, whereas non-enveloped viruses are removed by the 20-nm nanofilter. The measures taken by Octapharma to control other adventitious agents in the manufacture of Fibryna 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.