# Summary Basis for Regulatory Action

**Date:**

**From:** Alexey Khrenov, PhD, Chair of the Review Committee

***BLA*:** STN 125660/0

**Applicant Name:** Octapharma Pharmazeutika Produktionsges.m.b.H

**Date of Submission:** July 31, 2017

**Goal Date:** May 31, 2018

**Proprietary Name/Established Name:**
Plasma Cryoprecipitate (For Further Manufacturing Use)

**Indication: N/A**

**Recommended Action:**
The Review Committee recommends approval of this BLA.

**Review Office(s) Signatory Authority:** Wilson Bryan, MD, Director, Office of Tissues and Advanced Therapies

☐ **I concur with the summary review.**

☐ **I concur with the summary review and include a separate review to add further analysis.**

☐ **I do not concur with the summary review and include a separate review.**

The table below indicates the material reviewed when developing the SBRA

| **Discipline Reviewed** | **Reviewer** |
|---|---|
| **CMC**<br>• *Product Quality (OTAT/DPPT)*<br>• *Facilities (OCBQ/DMPQ)* | Alexey Khrenov<br>Chad Burger |

## 1. INTRODUCTION

Octapharma Pharmazeutika Produktionsges.m.b.H (Octapharma) located in Vienna, Austria, submitted an original Biologics License Application (BLA) for licensure of Plasma Cryoprecipitate (For Further Manufacturing Use) (Cryoprecipitate (FFMU)). The product is not intended for direct administration into humans, but is for further manufacture into a licensed final drug product. It is intended to be used as the starting material for the (b) (4) component of (b) (4) manufactured by (b) (4) licensed under (b) (4).

(b) (4) submitted a Prior Approval Supplement (PAS) under STN (b) (4), to request the use of the Octapharma Cryoprecipitate (FFMU) as an alternative starting material for (b) (4). The PAS was submitted concurrently with this BLA on (b) (4) and received a Complete Response (CR) Letter because the review of this BLA was not completed by the action due date of the PAS. (b) (4) has recently submitted a response to the CR Letter, and the approval of both submissions will be coordinated.

Cryoprecipitate is manufactured as an intermediate for Octapharma's US licensed product (b) (4) The manufacturing process of Cryoprecipitate (FFMU) and the cryoprecipitate used for (b) (4) are identical.

Cryoprecipitate (FFMU) is manufactured by an already licensed process, and Octapharma has provided sufficient data and information to support its licensure. Hence, the Review Committee recommends approval of this BLA.

## 2. BACKGROUND

Cryoprecipitate is the insoluble proportion of human plasma, which contains proteins precipitated at low temperature. It contains most of plasma-derived Factor (F) VIII and von Willebrand Factor (vWF), and is commonly used for the production of FVIII and vWF concentrates. It is also suitable to produce fibrinogen.

The starting material, human plasma, used in the manufacture of Cryoprecipitate (FFMU) is obtained from U.S. based plasmapheresis centers and community blood banks. All donations used by Octapharma comply with the requirements of 21 CFR 640.30 and 21 CFR 640.60. The plasma pool is processed to obtain Cryoprecipitate (FFMU), that could directly be manufactured into final product, or frozen immediately and stored until further use.

The manufacturing process is performed at the Octapharma facility in Vienna, Austria. All in-process control (IPC) testing is carried out by the Octapharma laboratories in Vienna, Austria, except for nucleic acid testing (NAT) for viral markers in the plasma pool, which is performed by the Octapharma laboratories in either Frankfurt, Germany or Stockholm, Sweden.

## 3. CHEMISTRY, MANUFACTURING AND CONTROLS (CMC)

### a) Product Quality

Description of Manufacturing Process
Each batch of Cryoprecipitate (FFMU) is manufactured from (b) (4)

In-process controls
(b) (4)

**Table 1. In-Process control test methods and acceptance criteria**

(b) (4)

Process Validation
The process was validated previously for the manufacture of (b) (4) with the latest Process Performance Qualification (PPQ) performed in 2013-2014. In this BLA, Octapharma submitted a report for the PPQ campaign consisting of (b) (4) batches: (b) ( batches were manufactured at the maximum processing time, and (b) ( batches at the minimum processing time.

All IPC results were within the specified limits and comparable to the results of the previous PPQ. Neither the minimum nor maximum processing times have any negative impact on product quality.

The cryoprecipitate PPQ batches in the report were part of (b) (4) process validation, and were not specifically intended to validate the manufacture of Cryoprecipitate

(FFMU). However, Octapharma provided data for (b) (4) different batches, manufactured for further manufacturing use that were tested per specification. All results met acceptance criteria.

Specifications
Release specifications for Cryoprecipitate (FFMU) include the following parameters and acceptance criteria:

| | |
|---|---|
| (b) (4) | (b) (4) Cryoprecipitate |
| (b) (4) | (b) (4) Cryoprecipitate |
| (b) (4) | (b) (4) Cryoprecipitate |

In addition, the Cryoprecipitate appearance must meet the following description:

"The cryoprecipitate (b) (4) has the appearance of (b) (4) and no signs of thawing."

The specifications are acceptable and sufficiently justified.

Analytical Methods
Octapharma provided descriptions and the validation reports for all methods used for the IPC and release testing of the cryoprecipitate. All validations were performed previously for the testing of the cryoprecipitate as an intermediate in the manufacture of (b) (4). No issues were identified in the analytical procedures or their validations.

Stability
To establish product stability under the proposed storage conditions (up to (b) (4), a stability study involving 3 batches of cryoprecipitate manufactured in (b) (4) was conducted. The samples were stored at (b) (4) To confirm the stability during transport, an excursion study was performed at (b) (4) All results met the specification. Octapharma stated that generally, the results show the same behavior as in earlier studies performed on cryoprecipitate. All biochemical parameters tested exhibited significant variability, which is to be expected and most likely due to the difficulties in preparing (b) (4) samples from the cryoprecipitate. The stability results support the specified shelf-life of (b) (4) when stored at (b) (4)

**b) CBER Lot Release**

Because Cryoprecipitate (For Further Manufacturing Use) is an intermediate intended for further manufacture into a drug product, it will not be subject to CBER lot release.

**c) Facilities review/inspection**

Facility information and data provided in the BLA were reviewed by CBER and found to be sufficient and acceptable. The activities performed and inspectional histories are noted in the table below and are further described in the paragraphs that follow.

**Manufacturer/Facilities Table**

| Name/Address | FEI number | DUNS number | Inspection / waiver | Justification /Results |
|---|---|---|---|---|
| Drug Substance Manufacturing, In-Process Testing/Batch Release, Package and Labeling<br><br>Octapharma Pharmazeutika Produktionsges.m.b.H.<br>Oberlaaer Strasse 235<br>Vienna, Austria, 1100 | 3002809097 | 301119178 | Waived | Team Biologics Jan. 9-17, 2017 VAI |

Team Biologics last surveillance inspection of the Octapharma manufacturing facility was conducted from January 9 - 17, 2017. All 483 issues were resolved and the inspection was classified as voluntary action indicated (VAI).

### d) Environmental Assessment

The BLA included a request for categorical exclusion from an Environmental Assessment under 21 CFR 25.31(c). The FDA concluded that this request is justified as the manufacturing of this product will not alter significantly the concentration and distribution of naturally occurring substances and no extraordinary circumstances exist that would require an environmental assessment.

### e) Product Comparability

Not applicable

## 4. NONCLINICAL PHARMACOLOGY/TOXICOLOGY

Not applicable

## 5. CLINICAL PHARMACOLOGY

Not applicable

## 6. CLINICAL/STATISTICAL/PHARMACOVIGILANCE

Not applicable

## 7. SAFETY

Not applicable

## 8. ADVISORY COMMITTEE MEETING

Not applicable

## 9. OTHER RELEVANT REGULATORY ISSUES

No other issues

## 10. LABELING

Cryoprecipitate (FFMU) is stored and shipped at (b) (4)

The labels contain the following information:

*Front side:*
Cryoprecipitate – for further manufacturing use
Octapharma Pharmazeutika Produktionsges.m.b.H.
Oberlaaer Strasse 235
A-1100 Vienna Austria
U.S. License Number 1646

*Back side:*
Name of Material: Cryoprecipitate FFMU
Material Number Octapharma: (b) (4)
Package Number:
Manufacturing Batch Number:
Storage Conditions: (b) (4)
Label Printing Date:
Version Number Printing Report / Release Date Printing Report:
Incoming Date / Manufacturing Date:
Expiry Date:
Weight, kg

## 11. RECOMMENDATIONS AND RISK/ BENEFIT ASSESSMENT

### a) Recommended Regulatory Action

CBER review committee unanimously recommends approval of this BLA.

### b) Risk/Benefit Assessment

There is no risk/benefit assessment since the product is for further manufacturing use.

### c) Recommendation for Postmarketing Activities

No post-marketing activities recommended.