DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food & Drug Administration
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To	STN 125612/0
Through	Lokesh Bhattacharyya, DBSQC/OCBQ
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Product	Fibryna (Octafibrin)
Sponsor	Octapharma
Subject	Primary Discipline Review Memo for Biological License Application for Quality Control Lot-Release Test Methods for the Drug Substance and Drug Product for Fibryna (Octafibrin)

Summary of Review

The Biologic License Application (BLA) for Fibryna (STN: 125612) was submitted by Octapharma. This Primary Discipline Review memo applies to the following analytical methods and validations as used for the lot release of the drug product:

1. Determination of Fibrinogen by (b) (4)
2. Visual Inspection of Freeze-Dried Products and Verification of Solubility of Freeze-Dried Products

The validation was carried out at the Octapharma OPG (Vienna) site, with method transfer for the Determination of Fibrinogen by (b) (4) from Octapharma OPG to the Octapharma ODE (Dessau) and OAB (Stockholm) sites. These latter sites were withdrawn as part of the BLA submission; hence Fibryna is tested solely at the OPG site. The Determination of Fibrinogen by (b) (4) method was revised considerably and revalidated. The two above-mentioned methods have been described and validated adequately and may be used for lot-release testing of Fibryna at the Octapharma – Vienna (OPG) site.

Background

Fibryna is proposed for treatment of acute bleeding episodes (b) (4) in adult and pediatric patients with congenital fibrinogen deficiency, including afibrinogenemia and

hypofibrinogenemia. Fibryna is purified from human plasma, and since the manufacture is a (b) (4) . It is supplied as a 1g dose. Upon reconstitution in 50 mL water for injection, the formulation is 20 mg/mL fibrinogen. The drug product is to be administered intraveneously.

Submitted Information Reviewed

This is an electronic submission. Information submitted and reviewed includes:

-125612/0 3.2.S.4.2 – Analytical Procedures

- 130SOP111/06 Determination of Fibrinogen by (b) (4)
- 130SOP006/07 Visual inspection of freeze-dried products, (b) (4) and WFI used for reconstitution and verification of solubility of freeze-dried products
- 130SOP115/04 Visual Control of Liquid Preparations and Short Term Stability of (b) (4)

-125612/0 3.2.P.5.1 – Specifications

-125612/0 3.2.P.5.3 – Validation of Analytical Procedures

- 000VAL111 FC 347/01 Analytical Method Validation Report for the Determination of Fibrinogen in Fibrinogen FC Samples by (b) (4)
- 000VAL111 FC 347 348/00 MCR OPG-ODE/00 Method Comparison Report between QC OPG (Vienna) and QC ODE (Dessau) for the Identification of Fibrinogen in Fibrinogen Final Product by (b) (4)

-125612/0 3.2.P.6 - Reference Standard or Materials

-125612/0.11 1.2 – Cover Letters

- Response to FDA information request – September 19, 2016

-125612/0.15 3.2.P.5.3 – Validation of Analytical Procedures

- 000VAL111 FC 347 348/00 MTR OPG-OAB/00 Method Transfer Report from QC OPG (Vienna) to QC OAB (Stockholm) for the Determination of Fibrinogen in FIBRINOGEN Final Product by (b) (4)

-125612/0.20 1.2 – Cover Letters

- Response to FDA information request – November 18. 2016

-125612/0.27 1.2 – Cover Letters

- Response to FDA information request – December 21, 2016

-125612/0.33 1.2 – Cover Letters

- Response to FDA information request – January 27, 2017

-125612/0.36 1.2 – Cover Letters

- Response to FDA information request – December 21, 2016

-125612/0.36 3.2.P.5.2 – Analytical Procedures

- 130SOP111/07 Determination of Fibrinogen by (b) (4)

-125612/0.36 3.2.P.5.3 - Validation of Analytical Procedures

- 000VAL111 FC 34x/0.2.rep Analytical Method Validation Report for the Determination of Fibrinogen in Fibrinogen FC Samples by (b) (4)

-125612/0.45 1.2 – Cover Letters

- Response to FDA information request – April 6, 2017

-125612/0.45 3.2.P.5.3 - Validation of Analytical Procedures

- 000VAL111 FC 34x/03.rep Analytical Method Validation Report for the Determination of Fibrinogen in Fibrinogen FC Samples by (b) (4)

Review Narrative

1. **Determination of Fibrinogen by** (b) (4)

This assay, based on the (b) (4) method, is used to measure the fibrinogen concentration of (b) (4) final drug product samples. The proposed specifications are (b) (4). The sponsor provided an analytical procedure, 130SOP111/06, a validation report, 000VAL111FC 347/01, and a method comparison report, 000VAL111FC 347 348/00.

Method

(b) (4)

Method Validation

(b) (4)

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

(b) (4)

Conclusion

The SOP and validation have undergone significant revision. The changes to the SOP and the additional validation studies indicate that this method is suitable for use for lot-release testing at the OPG site.

2. Visual Inspection of Freeze-Dried Products and Verification of Solubility of Freeze-Dried Products

The proposed specifications for Visual Inspection (Characters) of the lyophilized product are white or pale yellow, hygroscopic powder or friable solid; for Solubility, the drug product dissolves within (b) (4) mins at 20°C - 25°C, and the reconstituted solution is almost colorless and slightly opalescent; and for Stability of Solution (at 20°C - 25°C), (b) (4) . The sponsor provided analytical procedures, 130SOP006/07 and 130SOP115/04.

Method

The contents of the lyophilized material are visually examined for appearance and color as described in (b) (4) . The sample is then reconstituted in water for injection and the time taken for complete dissolution is recorded. The visual appearance is again recorded. The vial is left at 20°C - 25°C for (b) (4) mins and the stability after reconstitution, such as (b) (4) , is recorded. Visual inspection is appropriate to verify the appearance of the lyophilized material and reconstituted solution and validation of this method is not necessary.

Conclusion

These assays are approvable as test methods as part of this application.