

Memorandum

**Food and Drug Administration
Center for Biologics Evaluation and Research
Office of Compliance and Biologics Quality
Division of Manufacturing and Product Quality**

To: 125523/0 Fibrin Sealant (Human)

Alexey Khrenov, Chair, OBRR/DH/LH/ HFM- 392

Tracey Tilghman, RPM, OBRR/DBA/RPMB/ HFM-380

Cc: Review Committee Members

From: Susan Yu, OCBQ/DMPQ/B1/HFM-675

Through: Carolyn Renshaw, Branch Chief, OCBQ/DMPQ/B1/ HFM-675

Subject: BLA Review Memo

Indication: Aid to surgical hemostasis for mild to moderate bleeding from small vessels when control of bleeding by standard surgical techniques is ineffective or impractical

Applicant: ProFibrix, BV

Due Date: January 31, 2015

Recommendation

This application requires a pre-license inspection and follow-up of issues after inspection. The inspection is scheduled for (b) (4). After completion of the inspection and review of outstanding issues, a recommendation regarding approval of this application can be made.

Summary

ProFibrix, BV, the applicant, submitted a Biologics License Application (BLA) on January 31, 2014 and was received by FDA January 31, 2014. The final drug product is a spray dried powder mixture of thrombin and fibrinogen in glass vials. The powder can be sprinkled directly on to an open wound, used with a sponge, or used with a device which sprays the product on the wound. ProFibrix does not own any of the manufacturing facilities and contracts out all manufacturing. (b) (4) (Thrombin (b) (4) and Fibrinogen) are manufactured by (b) (4) and have been previously approved and licensed. Thrombin and fibrinogen manufacture are not part of this review. The drug product is manufactured a (b) (4). The manufacturing at (b) (4) includes the following: The thrombin and fibrinogen are (b) (4) sterile (b) (4), spray dried into a powder within (b) (4) for fibrinogen and (b) (4) for thrombin, stored in glass (b) (4) blended together (b) (4) filling, (b) (4) stoppered, (b) (4) over sealed, visually inspected, labeled, and placed in a foil pouch. After release testing, the drug product in the foil pouch is sent to (b) (4) for final labeling, and final packaging. A pre-license inspection will be performed at the (b) (4) facility. A decision was made by management not to inspect (b) (4).

Information Requests

Information requests (IR) dated March 25, 2014 and March 31, 2014 were sent to ProFibrix. These IR were sent to (b) (4) via ProFibrix to submit information that was not in the original BLA but is recommended in the FDA CMC guidance. Section 3.2.A was updated with responses in amendments 125523/0.004 and 125523/0/005. The review of the responses with comparison review of documents during the pre-license inspection will determine the adequacy of the response.

Review

The BLA was reviewed per “SOPP 8401.4: Review Responsibilities for the CMC Section of Biologic License Applications and Supplements” and the CMC and sterilization guidance documents. The applicant submitted the BLA using format and information outlined in ICH “Guidance for Industry M4Q: The CTD – Quality”. We have deferred review responsibilities to the Product Office or other appropriate office as outlined in SOPP 8401.4.

The BLA was designated as a combination product on February 25, 2014 after an inquiry to the CBER Ombudsman to the Office of Combination Products (OCP). OCP asked that CBER code this as a combination product (category 7), for reporting purposes because of the cross-labeling between the biologic and the dedicated delivery system. While the product can be used alone without the delivery system, since it is cross labeled with a specific device OCP indicated that it should be captured as a combination product in our reporting system. ProFibrix BV was notified of this designation.

Submission Content

The following is not a complete listing of submission content, but only sections of the contents I reviewed or read as an overview per “SOPP 8401.4: Review Responsibilities for the CMC Section of Biologic License Applications and Supplements” for DMPQ review. Some areas of this BLA are evaluated or followed up on the pre-license inspection as documented in SOP 8401.4.

Module 1 Regional Administrative Information

1.2 Cover Letter, Reviewers Guide

1.4.1 Letters of Authorization from (b) (4)

1.6 Meetings – Meeting Background Materials and Correspondence 5/8/09-10/08/13

1.12 Environmental Analysis – Categorical Exclusion

Module 2 Summary

2.2 Introduction

2.3.S (b) (4) – section not documented

2.3.P Drug Product Summary – description composition, development, manufacture, excipients, control of drug product, reference standards, stability

2.3.A Appendices – Facilities and equipment, adventitious agents safety evaluation

Module 3 Quality

Section 3.2.S (b) (4) – The (b) (4) Section 3.2.S does not exist.

Section 3.2.P Drug Product

3.2.P.1 Description and Composition

Components of the Drug Product

Drug Product

3.2.P.2 Pharmaceutical Development

Manufacturing Process Development

FMEA

Design Summary

(b) (4) Stability

DOE Study Blending

(b) (4)

Container Closure

Microbial Attributes

Compatibility

3.2. P.3 Manufacture

3.2. P.3.1 Manufacturers

3.2. P.3.2 Batch Formulation

3.2. P.3.3 Description of Manufacturing Process and Process Controls

3.2. P.3.4 Control of Critical Steps and Intermediates

3.2. P.3.5 Process Validation and / or Evaluation

Process Validation and / or Evaluation

PRO1065 Cleaning Validation Report

PRO1066 Process Performance Qualification

PRO 1067 Aseptic Process Validation

Validation Report MET 1262 Fibrinogen Cleaning Method

Validation Report MET 1289 (b) (4) Thrombin Residues

Validation Report MET 1290 – (b) (4) for Fibrinogen Results

3.2.P.4 Control of Excipients

3.2.P.5 Control of Drug Product

3.2.P.5.1 Specifications

3.2.P.5.2 Analytical Procedures

Endotoxin, (b) (4), Appearance, Moisture Content, Sterility

3.2.P.5.3 Validation of Analytical Procedures

3.2.P.5.4 Batch Analysis

3.2.P.7 Container Closure

3.2.P.8 Stability (overview only)

3.2.A Appendices

3.2.A.1 Facilities and Equipment

(b) (4)

1. Powder Risk Assessment

2. Layouts

3. Drawings (b) (4) Spray Dryer, Blend (b) (4), Blending System, Formulation and (b) (4), Spray Dryer Nozzle

4. 3.2.A.2 Adventitious Agents Safety Evaluation

5. 3.2.R Regional Information

6. Device Sprayer Information – informational read only, CDRH review as 510(k)

Section 3.2.A Appendix

Section 3.2.A was updated in 125523/0.004 and 125523/0/005. These amendments were responses to information requests dated March 25, 2014 and March 31, 2014. These IR were sent to (b) (4) via ProFibrix to submit information that was not in the original BLA but is recommended in the FDA CMC guidance. Because of the limited time frame to submit the information, we suggested (b) (4)/ ProFibrix submit standard operating procedures, qualification reports, and validation reports for the facilities, equipment, cleaning, and sterilization. Reviews of these documents are documented in this review, to follow with more comments during the addendum review, or on inspection.

Narrative

Module 1 Regional Administrative Information

1.2 Cover Letter, Reviewers Guide

The reviewers guide provided links to the CTD modules within the electronic BLA which were high level.

1.4.1 Letters of Authorization from (b) (4)

The BLA references the (b) (4). They are Thrombin (Human) (b) (4) Fibrinogen (b) (4) (Human) (b) (4) ProFibrix BV submitted (b) (4) letters of authorization both dated January 8, 2014 to allow reference to the (b) (4) BLAs and supplements.

1.6 Meetings – Meeting Background Materials and Correspondence 5/8/09-10/08/13

This section was a submission of documentation of all the meetings held with FDA from 5/8/09-10/08/13.

1.12 Environmental Analysis – Categorical Exclusion

The categorical exclusion submitted by ProFibrix claimed categorical exclusion based on 21 CFR 25.31 (e) was incorrect. In a response to the March 25, 2014 information request, ProFibrix submitted a categorical exclusion under 21 CFR § 25.31(c). The applicant states that to the applicant's knowledge, no extraordinary circumstances exist. Approval of this naturally occurring product is not expected to significantly alter the concentration or distribution of the substance, its metabolites, or degradation products in the environment. The categorical exclusion claim is accepted.

Module 2 Summary

2.2 Introduction

2.3.S (b) (4) – section not documented

2.3.P Drug Product Summary – description composition, development, manufacture, excipients, control of drug product, reference standards, stability

2.3.A Appendices – Facilities and equipment, adventitious agents safety evaluation

Module 3 Quality

Section 3.2.S (b) (4) – The format of the ProFibrix BV BLA for the (b) (4), Section 3.2.S in Module 3 does not exist. The relevant information regarding the (b) (4) are embedded in various sections of the drug product Section 3.2.P.

Section 3.2.P Drug Product

3.2.P.1 Description and Composition

The Drug Product (DP) is a dry powder combination of human fibrinogen and human thrombin. The DP is single strength 79 mg/g fibrinogen and (b) (4) human thrombin gram of powder. The presentations are 0.5g, 1.0g, and 2.0g with no overfill and a filling (b) (4). The DP can be applied directly on a wound, on a sponge placed over the wound, or from a sprayer manufactured specifically for this DP under review as a 510(k). The composition of one gram of the DP was shown in Table 1, page 3 and is provided below:

Table 1: Composition of Fibrocaps (per gram powder)

Component	Function	Quantity	Unit	Reference
Human Fibrinogen (INN)	Active	79 (b) (4) (b) (4)	mg/g	(b) (4)
Human Thrombin (INN)	Active	(b) (4) (b) (4)	IU/g	(b) (4)

Trehalose	(b) (4)	(b) (4) ^(b)	mg/g	(b) (4)
Calcium chloride	(b) (4)	11.0	mg/g	(b) (4)
Human albumin	(b) (4)	(b) (4) ^(b)	mg/g	(b) (4)
Sodium chloride	(b) (4)	(b) (4) ^(b)	mg/g	(b) (4)
Sodium citrate	(b) (4)	(b) (4) ^(b)	mg/g	(b) (4)
L-Arginine hydrochloride	(b) (4)	(b) (4) ^(b)	mg/g	(b) (4)

^a Based on label claim drug product

^b Nominal value based on target specifications of actives, actual value is calculated per lot active

^c 100% theoretical calculation (not determined) using the target specification (and ranges) as supplied on the Certificate of Analysis of the (b) (4)

The DP container closure includes: a 6 mL (b) (4) 1 clear glass vial manufactured by (b) (4) rubber stopper (b) (4) white crimp cap / seal (flip tear up). The container closure is discussed in more detail in section 3.2.P7.

3.2.P.2 Pharmaceutical Development

Components of the Drug Product

The components and ingredients of the (b) (4) are discussed in this section. Both the thrombin (b) (4) and fibrinogen (b) (4) manufacture are approved products in final containers (vials). Each vial of (b) (4) thrombin (b) (4) thrombin and each vial of (b) (4) fibrinogen (b) (4) contains (b) (4) fibrinogen. Tables 2 and 3, page three shows the individual potency for each vial. Table 4, page 4 includes the excipients in the (b) (4) present per gram of DP powder. Excipients in the DP formulation per gram of powder are trehalose (b) (4) used as a (b) (4) agent and calcium chloride (11.0 mg/g) used as a (b) (4). Table 5 page 5 shows the microbiological specification for trehalose with (b) (4). The trehalose is (b) (4). **Follow up on the high (b) (4) specification for trehalose, the (b) (4) testing, the (b) (4) of the process, and the post (b) (4) specifications later in the review or on inspection.** There was no mention of the calcium chloride specifications in this section.

Certificate of Analysis and Characterization

This section is under the review of the product reviewers in OBRR. The certificate of analysis provided for the DP was dated June 23, 2011, which should be updated.

Manufacturing Process Development

There were changes in the development and manufacture of the DP as outlined in this section from Phase 1, Phase 2 to Phase 3. (b) (4)

(b) (4)

The lots were characterized by testing with summaries of results provided in this section. The comparability of the characterization and specifications will be reviewed by the product office. There was no information in this section regarding the comparability of critical process parameters with regard to manufacturing.

FMEA

ProFibrix states that it had incorporated (b) (4) and Quality Risk Management principles to develop design space, product specifications, and critical process parameters based on ICH guidance in the PPQ lot manufacture. ProFibrix used Failure Mode and Effects Analysis (FMEA) based on the ICH to evaluate the risks to the product during the product life cycle. DEV011 was submitted as an update FMEA review of the ProFibrix manufacturing process. Table 1 page 6 includes DP components, critical quality attributes (CQA), and impact. CQA include thrombin and fibrinogen content, moisture content, particle size, endotoxin, sterility, and active content uniformity. Table 2 page 7 defines critical and non-critical process parameters, and Table 3 pages 8-9 classifies the results based on risk mitigation studies and results of the PPQ lots. Table 3 is recreated below:

Manufacturing Step	(b) (4)
Reconstitution and Filtration	
Spray drying	
Blending	
Filling	

(b) (4)

The FMEA process, including grading of the risk with each process, is summarized from pages 10-25 and includes links to the studies and references. Each process is graded on severity, risk and detection and given a risk probability number (RPN). The process with the highest was the blockage of the spray drying nozzles.

Design Summary

This section provides a summary of process validation developed based on the ICH process validation guidance following (b) (4) recommendations for development and (b) (4)

Table 2 page 13-14 summarizes the changes in manufacturing from pre-clinical to commercial scale. The commercial scale, with final manufacturing facility at (b) (4) aseptic processing, was not initiated until 2011. The original pre-clinical studies were performed from 2001-2008, phase 2 studies were performed 2009-2010 at (b) (4) of the DP. Table 3 listed CQA for spray dried thrombin and fibrinogen, blend, and DP include (b) (4) solution CQA are (b) (4) CPP that are critical affect the CQA and can be controlled within the design space. Key or general process parameters do not affect CQA but could affect robustness or reproducibility.

Design of experiment (DOE) studies and consistency batches were manufactured that included (b) (4) spray dried lots for thrombin and fibrinogen and (b) (4) blended lots at development scale. (b) (4) consistency lots were performed. A second DOE was performed using GMP criteria and operating within a design space using (b) (4) batches and then (b) (4) lots using GMP process parameters at the developmental scale. Results were shown to be within the established criteria.

Technology transfer from (b) (4) at Phase 3 in 2011 included transfer of analytical testing and manufacturing process technology. Transfer of manufacturing included manufacture at commercial lot size, new equipment, and DP manufacture using aseptic processing at formulation and filling (b) (4). An equipment comparison was provided in Table 21 pages 39-40. The significant changes included the (b) (4) nozzle with the (b) (4) nozzle design at (b) (4) stated to provide enhanced protection of thrombin (b) (4) which results in greater retention of thrombin activity post spray drying. Another significant change included the (b) (4), airflow, and feed rate because the different nozzle used at (b) (4) resulted in a different airflow to pressure ratio and feed rate. The final significant changed noted was a change to a (b) (4) filling line (b) (4) with (b) (4) and filling occurring in a (b) (4). Table 22 pages 44-45 listed the developmental studies to support commercial manufacturing. The next sections compare the product in-process tests and specifications using the new equipment, filters, and aseptic processing techniques with final results to support that the DP remains the same or improved. Changes documented included studies regarding (b) (4) hold time studies, (b) (4) for optimal particle size, blending (b) (4) and filling with (b) (4) equipment. An engineering batch for the entire manufacturing process was run at about (b) (4) (b) (4)

Before the Phase 3 products were (b) (4)

. These media fills were stated to be successful.

(b) (4) Stability

DEV014 was a DoE study to establish the thrombin and fibrinogen (b) (4) using manufacturing process at (b) (4) studies were performed at (b) (4) fibrinogen only) (b) (4). Testing was performed at (b) (4) of manufacture including the spray dried product, intermediate blend, and DP within established parameters. A deviation included fibrinogen forming a gel clot at (b) (4) (page 166). Because the evaluation is based on analytical testing during the (b) (4), I read this study but will defer the review to OBRR reviewers. The stability of the thrombin (b) (4) was stated to be demonstrated up to and including (b) (4) storage at (b) (4) and stability of the fibrinogen (b) (4) is demonstrated up to and including (b) (4) storage at (b) (4).

DOE Study Blending

DoE study DEV015 Blending Study on the Blending Process and to Fill Weight Configurations dated Nov. 8, 2012 was a study that established blending process parameters for the DP. Blending was performed at (b) (4) measured (b) (4), and at various (b) (4) blend sizes of thrombin and fibrinogen. Samples were (b) (4). Data summaries submitted indicate current operating settings for the blend settings for time and speed (b) (4) (maximum) were supported by the study.

(b) (4)

Container Closure – DMPQ reviewer Christine Harman has reviewed container closure in a separate review.

(b) (4)

The (b) (4) were provided in this section. The (b) (4) levels appear high for the trehalose and calcium chloride. These specifications were discussed with the OBRR reviewer and will be followed up. The fibrinogen (b) (4) is sterile, but the thrombin (b) (4). The trehalose and calcium chloride are (b) (4) and results of the (b) (4) components should be followed up on inspection and later in this review. T

Follow up on the high (b) (4) specification for trehalose and calcium chloride, the (b) (4) testing, the (b) (4) of the process, and the (b) (4) specifications later in the review or on inspection in conjunction with the OBRR reviewer. Specifications after (b) (4) and spray drying are that the intermediate and final DP are sterile.

(b) (4)

(b) (4)

(b) (4)

(b) (4)

Microbial Attributes Fibrocaps Drug Product

Test 1	Method	Specifications
Endotoxin	(b) (4)	(b) (4)
Sterility	(b) (4)	(b) (4)
Pyrogenicity	(b) (4)	(b) (4)

1 Waiver requested for General Safety Test (21 CFR 610.11) in this BLA, see Section 3.2.P.5.6

Compatibility

This section summarizes the compatibility of the fibrin sealant use with device or the sponge. This section's review expertise is with OBRR reviewers.

3.2. P.3 Manufacture

3.2. P.3.1 Manufacturers

The following facility sites were listed in the submission as manufacturing sites for the DP. The original filing memo stated an inspection would be performed at (b) (4). The facility has never been

inspected by FDA. I was informed by management I should not perform inspection because only labeling and packaging is performed at (b) (4).

Drug Product Manufacturer and Responsibility

Nova Laboratories Ltd.

(b) (4)

Drug Product Manufacturer and Responsibility

(b) (4)

Drug Product Testing and Responsibility

(b) (4)

3.2. P.3.2 Batch Formulation

The batch formula of the DP of a batch of (b) (4) of Fibrocaps drug product was included in this section. The DP mix is (b) (4) weight ratio of spray dried fibrinogen and thrombin.

Batch Formula Drug Product

Component	Amount		Function	Reference
	Fibrinogen Batch	Thrombin Batch		
Human Fibrinogen (b) (4)	(b) (4)	-	Active	(b) (4)
Human Thrombin (b) (4)	-	(b) (4)	Active	(b) (4)
Trehalose	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Calcium chloride	-	(b) (4)	(b) (4)	(b) (4)
Human albumin	(b) (4)	-	(b) (4)	(b) (4)
Sodium chloride	(b) (4)	-	(b) (4)	(b) (4)

Sodium citrate	(b) (4)	(b) (4)	(b) (4)	(b) (4)
L-Arginine hydrochloride	(b) (4)		(b) (4)	(b) (4)

1 Based on supplier CoA, number of vials calculated based on actual value CoA

2 (b) (4)

3 (b) (4) theoretical calculation (not determined) using the nominal specification as supplied on the Certificate of Analysis of the drug substances

3.2. P.3.3 Description of Manufacturing Process and Process Controls

This section provided a high level overview of the manufacturing performed at the (b) (4) facility.

Manufacturing includes (b) (4)

In **Attachment 1 – Manufacturing Process with Equipment**, of this review, I compiled a detailed table of the manufacturing process based on this section, in manufacturing process order that includes room number, equipment, in-process testing and information related to the equipment. The follow-up questions I have in the table will be addressed on inspection or later in this review.

3.2. P.3.4 Control of Critical Steps and Intermediates

This section provides an explanation of the process, the in-process controls method used, and the product specifications. (b) (4) Process Design included are (b) (4)

The testing performed is documented in Attachment 1 of the review. The specifications and the acceptance ranges are listed in this section. The microbial attribute specifications are documented previously in this review, which are reviewed by DMPQ. OBRR and DBSQC have the review responsibility for other in-process and final testing used to determine if specifications are met and methods validation. (b) (4)

(b) (4) samples fibrinogen and thrombin (b) (4)

issued February 5, 2013 for (b) (4) at defined temperatures. SOP 1140 is stated to follow the USP and (b) (4). Samples are taken during the (b) (4). The submission states “As this is a (b) (4) sterility test, validation of the test is not required” This does not appear to be correct per the CMC guidance. **Please clarify the statement regarding (b) (4) sterility testing not requiring test validation. This will be followed up during the (b) (4).**

(b) (4) of intermediate blend is carried out (b) (4)

test method is performed as described for drug product, including the (b) (4) treatment of the intermediate blend to form the (b) (4)

The validation of the method is described in Section 3.2.P.5.3.

Method (b) (4) is the endotoxin test method stated to be performed in accordance with (b) (4) described in Section 3.2.P.5.2 for the DP. The spray dried thrombin, spray dried, fibrinogen, intermediate blend, and DP (b) (4) prior to use in the endotoxin test. The endotoxin limit for (b) (4)

as defined for the drug product (based on the worst case assumption maximum use of (b) (4))

Fibrocaps drug product for the patient in (b) (4) It was stated (b) (4)




. The validation method is the same as for final product testing and is reviewed by CBER / OBCQ / DBSQC.

Table 25 includes other changes to analytical procedures which are stated to have minor impact.


3.2. P.3.5 Process Validation and / or Evaluation

The process validation is covered in more detail by OBRR reviewers and a second DMPQ reviewer in a separate review.

ProFibrix has adopted a (b) (4) Process Validation approach building on product development performed at both (b) (4)



(b) (4)



(b) (4)

Hold times are documented in Attachment 1 Manufacturing Process with Equipment of this review.

“PRO1066 Performance Qualification Report” was signed off as completed January 24, 2014. PRO1066 will also be reviewed by OBRR product reviewers and a second DMPQ reviewer assigned to this BLA. The information provided was for (b) (4) manufacture of the PPQ lots. PPQ (b) (4) (Clinical batch for the clinical Phase 3 study FC-004) was manufactured at the (b) (4) scale per spray dried active and (b) (4) blending scale. The subsequent batches (b) (4) were manufactured at the commercial launch scale of (b) (4) per spray dried active and (b) (4) blending scale. The (b) (4) PPQ batch both comprised an additional blend at (b) (4), filled at (b) (4) after an additional (b) (4) period (post blending / prior to filling) of the intermediate blend.

(b) (4) was proposed in this report to (b) (4)
The program involves (b) (4) for each of the (b) (4).

(b) (4)

Table 5 (page 18) shows Process Parameters during Manufacture of Thrombin (b) (4) and Spray Dried Thrombin of PPQ Batches. Table 6 (page 21) showed fibrinogen spray drying process and parameters. Table 7 (page 23-24) showed the process parameters and results for the blending and filling. PRO1066 goes on

to document the results for the raw materials and in-process controls for upstream processes. (b) (4) were met for the thrombin and a (b) (4) result was OOS in PPQ^{(b) (4)} due to error in (b) (4). This deviation, GMP11457 can be followed up on inspection. (b) (4) for the fibrinogen was “pass” (b) (4) specimen samples were tested by (b) (4) method due to (b) (4) blockage and should be (b) (4). Table 14 (page 34) included bottles of spray dried product collected. IPC for spray dried Thrombin was in Table 15 (page 35) and spray dried Fibrinogen Table 16 (page 36). Table 17 (page 37) were blending IPC with (b) (4) to be followed-up, but the final specifications met criteria of (b) (4). Table 18 (page 38) IPCs for filling, labeling, and packaging, There was one labeling discrepancy under GMP2. Table 19 (page 39-41) documents release testing results. There was an OOS for (b) (4) in PPQ for documented in OOS (b) (4), but results are in specification. Table 20 (page 42) was blending assessment data, Table 21 (page 43) blended product stability results.

The filling process was evaluated for consistency, and (b) (4) of the blend over time. (b) (4) was (b) (4) filled (i.e. (b) (4) vial for PPQ^{(b) (4)} and every (b) (4) vial for PPQ^{(b) (4)}, PPQ^{(b) (4)} and PPQ^{(b) (4)} and (b) (4) vials was confirmed for fill weight on an independent balance. The (b) (4) vials were analyzed for (b) (4)

In addition, one vial was (b) (4) after each (b) (4) and at the (b) (4) for PPQ^{(b) (4)} onwards, to demonstrate that their product characteristics were comparable to the remainder of the batch. These after the (b) (4)” vials were analyzed in the same manner. The QC results of the (b) (4) the fill” and the “following the (b) (4)” vials of each batch were shown in Figure 5 to Figure 40. The individual results are provided in Appendix 25 and Appendix 26. The results demonstrated that the product characteristics for both (b) (4) the fill “and” following the (b) (4) “vials were comparable to the QC results obtained for release testing of the batch (see Section 5.7.6). For some (b) (4) the fill”/ “following the (b) (4) ” (b) (4) the (b) (4) could not be determined for batch (b) (4) due to insufficient sample. There were (b) (4) out of specifications (OOS) results: one (b) (4) the fill “for batch (b) (4) (see OOS (b) (4) in Section 6.2) and two “following the (b) (4) for batches (b) (4) (see OOS (b) (4) in Section 6.3 and OOS (b) (4) in Section 6.4, respectively). The (b) (4) of the “following the (b) (4) vials was between (b) (4), which is slightly higher than the (b) (4) the fill” (b) (4)

Comparison of (b) (4) product was presented. This is deferred to OBRR review. Documentation, guidance, and SOPs used in the PPQ were listed on pages 96-99. Environmental monitoring was stated to be met except for (b) (4) during the manufacture of spray dried fibrinogen due to forgetting to read the (b) (4)

Section 6 of PRO1066 discussed deviations (pages 54-64). Deviations mentioned previously in this review and in this section should be followed up on inspection based on risk and if the resolution of the deviation appears problematic. Deviations associated with each aspect of manufacturing were discussed and actions to correct manufacturing problems were implemented. Detailed listings of deviations were listed in deviation section of “PRO1066 Performance Qualification Report” and individual sections. Deviations associated with (b) (4) and filling included: change from (b) (4) addition of trelahose and CaCl for thrombin; fibrinogen sterilizing (b) (4) was clogging so a (b) (4) were added; and (b) (4)

temperature rise due to temperature probe positioning – no action taken because still within CPP. Deviations associated with spray drying included: top sampling of last PPQ^{(b) (4)} was out of specification, due to foam, others within specification; start use of dedicated housing and nozzles; nozzle blockages for fibrinogen changed position and replaced nozzle;^{(b) (4)} rate was high for PPQ^{(b) (4)} thrombin batch; ^{(b) (4)} within the lower quarter for thrombin because in spray dried thrombin the ^{(b) (4)} amount relative to the ^{(b) (4)} amount is less than ^{(b) (4)} when compared to the ^{(b) (4)} amount, in spray dried fibrinogen of ^{(b) (4)} relative to ^{(b) (4)} amount ^{(b) (4)}. Deviations noted for blending: none. Filling deviations included: two ‘after a break’ samples were out of specification for ^{(b) (4)} Both ^{(b) (4)} occurred at the ^{(b) (4)} of the filling process. The assessments are documented in PRO1066 and concluded that the start and end of fill event were not replicated in the two other PPQ batches, included in each filling process investigation. There was no follow-up except to say that during ^{(b) (4)} to analyze further. In addition, no breaks ^{(b) (4)} will be allowed in these relevant volumes of batch. **Inspection follow-up: Follow up on PPQ deviation corrections. Discuss with OBRR the manufacture of ^{(b) (4)} depending on the lots manufactured and not submitted or discussed in the BLA.**

Section 5.4.7 included chart results in chart form of results of ^{(b) (4)} was not tested. OBRR will provide comments on the requirement. Section 5.4.8 Table 5 is a listing of results recovery for ^{(b) (4)} COA values and ^{(b) (4)} QC results.

Section 5.5 provided an overview of aseptic processing validation using media simulation. The media simulation is from ^{(b) (4)}. Table 7 shows the scale and Table 8 spray drying results for length of time for media fills. Media Simulations are described in detail in “*PRO 1067 Fibrocaps Aseptic Processing Validation Report Spray Drying, Blending, Filling and Closing Operations*”. In the report results for ^{(b) (4)} media simulations were presented. Deviations were summarized in Section 8. The first media simulation failed due to a catastrophic glove failure where the glove came off next to the product ^{(b) (4)} during spray drying of the media ^{(b) (4)} (Deviation GMP11316). There was sterility failure of the bulk and of ^{(b) (4)} samples failed. An additional ^{(b) (4)} spray dried media simulations were performed with failed date 9/9/11-9/23/11, then ^{(b) (4)} consecutive 10/6/11-10/20/11, 11/4/11-10/20/11, 12/2/11-12/19/11, revalidation 7/23/12-8/7/12 and 2/22/13-3/13/13. Blending and filling dates include 10/21/11-11/14/11, 12/9/11-12/22/11, 1/27/12-2/20/12, 8/9/12-9/7/12, and 5/3/13-6/6/13. Deviation GMP11404 included ^{(b) (4)} positive viable air samples during filling of the first revalidation. The canopy was breached at the bottom of the ^{(b) (4)} base. None of the samples were positive. **Inspection follow-up: Follow up on ^{(b) (4)} deviation corrections and follow up on ^{(b) (4)} not provided in the BLA including the most recent.**

Section 5.6 Equipment Cleaning Validation was performed for the ^{(b) (4)} PPQ batches and described in PRO1065 Cleaning Validation Report. Table 12 provided a summary of the cleaning. Equipment cleaning, method, and detection method are documented in Attachment 1 Manufacturing Process with Equipment of this review. The worst case and rational for the methods chosen are summarized in Section 5.6.2 and 5.6.3. The methods chosen reflected detection capability and cleaning ability for both ^{(b) (4)}. Thrombin residue is detected by ^{(b) (4)} and Fibrinogen by ^{(b) (4)} as explained in this section. Section 5.6.4 included Table 13

with dirty (b) (4) of (b) (4). Section 5.6.5 states the maximum allowable carryover (MAC) based as the lesser of either (b) (4) of the minimum daily dose for thrombin and (b) (4) for fibrinogen (plus equipment has to be confirmed as visually clean). The (b) (4) criterion applies to the thrombin residues, and equates to a safety factor of (b) (4). The (b) (4) criterion applies to the fibrinogen residues. The most stringent MAC was stated to be used as shown in Table 14 and are based on No Observed Adverse Effect Level (NOAEL) studies performed in animals for thrombin. Fibrinogen NOAEL studies were not performed because there were no literature studies to base testing on, since there are such high levels of fibrinogen in humans anyway. Section 5.6.6 Table 15 lists the calculation of acceptable residue limits, stated to be the worst case for the (b) (4) spray dryer. The maximum allowable residue per batch for thrombin and fibrinogen are listed with sample type, sample location, test method, limit of quantitation (LOQ) or limit of detection (LOD) for the test method, and validation reference. The LOQ for thrombin (b) (4) (conversion between thrombin as (b) (4) The LOD/LOQ for fibrinogen (b) (4) was LOD: (b) (4) LOQ: (b) (4) Fibrinogen (b) (4) LOQ was (b) (4) (Conversion for fibrinogen as (b) (4) Section 5.6.7 summarized the cleaning validation. Figures 37, 38, 39, and 40 depicted cleaning sampling sites for the spray dryer, formulation / (b) (4), blend (b) (4), and filling unit. The sampling was performed during the (b) (4) PPQ lots as shown in Table 16 for multiuse spray dryer equipment, (b) (4) and Table 17 for dedicated equipment (formulation, product (b) (4), nozzle inserts, blend (b) (4)). Results were within established limits. Some samples were missed or not tested. Cleaning in some cases was adjusted during PPQ^(b) to ensure cleaning levels were met. Section 5.6.8 discussed the clean (b) (4) for (b) (4) cleaned pieces of equipment, but did not mention what equipment was evaluated. The time of (b) (4) appears to apply to most equipment. The study was (b) (4) Report INV309. The equipment is recleaned per SOP 1367 'Cleaning and preparation of equipment by (b) (4) and 'Preparation of equipment, including (b) (4), glassware, tools & seals for use in manufacturing (Amendment 4). This study was for (b) (4) cleaned production equipment. (b) (4) samples and (b) (4) taken from the equipment were stated to comply to the set specifications of (b) (4) for (b) (4) for (b) (4). The (b) (4) should be followed up in during the pre-license inspection.

Section 5.7 was a comparison between the CQAs between (b) (4) for the spray dried intermediates and the drug product. This section is OBRR's area of review expertise. Section 5.8 was a summary of (b) (4) with the (b) (4) PPQ lots manufactured at (b) (4) which helped confirm manufacturing (b) (4). The batch size for commercial scale was provided in Table 25. Spray dried fibrinogen, thrombin, and intermediate blend (b) (4) batch size is up to (b) (4) and the drug product batch size is up to (b) (4), fill weight of (b) (4) will include standard QC testing (as outlined Section 3.2.P.3.4 for intermediates) and Section 3.2.P.5.1 (for drug product) and (b) (4) to verify performance and state of control. The (b) (4) plan should be followed-up and evaluated if performed. The following are the (b) (4)

- (b) (4)

- (b) (4)

“Validation Report MET 1262 Fibrinogen Cleaning Method – Method Validation of the (b) (4) Procedure and (b) (4) Analysis for Fibrinogen Residues.” The recovery is to support verification of cleaning from (b) (4) surfaces. (b) (4) was for (b) (4) for (b) (4). For (b) (4), the % recovery and RSD% were low. As recovery was (b) (4) a recovery factor of (b) (4) was the calculated corrected value used as an acceptance limit. The LOD was (b) (4) and the LOQ was (b) (4) criteria was met for the (b) (4) “Validation Report MET 1289 (b) (4) Thrombin Residues” – is a validation of the (b) (4) method of the (b) (4) and (b) (4) to test for thrombin residue with (b) (4) and dedicated equipment. The validation is for (b) (4) batches of (b) (4) g. Maximum allowable carryover (MAC) was calculated, then for (b) (4) samples. The recovery of the (b) (4) were completed meeting acceptance criteria. The (b) (4) was too low using the (b) (4) test method, to provide meaningful results. “Validation Report MET 1290 – (b) (4) for Fibrinogen Residues” is a validation of the (b) (4) procedures to test for fibrinogen residues for (b) (4) batches on the (b) (4) and dedicated equipment. The (b) (4) were for the (b) (4) batch and the (b) (4) only for the (b) (4) MAC was calculated, LOQ was determined and results were met for recovery and RSD% criteria for (b) (4) batches and (b) (4)

3.2.P.4 Control of Excipients – OBRR review

3.2.P.5 Control of Drug Product – OBRR review

3.2.P.5.1 Specifications – OBRR review

3.2.P.5.2 Analytical Procedures – OBRR review and DBSQC review

Endotoxin, (b) (4), Appearance, Moisture Content, Sterility

3.2.P.5.3 Validation of Analytical Procedures – OBRR review and DBSQC

3.2.P.5.4 Batch Analysis (overview only)

3.2.P.7 Container Closure – reviewed by second DMPQ reviewer

3.2.P.8 Stability (overview only)

3.2.A Appendices

3.2.A.1 Facilities and Equipment

There is one location for the applicant, one location involved in the manufacture of the Fibrin Sealant (b) (4) two facilities involved in the manufacture of the drug product, and one facility for the manufacture of the device.

The applicant, ProFibrix BV, located in Leiden, Netherlands, will not be inspected but may require review of documents. Since ProFibrix BV is a virtual manufacturer, a review of the processes and documents shared with (b) (4) is to be reviewed on inspection (b) (4) is the primary manufacturing site which handles most all the CGMP process. Generally, CBER will not inspect a company that is a virtual company. The relationship and contract between ProFibrix and (b) (4) will need to be reviewed to be sure the FDA regulations and CGMPs are met. ProFibrix was purchased by the (b) (4) / Medicines Company in August 2013. Complaints are sent to the (b) (4) / The Medicines Company / ProFibrix (Seattle) which then sends complaints to on to ProFibrix NL (Netherlands). ProFibrix will notify either (b) (4) about any corrections that may need to be made. (b) (4) will respond to ProFibrix regarding corrections. **Per discussion with DMPQ management virtual companies do not require inspection. Profibrix states that (b) (4) performs batch record review, QA and QC for drug product release. The contract relationship between ProFibrix and (b) (4) will be followed up on inspection.**

The (b) (4) used to manufacture the DP are final approved products themselves. They are manufactured by (b) (4). In previous agreements between ProFibrix and FDA as documented in meeting minutes, the review of the (b) (4) would not be required to be reviewed as part of this BLA.

The drug product manufacturing facility is (b) (4) ORA conducted an FDA Pre-Approval and GMP inspection of (b) (4) for CDER for manufacture of (b) (4). The inspection was listed as VAI. The inspection of manufacturing was performed in (b) (4) and also covered the chemistry and microbiology laboratories in (b) (4). The manufacturing of the fibrin sealant is in (b) (4).

The (b) (4) labeling and packaging facility in (b) (4) has never been inspected by FDA, but a decision was made by management that a (b) (4) labeling and packaging facility does not require inspection. There is no information about this facility in the BLA. **Information will be reviewed during the pre-license inspection to cover the contract relationship with ProFibrix, BV, procedures used for the fibrin sealant, quality systems, CGMP, and general state of control of the facility.**

The sprayer has been submitted as a 510(k) and the facility will not require inspection. The sprayer originally sent for review to CDRH, was transferred to CBER for review as a 510(k). The option to submit as a 510(k) was agreed upon by ProFibrix and FDA during the pre-BLA meetings and documented in the minutes. Sterilization for 510(k)s are part of the 510(k) review and are inspected after clearance.

Several facilities are contract sterilizers. (b) (4), only has (b) (4) sterilizers on site. (b) (4) sends components such as stoppers and equipment which cannot withstand (b) (4) sterilization to (b) (4). The review of (b) (4) sterilization will be reviewed based on (b) (4) procedures, audits, and testing of the (b) (4) components. There is no inspection history in FACTs. Information regarding facilities and locations follow.

BLA Applicant and Responsibility

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Leiden, Netherlands 2333 CR
Phone +31 6 21216679 / + 31 88 7308303
FEI 408491294
QC activities, quality documentation repository

Drug Product Manufacturer and Responsibility

(b) (4)

Drug Product Manufacturer and Responsibility

(b) (4)

[Redacted]

(b) (4) **Manufacturer and Responsibility**

(b) (4)

[Redacted]

Manufacturer of Thrombin (Human) (b) (4)

Manufacturer of Fibrinogen (b) (4)

Medical Device Sprayer Manufacturer and Responsibility

(b) (4), package and assemble sprayer

CDRH 510 (k) review (b) (4)

[Redacted]

(b) (4) sterilization of sprayer

(b) (4)

[Redacted]

(b) (4)

[Redacted]

(b) (4)

[Redacted]

(b) (4)

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- (b) (4)

Risk Assessment / Powder Risk Assessment – OBRR Review

3.2.A.2 Adventitious Agents Safety Evaluation Powder – OBRR Review

3.2.R Regional Information

Device Sprayer Information – informational read only, OBRR review as 510(k)

Section 3.2.A Appendix Amendments

Section 3.2.A was updated in 125523/0.004 and 125523/0/005. These amendments were responses to information requests (IR) dated March 25, 2014 and March 31, 2014. These IR were sent to (b) (4) via ProFibrix to submit information that was not in the original BLA but is recommended in the FDA CMC guidance. Because of the limited time frame to submit the information, we suggested (b) (4) / ProFibrix submit standard operating procedures, qualification reports, and validation reports for the facilities, equipment, cleaning, and sterilization. These included SOPs for: water and (b) (4) monitoring, (b) (4) r compatibility and testing, use of (b) (4), sterilization, EM, (b) (4) preparation and follow-up at the contractor (b) (4), media simulation, HVAC monitoring, equipment cleaning, operation and cleaning of the spray dryer, (b) (4) of the (b) (4), line clearance, and equipment requalification. Qualifications / re-qualifications submitted included (b) (4) HVAC, sterilization (b) (4) equipment, spray dryer including (b) (4), blending equipment, formulation and (b) (4) equipment and components. Reviews of these documents are documented previously in this review, to follow, or on inspection.

The following documents were submitted in Amendment 4 regarding (b) (4) *Validation Thrombin* (b) (4) *Validation Fibrinogen* (b) (4) *Human Thrombin and Human Fibrinogen* (b) (4) *Chemical Compatibility*, (b) (4) (Chemical Compatibility). The validation of the (b) (4) sterile (b) (4) used to sterile (b) (4) the thrombin and fibrinogen, were summarized in DEV021 and DEV022. Thrombin (b) (4) is sterile (b) (4) the spray dryer (b) (4) and using a sterile (b) (4) the (b) (4) Fibrinogen included the use of a (b) (4), then (b) (4) sterile (b) (4) one (b) (4) the (b) (4) Bacterial retentions studies with (b) (4) as the test organism were performed by (b) (4), the suppliers of the sterile (b) (4). Worse case conditions were applied including contact time, filtration area, flow rate, flow rate for unit area, load per unit area and batch volume (ml) and weight (g) based on the (b) (4) manufacturing process using the manufacturing process set up. Table 2 in both studies showed the worst case conditions for the bacterial retention studies. Studies performed at (b) (4) using worst case conditions determined by the process were used during the manufacture of the PPQ lots. The PPQ (b) (4) conditions were listed in Table 2 of both studies with an explanation of comparability to the bacterial retention studies. The amount of generated filtrates were reported as volumes (ml) in the bacterial retention study (using density (b) (4) and as weight (kg) in the PPQ batch records. To allow comparison of bacterial retention data to the PPQ data, volumes are transferred to weight using a density of (b) (4). The bacterial retention study resulting filtrates were sterile for both thrombin and fibrinogen. Post (b) (4) sterility was “pass” for the PPQ lots. (b) (4)

Pre-license Inspection Follow-up

The following is a compilation of the pre-license follow-up questions in this memo provided in the mid-cycle reviewer memo. These general issues will be followed up during the inspection and include review of specific documents requiring verification in the BLA and review of facility and processes not covered in the submission.

(b) (4)

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

(b) (4)

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

(b) (4)

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

References (the following list includes references but is not all-inclusive)

- 21 CFR 600s
- 21 CFR 211s
- Guidance for Industry For the Submission of Chemistry, Manufacturing and Controls and Establishment Description Information for Human Plasma-Derived Biological Products, Animal Plasma or Serum-Derived Product February 1999
- Guidance for Industry Sterile Drug Products Produced by Aseptic Processing, Sept. 2004
- Guidance for Industry Container Closure Systems for Packaging Human Drugs and Biologics May 1999
- Guidance for Industry Process Validation: General Principles and Practices January 2011
- Guidance for Industry for the Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products November 1994
- ICH Common Technical Document Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients Q7A
- ICH Common Technical Document for the Registration of Pharmaceuticals for Human Use: Quality M4Q (R1) 12 September 2002
- Compliance Program Guidance Manual Chapter – 45 Biological Drug Products Inspection of Biological Drug Products (CBER) 7345.848 October 1, 2010

Review History

Date Initiated: April 25, 2014; updated; August 25, 2014; completed September 5, 2014

Date Commented: September 2, 2014

Date Final: September 5, 2014

(b) (4)

