

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/DHHR/LH

Sonday Kelly, RPM, OBRR/IOD/RPMS

Cc: Review Committee Members

From: Susan Yu, OCBQ/DMPQ/B1

Through: Carolyn Renshaw, Branch Chief, OCBQ/DMPQ/B1
John A. Eltermann, Jr., R.Ph., M.S., Director, OCBQ/DMPQ

Subject: BLA Addendum 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: April 30, 2015

Recommendation

I recommend approval of this BLA based on the original application, subsequent amendments, the pre-license inspection at (b) (4) for the drug product, review of information request responses, concurrence of OCBQ and DMPQ management, and concurrence of OBRR.

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 (b) (4) (Thrombin (b) (4) and Fibrinogen) are manufactured by (b) (4) and have been previously approved and licensed. The drug product is manufactured at (b) (4). CBER performed a pre-license inspection at the (b) (4) facility (b) (4) and issued a FDA FORM 483 with eight observations. The labeled vials, which are sealed in unlabeled individual foil pouches, are sent to (b) (4) for final labeling of the pouches, and final packaging. The (b) (4) was not inspected. The final product can be used in three ways – sprinkled from the vial on to the open surgical site, placed on a sponge then applied to the site, or sprayed on to the site using a spray dryer. The spray dryer is manufactured under the ProFibrix label and under 510 (k) review by OBRR. Because of the cross label with the dedicated spray dryer, the product was designated a combination product.

Information Requests

At this time further information requests (IR) are not required.

Addendum Review

The original 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. When the original BLA was submitted, not all of the information was submitted as recommended by the CBER CMC guidance. Information requests were requested by DMPQ March 25, 2014 and March 31, 2014 with responses submitted by ProFibrix in amendments 004 and 005. The information submitted in the amendments was reviewed in the first BLA review memo, with some additional outstanding issues requiring follow up. The outstanding issues were followed up by the CBER inspection team during the pre-license inspection and additional information requests. Shipping validation, which was not submitted in the original BLA, was submitted in Amendment 17 received in CBER October 24, 2014. Shipping of the drug product from (b) (4) was reviewed during the pre-license inspection.

The follow up items were documented to be reviewed during the pre-license inspection or required further review in the first BLA review memo. The numbering of the follow up items in this memo, do not match the first memo, because some items were combined. The follow-up / further review items are in bold, followed by my review and discussion.

1. Follow up on the (b) (4) specification for trehalose and calcium chloride, the (b) (4) testing, the (b) (4) of the process, and the (b) (4) specifications. DMPQ Follow-Up: The (b) (4) specifications meet the USP suggested specifications for these raw materials. The (b) (4) process (b) (4) includes a series of (b) (4) steps prior to spray drying. OBRR is in agreement with that the raw material specifications are acceptable.

2. Please clarify the statement regarding (b) (4) sterility testing not requiring test validation. DMPQ Follow-Up: The (b) (4) sterility testing is performed per “SOP 1140 Sterility Testing of Products Using the (b) (4)”. SOP 1140 is stated to follow (b) (4) and (b) (4) CFR 601.12, methods that are acceptable when followed and do not require further validation.

3. Follow up on PPQ deviation corrections. Discuss with OBRR the manufacture of additional conformance lots and more testing on the lots, depending on the lots manufactured and not submitted or discussed in the BLA. DMPQ Follow-Up: During the time of submission, there were limited lots manufactured, (b) (4) PPQ and (b) (4) for marketing. During the inspection, (b) (4) was manufacturing another marketing size lot. Many of the deviations were procedural, and did not appear to impact the final product. OBRR is not requiring any additional lots to be manufactured prior to approval.

4. Follow up on media simulation deviation corrections and follow up on media simulations not provided in the BLA including the most recent. DMPQ Follow-Up: media simulations were followed up at (b) (4) including the most recent records. The deviations submitted to the BLA were the first media simulations performed where they encountered problems, but with no contaminations except for catastrophic failures when the study was aborted. The most recent media fills appeared to have fewer deviations with no media fill contaminations. Overall, the media simulations at (b) (4) are well documented and appear robust.

5. Profibrix states that (b) (4) performs batch record review, QA and QC for drug product release.

6. Review contract relationship between ProFibrix, BV and (b) (4) and procedures used for communication and notification for the fibrin sealant, quality systems, CGMP, deviations and general state of control of the facility. Review contract relationship between ProFibrix, (b) (4).

DMPQ Follow-Up for #5 and #6: Please see the EIR for a more detailed explanation of the ProFibrix, (b) (4) Clinical relationship, which includes flow charts in the exhibits, outlining the process. (b) (4) releases the drug product to (b) (4), and (b) (4) releases the labeled and packaged product. The ProFibrix representatives stated (b) (4) performs the following: final packaging, storage, inspect and affix labeling from (b) (4), send deviations to ProFibrix BV in Leiden, Netherlands and (b) (4), and throw away outdated and scrapped material. QC log sheets are sent from (b) (4) follows SOPs and is audited (b) (4) also stores and distributes the medical device used to spray the fibrin sealant. ProFibrix will perform a final QA review, and sends notification to both (b) (4) for final release of the batch to the US.

7. Follow-up on all products manufactured in (b) (4) and possibility of contamination or cross-contamination that might impact the drug product; Review line clearance, labeling, cleaning, storage of equipment, segregation of intermediates and product, concurrent manufacturing, and other areas with regard to manufacturing, release, and quality. DMPQ Follow-Up: During the pre-license inspection, the inspection team was able to observe the areas mentioned. Please see the EIR for a more detailed discussion. We reviewed documentation with regard to the mentioned areas for follow up. We performed an inspection walk through and were able to observe the manufacturing rooms and manufacturing process. The manufacturing areas are generally orderly and clean. The most critical manufacturing is performed in (b) (4), which if working correctly, provide a controlled, aseptic environment with low risk of cross contamination. Concurrent manufacturing of some products do occur, but are well segregated and at steps in the process dissimilar to the fibrin sealant manufacturing process. Line clearance procedures appear acceptable. Due to the number of days allowed for the inspection, we could only perform a representative review of the documents available. Documents reviewed included qualification, validation, cleaning logs, and manufacturing batch records.

8. Clarify if thrombin and fibrinogen manufactured in different areas concurrently; find out the order and segregation. DMPQ Follow-Up: The manufacturing of thrombin and fibrinogen is no performed at the same time. (b) (4) spray drying of thrombin and fibrinogen.

9. Check on the (b) (4) filling, stoppering, and labeling processes, quality, clearance and cleaning process. Since labeling may include generation of particulates, follow-up on segregation and monitoring within the (b) (4). DMPQ Follow-Up: During the pre-license inspection, the inspection team was able to observe the areas mentioned. Please see the EIR for a more detailed discussion. The inspection team was able to observe the filling, stoppering, and labeling procedures. The generation of any particulates from the labels is minor, because the final drug product is powder and is (b) (4) filled using an (b) (4) filling system from a (b) (4) into the vial. The particulates with in the (b) (4) are so numerous, only a baseline count can be obtained prior to manufacture. Because of the particulates generated, (b) (4) stated any particulate monitor would be overwhelmed and destroyed. The current process included (b) (4) Due to the number of days allowed for the inspection, we could only perform a representative review of the documents available. Documents reviewed included qualification, validation, cleaning logs, and manufacturing batch records.

10. (b) (4) : Follow-Up on (b) (4) qualification, validation, cleaning, sanitization, and requalification and revalidation especially change over between products in (b) (4) used for filling. Qualification / validation for (b) (4) : Follow up by reviewing validation data, revalidation using (b) (4) worst case, media simulation, environmental monitoring, and sanitization of permanent equipment. DMPQ Follow-Up: During the pre-license inspection, the inspection team was able to observe the areas mentioned. The (b) (4) used in the fibrin sealant manufacturing process have been qualified and undergo periodic requalification to show if (b) (4)

Media simulation batch records and environmental monitoring results were reviewed. Please see the EIR for a more detailed discussion. Due to the number of days allowed for the inspection, we could only perform a representative review of the documents available. Documents reviewed included qualification, validation, cleaning logs, and manufacturing batch records.

11. Water:

- Follow up on differences between (b) (4) which can have different suggested specifications. Also check on testing and audit process. Since (b) (4), ask for information supporting that assures water meets specifications.
- Check on testing, deviations, and audit process of water for irrigation.
- Check on testing and deviations for (b) (4) water system.

DMPQ Follow-Up: During the pre-license inspection, an inspection team member was able to observe the areas mentioned. There were no observations regarding water use a (b) (4). Please see the EIR for a more detailed discussion.

12. Follow-up on any computer systems as part of the spray dryer and blender, and computer systems that are not listed including (b) (4), others as they are found. DMPQ

Follow-Up: During the pre-license inspection, an inspection team member was able to follow up on computer systems. (b) (4) is still mainly using a paper based system for batch records and quality systems, although they have started to transition to electronic records. There were no observations regarding the current computer system use at (b) (4). Please see the EIR for a more detailed discussion.

13. The process includes some extended (b) (4) thrombin (b) (4) fibrinogen (b) (4) blended product prior to the (b) (4), and it is not clearly explained how long the entire (b) (4) process will take, since it is a (b) (4) process. The equipment used should be shown to be able to support the (b) (4) and extended (b) (4). More detailed information will follow after inspection. Follow up on critical equipment qualification, validation, cleaning, and sterilization on inspection. DMPQ Follow-Up:

During the pre-license inspection, the inspection team was able to observe the areas mentioned. Please see the EIR for additional information. The process validation the (b) (4) and blended products have been validated. The blending and filling process in (b) (4) can take up to (b) (4) or more. The blending process (b) (4) after the thrombin and fibrinogen (b) (4) process, because it is a (b) (4), mostly (b) (4) process, can take over a (b) (4). During the (b) (4). The current data supports this process, based on media simulations and conformance lot product data. Due to the number of days allowed for the inspection, we could only perform a representative review of the documents available. Documents reviewed included qualification, validation, cleaning logs, and manufacturing batch records.

14. The Fibrocaps aseptic process validations are documented in PRO1067. The process appears appropriate as an overall procedure. Verify if media fills represent the current and worst case process

for ProFibrix DP manufacturing. Verify if aseptic processing includes labeling and capping, because it occurs in the (b) (4). DMPQ Follow-Up: During the pre-license inspection, the inspection team was able to observe the areas mentioned including media simulation batch records. The DMPQ follow up comments to #4 addresses the media simulations and # 9 addresses the labels within the (b) (4). Capping machinery can generate particulates. In the case of this filling line, the caps are (b) (4)

(b) (4). Please see the EIR for additional information. Media simulations appear are worst case and well documented. The contract agreement between (b) (4) and ProFibrix is that the maximum number of vials filled in a media simulation every (b) (4), is the maximum vial fill allowed for the fibrin sealant drug product. As an example, if (b) (4) is the maximum drug product vial fill. If the next media simulation is (b) (4) is the maximum drug product vial fill until the next media simulation.

17. The last requalifications of (b) (4) are provided in VAL1153-10 PQ and VAL1337-07 PQ, respectively. During the last re-qualifications, all (b) (4) were stated to be successfully re-qualified with no deviations. Inspection Follow-Up: follow up on the (b) (4)
Review initial qualification and latest requalification. Find out what compendial sterilization and depyrogenation processes are used and if parameters are met. DMPQ Follow-Up: During the pre-license inspection, the inspection team was able to observe the areas where the (b) (4) are used. (b) (4) does not use (b) (4), but uses (b) (4) if equipment can withstand the rigors of (b) (4). Components and equipment that cannot undergo (b) (4) are (b) (4). There are a total of (b) (4) and review of requalification documentation of (b) (4) and (b) (4) occurred during the inspection. Requalifications were performed using (b) (4) met current CGMP requirements. Due to the number of days allowed for the inspection, we could only perform a representative review of the (b) (4) and documents available. Documents reviewed included qualification and manufacturing batch records.

18. Spray Dryer: Follow up on (b) (4) and other sterilization processes for the spray dryer. According to the information submitted in the equipment table (Section 3.2.A, Table 11) VAL1289 is for the (b) (4) process, VAL 1290 and PRO1065 are for the (b) (4) process, and there is also a (b) (4) process for some (b) (4)
The cleaning validation of the spray dried intermediates (equipment) is described in Section 3.2.P.3.5. Follow-up on cleaning of spray drying (b) (4) and parts. The information submitted does not clarify what is followed by sterilization. DMPQ Follow-Up: During the pre-license inspection, the inspection team was able to clarify the process and review representative procedures and records. (b) (4) for sterilization of equipment that can undertake the rigors of (b) (4). Components and equipment that cannot undergo (b) (4) sterilization are (b) (4). After sterilization (b) (4) of equipment and components and (b) (4) of the large (b) (4) of the spray dryer, everything in the (b) (4) undergoes (b) (4).

19. (b) (4) : Follow-up on how (b) (4) / sterilized products are prepared for sterilization, shipped and returned, are evaluated, the verification testing that is performed, tracking, data to support (b) (4). Follow up on testing, clean (b) (4) after (b) (4) of stoppers, caps, tubing, lids, seals, (b) (4). DMPQ Follow-Up: During the pre-license inspection, an inspection team member was able to review the process and review representative procedures and records. Equipment and components are wrapped in polyethylene bags with (b) (4) included, and sent to (b) (4) for (b) (4). Mapped dosing was qualified under “VAL1795-01PQ (b) (4)” and

reviewed under “SOP 1153 Receipt and Inspection of Materials Returned from (b) (4)”. Prior to sterilization or (b) (4), certain equipment undergoes (b) (4) cleaning. Please see the EIR for more detailed information.

20. There was no information as to how environmental monitoring schedule was determined and if criteria were based on worst case conditions. Also follow up on particulate monitoring that is performed before and after operation. The (b) (4) area surrounding the (b) (4) is not monitored in operation and has no action limit. Review trends. DMPQ Follow Up: During the pre-license inspection, an inspection team member was able to review the process and review representative procedures and records. The spray drying, blending, and filling manufacturing all occur in (b) (4). The surrounding areas are (b) (4). There was a 483 observation regarding the (b) (4) area surrounding the (b) (4) blending and filling (b) (4), that was resolved, but brought attention to (b) (4) that more trending and follow up of environmental excursions was needed. The follow up response #9 addresses the particulates. Due to the number of days allowed for the inspection, we could only perform a representative review of the environmental monitoring documents available. Please see the EIR for more detailed information.

21. Review how deviations are reviewed and investigated, follow up on manufacturing deviations in general, review SOPs, and evaluate if these procedures are effectively reviewed by QA. DMPQ Follow-Up: During the pre-license inspection, the inspection team was able to review the process and review representative procedures and records. There was a 483 observation regarding follow up and close out of GMP deviations. The response was satisfactory. (b) (4) has been using mostly paper based records and had recently added an electronic software system to track their quality records. Due to the number of days allowed for the inspection, we could only perform a representative review of the deviations. Please see the EIR for more detailed information.

22. Follow up on the inspection for damage procedure after (b) (4) sterilization, drying (b) (4), sterilization (b) (4) for vials, sample vials, (b) (4), filling unit, tools, spray dryer components, (b) (4). DMPQ Follow-Up: During the pre-license inspection, the inspection team was able to review representative procedures and records regarding the components and equipment. Vials are (b) (4). Because of the (b) (4) technology used, vials, sample (b) (4), and (b) (4) within the (b) (4). Final product vials are the most critical with regard to defects and are inspected individually as part of the (b) (4) process. Spray drying equipment and filling equipment is either sterilized or (b) (4) then the entire contents undergoes a validated (b) (4) process within the (b) (4). Please see the EIR for more detailed information.

23. Review line clearance SOP 1904 ‘Line Clearance’ in the multi-product areas, cleaning validation, cleaning verification, and recent results, including clean (b) (4) and including start up after prolonged shut down. DMPQ Follow-Up: During the pre-license inspection, the inspection team was able to review the process and review representative procedures and records. Please see the EIR for more detailed information. Because critical manufacturing occurs within (b) (4), there is complete change over with equipment and components removed for cleaning and sterilization and (b) (4) after their return. The (b) (4) manufacturing (b) (4) appear clean and orderly, and could be easily cleared before and after use.

24. Follow up if sterilization clean (b) (4) and dirty (b) (4) are supported by data. During the pre-license inspection, the inspection team was able to review the process and review representative qualification, validation, procedures, and records. DMPQ Follow-Up: Clean and dirty (b) (4) for equipment were validated as part of the cleaning validation, media simulations, and the manufacture of the PPQ

lots. Cleaning verification is performed every time for most (b) (4) cleaned product contact equipment. The equipment including the spray dryer and blender have a dirty (b) (4) and clean (b) (4). Due to the number of days allowed for the inspection, we could only perform a representative review of equipment qualification. Please see the EIR for more detailed information.

25. Cleaning of the facility: Follow up by reviewing verification and validation protocols, cleaning logs, and data including (b) (4) review of cleaning agents and disinfectants. DMPQ Follow Up: During the pre-license inspection, the inspection team was able to review the process and review representative qualification, validation, procedures, and records. Due to the number of days allowed for the inspection, we could only perform a representative of cleaning logs and verification. Please see the EIR for more detailed information.

26. Follow up on small component and tool cleaning. It appears that these items are non-product contact and only undergo (b) (4). DMPQ Follow Up: During the pre-license inspection, the inspection team was able to review the process and review representative qualification, validation, procedures, and records. Due to the number of days allowed for the inspection, we could only perform a representative review of documents. The drying time meets regulatory requirements and the (b) (4) undergo required requalification. Cleaning verification is performed every time for product contact equipment. Cleaning SOPs were reviewed. A 483 observation regarding the cleaning time was issued and satisfactorily addressed. Please see the EIR for more detailed information.

27. Follow Up on product dedicated or non-dedicated (b) (4). The information submitted does not clarify which (b) (4) are included in this category in which some are stated to only require washing. DMPQ Follow Up: The product contact equipment (b) (4) were dedicated to this product.

28. Follow up in shipping of (b) (4) and drug product including shipping validation to US market.


Transport validation studies were completed and results were submitted in BLA Amendment 17. The OBRR reviewer reviewed the stability studies associated with the shipping validation and found the data acceptable.

Information was provided in “Summary Report Validation Summary Report SR-FC-P116 Overview of Shipment and Validation Studies Raplixa® and Raplixa® Delivery Kit” (version 01 21 Oct 2014). The validation is stated to be applicable for transport / transshipment by road, air and sea. The validation activities also addresses bulk shipment transport from the manufacturing site in the UK, shipment to the distribution center in the US, and the shipment from the distribution center in the US to the hospitals in the US. The packaging combination of final drug product and the sprayer delivery kit were tested to see if they were sufficient to resist the hazards encountered during transport, storage and transshipment. The packaging combination was exposed to stress conditions that might occur during distribution in climate (b) (4). The studies were conducted in accordance with (b) (4).

The following studies were performed:

Temperature excursion study: Impact assessment of stress conditions on the drug product stability was summarized in “Research Study Plan SP-FC-P115(version 01 01 July 2014) Impact Assessment of Stress Conditions on Fibrocaps Drug Product Stability / Study Report” and “SR-FC-P115 Impact Assessment of Stress Conditions on Fibrocaps drug product Stability (version 01 26 Sept 2014)”. The study included:

(b) (4)



All requirements of the transport simulation study were stated to be met. In conclusion, the packaging combinations of drug product and spray device kit appear validated for transport, storage and transshipment in

(b) (4) Section 3.2.P.3.5 of the BLA was updated to include a summary of the results.

The following components of the packaging combination were stated to be validated:

1. Raplixa Drug Product Kit carton
2. Raplixa Delivery Kit carton (which includes RaplixaSpray)
3. Shipment box
4. Pallet
5. Temperature data loggers
6. Stress temperature range of the product during shipment

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: February 27, 2015; first draft: March 14, 2015;

Date Commented: March 20, 2015 CRenshaw

Date Final: March 26, 2015 SYu

Date Updated: March 30, 2015 SYu (add J. Eltermann)