# Summary Basis for Regulatory Action

**Date: April 3, 2015**

**From:** Alexey Khrenov, Chairperson of the Review Committee

**BLA #: BL 125523/0**

**Applicant Name:** ProFibrix, BV

**Date of Submission:** January 31, 2014

**PDUFA Goal Date:** May 1, 2015

**Proprietary Name / Established Name:** Raplixa / Fibrin Sealant (Human)

**Indication:** An adjunct to hemostasis in adults undergoing surgery when control of bleeding by standard surgical techniques (such as suture, ligature, and cautery) is ineffective or impractical.

**Recommended Action:** Approval

**Signatory Authorities Action:**

**Offices Signatory Authority:**

Jay S. Epstein, MD
Director
Office of Blood Research and Review

☐ 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.

Mary Anne Malarkey
Director
Office of Compliance and Biologics Quality

☐ 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.

| **Discipline** | **Reviewer** |
|---|---|
| Clinical | Charles Maplethorpe |
| Clinical Pharmacology | Carl-Michael Staschen |
| Statistics | Boris Zaslavsky |
| Bioresearch Monitoring | Anthony Hawkins |
| Pharmacology/Toxicology | La'Nissa Brown-Baker |
| Chemistry, Manufacturing and Controls | Natalya Ananyeva, Christine Harman, Alexey Khrenov, and Susan Yu |
| Pre-License Inspection | Christine Harman, Alexey Khrenov, and Susan Yu |
| In-Support and Lot Release Testing | Lokesh Bhattacharyya, Karen Campbell, Alfred Del Grosso, Cheryl Hulme, Hsiaoling Wang, and Claire Wernly |
| Pharmacovigilance | Faith Barash |
| Labeling | Kristine Khuc |
| Regulatory Project Management | Sonday Kelly |
| Advisory Committee Transcript | Product was not presented to an Advisory Committee |

# 1. Introduction

ProFibrix BV (ProFibrix), a wholly owned subsidiary of The Medicines Company, submitted an original Biologics License Application (BLA) to seek U.S. licensure for Fibrin Sealant (Human), with the proprietary name Raplixa. The active components in this product are fibrinogen and thrombin derived from human plasma collected in the United States from healthy donors. These biological components are individually (b) (4) using a manufacturing process that consists of validated virus inactivation and removal steps. The (b) (4) proteins are formulated, sterile-(b) (4), and spray-dried separately under aseptic conditions.

The sterile, spray-dried powder is blended and filled in single-use glass vials and packed in a foil pouch. Each vial is filled with 0.5, 1 or 2 g of a mixture containing nominally 79 mg/g of fibrinogen and 699 IU/g of thrombin. The powder is applied directly, from the vial or using an optional spraying device, onto a bleeding site. The product dissolves in blood and starts the reaction between fibrinogen and thrombin, which results in the formation of a blood clot and stops the bleeding. The 510(k) application BK140119 was submitted for the optional RaplixaSpray spraying device (sold separately). The 510(k) application is cleared concurrently with the approval of this BLA.

Raplixa is indicated as an adjunct to surgical hemostasis in adults undergoing surgery when control of bleeding by standard surgical techniques (such as suture, ligature, and cautery) is ineffective or impractical. Raplixa may be used in conjunction with an absorbable gelatin sponge (USP).

The safety and efficacy of Raplixa were evaluated in a prospective, multicenter clinical trial of 719 adult subjects undergoing hepatic resection, soft tissue dissection, spinal surgery, or vascular surgery. The time-to-hemostasis (TTH) for the Raplixa with gel sponge arm (480 subjects) was shorter than the TTH for the gel sponge alone arm (239 subjects) for all four surgical categories. No safety concerns were identified in the trial.

The overall study population was generally balanced with regard to sex (female = 46%) and the majority were white (88%). Median age at enrollment was 59.0 years (range, 19–91years). The majority of subjects were < 65 years (461/721; 64%), 260/721 subjects (36%) were ≥ 65 years, and 79/721 (11%) were ≥ 75 years. The two treatment groups did not differ significantly in the distribution of age, sex, or race.

# 2. Background

Fibrin sealants recreate the final stage of the blood coagulation cascade via the reaction of thrombin and fibrinogen at the site of bleeding to form a fibrin clot. They are generally indicated as an adjunct to hemostasis when control of bleeding by standard surgical techniques is ineffective or impractical. The two-component fibrin sealants, in (b) (4) have a long history of clinical use, including FDA-licensed products – TISSEEL and ARTISS (Baxter Healthcare Corp.), and EVICEL (Omrix Biopharmaceuticals, Ltd.). Additionally, two fibrin sealant patch products, for which thrombin and fibrinogen are

embedded into an absorbable backing layer, are licensed in the U.S.: EVARREST by Omrix Biopharmaceuticals and TachoSil by Takeda Pharmaceuticals International. Two thrombin only products, EVITHROM (Ethicon) and RECOTHROM (The Medicines Company) are also approved for the same indication.

Raplixa consists of a blend of fibrinogen and thrombin in a ready-to-use powder form, which can be stored at room temperature and applied directly onto a wound surface without the need for reconstitution or mixing. The manufacturing of a powder with the desired physical properties was achieved by proper formulation and utilization of a spray drying process. Fibrinogen and thrombin are (b) (4) trehalose (b) (4) , sterile (b) (4) and spray-dried separately under aseptic conditions. The resultant (b) (4) are subsequently blended, filled in vials and packaged. Upon application of the powder onto the bleeding site, the product dissolves in blood allowing for thrombin to react with fibrinogen resulting in the formation of a fibrin clot that stops the bleeding. Raplixa is the first biological product to be licensed in the U.S. that is manufactured by spray drying.

Both biological components of Raplixa, human fibrinogen and human thrombin, are manufactured by (b) (4) and licensed by the FDA. Fibrinogen (b) (4) (Human) is licensed for the treatment of acute bleeding episodes in patients with congenital fibrinogen deficiency (b) (4) and Thrombin is licensed for (b) (4) with this BLA.

Raplixa was developed under Investigational New Drug (IND) application, IND 14385, originally submitted by ProFibrix in September 2010. ProFibrix was acquired by The Medicines Company in August 2013 and continues to operate as its wholly owned subsidiary, with The Medicines Company as their U.S. agent.

## *Regulatory History*

The BLA was submitted electronically on January 31, 2014, and reviewed under the standard 12-month review schedule of the PDUFA V program.

During the review, FDA requested ProFibrix to make substantial revisions to the Drug Product Specification and provide justifications for the specifications based on the company's manufacturing experience. In response, ProFibrix submitted Amendment October 16 and 17, 2014, which contained a large amount of new information. This submission was classified as a *Major Amendment*, and the action due date was extended to May 2, 2015.

The data contained in the BLA and its amendments support the consistency and robustness of the manufacturing process to produce Raplixa lots that meet pre-defined acceptance criteria. In addition, all the issues identified during the pre-license inspection (PLI) of (b) (4) the contract manufacturer of the final drug product, in (b) (4) , were satisfactorily addressed.

The clinical data demonstrate the safety and efficacy of Raplixa for the proposed indication. Bioresearch Monitoring inspections support the validity of the clinical data. Raplixa will be the first spray-dried biological product licensed by CBER/FDA. Raplixa is not currently approved or marketed in any other country. On January 22, 2015, the European Medicines Agency Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending the granting of a marketing authorization for Raplixa in the European Union.

**Table 1: Review Milestones**

| Milestone | Date |
|---|---|
| Received | January 31, 2014 |
| Filed | April 1, 2014 |
| Mid-Cycle Communication | July 30, 2014 |
| Major Amendment | October 17, 2014 |
| Late-Cycle Meeting | Cancelled by the company |
| Action Due Date | May 2, 2015 |

# 3. Chemistry, Manufacturing and Controls (CMC)

## a) Product Quality

*Manufacturing Process*

The Raplixa final drug product (FDP) is manufactured at (b) (4) . The FDP manufacturing process is comprised of separate spray drying of formulated and sterile-(b) (4) fibrinogen and thrombin solutions to form (b) (4) of a desired size, followed by blending of the two protein powders and filling of the mixture in single-use vials. These operations are performed under aseptic conditions.

Raplixa is manufactured from (b) (4) - Thrombin (Human) ((b) (4) and Fibrinogen (b) (4) (Human) - supplied by (b) (4). Other components used in the FDP are trehalose and calcium chloride.

The thrombin (b) (4) in a trehalose/(b) (4) , and the fibrinogen (b) (4) - in a trehalose (b) (4) , which provides an aseptic environment.

Sterile-(b) (4) thrombin and fibrinogen (b) (4) are spray-dried separately into a powder (b) (4) . Spray drying is

(b) (4)

The spray-dried thrombin and fibrinogen powders (b) (4) and sealed in aluminum pouches. Stability data support the storage of the powder up to 24 month at 25 °C.

The spray-dried thrombin and fibrinogen powders are blended (b) (4) The blended product (b) (4) 6-mL glass vials (b) (4) . The target fill weight is 0.5, 1.0 or 2.0 g/vial. The vials are (b) (4) stoppered, (b) (4) over-sealed, visually inspected, labeled, and sealed in a foil pouch. All steps from blending to pouching occur aseptically in a Class (b) (4) .

The unit operations and process controls are designed to allow for adjustment of process parameters during manufacture to minimize wastage of raw materials and the potential of failure of the final DP.

## *Source Material - Quality and Control*

(b) (4) thrombin is supplied by (b) (4) in vials with a nominal (b) (4) of (b) (4) . Upon receipt, the *Certificate of Analysis* (CoA) is checked for compliance with raw material specification, and thrombin (b) (4) are tested at (b) (4) fibrinogen is supplied by (b) (4) in vials with a nominal fibrinogen (b) (4) of (b) (4). Upon receipt, the CoA is checked for compliance with raw material specification, and fibrinogen (b) (4) are also tested a (b) (4) . The shipping of fibrinogen and thrombin (b) (4) was validated, monitored, and controlled by (b) (4). Per FDA's request, the acceptance criteria for fibrinogen (b) (4) and thrombin (b) (4) were revised based on previous experience to allow for better control over potential degradation of these proteins during shipping and storage.

Trehalose and calcium chloride are supplied as (b) (4) from qualified vendors. Upon receipt, the CoAs are checked for compliance with raw material specifications, and the materials are tested for (b) (4).

## *In-Process Controls and Hold Times*

Early development studies and risk management tools were used to identify critical process parameters (CPPs) and manufacturing unit operations that can impact the critical quality attributes (CQAs) of the intermediates and FDP. The obtained information was used to

develop in-process controls and FDP specifications for the manufacturing process. Each process parameter was evaluated to assess its impact on the identified CQAs. All CPPs were defined in this way, and control strategies were then developed and implemented.

Since the quality of the Raplixa FDP is dependent on the efficiency of the spray drying process and blending of the thrombin and fibrinogen powders, the controls for these intermediates are critically important. As requested by the FDA, the justifications for in-process control specifications were re-evaluated and the acceptance criteria were revised based on manufacturing experience for the following parameters: thrombin (b) (4) spray-dried thrombin; fibrinogen (b) (4), fibrinogen (b) (4) spray-dried fibrinogen.

Additionally the possibility of adding the in-process specifications for (b) (4) and (b) (4) was considered and discussed with the company. As requested by FDA, tests for (b) (4) were validated and performed on Process Performance Qualification (PPQ) batches to confirm that these parameters are consistent with the theoretical content, and consistent between the batches. The nature of the manufacturing process, provided data and the fact that other in-process control parameters act as surrogate controls for (b) (4) deemed these in-process specification redundant.

All in-process (b) (4) were validated in prospective stability studies that demonstrated that the CQAs of the intermediates were not negatively affected during the established time periods. Thus, we found the CPPs and in-process specifications to be adequate to provide control over the process to manufacture product lots of consistent yield, purity and potency.

## *Process Validation*

ProFibrix has adopted a (b) (4) process validation approach which is based on their understanding of the process accumulated during product development performed at both (b) (4); up to phase 2 clinical trial) and (b) (4) Phase 3 clinical trial and commercial manufacturing site).

- (b) (4)
- (b) (4) .
- (b) (4)

The commercial manufacturing process has been defined using a development strategy based on the principles of (b) (4) Emphasis was put on using information gained from process development studies to identify potential CQAs of spray-dried fibrinogen and thrombin and intermediate blends that were linked to the CQAs of Raplixa FDP.

Risk management and data evaluation were subsequently used to identify the CPPs and the unit operations that could impact the CQAs of Raplixa FDP and its intermediates. Following its design, review of the manufacturing process and risk assessment of all steps were performed to identify control strategies to ensure consistent, reproducible process performance and FDP quality.

Statistical comparisons of CQAs were made using a linear mixed effects regression model between development batches (b) (4) for the spray-dried fibrinogen, thrombin, and FDP. Overall, the statistical analyses confirmed comparability between materials manufactured at (b) (4)

In total, (b) (4) batches were successfully produced at commercial scale, under a prospective process validation protocol, to demonstrate process consistency at (b) (4) , the intended commercial manufacturing site. Enhanced testing regimens were implemented during the different manufacturing steps which comprised (b) (4) The results demonstrated the capability and robustness of the process to routinely produce FDP batches with the desired quality attributes.

## *Final Drug Product: Composition and Presentation*

Raplixa is supplied as a sterile, spray-dried, ready-to-use powder in single-use glass vials packed in a foil pouch. Each vial is filled with 0.5, 1 or 2 g of the product containing nominally 79 mg/g of human fibrinogen and 699 IU/g of human thrombin.

In addition to fibrinogen and thrombin, 824 mg/g trehalose and 11 mg/g calcium chloride were added to manufacture the FDP. The following components are carried over to Raplixa FDP as part of the formulations in the fibrinogen and thrombin (b) (4) human albumin, (b) (4) sodium chloride, (b) (4) sodium citrate, and (b) (4) L-arginine hydrochloride.

## *Companion Device*

The product may be delivered using the gas operated RaplixaSpray spraying device. The device comes in a kit, containing separately sterile-packed sprayer with attached rigid nozzle, flexible nozzle, and air filter. The device is not packaged with the product and is supplied separately.

The 510(k) premarket notification BK 140119 was submitted to FDA for the device. The review of the 510(k) did not raise safety or efficacy concerns. RaplixaSpray is operated at significantly lower pressure than other fibrin sealant delivery devices and poses lower risk of air embolism. The additional risks associated with device use are described in the Risk/Benefit

Assessment section of this document. The device is expected to be cleared for marketing concurrently with the approval of this BLA.

## *Container Closure System*

The container closure system for Raplixa consists of the following components:

- 6-mL clear (b) (4) glass vial (b) (4) Type (b) (4) glass specification
- (b) (4) rubber stopper ((b) (4)
- (b) (4) white crimp seal ('Flip Tear Up') consisting of an aluminum shell (b) (4)
- (b) (4) Aluminum/(b) (4) ) peelable foil pouch (b) (4) aluminum (b) (4) . This material meets the requirements of ISO 11607-1.

## *Product Characterization and Comparability*

The mechanisms of action of fibrin sealants are well studied and the (b) (4) fibrinogen and thrombin (b) (4) have been reviewed in previous applications, therefore, the active components do not require additional characterization. However, in other fibrin sealant products, the thrombin and fibrinogen components are filled and stored separately to avoid premature reaction before their application to a bleeding site. In Raplixa, the fibrinogen and thrombin powders are blended, vialed, stored at room temperature, and can be applied onto a bleeding or oozing wound without the need of reconstitution or mixing. This is achieved by proper formulation and spray drying. Since this is the first application of spray drying to the manufacture of a biological product, characterization studies were undertaken to evaluate the effects of spray drying on the structural and functional properties of fibrinogen and thrombin, the stability of the blend, and the physical properties of the powder.

Structural (b) (4) of fibrinogen and thrombin and absence of premature conversion of fibrinogen to fibrin were confirmed by (b) (4) (for thrombin). (b) (4)

Additionally, although thrombin is supplied by (b) (4) and is a licensed product, ProFibrix performed characterization studies of this material, including analysis of (b) (4)

The current manufacturing process for Raplixa was used for the manufacture of phase 3 clinical batches. In the early stage of product development, (b) (4) . also used a similar process. The difference is that it was not performed under aseptic conditions and the final FDP was sterilized by (b) (4) . ProFibrix compared the (b) (4) phase 2 product and the (b) (4) phase 3 aseptically manufactured product. In addition to the characterization methods described above, the studies included a (b) (4) All test results demonstrated comparability between Raplixa batches used in the nonclinical and clinical studies and the commercial product. The material used in Phase 3 clinical trials is representative of that manufactured by the commercial manufacturing process.

## *Analytical Methods*

Suitable analytical methods have been validated to support in-process control, FDP release and stability testing. All identified issues were adequately resolved in the course of the review through requests of supplemental data, additional documentation, or method re-validation, as well as responses to Form FDA 483 items from the PLI of (b) (4) . In particular:

- (b) (4) of Thrombin in Raplixa FDP (b) (4)

  During the Pre-license Inspection (PLI), FDA also found recurrent out-of-specification (OOS) results in this assay. ProFibrix has since changed the sample (b) (4) procedure which resulted in consistent and acceptable thrombin recovery values. ProFibrix also carried out additional validation which showed improvement in repeatability and intermediate precision.

- *The* (b) (4) of Thrombin in Raplixa FDP and (b) (4) is measured by a (b) (4) . Several deficiencies in method validation were identified by FDA during the review and the PLI. To address these issues, ProFibrix improved the sample (b) (4) procedure; control of standard solutions; pipetting techniques; control of temperatures of solutions and equipment; and assay procedure by introducing a thrombin (b) (4) . The method was re-validated with improved repeatability and intermediate precision. Linearity and accuracy were re-validated using a (b) (4) FDP; and the range of the assay was established based on linearity, accuracy and precision results. Method robustness was also adequately confirmed.

- (b) (4) of Fibrinogen in Raplixa FDP and (b) (4) are determined using a (b) (4) . At FDA's request, ProFibrix performed validation of specificity that included a (b) (4) ,

(b) (4)
accuracy using the actual FDP. The assay range is now in accordance with the specification range for the FDP.

- The absence of premature fibrin formation, critical for maintaining product efficacy, is ensured through control of residual moisture content and fibrinogen integrity in FDP. The *Moisture Content* in Raplixa FDP is determined using a (b) (4) At FDA's request, the method was re-validated using the actual FDP and the range of the assay was re-established to cover the upper specification limit and reflect the manufacturing capability.

- (b) (4) implemented based on FDA feedback. Also, per FDA's recommendation, ProFibrix updated the specification to establish quantitative upper limits for *Fibrinogen* (b) (4) .

An acceptable (b) (4) qualification program has been established for (b) (4) for Fibrinogen (b) (4) which is qualified against the (b) (4) for Fibrinogen (b) (4) . As a (b) (4) for Thrombin, ProFibrix currently uses (b) (4) Thrombin and qualifies it against the current (b) (4) Due to issues with the performance of this standard identified during review and in-support testing by CBER, ProFibrix will establish, as a Post-Marketing Commitment, a (b) (4) Thrombin using a (b) (4)

As a result of our review, all the test methods are sufficiently described in their respective SOPs, adequately validated in accordance with ICH Guideline Q2R1, successfully transferred from (b) (4) , and deemed suitable for their intended use as FDP release tests.

## *Drug Product Release Specification*

The specification for Raplixa FDP is established in accordance with ICH Guidelines Q6A and Q6B. The parameters are selected from CQAs determined in the process development studies and risk assessments. Acceptance ranges/limits are established based on manufacturing capability, clinical outcome, analytical variability, and stability data. Manufacturing capability was assessed through analysis of release data for the Phase 3 clinical and process validation batches. The following substantive issues were resolved in the course of the review:

*Justification of Specification*
Justification of Specification for Raplixa FDP submitted in the original BLA was deemed insufficient. Initially, the key parameters of specification were established arbitrarily and were

not based on manufacturing capability. As requested by FDA, ProFibrix re-evaluated the ranges and limits for all quantitative parameters in the specification based on statistical analysis of data acquired from testing all FDP lots. As a result, ProFibrix revised the limits for fibrinogen potency, fibrinogen content, moisture content, and endotoxin.

(b) (4)

The final FDP Release Specification, as summarized in Table 2, is considered adequate to control the identity, purity, activity, and safety of Raplixa. As the specification is (b) (4) based, the specifications provided in the Table below apply to FDP filled at 0.5, 1.0 or 2.0 g per vial. These specifications are used both for FDP release and monitoring of product stability throughout its shelf-life.

**Table 2: SPECIFICATION FOR FINAL DRUG PRODUCT**

| Test | Method | Specification for Release and Stability |
|---|---|---|
| Appearance | Visual Determination of Appearance | White to off-white powder, no visible agglomerates |
| Identity Fibrinogen | (b) (4) | (b) (4) |
| Identity Thrombin | (b) (4) | (b) (4) |
| Fibrinogen potency | (b) (4) | (b) (4) |
| Thrombin potency | (b) (4) | (b) (4) |
| Fibrinogen content (b) (4) | (b) (4) | (b) (4) |
| Thrombin content (b) (4) | (b) (4) | (b) (4) |
| Fibrinogen content | (b) (4) | (b) (4) |
| Thrombin content | (b) (4) | (b) (4) |
| Moisture content | (b) (4) | (b) (4) |

| | | |
|---|---|---|
| Total protein content | (b) (4) | (b) (4) |
| (b) (4) | (b) (4) | (b) (4) |
| Fibrinogen integrity | (b) (4) | (b) (4) |
| Fibrinogen integrity | (b) (4) | (b) (4) |
| Premature fibrinogen (b) (4) | (b) (4) | (b) (4) |
| Thrombin integrity | (b) (4) | (b) (4) |
| Sterility | (b) (4) | (b) (4) |
| Pyrogenicity | (b) (4) | (b) (4) |
| Endotoxin | (b) (4) | (b) (4) |

## *Batch Analyses and In-Support Testing*

The BLA contains results of release testing of (b) ( FDP batches (representative of (b) ( (b) (4) , manufactured from (b) ( batches of spray-dried fibrinogen and (b) ( batches of spray-dried thrombin. The results for all batches are within FDP release specifications.

The Division of Biological Standards and Quality Control (DBSQC) in the Office of Compliance and Biologics Quality (OCBQ), CBER, FDA, performed in-support testing of the (b) ( Process Performance Qualification (PPQ) batches of Raplixa. The results for all (b) (4) batches are consistent with the FDP release specifications.

The in-support testing results confirmed the suitability of the test methods for their intended use as release tests of the FDP.

## *Stability Studies*

The stability program for Raplixa included studies under long-term storage (25 ºC / (b) (4) conditions. The stability program is extensive and included studies on the FDP, spray-dried fibrinogen, spray-dried thrombin, and the intermediate blend.

The available stability data revealed no negative trends during the observed long-term storage period. The data support the proposed shelf-life of 24 months for the Raplixa final container when stored at 25 ± 2 °C / (b) (4) . No photo-stability studies were performed, as the

product vials are packed in foil pouches and the FDP is not exposed to light until the vial is removed from the carton and pouch.

In-use stability studies were performed at (b) (4) to simulate the worst-case scenario. The data support FDP stability for 1 h after the vial is opened. Absorption of moisture by the FDP results in caking of the powder, and makes it difficult to apply the product to the wound. ProFibrix claimed that the data support the use of FDP within (b) (4) after the vial is opened. However, the moisture content in the FDP lots used in these studies is only (b) (4), which is significantly lower than the (b) (4) limit of the FDP specification. Thus, the label will state that the product should be usedwithin 1 h after opening..

The dating period for Fibrin Sealant (Human) should not exceed the dating periods for spray-dried thrombin and fibrinogen intermediates (whichever is the earliest) when stored at 25 °C. The dating periods for spray-dried thrombin and fibrinogen intermediates should be 24 months from the date of (b) (4) thrombin and fibrinogen (b) (4) when stored at 25 °C, and should not exceed the manufacturer-specified expiration dates for these (b) (4)

Post-approval Stability Protocol and stability commitment were reviewed and found to be adequate to monitor FDP stability post-approval.

*Evaluation of Safety Regarding Adventitious Agents*

Raplixa is manufactured using licensed fibrinogen and thrombin from (b) (4). In summary, the risk of these proteins in transmitting viruses has been reduced by the screening of plasma donors for prior exposure to certain viruses and by testing donations for the presence of current specific virus infections using FDA-licensed serological assays and nucleic acid testing (NAT) assays for HBV, HIV-1/2, and HCV. Furthermore, the manufacturing process for fibrinogen and thrombin include (b) (4) which have been validated in *in vitro* experiments and shown to be effective to inactivate and/or remove both enveloped and non-enveloped viruses.

For the manufacture of Raplixa, human fibrinogen and thrombin are formulated, sterile-(b) (4), and spray-dried separately under aseptic conditions. The spray-dried thrombin and fibrinogen powders are then blended, filled into glass vials, stoppered, over-sealed, visually inspected, labeled, and sealed in a foil pouch. All steps from blending to pouching occur aseptically in a Class (b) (4). Finally, the quality of the FDP is controlled by release testing, which includes safety parameters for sterility, pyrogenicity and endotoxin contents.

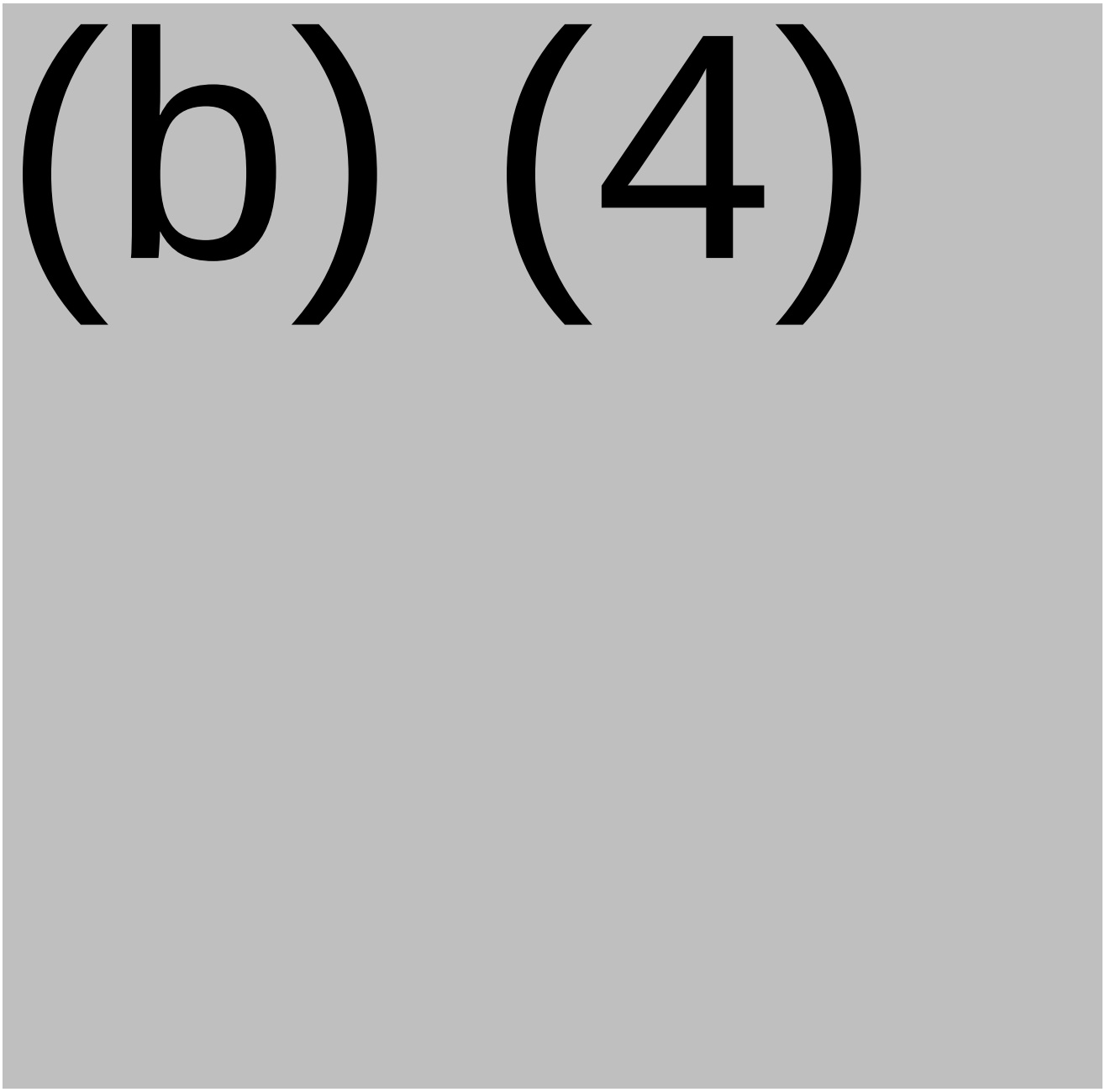
## b) CBER Lot Release

Raplixa is manufactured from plasma-derived human proteins and is subject to routine lot-by-lot release by CBER. The *Lot Release Protocol* for final FDP was submitted as part of the BLA and is found to be adequate. For routine lot release, the applicant will submit final

container samples together with lot release protocols. Testing will be performed according to a lot testing plan that was developed by CBER and will be used for routine lot release.

## c) Facilities review/inspection

The facilities involved in the manufacture of the FDP for Fibrin Sealant (Human) [Raplixa] are listed in Table 3, below. The activities performed and inspectional histories are noted in Table 3 and further described in the paragraphs that follow.



A pre-license inspection was conducted at (b) (4) ProFibrix BV (Leiden, Netherlands), which is owned by The Medicines Company (Seattle, WA). (b) (4) . Observations were related to the laboratory control system, production system, quality systems, facilities and equipment, and materials systems. The (b) (4) responses were submitted and found to be adequate. All inspectional issues are considered to be satisfactorily resolved.

(b) (4) manufactures the (b) (4) used in the manufacture of the fibrin sealant biologic drug product (Raplixa™). The (b) (4) Thrombin (b) (4) and Fibrinogen (Human) are approved FDA drug products. The (b) (4) facility was inspected (b) (4) by Team Biologics for a biennial surveillance inspection. The inspection was designated as Voluntary Action Indicated (VAI).

(b) (4) testing on the final drug product. (b) (4) facility was inspected by Team Biologics (b) (4) . The inspection was designated as Voluntary Action Indicated (VAI).

Facility information and data provided in the BLA were reviewed by OCBQ/CBER and found to be sufficient and acceptable.

### d) Environmental Assessment

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

## Recommendation

The manufacturing process for Raplixa is considered to be adequately validated at the commercial scale and is sufficiently controlled to assure consistent manufacture of the commercial product that meets acceptable release specifications. All inspectional issues were adequately addressed. The reviewers from the Division of Hematology Research and Review, OBRR; the Division of Manufacturing and Product Quality and the Division of Biological Standards and Quality Control, OCBQ, conclude that ProFibrix BV has provided sufficient data and information on chemistry, manufacturing and controls to support the licensure of Raplixa.

# 4. Nonclinical Pharmacology/Toxicology

***General Considerations***

The established pharmacologic class for Raplixa is Fibrin Sealant, and the non-proprietary name is Fibrin Sealant (Human). The proposed indication (from the **INDICATIONS AND USEAGE** section of the ProFibrix's labeling) is "as an adjunct to hemostasis in adults undergoing surgery when control of bleeding by standard surgical techniques (such as suture, ligature, and cautery) is ineffective or impractical. Raplixa may be used in conjunction with an absorbable gelatin sponge (USP)."

Nonclinical data to support the safety and effectiveness of Raplixa as a topical hemostatic agent for use in surgery were obtained from Good Laboratory Practice (GLP) compliant and non-GLP nonclinical studies, following the guidance provided in the ICH S6 *Preclinical Safety Evaluation for Biotechnology-Derived Pharmaceuticals* and the ICH S6(R1) *Addendum*. The safety and effectiveness of Raplixa were characterized in a nonclinical program that included in vivo investigation of safety pharmacology in mice, guinea pigs, swine, and rabbits, nonclinical effectiveness in surgical models in swine, rabbits and sheep, local tolerance in pigs, antigenicity in guinea pigs and rabbits with limited immunogenicity characterization in guinea pigs, and acute and repeat-dose toxicity studies in swine and rabbits. A risk assessment and in vitro and in vivo testing to qualify the safety of the Raplixaspray™ delivery device were conducted as per the ISO 10993 *Biological Evaluation of Medical Devices Part 1: Evaluation and Testing* standards. ProFibrix provided an assessment and limited nonclinical data to address potential long-term adverse effects, including the potential risk of carcinogenicity, from Raplixa product use. Lastly, nonclinical data to address the comparability of the final commercial Raplixa product with the product used in nonclinical and clinical testing were also provided in the BLA submission for review.

Previous experience with similar, human plasma-derived fibrin sealant products has demonstrated that the toxicities of exogenously administered topical thrombin and fibrinogen in animals are extensions of their pharmacologic activity in facilitating coagulation, i.e. hypercoagulability of blood, thrombosis, and thromboembolus formation in treated animals. Additional expected nonclinical findings are development of neutralizing and non-neutralizing antibodies directed against the human fibrinogen and thrombin proteins (i.e., immunogenicity), with the potential to cross-react and neutralize endogenous thrombin and fibrinogen in wild-type animals. The findings with Raplixa, as compared with other, marketed topical fibrin sealant products that were included in the testing as part of the Raplixa nonclinical program, are discussed in the section below.

***Pharmacology and Toxicology Findings***

*Pharmacology*

Nonclinical pharmacology studies with Raplixa were conducted in surgically-induced splenic bleeding in swine, (b) (4) vascular grafts in sheep, cancellous bone breaks in rabbits, and hepatic resection (i.e., liver bleeding) models in rabbits and pigs. In all in vivo animal models of surgically-induced bleeding, application of Raplixa either as the dry powder, with a (b) (4) or gelatin sponge as the carrier, or using the Raplixaspray delivery device improved time to hemostasis, decreased blood loss and promoted the healing process as compared to the standard of care (SoC; i.e, gauze and manual compression), and was comparable in

effectiveness to other, approved topical hemostatic agents used as positive controls in each study. Specifically, in a surgically-induced splenic bleeding model (i.e. 6 mm punch biopsy) in (b) (4) swine, treatment with Raplixa alone or in combination with (b) (4) gelatin sponges at approximately the clinical dose resulted in a 3-fold decrease in time to hemostasis (TTH) and decreased blood loss compared to the group treated with the SoC alone. However, there were no significant, additive or potentiation of effects on either TTH or decreased blood loss in the groups treated with Raplixa plus the gelatin sponges when compared to the (b) (4) alone treated groups, or the group treated with Raplixa alone.

Similar decreases in TTH and blood loss were achieved in the swine spleen bleeding model when Raplixa applied to (b) (4) sponges was compared to (b) (4) plus other, FDA-approved topical fibrin sealants (e.g. (b) (4) or other FDA-approved gelatin sponges as the carrier material (e.g., (b) (4) In this same model, Raplixa delivered using the Raplixaspray device and the (b) (4) resulted in an apparent 40% improvement in TTH and a 3-fold decrease in blood loss, when compared to pigs treated at the wound site with (b) (4) alone. The effectiveness of Raplixa produced for the Phase 2 clinical trials and following (b) (4) in manufacturing site and (b) (4) (Phase 3 (b) (4) was comparable in the swine spleen bleeding model.

The effectiveness of Raplixa alone or in combination with an approved hemostat (i.e., (b) (4) was also evaluated in liver bleeding models in (b) (4) rabbits and (b) (4) swine. In the rabbit models with up to 4, 1-cm liver resections per animal, (b) (4) sponges alone, Raplixa alone and Raplixa plus (b) (4) improved TTH, as compared to (b) (4) alone or SoC. Blood loss was not appreciably improved over the SoC dose group in any of the gelatin sponge or Raplixa-treated groups.

Application of Raplixa in combination with gelatin sponges in a liver bleeding model (i.e., 10 mm punch biopsy at 4 sites) in (b) (4) swine resulted in a 2-fold improvement in TTH compared to the gelatin sponge alone, and was similar in effectiveness to the gelatin sponge plus human thrombin. All three treatments decreased TTH greater than 5-fold, as compared to SoC (manual compression and gauze). Using this same liver bleeding model in swine, the effectiveness of Raplixa applied using the RaplixaSpray device in achieving hemostasis at the wound sites was similar to that of topically applied Raplixa, using either the dry powder or gelatin sponge carrier. These data provided proof-of-concept to support the use of the RaplixasSpray delivery device for application of Raplixa during clinical trials.

A pilot pharmacology study demonstrated that Raplixa applied with the RaplixaSpray device to the site of anastomosis in a (b) (4)[(b) (4)] vascular graft model in (b) (4) sheep adhered to the synthetic graft, and was effective in controlling both mild and moderate bleeding at either arterial or venous anastomotic sites. A separate pilot pharmacology study in an abdominal (retroperitoneal) bleeding model in (b) (4) swine showed that the RaplixaSpray device could deliver Raplixa without risk of thrombus or air embolus, and effectively control bleeding in this model. These data were used to optimize the pressure, device distance and angle of Raplixa delivery using the Raplixaspray device prior to testing the device configuration in clinical trials.

There were no in vitro or in vivo nonclinical studies to support the proof-of-concept or safety of use of Raplixa in spinal surgeries.

Because the potential adverse effects of the topically applied, human thrombin and human fibrinogen in Raplixa are related to its pharmacologic activity as a hemostat, limited toxicology endpoints were incorporated into the pharmacology studies described above. There were no apparent adverse effects of Raplixa, applied topically with or without the different gelatin sponges, or applied with the RaplixaSpray on body weights, food and water consumption, measured hematology endpoints (i.e., active clotting time), or cardiac safety pharmacology endpoints (blood pressure, heart rate, electrocardiogram where measured) in the above studies. In the majority of studies, histopathology and clinical chemistry analyses were not performed. The safety profile of Raplixa in these surgical animal models was similar to that of the active comparator control fibrin sealants or gelatin sponge pads, and to that obtained for the SoC controls.

In summary, animal studies with Raplixa showed the expected pharmacologic (pro-coagulant) activity in multiple animal models of surgically induced bleeding, and the results were similar to those obtained with other, approved fibrin sealant products. There was no evidence of undesirable secondary pharmacologic activity, i.e., thrombogenesis, or other clinical signs of toxicity in the Raplixa-treated animals at doses to up to 11-fold greater than the estimated human Raplixa dose. These data were used as proof-of-concept to support the entry of Raplixa into clinical trials.

*Pharmacokinetics*
Pharmacokinetic studies demonstrated that following application of Raplixa alone to the wound as dry powder, biodegradation of its components begins within minutes, and the systemic absorption of human thrombin and fibrinogen is negligible. Additional nonclinical studies in swine and rabbit liver bleeding models showed that when applied with the gelatin pad, small remnants of Raplixa and the carrier gelatin pad are detectable up to 12 weeks after application. Specifically, in animal studies approximately 5 to 10% of the patch remained at the application site at study termination 12 weeks after surgery. These data are appropriately reflected in Section 13.2, Animal Toxicology and/or Pharmacology, of the product labeling.

*Toxicology*
Overall, the nonclinical safety profile of Raplixa did not identify any unexpected findings or significant concerns in single and repeat-dose toxicity studies conducted in healthy, normal mice, rabbits, guinea pigs and swine. Previous experience with similar, approved fibrin sealant products suggests there is the potential for post-operative re-bleeding, neutralizing antibody formation, and minimally likely, thromboembolic events following Raplixa administration. Raplixa was tested in the nonclinical safety program in both normal animals and the aforementioned surgical animal models at doses of up to 11 times the intended clinical dose (approximately (b) (4) or gelatin USP pad per animal per surgery, and for durations of up to 12 weeks without any serious adverse events reported. Raplixa was well-tolerated in all species and test models, with no mortalities and no evidence of systemic toxicities reported.

Adhesions of mild to moderate severity were present in the majority of animals treated with Raplixa as well as the active comparator controls with no apparent increase in either incidence or severity between the dose groups, and regardless of whether application of Raplixa was peformed with or without the gelatin sponge carrier, or with or without the RaplixaSpray device. Limited, GLP-compliant toxicology studies to determine local tolerability and irritation potential of Raplixa in normal rabbits, antigenicity and potential for allergic or immune-mediated toxicities in healthy guinea pigs, and acute systemic toxicities in normal mice showed no severe toxicities or other treatment-related adverse effects compared to either the negative or active comparator controls. Lastly, evaluation of the RaplixaSpray device in in vitro and in vivo GLP-compliant safety studies conducted under "worst-case" or 'misuse' conditions (i.e., increased pressure, high dose, or application close to large bleeding vessels or tissues), including in the rabbit liver resection model described above, did not induce air emboli or other treatment-related adverse effects.

There were no animal studies for carcinogenicity, fertility, reproductive toxicity or teratogenicity conducted with Raplixa. Raplixa is composed of human thrombin and human fibrinogen; human proteins administered as repeated doses to animals result in development of antibodies that both accelerate clearance of the protein and in some cases, neutralize its pro-coagulant activity. Therefore, long-term, repeat-dose toxicity studies as well as the standard carcinogenicity bioassay (i.e. 2 years of daily Raplixa dosing in both rats and mice) were not feasible to conduct.

No nonclinical reproductive or developmental toxicity studies were conducted in support of this submission. Raplixa received a Pregnancy Category C designation in the labeling that includes a statement that nonclinical reproductive and developmental toxicity studies with Raplixa have not been conducted, and the product should be used only if clearly needed. This labeling is consistent with that included in the prescribing information for other topically applied fibrin sealant products indicated for use as an adjunct to surgical hemostasis.

Because Raplixa is composed of human proteins, the standard battery of genotoxicity testing as recommended in the International Conference on Harmonisation (ICH) S2 guidance documents would not provide information that will address potential mutagenicity of Raplixa, and as per the ICH S6 guidance on biotechnology-derived protein therapeutics, these studies were not required. However, ProFibrix conducted (b) (4) on the components of Raplixa, and the results were negative for genotoxicity. The lack of carcinogenicity and chronic toxicity data, and the negative mutagenicity data in the (b) (4) are addressed in the appropriate sections of the labeling.

*Special Toxicology Studies*

A toxicological risk assessment analysis, providing identification and qualification of the safety of the extractable and potential leachable substances from the components used in the Raplixa manufacturing process and for the Raplixaspray device as per the ISO 10993 standards, was also provided. The results of this risk analysis indicated that the levels of potential leachable or extractable impurities appear acceptable, as they were significantly lower than the maximally allowed daily exposure levels identified from extensive clinical and

nonclinical experience. Additionally, the safety of these extractable and leachable compounds can be considered adequately qualified because several lots of the Raplixa (b) (4) were used in the nonclinical toxicology testing, at doses that exceeded the recommended clinical dose by up to 11-fold. The risk of these compounds to patients treated with Raplixa as an adjunct for surgical hemostasis at the prescribed levels is considered minimal and acceptable.

***Recommendations***
The results from the nonclinical program suggest that treatment with Raplixa will be reasonably safe for use for the labeled clinical indication as "an aid to surgical hemostasis for mild to moderate bleeding from small vessels, when control of bleeding by standard surgical techniques is ineffective or impractical"; specifically for retroperitoneal, soft tissue, and vascular surgeries. The results from both the toxicological risk assessments and the nonclinical studies conducted by ProFibrix support the approval of Raplixa.

# 5. Clinical Pharmacology

Specific clinical pharmacology or formal pharmacokinetic studies of Raplixa have not been performed as Raplixa is applied topically, acts locally and as such there is little to no biodistribution to other tissues including blood.

# 6. Clinical/ Statistical

## a) Clinical Program

Raplixa has been studied in two phase 2 studies [FC-002 (US) in the United States with 70 subjects, and FC-002 (NL) in The Netherlands with 56 subjects]. The results of the phase 3 study FC-004 that enrolled 721 subjects are discussed below.

Profibrix chose to pursue a clinical development program to support an indication for use of Raplixa as an adjunct to hemostasis in general surgery. Therefore, the pivotal study FC-004 enrolled subjects undergoing one of four types of surgery: soft tissue dissection, hepatic, vascular, or spinal surgery. The following table further describes these four surgery types:

**Table 4: Types of Surgery**

| | |
|---|---|
| Spinal Surgery | Cervical, thoracic, or lumbar discectomy; corpectomy; laminectomy; lateral or interbody fusion; bleeding site not confined within a bony cavity |
| Vascular Surgery | Arterial bypass surgery; arteriovenous graft formation for hemodialysis access; carotid endarterectomy |
| Hepatic Resection | Hepatic wedge resection or anatomic resection of 1 to 5 contiguous hepatic segments, which may be combined with surgical procedures involving the pancreas, gall bladder, bile duct or intestines. |
| Soft Tissue Dissection | Primary procedure may include, but not limited to, abdominoplasty, lower anterior resections, abdominal perineal resections, distal |

| | |
|---|---|
| | pancreatectomy, esophagectomy, donor skin graft site in limited burn patients, and mastectomy |

Adapted from STN125523 Protocol FC-004 v4.3 page 6

Subjects were adults without known allergies to study agent components (plasma-derived thrombin and fibrinogen, (b) (4) gelatin). The protocol excluded subjects who had any clinically-significant coagulation disorder that could interfere with the assessment of efficacy or pose a safety risk to the subject according to the investigator, or baseline abnormalities of the International Normalized Ratio (INR) of the prothrombin time greater than 2.5, or an activated partial thromboplastin time (aPTT) greater than 100 seconds during screening that are not explained by current drug treatment (e.g., warfarin, heparin); subjects who had aspartate aminotransferase (ASAT/AST ) or alanine aminotransferase (ALAT/ALT) greater than three times the upper limit of normal range during screening, except for subjects undergoing liver resection surgery or with a diagnosis of liver metastases where there is no upper limit for
these analytes due to the nature of their disease; and subjects who had a platelet count less than 100 times$10^9$ platelets per liter during screening.

The study design planned to enroll approximately 180 subjects into each surgery type using a 2:1 randomization to the test arm (Raplixa with gelatin sponge or RaplixaSpray device, depending on the location of the bleeding site) or the control arm (gelatin sponge alone). A target bleeding site (TBS) with area less than 100 square centimeters was identified during surgery; the bleeding from the TBS had to be characterized as mild or moderate bleeding/oozing not controllable by conventional surgical techniques (suture, ligature, or cautery). Raplixa could be applied in one of three ways, depending on the nature of the TBS: 1) by sprinkling on the TBS followed by application of the gelatin sponge, 2) by sprinkling of Raplixa onto the gelatin sponge, and then application of this to the TBS, or 3) by using the Raplixaspray device.

The primary endpoint was time-to-hemostasis (TTH), censored at 5 minutes. Secondary endpoints included proportion of subjects achieving hemostasis at the TBS at 3 and 5 minutes, use of alternative hemostatic agents at the TBS, transfusion requirements through day 29, and re-operation of the TBS for bleeding.

**Study FC-004 Results.**

**Subject Disposition and Demographics.** A total of 957 potential subjects were screened; of these, 721 subjects (75%) were enrolled and randomized at 28 sites in the U.S. and 29 sites in the EU (the Netherlands, Belgium, and the United Kingdom). Of the 721 randomized subjects, 482 (67%) were randomized to the Raplixa plus gelatin sponge group and 239 (33%) were randomized to the gelatin sponge only group. Two subjects randomized to the Raplixa plus gelatin sponge group were discontinued from the trial before receiving treatment (one because of lack of an appropriate TBS and the other for receiving blood product after randomization, which was a protocol violation). However, these two subjects are part of the 721 subjects in the intent-to-treat (ITT) population used in sensitivity analyses. The safety population (defined as all subjects who were randomized and received study treatment) and

efficacy population (defined as all subjects who were randomized, received study treatment, and had a TTH assessment) were identical and consisted of 719 subjects.

Among the 480 subjects treated with Raplixa plus gelatin sponge, 122 underwent spinal surgery, 117 underwent vascular surgery, 119 underwent hepatic resection, and 122 underwent soft tissue dissection. Among the 239 subjects treated with gelatin sponge alone, 61 underwent spinal surgery, 58 underwent vascular surgery, 61 underwent hepatic resection, and 59 underwent soft tissue dissection.

The majority of subjects (695/719; 96%) completed the Day 29 safety assessments. Of the 24 subjects who prematurely discontinued from the trial after receiving treatment, 15 were in the Raplixa plus gelatin sponge group and nine were in the gelatin sponge alone group. Reasons for premature discontinuation were death (10 subjects: eight Raplixa plus gelatin sponge, two gelatin sponge alone), lost to follow-up (10 subjects: six Raplixa plus gelatin sponge, four gelatin sponge alone), withdrawal of consent (two subjects: one Raplixa plus gelatin sponge, one gelatin sponge alone), “other” (one subject: gelatin sponge alone; subject did not return for his or her final follow-up visit), and non-compliance (one subject; gelatin sponge alone).

The overall study population was generally balanced with regard to sex (female = 46%) and the majority were white (88%). Median age at enrollment was 59.0 years (range, 19–91 years). The majority of subjects were < 65 years (461/721; 64%), 260/721 subjects (36%) were ≥ 65 years, and 79/721 (11%) were ≥ 75 years. The two treatment groups did not differ significantly in the distribution of age, sex or race.

**Study FC-004 Efficacy**

The results for the primary endpoint, time-to-hemostasis within 5 minutes, are shown in the following table:

**Table 5: Time to Hemostasis by Surgery Type and Treatment**

| | Raplixa Plus Gelatin Sponge Median TTH, min. (95% CI) | Gelatin Sponge Alone Median TTH, min. (95% CI): | Cox Proportional Hazard Ratio | p-value[a] |
|---|---|---|---|---|
| **Spinal[b] (n=183)** | 1.0 (-, -) | 2.5 (2.0, 3.0) | 3.3 | <0.0001 |
| **Vascular[c] (n=175)** | 2.0 (1.5, 2.5) | 4.0 (3.0, 5.0) | 2.1 | <0.0001 |
| **Hepatic Resection[d]** | 1.0 (1.0, 1.5) | 2.0 (1.5, 2.5) | 2.3 | <0.0001 |
| **Soft Tissue Dissection[e] (n=181)** | 1.5 (1.0, 1.5) | 2.5 (2.0, 3.5) | 3.4 | <0.0001 |

[a] Log-rank test
[b] Raplixa + Gelatin Sponge n= 122; Gelatin Sponge Only n=61
[c] Raplixa + Gelatin Sponge n= 117; Gelatin Sponge Alone n=58
[d] Raplixa + Gelatin Sponge n= 119; Gelatin Sponge alone n= 59
[e] Raplixa + Gelatin Sponge n= 122; Gelatin Sponge alone n= 59
Source: STN125523 Sudy FC-004 Clinical Report page 44

Results for the secondary endpoints were either favorable for Raplixa, or not different from the control results. Raplixa had statistically significant better results for TTH at 3 and 5 minutes; had the same extent of use of alternative hemostatic agents at the TBS (1 percent vs. 3 percent for the control); had the same extent of RBC transfusion requirements through day 29 (8 percent vs. 9 percent for the control); and had no re-operations at the TBS for bleeding, whereas the control arm had one subject re-operated for bleeding at the TBS.

**Bioresearch Monitoring (BIMO) Inspections**

BIMO inspections of five clinical study sites were performed in support of the BLA and were conducted in accordance with FDA's Compliance Program Guidance Manual (CPGM) 7348.811, Inspection Program for Clinical Investigators. The number of subjects selected for data verification and enrolled at the selected sites represents 15 percent of subjects enrolled in the pivotal study FC-004.

The inspection reports did not reveal significant problems that impact the corresponding data submitted in the BLA.

### b) Pediatrics

Pediatric studies for all age groups are deferred, as approved at the March 5, 2015, meeting of the Pediatric Research Committee (PeRC).

### c) Other Special Populations

There were no other special population results associated with this BLA.

### d) Overall Comparability Assessment

The current manufacturing process for Raplixa was used to manufacture the (b) (4) batch used in the Phase 3 clinical trial. In early stage of product development, (b) (4) . used a similar manufacturing process. The difference is that it was not performed under aseptic conditions and the final FDP was sterilized by (b) (4) .

ProFibrix conducted comparability and characterization studies of (b) (4) Phase 2 product and the (b) (4) Phase 3 aseptically manufactured product and provided sufficient data to demonstrate biochemical and functional comparability between Raplixa batches used in the nonclinical and clinical studies and the commercial product. The material used in the Phase 3 clinical trials is representative of that manufactured by the commercial manufacturing process.

# 7. Safety

The safety database is derived from the 480 subjects who were treated with at least one vial of Raplixa while undergoing spinal surgery, vascular surgery, hepatic resection, or soft tissue dissection. The method of exposure is summarized in the following table:

**Table 6: Study FC-004 for Target Bleeding Site: Number of Subjects in Administration Type by Surgery Type**

| | **Sprinkled Directly from Vial** | **Raplixa Applied to Moist Gelatin sponge** | **RaplixaSpray Device Used** | **Other[1]** |
|---|---|---|---|---|
| Spinal surgery | 8 | 83 | 28 | 4 |
| Vascular surgery | 48 | 82 | 1 | 2 |
| Hepatic resection | 8 | 1 | 124 | 0 |
| Soft tissue dissection | 4 | 4 | 122 | 0 |
| **Total** | 68 | 170 | 275 | 6 |

[1]In spinal surgery: in 1 subject Raplixa applied with dry gelatin sponge, in 1 subject Raplixa applied with (b) (4) , in 2 subjects Raplixa was underdosed from protocol recommendation; in vascular surgery: in 1 subject Raplixa applied with dry gelatin sponge, in 1 subject Raplixa only 25 percent of dose applied.

In the adult study FC-004 (randomized 2:1 Raplixa + gelatin sponge vs. gelatin sponge alone), treatment-emergent adverse events (i.e. adverse events that occurred after exposure to the study agent and during the next 29 days) were experienced by 426 of 480 subjects in the Raplixa + gelatin sponge arm, and 214 of 239 subjects in the gelatin sponge alone arm.

**Deaths.** There were 10 deaths during the 30-day follow-up period (and 1 death in the post-study period). None of the deaths are attributable to the study agents, but appear to be caused by the underlying medical conditions.

Intensity of adverse events was assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 or using the following scale for items not listed in the CTCAE v4.0:

- Mild (awareness of sign or symptom, but easily tolerated)
- Moderate (discomfort sufficient to cause interference with normal activities)
- Severe (incapacitating, with inability to perform normal activities)
- Life-threatening (subject is at risk of death due to AE)
- Death

Most adverse events were grade 1 or 2 severity; adverse events of ≥ grade 3 were experienced by 105 of 480 subjects in the Raplixa + gelatin sponge arm, and 44 of 239 subjects in the gelatin sponge alone arm but these were not considered to be adverse reactions to the product.[1] The most commonly reported adverse events (> 5 % subjects) were nausea, constipation, post-operative pain, pyrexia, and low blood pressure, with the majority considered mild in intensity. The following table shows the frequency of these adverse events in the four surgical categories by treatment:

[1] As stated in the CTCAE v4.0:
Grade refers to the severity of the AE. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline:

| | |
|---|---|
| Grade 1 | Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated. |
| Grade 2 | Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental Activities of Daily Living (ADL) -- instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc. |
| Grade 3 | Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL -- refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.. |
| Grade 4 | Life-threatening consequences; urgent intervention indicated. |
| Grade 5 | Death related to AE. |

**Table 7: Commonly reported Adverse Reactions (> 5% subjects) in Raplixa Clinical Trials**

| | Phase 2[a)] | | Phase 3[b)] | | Total | |
|---|---|---|---|---|---|---|
| **N (%) of Patients Preferred Term** | **FC+ G[d] (N=86)** | **G[d] (N=39)** | **FC+ G[d] (N=480)** | **G[d] (N=239)** | **FC+G[d] (N=566)[c)]** | **G[d] (N=278)** |
| Procedural pain | 40 ( 47) | 16 ( 41) | 257 ( 54) | 134 ( 56) | 297 ( 52) | 150 ( 54) |
| Nausea | 26 ( 30) | 13 ( 33) | 120 ( 25) | 48 ( 20) | 146 ( 26) | 61 ( 22) |
| Constipation | 21 ( 24) | 9 ( 23) | 72 ( 15) | 31 ( 13) | 93 ( 16) | 40 ( 14) |
| Incision site pain | 5 ( 6) | 3 ( 8) | 63 ( 13) | 32 ( 13) | 68 ( 12) | 35 ( 13) |
| Pyrexia | 7 ( 8) | 5 ( 13) | 37 ( 8) | 11 ( 5) | 44 ( 8) | 16 ( 6) |
| Anaemia | 4 ( 5) | 2 ( 5) | 33 ( 7) | 17 ( 7) | 37 ( 7) | 19 ( 7) |
| Vomiting | 11 ( 13) | 2 ( 5) | 26 ( 5) | 12 ( 5) | 37 ( 7) | 14 ( 5) |
| Hypotension | 2 ( 2) | 2 ( 5) | 38 ( 8) | 16 ( 7) | 40 ( 7) | 18 ( 6) |
| Pruritus | 3 ( 3) | 1 ( 3) | 33 ( 7) | 8 ( 3) | 36 ( 6) | 9 ( 3) |
| Hypertension | 1 ( 1) | 0 | 25 ( 5) | 10 ( 4) | 26 ( 5) | 10 ( 4) |

[a] FC-002 US and FC-002 NL clinical trials combined
[b] FC-004 Pivotal Phase 3 clinical trial
[c] Sorted on Total Raplixa + Gelatin Sponge subjects
[d] FC+G = Raplixa + Gelatin Sponge; G= Gelatin sponge alone
Source: Raplixa package insert

**Serious Adverse Events (SAEs).** A total of 110/719 subjects (15%) experienced an SAE: 81/480 subjects (17%) treated with Raplixa and 29/239 subjects (12%) treated with gelatin sponge alone. All SAEs were reported in <5% of subjects in either treatment group within each surgical setting and the frequencies and the types of events were similar between the two treatment groups. No SAEs were considered by the clinical reviewer to be related to study treatment.

**Viral Safety.** There were two subjects with treatment-emergent positive hepatitis C antibody test results. Subject 402-019, 55 y.o. African-American male, (Raplixa + sponge arm) had a positive result on November 9, 2012. Subject 402-003, 47 y.o. white male, (sponge alone arm) had a positive result on September 29, 2012. Both subjects were enrolled at Washington University, St. Louis MO. Both subjects were undergoing amputations (below-the-knee or partial foot) and were enrolled in the soft tissue dissection category of study FC-004.

> ***Reviewer's comment:*** These two hepatitis C seroconversions are most likely community-acquired, because the plasma-derived components are licensed products that have undergone viral safety validation procedures during manufacturing, and there are no additional cases that could implicate this product, or the licensed products from which it is made.

***Thrombogenicity***

Thrombogenicity potential might be suspected due to the pharmacologic mode of action. Clinical studies did not show any increased incidence of thromboembolic events (see Table 7). In addition, the rates of occurrence of the following adverse events were similar in both Raplixa and placebo arms: AV fistula thrombosis, vascular graft thrombosis, intestinal ischemia, vena cava thrombosis, cardiac arrest, myocardial infarction, myocardial ischemia, acute coronary syndrome, silent MI, cerebral infarction and cerebrovascular accident. According to ProFibrix, topical administration to a small area that is the site of bleeding, combined with rapid inactivation, results in no systemic exposure to active thrombin/fibrinogen.

# 8. Advisory Committee Meeting

The Division of Hematology Research and Review and the Division of Hematology Clinical Review in the Office of Blood Research and Review reviewed the information in this application and determined that referral to the Blood Products Advisory Committee prior to product approval was not needed.

The notable issues raised in the course of the review are described in the respective sections of this document, and they have been satisfactorily resolved through information requests and teleconferences. There are no other relevant regulatory issues.

# 9. Labeling

The proposed proprietary name, Raplixa, was reviewed by the Advertising and Promotional Labeling Branch (APLB) from a promotional and comprehension perspective on January 2, 2014. The proprietary name was determined to be acceptable.

The FDA comments regarding product labeling were conveyed on March 24, 2015. The final Full Prescribing Information (FPI) was submitted on April 21, 2015 and was determined to be acceptable. Carton and container labels submitted to the BLA on April 27, 2015 were considered acceptable

# 10. Recommendations and Risk/Benefit Assessment

**a) Recommended Regulatory Action**

The CBER review committee recommends **APPROVAL** of this BLA. The manufacturing process for Raplixa, Fibrin Sealant (Human), is considered validated and adequately controlled. Efficacy and safety clinical data for Raplixa support a favorable benefit/risk determination for the proposed indication as an adjunct to surgical hemostasis for adults

undergoing surgery when control of bleeding by standard surgical techniques is ineffective or impractical.

**b) Risk/Benefit Assessment**

Surgery creates large areas of bleeding that must be addressed before surgical closure. There are several fibrin sealant products available for use as an adjunct to hemostasis in various surgical settings.

Fibrin sealant products, when used as adjuncts to hemostasis, have not been able to demonstrate a traditional clinical benefit based on mortality or morbidity endpoints. For this reason, CBER decided to accept the surrogate endpoints of time-to-hemostasis or percent of subjects achieving hemostasis at a defined time point as acceptable primary endpoints for licensure. Perhaps the major benefit from the licensure of these products has been the decreased use of the surgical practice of "home brew" fibrin sealants made from fresh frozen plasma and licensed thrombin. These "home brew" products are thought to have a greater risk compared licensed fibrin sealant products that are validated to be virally safe.

There is no unmet medical need because the clinical studies have not demonstrated a more significant clinical benefit from the use of Raplixa compared to that of other adjunct to hemostasis products. All the evidence indicates that the risk associated with the use of Raplixa as an adjunct to hemostasis is minor. There is no evidence of an increased risk for thrombogenicity or increased immunogenicity; however, continued surveillance for these events is advisable.

There is a potential risk for air embolism if the Raplixaspray application device (510(k) premarket notification BK140119) is used inappropriately. This potential risk is addressed through labeling for appropriate use. Routine surveillance will identify whether this risk management approach is sufficient to address the potential risk of air embolism.

The benefit-risk assessment for Raplixa is favorable.

**c) Recommendation for Post-marketing Risk Management Activities**

The review of the clinical data did not raise major safety concerns. Therefore, there is no *Risk Evaluation and Mitigation Strategies* (REMS), post-marketing commitment or post-market requirement for this product. ProFibrix has proposed enhanced pharmacovigilance and risk communication activities for air embolism adverse events. ProFibrix will conduct targeted follow-up, by questionnaire, of events that may be indicative of air or gas embolism. They will attempt examination of the RaplixaSpray device if such incidents are reported, and review product complaints for the RaplixaSpray devices with the same lot number.

Thrombogenic potential might be suspected due to the pharmacologic mode of action, however the studies conducted by the applicant showed no thrombosis safety signal. According to ProFibrix, topical administration to a small area at the site of bleeding, combined with rapid inactivation, results in no systemic exposure to active thrombin/fibrinogen.

The Warnings and Precautions section of the label states "Do not apply Raplixa directly into the circulatory system. Intravascular application may result in a life-threatening result."

**d) Recommendation for Post-marketing Activities**

The licensure of Raplixa includes a post-marketing commitment and the deferred pediatric study FC-007 as describe below.

As stated in Amendment 32 dated April 17, 2015, ProFibrix commits to the following:

1. To establish, following a prospectively defined protocol, its (b) (4) for thrombin for the *Thrombin* (b) (4) *Thrombin* (b) (4) Thrombin (Human) (b) (4) [Thrombin ((b) (4) used for the manufacture of Raplixa. This (b) (4) thrombin standard, and (b) (4) international units (b) (4)

   ProFibrix will establish the protocol and will select, calibrate and qualify a (b) (4) Thrombin (b) (4) for the appropriate assays. ProFibrix will submit the full package to the FDA for review by November 30, 2015 as a Post Marketing Commitment Final Study Report.

A Pediatric study protocol FC-007 was proposed to support the use of Raplixa in pediatric populations. Protocol FC-007 was submitted on 1 July 2014 with the objective of characterizing safety for achieving hemostasis in pediatric patients undergoing hepatic, soft tissue or vascular surgery. The approval letter for STN125523/0 contains the following PREA post-marketing requirement:

2. Deferred pediatric study under PREA for use as an adjunct to surgical hemostasis for mild to moderate bleeding from small vessels when control of bleeding by standard surgical techniques is ineffective or impractical in pediatric patients ages 0 to 18 years.

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   | Final Protocol Submission: | January 2014 |
   | Study Completion Date: | September 2015 |
   | Final Report Submission: | March 2016 |