



Department of Health and Human Services  
Public Health Service  
United States Food and Drug Administration  
Center for Biologics Evaluation and Research



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**Pharmacology / Toxicology Primary Discipline Review**

**To:** File (Original BLA 125523/0)

**From:** La’Nissa A. Brown, PhD, Pharmacologist, Division of Hematology Clinical Review (DHCR)/ Office of Blood Research and Review (OBRR)

**Through:** Anne M. Pilaro, PhD, Supervisory Toxicologist, DHCR/OBRR

**Subject:** STN BLA 125523/0 – ProFibrix BV’s Original Biological License Application (BLA) for *Raplixa*™, Human plasma-derived fibrin sealant, spray dried

**Indication:** As an adjunct to surgical hemostasis in adults for mild to moderate bleeding from small vessels when control of bleeding by standard surgical techniques is ineffective or impractical. Raplixa may be used in conjunction with an absorbable gelatin sponge (USP).

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This memorandum is the final primary review of the nonclinical program based on pharmacology/toxicology data submitted in the Original Biological License Application (BLA) STN 125523/0 for Raplixa™, Human plasma-derived fibrin sealant spray dried. Raplixa is indicated “as an adjunct to surgical hemostasis in adults for mild to moderate bleeding from small vessels when control of bleeding by standard surgical techniques is ineffective or impractical.”; specifically in spinal, retroperitoneal, soft tissue, and vascular surgeries. From the toxicology/pharmacology reviewer perspective, this original biological application STN 125523/0 is recommended for approval.

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**Cross reference:** 510K #BK140119/0 FibroSpray Device to deliver Fibrocaps

**I. Recommendations**

The results from the nonclinical program suggested that treatment with Raplixa™ will be reasonably safe for use for the labeled clinical indications for treatment for “an aid to surgical hemostasis for oozing blood and mild to moderate bleeding from small vessels when control of bleeding by standard surgical techniques is ineffective or impractical” specifically spinal, retroperitoneal, soft tissue, and vascular

surgery. The Pharmacology/Toxicology Reviewer, La’Nissa A. Brown PhD, recommends that the Biological License Application (BLA) 125523/0 for Raplixa™ be approved, based on the results from both the toxicological risk assessment, and the nonclinical studies conducted by the Applicant.

## **II. Summary Basis for Regulatory Action (SBRA) for Nonclinical Data**

### **Official Summary Basis for Regulatory Action (SBRA)**

#### **4. Non-clinical Pharmacology/Toxicology**

##### ***General Considerations***

Raplixa™ was determined to be safe for its intended use as a hemostatic agent, based on Good Laboratory Practice (GLP) compliant and non-GLP nonclinical studies, and on its experimental use in surgical settings during clinical trials conducted in the United States. The nonclinical program consisted of a battery of studies to demonstrate the safety and effectiveness of Raplixa; these studies included investigation of safety pharmacology in mice, guinea pigs, swine, and rabbits, nonclinical efficacy 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. The Applicant has also completed a risk assessment analysis to qualify the safety of the Raplixa delivery device as per the ISO 10993 standards, and provided an assessment and limited nonclinical data to address potential long-term adverse effects, including the potential risk of carcinogenicity, from product use.

##### ***Pharmacology and Toxicology Findings***

The nonclinical safety profile determined for Raplixa™ is sufficient to support BLA approval. 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 program 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. Nonclinical studies in surgically-induced splenic bleeding in swine, (b) (4) vascular grafts in sheep, and partial hepatectomy (i.e., liver bleeding) models in rabbits and pigs demonstrated that application of Raplixa™ improved time to hemostasis and promoted the healing process, when compared to the standard of care and to other, approved topical hemostats. Pharmacokinetic studies demonstrated that following application of Raplixa alone to the wound as dry powder, degradation of its components begins within minutes. However, when applied with the gelatin pad, small remnants of Raplixa and the carrier gelatin pad may be present up to 12 weeks after application. Specifically, in animal studies greater than 5% of the patch was remaining at the application site at study termination 12 weeks after surgery. A potential safety concern is possible immunogenic responses to the foreign components of Raplixa, and for potential obstructions due to adhesions until complete degradation of both Raplixa and the gelatin pad occur. These safety concerns have been appropriately monitored in clinical trials, and are addressed in the labeling. A risk assessment of the potential leachable and extractable components present in Raplixa and of the excipients used in the final drug product was conducted as per ISO 10993 standards, and the results were acceptable.

##### ***Recommendations***

The results from the nonclinical program suggest that treatment with Raplixa™ will be reasonably safe for use for the labeled clinical indications as treatment for “an aid to surgical hemostasis for oozing blood and mild to moderate bleeding from small vessels, when control of bleeding by standard surgical techniques is ineffective or impractical”; specifically for spinal, retroperitoneal, soft tissue, and vascular

surgeries. Based on the results from both the toxicological risk assessments and the nonclinical studies conducted by the Applicant, this submission is recommended for approval.

### **III. Nonclinical Labeling for the Package Insert (PI) for STN 125523/0**

The label was revised to reflect current labeling guidelines and the relevant information for prescribing data based on nonclinical and clinical experience using RAPLIXA<sup>TM</sup>

#### **Clean Revised Version of Label for Nonclinical**

##### **8.1 Pregnancy**

Animal reproduction studies have not been conducted with Raplixa. It is also not known whether Raplixa can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Raplixa should be given to a pregnant woman only if clearly needed.

##### **8.3 Nursing Mothers**

It is not known whether Raplixa is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercise when Raplixa is administered in a nursing woman.

##### **12.1 Mechanism of Action**

Raplixa contains a spray-dried mixture of human fibrinogen and human thrombin powders that are designed to mimic the final steps in the coagulation cascade. Raplixa dissolve readily on contact with aqueous fluids (e.g., blood) activating thrombin which triggers an immediate conversion of fibrinogen into fibrin, and subsequent clot formation.

##### **12.3 Pharmacokinetics**

Pharmacokinetic studies have been performed. Because Raplixa is applied only topically, systemic exposure or distribution to other organs or tissues is not expected.

##### **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

Long-term studies in animals to evaluate the carcinogenic potential of RAPLIXA or studies to determine the effects of Raplixa on genotoxicity or fertility have not been performed. An assessment of the carcinogenic potential of Raplixa was completed and suggests minimal carcinogenic risk from product use.

##### **13.2 Animal Toxicology and/or Pharmacology**

There were single or multiple dose implantation studies up to 12 weeks after Raplixa plus gelatin sponge (USP) application into liver or spleen. These studies also demonstrated a progressive biodegradation of Raplixa consistent with metabolism based on fibrinolysis and phagocytosis.

#### **Labeling Revisions to Applicant's Label**

**Applicant's Language (Section edited):**

### **8 USE IN SPECIFIC POPULATIONS**

#### **8.1 Pregnancy**

Safety and efficacy studies have not been completed in pregnant woman.

**FDA Revision:** Section 8.1 was modified to reflect labeling guidelines as per 21 CFR 201.57.

### **8.1 Pregnancy**

Animal reproduction studies have not been conducted with Raplixa. It is also not known whether Raplixa can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Raplixa should be given to a pregnant woman only if clearly needed.

**Justification:** Revised the language to be consistent with that provided in the CFR to describe the Pregnancy designation for Raplixa™.

**Applicant's Language (Section edited):**

### **8.3 Nursing Mothers**

Safety and efficacy studies have not been completed in nursing mothers.

**FDA Revision:** Section 8.3 was modified to reflect labeling guidelines as per 21 CFR 201.57.

### **8.3 Nursing Mothers**

It is not known whether Raplixa is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercise when Raplixa is administered in a nursing woman.

**Justification:** Revised the language to be consistent with that provided in the CFR to describe the risks of use of Raplixa™ in nursing mothers.

## **12 CLINICAL PHARMACOLOGY**

**Applicant's Language (Section edited):**

### **12.1 Mechanism of Action**

Raplixa contains a spray-dried mixture of human plasma-derived fibrinogen and human plasma-derived thrombin powders that are designed to mimic the final steps in the common pathway of the coagulation cascade. Raplixa dissolve readily on contact with aqueous fluids (e.g., blood) activating thrombin which triggers an immediate conversion of fibrinogen into fibrin, and subsequent clot formation.

**FDA Revision:** Section 12.1 section was edited to convey important information that was omitted by the Applicant

### **12.1 Mechanism of Action**

Raplixa contains a spray-dried mixture of human fibrinogen and human thrombin powders that are designed to mimic the final steps in the coagulation cascade. Raplixa dissolve readily on contact with aqueous fluids (e.g., blood) activating thrombin which triggers an immediate conversion of fibrinogen into fibrin, and subsequent clot formation.

**Justification:** Section 12.1 section was edited to convey important information that needed to be added to the label to prevent misinterpretation.

### **Section 12.3 added**

**FDA Revision:** Section 12.3 made need to be added to describe lack of pharmacokinetic studies

### 12.3 Pharmacokinetics

Pharmacokinetic studies have been performed. Because Raplixa is applied only topically, systemic exposure or distribution to other organs or tissues is not expected.

**Justification:** Section 12.3 Pharmacokinetics was added to convey important information that was omitted by the Applicant and needed to be added to the label.

## 13. NONCLINICAL TOXICOLOGY

### Applicant's Language (Section edited):

#### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies to evaluate the carcinogenic potential of Fibrocaps have not been performed. The in vitro mutagenic potential of Fibrocaps has been evaluated in an (b) (4) mutagenicity study. Fibrocaps was found to be non-toxic and non-mutagenic in the (b) (4) assay. The effect of Fibrocaps on fertility has not been characterized.

#### FDA Revision: Section 13.1

#### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals to evaluate the carcinogenic potential of RAPLIXA or studies to determine the effects of Raplixa on genotoxicity or fertility have not been performed. An assessment of the carcinogenic potential of Raplixa was completed and suggests minimal carcinogenic risk from product use.

**Justification:** Section 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility section was edited to convey important information that was omitted by the Applicant (i.e. an assessment of carcinogenic risk was performed, although in vivo animal carcinogenicity testing was not conducted) and needed to be added to the label.

### Applicant's Language (Removed the entire Section 13.2, below):

#### 13.2 Animal Toxicology and/or Pharmacology

Overall, no clinical signs of overt toxicity were observed in the in non-clinical safety studies of Fibrocaps. Importantly, no clinical observations, clinical or anatomic pathologies (including evidence of emboli) were observed in single or multiple dose implantation studies of Fibrocaps plus gelatin sponge (USP) into liver or spleen. These studies also demonstrated a progressive biodegradation of Fibrocaps consistent with metabolism based on fibrinolysis and phagocytosis. Fibrocaps did not interfere with bone healing and had no evidence of incompatibility with bone tissue. ISO 10993 studies of Fibrocaps found no evidence of acute toxicity, genotoxicity or significant sensitization or irritation. Additional in vivo studies demonstrated that Fibrocaps had the expected pharmacology and was able to reduce time-to-hemostasis as compared to various control hemostatic agents.

**FDA Revision:** Language immediately under the header for Section 13.2 was removed.

**Justification:** Removed entire Section 13.2 due to redundancy. The product testing and findings in animals are not essential for clinical prescribing information; the Raplixa product was evaluated in clinical trials and the results and safety profile that occurred are appropriately described in the clinical sections of the label.

#### IV. Background

Profibrix BV Incorporated has manufactured a fibrin powder named Raplixa™, code name Fibrocaps, that is indicated as “An aid to surgical hemostasis for oozing blood and mild to moderate bleeding from small vessels when control of bleeding by standard surgical techniques is ineffective or impractical”; specifically, for use in spinal, retroperitoneal, soft tissue, and vascular surgeries. Fibrocaps is a ready-to-use fibrin dry powder consisting of a blend of human fibrinogen (b) (4) and plasma derived human thrombin (b) (4) particles spray dried with trehalose (b) (4), with a concentration of (b) (4) fibrinogen and (b) (4) thrombin per gram Raplixa in the product used in preclinical studies. Fibrocaps was developed for clinical use based on its unique formulation and improved handling properties, compared to other fibrin sealants. The Applicant claims that the dry powder formulation allows more irregular bleeding surface areas to be treated, and Raplixa can be shipped and stored at room temperature.

**Related Files: (if any) IND and/or STNs: IND 14385 and 510K 140119/0 Fibrospray Device**

#### V. Proposed Use and Doses

Raplixa is a fibrin sealant (spray dried) intended for use as an aid to surgical hemostasis for mild to moderate bleeding from small vessels when control of bleeding by standard surgical techniques such as suture, ligature, or cautery; and as a suture support in vascular surgery is ineffective or impractical. Raplixa can be applied with Fibrospray Delivery Device. Raplixa may be used in conjunction with an absorbable gelatin sponge, (USP). Raplixa is a ready-to-use fibrin dry powder consisting of a blend of human fibrinogen (b) (4) and plasma derived human thrombin (b) (4) particles spray dried with trehalose with a concentration of 79 mg human fibrinogen and (b) (4) human thrombin per gram Raplixa supplied in 0.5g, 1.0 g or 2.0g vials, with the treated area based on the physician's discretion following the guidelines below:

Maximum Surface Area Direct Application from Vial	Maximum Surface Area Application Using Fibrospray	Raplixa Package Size
25 cm <sup>2</sup>	50 cm <sup>2</sup>	0.5 g
50 cm <sup>2</sup>	100 cm <sup>2</sup>	1 g
100 cm <sup>2</sup>	200 cm <sup>2</sup>	2 g

#### V. General Comments

- Animal studies for fertility, reproductive toxicity or teratogenicity have not been conducted, as these were not required according to ICH S6 guidance.
- There were no special toxicity concerns identified for this product regarding impurities or unexpected toxic effects. A risk assessment analysis has been conducted on the carcinogenic potential of the product, and Fibrocaps is considered of minimal risk for tumorigenicity.
- There is clinical experience using this product, including in 566 patients in the clinical trials conducted to date. Clinical data on Fibrocaps degradation and immunogenicity will be used in lieu of requesting additional nonclinical studies to support and corroborate the safety profile of RAPLIXA for BLA licensure.

## **VI. List of Nonclinical Studies in STN BLA 125523/0**

### **Primary Pharmacodynamics**

- Study Report 1698-001- Non-GLP Pilot Study of Hemostasis in a Spleen Bleed Time Model in the Swine
- Study Report 1698-002 (SR-FC-P011) - Study of Fibrocaps in a Spleen Bleed Time Model in Swine
- Study Report 1698-003 (SP-FC-P013) - Acute Study of Fibrocaps + (b) (4) vs. (b) (4) Hemostasis in a Spleen Bleed Time Model in the Swine
- Study Report 1698-004 – Acute Study of Fibrocaps Compared to Two Hemostatic Agents in a Spleen Time Model in the Swine
- Study Report 1698-009 (SR-FC-054) - Acute Study of Fibrocaps in Spleen Bleed Time Model in The Swine
- Study Report SR-FC-004 – A Pilot Study to Assess the Hemostatic Properties of a Novel Plasma-Based Thrombin/ Fibrin Sealant in Sheep Vascular Graft Model
- Study Report SR-FC-P014 - Hemostasis Effect of Fibrocaps + Gelatin in a Swine Liver Bleeding Model
- Study Report SR-FCP015 - Pilot Study of Fibrocaps in a Sheep (b) (4) Vascular Graft Model
- Study Report SR-FC-P066 – Fibrospray Device Development: Interchangeable Flexible Nozzle Assessment in Swine Model

### **Toxicology**

- Study Report 90067 - Acute Systemic Toxicology Study in the Mouse (two extracts) According to ISO 10993 Standards on Fibrocaps, Batch (b) (4)
- Study Report 1698-007 - A 21-Day Study to Evaluate the Adhesion Formation Potential of Fibrocaps Following Intra-abdominal Application in the Rabbit
- Study Report 1698-0008 (SP-FC-P046) - A GLP Study to Evaluate the Risk of Air Embolism following Application of Fibrocaps in a Liver Edge Resection Model in Rabbits
- Study Report SR-PF-019 - Evaluation of tissue sealant Fibrocaps in an extremity a Bilateral Femoral Defect Model in (b) (4) Rabbits
- Study Report 1698-011 -A Repeat Dose Safety Study of Fibrocaps in Swine (GLP)

### **Other Toxicity Studies**

- Study Report 90069 – Evaluation of Mutagenicity: (b) (4) Extracts
- Study Report 87970 - Local Tolerance and Performance of Fibrocaps, a Hemostatic Agent, Following Functional Application in Pig for 3 to 12 weeks

## **VII. Summary of Nonclinical Studies in STN BLA 125523/0**

The 510(k) application for the Fibrospray device (BK#140119) was submitted in parallel with the original BLA STN 125523/0 for the Fibrocaps Fibrin Sealant. The following pivotal nonclinical studies for the Fibrospray delivery device are reviewed in totality below:

- Study Report SR-FC-P014 - Hemostasis effect of Fibrocaps + Gelatin in a Swine Liver Bleeding Model
- Study Report SR-FCP015 - Pilot Study of Fibrocaps in a Sheep (b) (4) Vascular Graft Model
- Study Report 1698-0008 - A GLP Study to Evaluate the Risk of Air Embolism following Application of Fibrocaps in a Liver Edge Resection Model in Rabbits

- Study Report 1698-007- A 21-Day Study to Evaluate the Adhesion Formation Potential of Fibrocaps Following Intra-abdominal Application in the Rabbit
- Study Report 1698-0008 (SP-FC-P046) - A GLP Study to Evaluate the Risk of Air Embolism following Application of Fibrocaps in a Liver Edge Resection Model in Rabbits
- Study Report SR-FC-P066 – Fibrospray Device Development: Interchangeable Flexible Nozzle Assessment in Swine Model

#### **Study Report 1698-001- Non-GLP pilot study of hemostasis in a spleen bleed time model in the swine**

The aim of this study was to obtain preliminary data on the effectiveness of Fibrocaps and other, comparator fibrin sealants and surgical (b) (4) carriers in a swine proximal bleeding spleen model. The Applicant tested the following products and /or combination of products in each dose group: (b) (4) soaked in thrombin (b) (4); Fibrocaps + (b) (4) soaked in saline, + Dry (b) (4); Fibrocaps + (b) (4) soaked in saline; or Fibrocaps + (b) (4) non-adherent pad (b) (4) swine (n=2 F/group) underwent midline laparotomy for 6 mm biopsy punch of the spleen, followed by application of the designated treatment regimen. Treated swine were monitored for clinical signs including morbidity, mortality, injury, food and water consumption and activated clotting time (ACT), then following application of the test article, time to hemostasis (TTH) and mean arterial pressure. Standard of care (SoC) was used as the negative control, and consisted of manual pressure applied for 1 to 2 minutes, followed by evaluation of hemostasis every 30 seconds for up to 10 minutes. Gelatin pads were cut to approximately 2 cm X 2 cm size and 0.25 g Fibrocaps was added, then manual pressure (pads only groups) was applied. Time to hemostasis occurred most quickly with Fibrocaps use (2:31 min), vs. (b) (4) and (b) (4) (6:16 mins). Blood loss was proportional to TTH for all treatment selections, with the greatest effectiveness performance reported with use of Fibrocaps as a component of the combination of treatment regimen (TTH less than 10 min). The reduction in TTH with Fibrocaps was similar to that reported with the (b) (4) and thrombin (b) (4) combination when either the (b) (4) or the (b) (4) Pad were used to apply light manual pressure after Fibrocaps application. This study was completed in May 2009 at (b) (4) and was non-GLP compliant.

#### **Study Report 1698-002 (SR-FC-P011) Study of Fibrocaps in a spleen bleed time model in swine**

The aim of this study was to evaluate the bleeding time in a spleen bleeding model in swine, following treatment with Fibrocaps (FC) alone and in combination with other hemostat agents (b) (4) that are dry or “wet” (pre-soaked with saline) prior to application, versus SoC (gauze & light manual pressure). (b) (4) swine (n = 2 F/group) underwent midline laparotomy for spleen 6 mm biopsy punch, followed by the designated treatment regimen. Standard of care was manual pressure applied for 1 to 2 min, followed by hemostasis evaluation every 30 seconds for up to 10 minutes. Swine were monitored for clinical signs including morbidity, mortality, injury, food and water consumption, ACT, TTH, and mean arterial pressure. There were no overt toxicities or serious adverse events noted in this study. Time to hemostasis in all pigs treated with FC alone or in combination with the (b) (4) products, as well as those animals treated with the gelatin sponges alone achieved hemostasis within 3 minutes of application, as compared to greater than 10 minutes In those pigs treated by SoC. There were no significant differences in TTH or blood loss between the groups of swine treated at the wound site with (b) (4) plus FC, (b) (4) alone, (b) (4) plus FC or (b) (4) alone, or for dry versus wet carrier application. The results of this study indicated that treatment with Fibrocaps with any carrier agent pre-wet or dry is effective in achieving hemostasis over SoC. This study was completed February 2010 at (b) (4) and was non-GLP compliant.



**Study Report 1698-003 (SP-FC-P013) - Acute Study of Fibrocaps + (b) (4) Hemostasis in a Spleen Bleed time Model in the Swine**

The aim of this study was to evaluate the hemostatic efficacy of Fibrocaps in combination with (b) (4), versus (b) (4) alone only in the swine spleen bleeding model described above. Fibrocaps was delivered to the spleen punch biopsy wound site in (b) (4) swine (n = 1 F/group) using the Fibrospray device, and the negative control for this study was folded gauze. Treated swine were monitored for clinical signs including morbidity, mortality, injury, food and water consumption, ACT, TTH and mean arterial pressure. Standard of care was manual pressure applied for 1 to 2 minutes, followed by hemostasis evaluation every 30 seconds for up to 10 minutes. There were no overt toxicities or serious adverse events noted in this study. Time to hemostasis was reduced to 3.5 min in the pig treated with FC + (b) (4), compared to 5 min in the pig treated with (b) (4) alone. Blood loss was greater for the pig treated with (b) (4) alone (6.40 g), compared to the pig treated with (b) (4) + FC (2.13g). The performance of (b) (4) alone appeared to be equivalent to gauze/manual pressure (SoC). This study was completed in November 2009 at (b) (4), and was non-GLP compliant.

**Study Report 1698-004 (SR-FC-P016) – Acute Study of Fibrocaps compared to two hemostatic agents in a spleen time model in the swine**

The aim of this study was to evaluate the hemostatic efficacy of Fibrocaps (FC) in combination with (b) (4) alone, (b) (4) or gauze/ manual pressure (SoC). (b) (4) swine (n=1F/group) underwent midline laparotomy for spleen 6 mm biopsy punch, followed by the designated treatment regimen. Standard of care was manual pressure applied for 1 to 2 min, followed by hemostasis evaluation every 30 seconds for 10 minutes. Swine were monitored for clinical signs including morbidity, mortality, injury, food and water consumption, ACT, TTH and mean arterial pressure. There were no overt toxicities or serious adverse events noted in this study. Interestingly, it appears that treatment at the wound site with (b) (4) achieved TTH (1:45 min) faster than treatment with FC + (b) (4) (2:52 min), and both worked better than SoC alone (greater than 5 min). Time to hemostasis in the (b) (4) group was 1:50 min; the Applicant claims that this difference in TTH is based on the reduced bleeding rate in the (b) (4) treated pig. This non-GLP compliant study was completed in March, 2010 at (b) (4).

**Study Report 1698-009 (SR-FC-054) - Acute Study of Fibrocaps in Spleen Bleed Time Model in the Swine**

The aim of this study was to evaluate the efficacy of FC in combination with (b) (4) in the spleen bleeding model in swine, as part of a comparability assessment between FC manufactured using the Phase 3 process (test article) at the new manufacturing site (b) (4) and prepared with and without (b) (4), compared to Phase 2 FC material manufactured by (b) (4). (b) (4) was used as the carrier for Fibrocaps. Gauze and manual compression (SoC) served as the control. (b) (4) swine (n =2 F/group; 20 wounds/spleen, 3 wounds/treatment) were treated with the designated regimen after the spleen wounds were created using a 6 mm biopsy punch following midline laparotomy. Time to hemostasis (TTH), blood loss, bleeding rate and whether or not hemostasis was achieved were evaluated in this study.

There were no overt toxicities or serious adverse events noted in this study. Fibrocaps produced by either manufacturing process, and with or without (b) (4) was effective, as all products achieved hemostasis (100% success rate). Additionally, all FC products tested were within the same window of TTH; specifically, the TTH for the (b) (4) Fibrocaps (b) (4) was approximately (~) 1:45 min; for (b) (4) TTH ~2:10 min; Fibrocaps (b) (4) Blend (b) (4) TTH was ~1:59 min; for Fibrocaps (b) (4) Blend 2 (b) (4) TTH ~1:28 min; Fibrocaps (b) (4) Blend 1 (b) (4) TTH was ~2:13min, and for Fibrocaps (b) (4) Blend 1 (b) (4), TTH was ~ 1:37 min. The SoC gauze only group did not achieve hemostasis within 3 minutes (0% success), therefore no TTH was reported. There

was a slightly faster TTH achieved using (b) (4) Fibrocaps versus (b) (4) Fibrocaps (mean TTH for (b) (4) estimated to be 30.89 sec longer than the mean TTH for the (b) (4) product). The faster TTH achieved in the (b) (4) group may be expected, as there was more thrombin present (514-772 IU/g) in the (b) (4) Fibrocaps material as compared to the (b) (4) Fibrocaps materials (361-541 IU/g). The manufacturing changes do not appear to have any significant effect on the efficacy of Fibrocaps used in combination with (b) (4), since TTH occurred within 4 mins for all treatment combinations. There were no signs of overt toxicity or adverse events noted. This study was completed in September 2011 at (b) (4), and was non-GLP compliant.

**Study Report SR-FC-004 – A Pilot Study to Assess the Hemostatic Properties of a Novel Plasma-Based Thrombin/ Fibrin Sealant in a Rabbit Wound Model**

The aim of this study was to evaluate the hemostatic properties of Fibrocaps (lot (b) (4)) in combination with (b) (4) (lot (b) (4)) or alone, compared to (b) (4) alone (lot (b) (4)) in a rabbit liver wound model. Gauze and manual compression (SoC) served as the control. (b) (4) served as carrier agent. (b) (4) rabbits (n = 8 F/group) underwent liver resection with 1 cm lesions created in the liver lobe (up to 4 lesions/animal). Fibrocaps dry powder (0.25 g) was applied directly to the wound site either alone, or in combination with a gelatin pad carrier. Time to hemostasis, blood loss, bleeding rate and whether or not hemostasis was achieved were evaluated in this study. Application of both (b) (4) alone or Fibrocaps plus (b) (4) reduced TTH faster than the (b) (4) pad alone, and all treatments achieved TTH faster than SoC. Blood loss was consistent between all groups, with no significant differences. There were no overt toxicities or serious adverse events noted in this study. The study design did not incorporate necropsy or histopathology reporting. This study was completed in April 2009 at (b) (4) and was non-GLP compliant.

**Study Report 87970 - Local Tolerance and Performance of Fibrocaps, a hemostatic agent, following functional application in pig for 3 to 12 weeks**

The aim of this study was to evaluate the long term effects of 4 batches of Fibrocaps on local tolerance, degradation, and hemostatic performance (hemostatic scoring), as compared to (b) (4) alone or (b) (4) alone, or in combination with each sponge type in a pig liver lesion wound model. Pigs (n=10 with 4 sites/animal liver for 3 week assessment and n=10 with 4 sites/animal liver for 12 week assessment, Total = 22 pigs) were surgically wounded on the liver surface at a total of 10 to 12 sites per test article, monitored daily for overt toxicity and assessed at necropsy 3 and 12 weeks after surgery. The study evaluated the following clinical signs: test article adhesion, limited histology (site of testing and surrounding liver tissue), limited microscopic evaluation of liver inflammation and wound healing (fibroblasts, macrophages, lymphocytes, giant cells, signs of necrosis), and also macroscopic analysis of the wounds (at each surgical site). Clinical monitoring signs included assessment of morbidity, mortality and behavior. Adhesion of the gelatin pads to the wound sites was good for all test articles, and no secondary detachment was noted. All combination of products appears to achieve time to hemostasis more quickly than test articles alone (no significant differences between groups of combinations). After 12 weeks, there was still some presence of product (residues of (b) (4) and gelatin pads) at the implantation sites. Evidence of granulomatous reaction, and fibrosis with and without encapsulation were present at 3 weeks and 12 weeks on microscopic evaluation of the liver, spleen or skeletal muscle (diaphragm); however, there were no apparent, increased safety risks associated with the use of the Fibrocaps product than with other, currently marketed products. The Fibrocaps batches Tested were: (b) (4). This study was completed in October 2012 at (b) (4), in accordance with the Good Laboratory Practice Regulations (i.e., GLP compliant).

**Reviewer comment:** This study does not adequately address concerns with pharmacokinetics or local tolerance of Fibrocaps, because the study design does not reflect the actual clinical intended application.

The pictures provided by the Applicant of the procedure are obscure, and cannot be reviewed to assess the reliability of the results. Important clinical observations, such as complete serum chemistry panel, immunogenicity and histopathology of other major organs were not assessed in this study.

**Study Report 90067 - Acute Systemic Toxicology Study in the mouse (two extracts) according to ISO 10993 standards on Fibrocaps, Batch (b) (4)**

The purpose of this GLP compliant study was to evaluate the acute systemic effects of Fibrocaps in the mouse model in a. Mice (n=5/gr, total of 5 groups) were dosed by intravenous or intraperitoneal injection with 0.2 g/mL or 0.1 g/mL (100X or 50X maximal human dose) of Fibrocaps ((b) (4) treated) in respective vehicles of 0.9% NaCl (saline) or (b) (4) or negative (saline only) control. Mice were monitored at 4, 24, 48, and 72 hrs after dosing and scored for toxic responses (0/ normal to 4 /death scale), and BWs were monitored at 24, 48, 72, and 96 hrs post-dose. There were no mortalities associated with systemic exposure to Fibrocaps, and no overt toxicities or changes in clinical observations were noted in the test groups. Mice in the NaCl groups did exhibit hypokinesia, but recovered within minutes after injection. Fibrocaps™ is apparently well-tolerated after systemic exposure, as determined by the limited parameters measured in this study. Of note, important clinical observations, including evaluation of a complete serum chemistry panel, histology, and immunogenicity were not assessed in this study.

**Study Report SR-PF-019 - Evaluation of tissue sealant Fibrocaps in an extremity a Bilateral Femoral Defect Model in (b) (4) Rabbits**

The purpose of this study was to evaluate the effect of Fibrocaps™ on bone healing, using a distal bilateral femoral condyle defect model in rabbits. (b) (4) rabbits (n = 10 animals/group, with test and control site on each animal) underwent surgery to create bilateral defects (5 x 5 mm) in the cancellous bone of the medial aspect of the distal femur. Rabbits were treated with Fibrocaps™ (~75 mg/g Fibrinogen and ~550 IU/g Thrombin) as dry powder with saline or wound left empty (cleaned only). The following parameters were be monitored via macroscopic, radiographic (microcomputer tomography) and histology appearance (defect site only) at 4 weeks and 8 weeks. Bone healing in the femurs treated with Fibrocaps™ appeared to occur more quickly than in the untreated side in each animal. There were no overt toxicities noted or significant changes in clinical signs. In this study, the Applicant reported that Fibrocaps™ was completely degraded after 4 weeks, and inflammatory and/or foreign body reactions were absent at that time. This study was completed in February 2010 at (b) (4) and was non-GLP compliant.

**Study Report 90064 - Incutaneous Irritation Test by Intradermal Injection in the Rabbit**

The purpose of this study is to test the ability of Fibrocaps™ to cause irritation in the rabbit model. Rabbits (n = 2/group, 5 sites/animal) were dosed 0.2 mL Fibrocaps™ ((b) (4) ) in 0.9% NaCl, or 0.2 mL of (b) (4) in same animal. The sites were monitored at 24, 48, and 72 hours after dosing, and graded for evidence of irritation based on a grading scale for erythema (i.e, 0/none to 4/severe erythema). There were no overt toxicities noted after Fibrocaps injection. Application of the Fibrocaps product did cause slight, but apparently tolerable irritation. The average erythema grades were 1-2 for the test article groups, and 0-1 for control, and no statistically significant differences between the test groups and the respective (b) (4) control sites were demonstrated. This study was completed in November 2009 at (b) (4) in accordance with Good Laboratory Practices (i.e., GLP compliant).

**Reviewer comment:** This was a poorly designed study, due to the small number of distinct animals for the number of groups tested.

**Study Report 90065 - Sensitization Study in the Guinea Pig**

The aim of this study was to evaluate the potential of delayed dermal contact sensitization in guinea pigs following application of Fibrocaps. Guinea pigs (n=10/group in test groups groups and n=4-5/control groups, T=38) were dosed intradermally or had Fibrocaps™ topically applied at using 0.9% NaCl (intradermal injection and patch application) or (b) (4) (intradermal injection and patch application) for drug delivery, or with a combination of (b) (4) (positive control), then allowed 24 or 48 hours for observation after patch application or injection. There were no overt toxicities reported for any of the test groups. There was no apparent sensitization resulting from topical application of the Fibrocaps test article in either the saline or (b) (4) (i.e., grade 0); however, there was evidence of sensitization following intradermal injection in saline (grade 5 inflammation). The results from this study suggest that Fibrocaps™ is tolerable following topical delivery, but does cause sensitization from intradermal delivery (resulting in increased immunization [tolerance] to product). This study was completed in November 2009 at (b) (4) in accordance with Good Laboratory Practices (i.e., GLP compliant).

**Study Report 90069 – Evaluation of Mutagenicity: (b) (4) extracts**

The purpose of this study was to evaluate the mutagenic potential of Fibrocaps™ in a bacterial (b) (4). Fibrocaps™ (b) (4), and the results were compared to those obtained following (b) (4) to determine the mutagenic potential of test article. Based on the results a (b) (4) Fibrocaps™ did not appear to be toxic or mutagenic in the bacterial (b) (4). The (b) (4) performed as expected, confirming the validity of the assay conditions. Fibrocaps™ or its components do not appear to be mutagenic or genotoxic based on these study results. This study was completed in November 2009 at (b) (4) in accordance with Good Laboratory Practices (GLP-compliant).

**Study Report 1698-0008 (SP-FC-P046) - A GLP Study to Evaluate the Risk of Air Embolism following Application of Fibrocaps in a Liver Edge Resection Model in Rabbits**

The aim of this study was to examine the worst case scenario of misuse of the Fibrospray device in surgical settings (i.e., misapplication); specifically, to test the potential risk of air embolism following the use of Fibrospray device for delivery of Fibrocaps in an actual surgical environment, using a rabbit liver wound model. (b) (4) Rabbits were randomized for use of Fibrocaps (human fibrin powder) at wound sites in a liver resection model. The animals were monitored for 72 hours to determine any adverse effects from product and/or device misuse. The groups of rabbits were designated as follows for the various differences in Fibrospray application pressure, spray distance, and Fibrocaps dose levels:

Experimental Scenario	Fibrocaps Dose	Pressure/distance from wound site	Number of animals	Number of sites/animal liver
Worst case	4.5 g/wound	5.2 bar/ 1 cm	3	4
Spray too close	1.5 g/wound	1.7 bar/2 cm	4	4
Apply too far	1.5 g/wound	1.7 bar/10 cm	4	4
Optimal conditions for device use	1.5g/ wound	1.7 bar/ 5 cm	2	4
High pressure (air only) – control	0 g/wound	5.2 bar/ 1 cm	4	4

Animals were observed for clinical signs including external disposition, body weight, morbidity/mortality, and macroscopic evidence of pathology at necropsy. Tissue sections from major organs were examined microscopically after necropsy. In the worst case scenario group, the results were the least favorable for product and device use; however, the results were not grossly disparaging for Fibrocaps and Fibrospray use. Misapplication of Fibrocaps (i.e., distance of Fibrospray from the wound being too close, too far, and/or if too much product [dose] was applied) resulted in adhesion formation in all groups tested. Hemorrhage (minimal to mild) and inflammation at treatment wound sites, and inflammation (subacute, mild, and present in approximately 25% of all treated animals) and fibrosis deposits in lungs occurred in all treatment groups; more severe responses were reported in the groups treated with the worst case scenario and the high pressure control groups. The results were slightly greater in effect for the test article groups than for control group (Fibrospray air only) and product use under normal conditions (optimal conditions with FC alone and with Fibrospray previously tested in other studies). There were little variations in the preclinical study results between the tested worst-case scenarios and normal (optimal conditions [submitted in original IND 14385/0]) Fibrocaps' use. This study was the pivotal proof of concept study to mimic potential misuse in the clinical surgical setting. This study was completed in March 2011 at (b) (4) in accordance with Good Laboratory Practices (i.e., GLP compliant).

**Reviewer comment:** The Instructions for Use for the Fibrospray device should be clearly labeled to advise users of the effects of inappropriate use or misuse of the device, and/or inappropriate application of Fibrocaps.

#### **Study Report SR-FC-P014 Hemostasis effect of Fibrocaps + Gelatin in a Swine Liver Bleeding Model**

The aim of this study was to evaluate the hemostatic effectiveness of Fibrocaps (FC) + gelatin sponge (b) (4), versus human thrombin (b) (4) + gelatin sponge in a swine liver bleeding model. Gelatin pad (b) (4) alone (pre-wetted with saline) served as the negative control for this study. Fibrocaps (b) (4) manufactured) was also delivered using the Fibrospray device. Large white (b) (4) swine (n = 3; n = 4 wounds/treatment) underwent midline incision and 10 mm punch biopsy of the liver, followed by the designated treatment regimen. Animals were observed for clinical signs including external disposition, body weight, moribundity/mortality, and TTH. Standard of care was manual pressure using folded gauze applied for 30 seconds, followed by hemostasis evaluation every 30 seconds for 5 minutes. Fibrocaps in combination with (b) (4) was able to reduce TTH (1:00 min) similarly to human plasma thrombin combined with (b) (4) (1:00 min). Use of (b) (4) alone resulted in a TTH of 1:51 min. Additionally, the Fibrospray delivery device (1.2 bar pressure) used for Fibrocaps application appears to show significant improvements over the previous prototypes, and was considered suitable for clinical delivery of FC for multiple clinical indications. This study demonstrated effective proof of principle for the Fibrospray device for delivery of Fibrocaps. This study was completed in April 2010 at ProFibrix Inc. in Seattle WA, and was non-GLP compliant.

#### **Study Report SR-FCP015 - Pilot Study of Fibrocaps in a Sheep (b) (4) Vascular Graft Model**

The aim of this study was to evaluate the efficacy of Fibrocaps (FC) for adherence, effects in a heparinized animal model, and the effectiveness of the Fibrospray device in a vascular graft model. This pilot study was designed to assess the efficacy of FC to adequately control bleeding at the site of anastomosis (n=4). (b) (4) sheep (n = 1 F) underwent several procedures including a (b) (4) graft to determine Fibrocaps adherence at the anastomosis wound sites. The study design used Fibrospray (normal application; 1-1.5 bar pressure; distance of use not stated) to deliver 0.25 g of Fibrocaps powder, followed by manual compression at the test site using a saline pre-wetted, (b) (4) sponge. The Applicant reports that there were no issues (i.e., no difficulty) with use of the spray device.

Bleeding time was reduced with sprayed FC, and bleeding was completely stopped after subsequent (b) (4) application. At another test site in the same animal a single needle hole was made in a graft, and bleeding was stopped with a single application of FC. Fibrocaps was able to adhere to the synthetic graft and stop moderate bleeding in the sheep vascular graft model in under 2 minutes at the arterial and venous anastomotic sites (n = 4), regardless of whether the occlusion loops were removed before or after Fibrocaps application. There were no overt toxicities noted in this study, although the animal's blood pressure did drop 30 points during the test. The Applicant claims that this change was related to the surgical procedure, and not related to FC use. This study was completed in April 2010 at (b) (4) and was non-GLP compliant.

#### **Study Report SR-FC-P066 – Fibrospray Device Development: Interchangeable Flexible Nozzle Assessment in Swine Model**

The aims of this study were to determine the feasibility of using the Fibrospray device to deliver the Fibrocaps product in an actual surgical environment, and to optimize the Fibrospray device flexible nozzle (b) (4) nozzle) and its efficacy in delivery of Fibrocaps for the treatment of wounds. This study is considered a proof of principle study based on study design. Large (b) (4) Swine (n = 1) were tested in liver and abdominal bleed wound models. Fibrocaps (Batch Number: (b) (4) ) was delivered using the Fibrospray device, with the pressure setting for delivery at 1.0 bar (~ 14.5 psi) and to not exceed a maximum of 1.7 bar (~ 24.7 psi), as this is the safety limit on the Fibrospray regulator. Historical references were used as a control for this study. The following parameters were assessed: vial evacuation, accuracy (amount and directional control) of delivery, delivery efficiency, dusting/drop off, and qualitative establishment of hemostasis based on TTH. Based on the results of this study, the Fibrospray device (b) (4) appears to be user-friendly and effective for the delivery of Fibrocaps. The Fibrospray device can deliver Fibrocaps easily and accurately to the target wound site from a variety of angles and at different distances from nozzle head, while maintaining sufficient user friendly control and ease of Fibrocaps application to the bleeding wound site. Fibrospray can deliver Fibrocaps up to 180 degrees wound target angles, with good visibility, good flexibility on nozzle with reasonable evacuation and powder retention for (b) (4) nozzle when compared to its predicate design (b) (4) . Additionally, the Fibrospray design (b) (4) has effective anti-clogging function, except when completely submerged in blood or fluid, which resulted in attenuated performance. There were no overt toxicities or serious adverse events noted in the treated pigs in this study. The study design did not incorporate necropsy or histopathology reporting. This study was completed in April 2012 at ProFibrix BV in The Netherlands at (b) (4) and was non-GLP compliant.

#### **Study Report 1698-007 - A 21-Day Study to Evaluate the Adhesion Formation Potential of Fibrocaps Following Intra-abdominal Application in the Rabbit**

The aim of this study was to determine the risk of adhesion formation following inadvertent application of Fibrocaps in the rabbit. Rabbits (n = 8 females/group) were dosed with 0.125 g of Fibrocaps (FC) using the Fibrospray device at 1 bar pressure, followed by manual pressure with pre-wetted gauze (saline) on top of a gelatin sponge (b) (4) [2x2 cm size], or air only (no FC) from Fibrospray (15-20 seconds) followed by manual pressure with pre-wetted gauze (saline) on top of gelatin sponge (b) (4) [2x2 cm size] on a biopsy punch wound on the liver lobe closest to the bowel, to simulate misapplication. The group without Fibrocaps use (air only from Fibrospray device) was considered the control group. General overt toxicities (e.g. morbidity/mortality) and external physical characteristics (e.g. injury) were monitored in the animals for 3 weeks, and major organs were examined by microscopic and macroscopic parameters after necropsy at 21 days post-surgery. Adhesions were found on the liver and omentum (wound site), but not in bowel in all study animals. The extent (<25%) and severity (minimal) of the adhesions were comparable in both study groups, without statistically significant differences. There were no abnormalities in major organ histopathology in either group tested. Based on these findings, there appears to be no greater risk for adhesion formation following inadvertent treatment with Fibrocaps versus control methods. General precautions and warnings regarding potential for adhesions should be

included in the Fibrocaps labeling, similar to those included for use of with similar fibrin sealant products. This study was completed in December 2010 at (b) (4) in accordance with Good Laboratory Practices (GLP compliant).

**Excipient Line Listing**

A risk assessment of the potential leachable and extractable in the final product was conducted. The excipients in the final Fibrocaps product have previously been evaluated, and approved for use in the (b) (4) Thrombin product under (b) (4). The concentration of excipients will be substantially less than that in (b) (4) product, and should not present any greater risk than the approved thrombin.

Excipients: Trehalose, calcium chloride, albumin\*, sodium chloride\*, Sodium citrate\*, L-arginine hydrochloride\*

\*These excipients are found in the (b) (4) but are not measured in the final product.