DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

Our STN: BL 125523/0 **BLA APPROVAL**

ProFibrix, BV
Attention: Linda Zuckerman, PhD
The Medicines Company
1144 Eastlake Avenue East
Suite 700
Seattle, WA 98109

Dear Dr. Zuckerman:

We are issuing Department of Health and Human Services U.S. License No. 1994 to ProFibrix BV, Leiden, Netherlands, under the provisions of section 351(a) of the Public Health Service Act controlling the manufacture and sale of biological products. The license authorizes you to introduce or deliver for introduction into interstate commerce, those products for which your company has demonstrated compliance with establishment and product standards.

Under this license, you are authorized to manufacture the product Fibrin Sealant (Human). Fibrin Sealant (Human) is indicated 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.

The review of this product was associated with the following National Clinical Trial (NCT) numbers: 02117349, 01527357, and 01256164.

Under this license, you are approved to manufacture Fibrin Sealant (Human) at your contract facility, (b) (4) Thrombin (b) (4) Fibrinogen (Human), (b) (4) The final drug product labeling and packaging are done at (b) (4) You may label your product with the proprietary name Raplixa and market it in fill sizes of 0.5 g, 1 g, and 2 g per vial.

We did not refer your application to the Blood Products Advisory Committee because our review of information submitted in your BLA, including the clinical study design and trial results, did not raise concerns or controversial issues which would have benefited from an advisory committee discussion.

The dating period for Fibrin Sealant (Human) shall not exceed the dating periods for your spray-dried thrombin and fibrinogen intermediates (whichever is the earliest) when stored at 25 °C. The dating periods for your spray-dried thrombin and fibrinogen intermediates shall be 24

months from the date of (b) (4) when stored at 25 °C, and shall not exceed the manufacturer-specified expiration dates for these (b) (4)

Your request for exemption from the General Safety test for Fibrin Sealant (Human) has been granted.

Please submit final container samples of the product in final containers together with protocols showing results of all applicable tests. You may not distribute any lots of product until you receive a notification of release from the Director, Center for Biologics Evaluation and Research (CBER).

You must submit information to your biologics license application for our review and written approval under 21 CFR 601.12 for any changes in, including but not limited to, the manufacturing, testing, packaging or labeling of Fibrin Sealant (Human) or in the manufacturing facilities.

You must submit reports of biological product deviations under 21 CFR 600.14. You should identify and investigate all manufacturing deviations promptly, including those associated with processing, testing, packing, labeling, storage, holding and distribution. If the deviation involves a distributed product, may affect the safety, purity, or potency of the product, and meets the other criteria in the regulation, you must submit a report on Form FDA-3486 to the Director, Office of Compliance and Biologics Quality, at the following address:

Food and Drug Administration
Center for Biologics Evaluation and Research
Document Control Center
10903 New Hampshire Ave.
WO71-G112
Silver Spring, MD 20993-0002

Please provide your final content of labeling in Structured Product Labeling (SPL) format and include the carton and container labels. In addition, please submit three original paper copies for carton and container final printed labeling. All final labeling should be submitted as Product Correspondence to this BLA at the time of use (prior to marketing) and include implementation information on FDA Form 356h.

In addition, please submit the final content of labeling (21 CFR 601.14) in SPL format via the FDA automated drug registration and listing system, (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Information on submitting SPL files using eLIST may be found in the guidance for industry titled, "*SPL Standard for Content of Labeling Technical Qs and As* at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

You may submit two draft copies of the proposed introductory advertising and promotional labeling with an FDA Form 2253 to the Advertising and Promotional Labeling Branch at the following address:

Food and Drug Administration
Center for Biologics Evaluation and Research
Document Control Center
10903 New Hampshire Ave.
WO71-G112
Silver Spring, MD 20993-0002

You must submit copies of your final advertisement and promotional labeling at the time of initial dissemination or publication, accompanied by Form FDA 2253 (21 CFR 601.12(f)(4)).

All promotional claims must be consistent with and not contrary to approved labeling. You should not make a comparative promotional claim or claim of superiority over other products unless you have substantial evidence or substantial clinical experience to support such claims (21 CFR 202.1(e)(6)).

ADVERSE EVENT REPORTING

You must submit adverse experience reports in accordance with the adverse experience reporting requirements for licensed biological products (21 CFR 600.80) and you must submit distribution reports as described in 21 CFR 600.81. You should submit postmarketing adverse experience reports and distribution reports to the Office of Biostatistics and Epidemiology, at the following address:

Food and Drug Administration
Center for Biologics Evaluation and Research
Document Control Center
10903 New Hampshire Ave.
WO71-G112
Silver Spring, MD 20993-0002

Prominently identify all adverse experience reports as described in 21 CFR 600.80.

PEDIATRIC REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are deferring submission of your pediatric study until March 2016 because this product is ready for approval for use in adults and the pediatric study has not been completed.
Your deferred pediatric study required under 505B(a) of the Federal Food, Drug, and Cosmetic Act is a required postmarketing study. The status of this postmarketing study must be reported according to 21 CFR 601.70 and section 505B(a)(3)(B) of the Federal Food, Drug, and Cosmetic Act. This required study is listed below:

1. 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.

   Final Protocol Submission: January 2014

   Study Completion Date: September 2015

   Final Report Submission: March 2016

Submit final study reports to this BLA. For administrative purposes, all submissions related to this required pediatric postmarketing study must be clearly designated **"Required Pediatric Assessment(s)."** Subsequent to the submission of these required final study reports, you must submit the data as a supplement(s) to this BLA 125523 with the proposed labeling changes you believe are warranted based on the data derived from these studies.

AGREED UPON POSTMARKETING COMMITMENTS

We acknowledge your written commitment as described in your letter dated April 17, 2015, as outlined below:

Postmarketing Studies not subject to reporting requirements of 21 CFR 601.70.

2. 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 its (b) (4) in international units (b) (4) (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 30 November 2015 as a Postmarketing Study Commitment – Final Study Report.

We request that you submit information concerning nonclinical and chemistry, manufacturing, and control postmarketing commitments and final reports to your BLA, STN 125523/0. Please refer to the sequential number for each commitment and the submission number as shown in this letter.

Please use the following designators to label prominently all submissions, including supplements, relating to these postmarketing study commitments as appropriate:

- **Postmarketing Study Correspondence**
- **Postmarketing Study Commitment – Final Study Report**
- **Supplement Contains Postmarketing Study Commitment – Final Study Report**

For each postmarketing commitment not subject to the reporting requirements of 21 CFR 601.70, you may report the status to FDA as a "PMC Submission – Status Update." The status report for each commitment should include:

- the sequential number for each study as shown in this letter
- the submission number associated with this letter
- describe what has been accomplished to fulfill the non-506B PMC; and summarize any data collected or issues with fulfilling the non-506B PMC

When you have fulfilled your commitment, submit your final report as PMC Submission – Final Study Report or Supplement Contains Postmarketing Study Commitment – Final Study Report.

PDUFA V APPLICANT INTERVIEW

FDA has contracted with Eastern Research Group, Inc. (ERG) to conduct an independent interim and final assessment of the Program for Enhanced Review Transparency and Communication for NME NDAs and Original BLAs under PDUFA V ('the Program'). The PDUFA V Commitment Letter states that these assessments will include interviews with applicants following FDA action on applications reviewed in the Program. For this purpose, first-cycle actions include approvals, complete responses, and withdrawals after filing. The purpose of the interview is to better understand applicant experiences with the Program and its ability to improve transparency and communication during FDA review.

ERG will contact you to schedule a PDUFA V applicant interview and provide specifics about the interview process. Your responses during the interview will be confidential with respect to the FDA review team. ERG has signed a non-disclosure agreement and will not disclose any identifying information to anyone outside their project team. They will report only anonymized results and findings in the interim and final assessments. Members of the FDA review team will be interviewed by ERG separately. While your participation in the interview is voluntary, your feedback will be helpful to these assessments.

Sincerely,

Mary A. Malarkey
Director
Office of Compliance and
Biologics Quality
Center for Biologics
Evaluation and Research

Jay S. Epstein, MD
Director
Office of Blood Research and Review
Center for Biologics
Evaluation and Research

Enclosure:
Final Approved Draft Labeling