

## Record of Telephone Conversation

**Application type and number:** original BLA, STN 125523/0

**Product name:** Fibrin Sealant, Human Fibrinogen Human Thrombin  
“Development” Name (previous Proprietary Name) – Fibrocaps  
Proposed Proprietary Name – Raplixa

**Proposed Indication:** Raplixa is indicated 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.

**Applicant:** ProFibrix BV, The Netherlands

**Telecon date & time:** Monday, December 8, 2014, 3:00 - 4:00 PM (EDT)

**RPM:** Tracy Tilghman

### Attendees:

Natalya Ananyeva	LH/DHRR/OBRR
Lokesh Bhattacharyya	LACBRP/DBSQC/OCBQ
Karen Campbell	QAB/DBSQC/OCBQ
Alexey Khrenov	LH/DHRR/OBRR
Tracy Tilghman	RPMS/IOD/OBRR
Hsiaoling Wang	LACBRP/DBSQC/OCBQ

### ProFibrix Attendees:

Linda Zuckerman, Ph.D. VP, Global Scientific Lead- Hemostasis  
Eliane Schutte, MSc., VP Global Product Development  
Sabrina Gu, MSc. Manager Regulatory Affairs  
Sabine Snaar, Ph.D. Director Quality Assurance  
Laurens van Pinxteren, Ph.D. Director Manufacturing & Supply  
(b) (4), (b) (6)

### Meeting Summary:

FDA requested a meeting with ProFibrix to discuss the (b) (4) assay that was part of Drug Product (DP) Specification in the original BLA submission, STN 125523/0. After reviewing the data submitted by ProFibrix in response to several information requests regarding the assay, FDA held an internal discussion and concluded that the (b) (4) assay cannot be used for its intended purpose (as a quality control release test, supplemental to the Moisture Content by the (b) (4)) for the following reasons:

1. The Applicant could not demonstrate consistent correlation between the results of the (b) (4) test and the Moisture Content determined by the (b) (4).

2. The assay is not precise enough when appropriate (i.e., experimentally generated) calibration model is used. FDA considers the approach used by ProFibrix for building the calibration line (generated by the computational interpolation of intermediate values from (b) (4) spectra) to be unacceptable.

FDA acknowledged that the other tests, proposed by ProFibrix for commercial release of Raplixa DP, allow adequate control of the product quality in relation to moisture content. The (b) (4) assay allows direct determination of the moisture content, and the (b) (4) analysis with (b) (4) quantification of the (b) (4) amount allows for control of premature fibrinogen activation, which is the major negative effect of the presence of excessive moisture in the product. As the (b) (4) test does not provide additional information, FDA recommended this method be removed as a quality control release test from DP Specification.

ProFibrix agreed with the FDA's comments and committed to remove the (b) (4) assay from the BLA and amend the relevant sections of the module 3.2.P.5 accordingly. The format for submitting the changes will be communicated to ProFibrix by FDA later that day.

Regarding the (b) (4) method for the determination of Moisture Content, the revised Justification of Specification is still under FDA review and the acceptance criterion (b) (4) may need to be revised based on the analysis of the manufacturing data.

Regarding the (b) (4) analysis of premature fibrinogen activation, FDA agreed that the use of the quantitative acceptance criterion (b) (4) as proposed in the revised Justification of Specification, will be more appropriate than the current qualitative/descriptive specification (b) (4) ”). FDA recommended ProFibrix to reserve the implementation of this change until FDA provides other comments regarding DP Specification, so that all comments can be addressed in one amendment.

**END**