Record of Internal 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: Fibrocaps 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

Meeting date & time: Wednesday, December 3, 2014, 4:00 - 5:00 PM (EDT)

RPM: Tracy Tilghman

Attendees:

Natalya Ananyeva	LH/DHRR/OBRR
Lokesh Bhattacharyya	LACBRP/ DBSQC/OCBQ
Karen Campbell	QAB/DBSQC/OCBQ
Alfred Del-Grosso	LACBRP/ DBSQC/OCBQ
Alexey Khrenov	LH/DHRR/OBRR
William McCormick	DBSQC/OCBQ
Tracy Tilghman	RPMS/IOD/OBRR
Hsiaoling Wang	LACBRP/ DBSQC/OCBQ

Teleconference discussion

The purpose of this internal teleconference was to discuss the data that has been provided by ProFibrix regarding the test for (b) (4) . At the Pre-IND stage, this method was selected as a complementary method to moisture content determination by (b) (4) based on the regulatory feedback from FDA. The (b) (4) method assesses trehalose phase (b) (4), i.e., the transformation from the (b) (4) form of materials, which is dependent on the moisture content, by means of a change in the (b) (4) of the sample. At the BLA stage, the assessment of this test as a potential quality control release test was provided in responses to the September 9, 2014 information request from FDA, the September 19, 2014 teleconference with ProFibrix, and the follow-up email on September 23, 2014 to the Applicant. Following these discussions, the Applicant agreed to provide information to the FDA on the relationship between the (b) (4) in the product and the moisture content. ProFibrix also agreed to change the test from a quantitative test to a limit test.

After reviewing the data provided by the Applicant in the amendment 17 (24 October 2014), FDA determined that the (b) (4) assay in its current condition cannot be used for its intended purpose (as a supplemental quality control release test) for the following reasons:

1. The sponsor could not show consistent correlation between the results of the (b) (4) test and the moisture content determined by (b) (4), which limits the value of the (b) (4) assay.

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. The company provided the data demonstrating that, if the experimental data are used from the (b) (4) product, the uncertainty of the results becomes excessive.

FDA staff was in agreement that the other tests currently used by the company for proposed commercial release of Raplixa allow adequate control of product quality in relation to moisture content. (b) (4) assay allows for controlling the moisture content directly, and the (b) (4) in combination with (b) (4) allows for direct control of the presence of premature fibrinogen activation which is the major negative effect of the presence of excessive moisture in the product. Of note, the (b) (4) test was implemented during the IND stage based on the FDA feedback. FDA staff was in agreement that the control over premature fibrinogen activation determined by the presence of (b) (4) appears appropriate and emphasized that the (b) (4) at the level or below the LOQ of the method (expressed as (b) (4) should be used as the specification limit in Drug Product specification for this parameter.

FDA staff discussed the possibility of the company to develop an alternative method to control for (b) (4) as a PMC. However, this was deemed unnecessary as it was concluded that the (b) (4) itself does not have a significant intrinsic value of product quality. FDA staff agreed that with the use of more suitable methods to adequately control moisture and premature fibrinogen activation, the (b) (4) test is not needed and FDA would advise the company to remove this test from the specification.

The question was raised during the discussion regarding the specification limit for the moisture content (b) (4) which was considered high by some participants. The Product Office staff noted that, while there are similar approved fibrin sealant products on the market with similar limits for residual moisture, the discussion of this issue is premature: (b) (4) The concern regarding the specification limit for the moisture content is also lessened

considering that the (b) (4) test for premature fibrinogen activation is proposed to be used for quality control of the product.

Based on the discussion, FDA felt it was necessary to hold a teleconference with ProFibrix to discuss the possibility of removing of the (b) (4) test as a quality control release test from Drug Product specification and submit appropriate amendment(s) to the original BLA file.