RECORD OF TELEPHONE CONVERSATION

Submission Type: BLA Submission ID: 125523/0 **Office:** OBRR

Product: Fibrin Sealant, Human Fibrinogen Human Thrombin

Applicant: ProFibrix, BV.

Telecon Date/Time: 14-Aug-2014 10:30 AM **Initiated by FDA?** Yes

Telephone Number: (b) (4)

Communication Categorie(s):

1. Other - Telecon to discuss testing of trehalose and calcium content in Drug Product

Author: Thomas J. Maruna

Telecon Summary:

Telecon to discuss testing of trehalose and calcium content in Drug Product

FDA Participants:
Natalya Ananyeva
Lokesh Bhattacharyya
Alfred Del-Grosso
Alexey Khrenov
Thomas J. Maruna

Non-FDA Participants:
Eliane Schutte (VP Global Product Development, ProFibrix, MCDO)
Sabrina Gu (Sr Regulatory specialist, ProFibrix, MDCO)
Sabine Snaar (Director QA, ProFibrix MDCO)
(b) (4), (b) (6)

Trans-BLA Group: No

Related STNs: None

Related PMCs: None

Telecon Body:
FDA requested a teleconference to clarify the need for the tests for trehalose and calcium (Ca) content in ProFibrix, BV's Fibrin Sealant, Human Fibrinogen Human Thrombin Drug Product (DP).

FDA requested clarification pertaining to the details of introduction of Ca into the product. ProFibrix indicated that Ca is added to the trehalose (b) (4), in which the (b) (4) for further processing into the DP; the purpose of which is to compensate for the presence of (b) (4) citrate in (b) (4). When the product is applied to the bleeding site, sodium citrate will chelate Ca present in blood thereby inhibiting clotting; therefore (b) (4) Ca is introduced into the (b) (4) formulation to neutralize this effect. FDA inquired whether Ca is present in the Thrombin (b) (4) received from (b) (4) as was stated previously by ProFibrix during April 7, 2014 teleconference. ProFibrix could not confirm if Ca is present in the (b) (4) or not.

The FDA stressed that the correct amount of Ca in the product is critical for its function and efficacy and emphasized the importance of controlling this parameter.

The manufacturing and testing process overview was described and is consistent with the description of the process in ProFibrix's April 8, 2014 amendment. The (b) (4) are received from (b) (4) is (b) (4) in a trehalose (b) (4) containing calcium chloride; Fibrinogen (b) (4) is (b) (4) in a trehalose (b) (4) the (b) (4) are spray-dried and then blended into DP. Sponsor proposes to measure (b) (4) content in the spray-dried thrombin intermediate for the 3 validation lots only.

The FDA stated that it is acceptable to perform (b) (4) tests on spray-dried thrombin and fibrinogen intermediates instead of final blended DP. However, to ensure process consistency, the (b) (4) tests should be conducted on a continuing basis during process verification stage; not just for the 3 validation lots. When process consistency has been verified, ProFibrix may submit, at a future date (a year or more later), an amendment requesting discontinuation of the (b) (4) testing for the spray-dried intermediates for FDA review.

At this time, FDA requested results from at least 3 validation lots to be submitted for review as an amendment to the BLA as agreed upon during April 7, 2014 teleconference and stated in April 14, 2014 amendment. ProFibrix committed to submit such amendment by August 31, 2014 containing:

- Description of the assays for (b) (4) content determination in spray-dried (b) (4)
- Validation Reports for these methods
- Batch results of the 3 PPQ batches including contents of (b) (4)
- Update of the respective Module 3 sections with the data

The extent of further testing for (b) (4) will be addressed after FDA reviews the submitted data.

END