

MEMORANDUM



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



To: Administrative File for BLA (STN 125523/0)
Alexey Khrenov, PhD, Chair of the Review Committee, Laboratory of Hemostasis (LH), Division of Hematology Research and Review (DHRR)/OBRR
Sonday Kelly, RPMS/IOD/OBRR

From: Natalya Ananyeva, PhD, LH/DHRR/OBRR

Through: Tim Lee, PhD, Acting Chief, LH/DHRR/OBRR

Basil Golding, MD, Division Director, DHRR/OBRR/CBER

Subject: Final review of analytical methods in the BLA for Fibrin Sealant (Human) [Raplixa] (Applicant – ProFibrix, BV, Leiden, The Netherlands)

INTRODUCTION

ProFibrix, BV (ProFibrix), a wholly owned subsidiary of The Medicines Company, Inc. submitted to the FDA an original Biologics License Application (BLA), STN 125523/0, on 31 January 2014 to seek U.S. licensure for Fibrin Sealant (Human), with the proposed proprietary name Raplixa. Raplixa consists of a blend of (b) (4) of human plasma-derived fibrinogen and human plasma-derived thrombin in a ready-to-use powder form, which can be stored at room temperature and applied directly onto a wound surface without the need for reconstitution or mixing.

Raplixa 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.

Both biological components of Raplixa, human fibrinogen and human thrombin (b) (4), are manufactured by (b) (4) and are licensed by the FDA. Fibrinogen (b) (4) (Human) is licensed for the treatment of acute bleeding episodes in patients with congenital fibrinogen deficiency (b) (4) and Thrombin (Human) (b) (4) [Thrombin (b) (4) is licensed (b) (4)]

fibrinogen and thrombin (b) (4) Raplixa. These (b) (4) with this BLA.

The Raplixa drug product (DP) is manufactured at (b) (4). The two (b) (4) biological components are formulated in a trehalose solution, sterile (b) (4), and spray-dried separately under aseptic conditions. The (b) (4) of spray-dried fibrinogen and thrombin are subsequently blended, and the resultant powder is filled in single-use glass vials and packed in a foil pouch. Each vial is filled with 0.5, 1 or 2 g of the mixture containing nominally 79 mg of fibrinogen and 699 IU of thrombin per gram of the blended powder.

Raplixa may be used in conjunction with an absorbable gelatin sponge (USP). The powder is applied either directly from the vial or using an optional spraying device, onto a bleeding site. The 510(k) application BK # 140119/0 was submitted for the RaplixaSpray spraying device and will be cleared concomitantly with this BLA. Upon application of the powder onto the bleeding site, the product dissolves in blood allowing for thrombin to react with fibrinogen resulting in the formation of a fibrin clot that stops the bleeding.

The product has been developed under Investigational New Drug (IND) application 14385 which was first submitted to the FDA in September 2010. During development, the product had a company designed code Fibrocaps. Raplixa is the first biological product to be licensed in the U.S. that is manufactured by spray drying.

The current memorandum summarizes my CMC review of the analytical methods used for in-process control testing of intermediates and release and stability testing of Raplixa DP. The review of most methods was performed jointly with the Division of Biological Standards and Quality Control (DBSQC) in the Office of Compliance and Biologics Quality (OCBQ), CBER, where in-support testing was carried out. The suitability of analytical procedures for their intended use and the Applicant's responses to information requests were discussed with Drs. Alexey Khrenov (Chair, DHRR), Tim Lee (DHRR) and Lokesh Bhattacharyya (DBSQC) on a regular basis throughout the review process.

RECOMMENDATION

The Applicant provided sufficient information on the analytical procedures used for in-process control and release testing of Raplixa DP and their validation. All identified issues were adequately resolved in the course of the review through requests of supplemental data, additional documentation, or method re-validation, as well as in response to 483 items from the pre-license inspection of the (b) (4) facility. As outcome of the review process, all test methods are sufficiently described in the respective updated SOPs, adequately validated in accordance with ICH Guideline Q2R1, have been successfully transferred from (b) (4), and are deemed suitable by FDA to support quality control testing throughout manufacture, final product release and stability monitoring of Raplixa DP. Therefore, I recommend **APPROVAL** of this BLA from the analytical methods perspective.

One remaining item (qualification of (b) (4) for thrombin) will be addressed in a Post-Marketing Commitment as confirmed by the Applicant in Amendment 32 dated 17 April 2015. This commitment will be included in the Approval Letter.

1. ProFibrix will establish, following a prospectively defined protocol, its (b) (4) for thrombin for the *Thrombin* (b) (4) and *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) international units (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 Post-Marketing Study Commitment – Final Study Report.

REVIEW SUMMARY

1. (b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

Reviewer's comments

Information Requests (IR) were sent to the Applicant on 24 June 2014 and 10 October 2014 to address minor deficiencies. The responses were received on 30 September 2014 as Amendment 14 and on 7 November 2014 as Amendment 19. Specifically:

(b) (4)

Method Improvement and Additional Method Validation

During the Pre-License Inspection (PLI) of (b) (4), repeated out-of-specification (OOS) results were noted with the (b) (4) assay, and the investigations failed to identify the root cause; the corrective and preventive actions (CAPA) taken were ineffective in preventing the recurrence of OOS results. Addressing this inspectional 483 item, ProFibrix conducted comprehensive investigation and concluded that the unsatisfactory (b) (4) was the root cause of the OOS results. The Applicant introduced a number of changes to the SOP 1840, ver. 03 (submitted in Amendment 24 on 20 January 2015), focusing on improving the (b) (4) procedure, and conducted a limited re-validation of the method (document MET 1380, ver. 2 submitted as Amendment 23 on 31 December 2014). The following changes were implemented to the (b) (4) procedure:

- (b) (4)

(b) (4)

- (b) (4)

(b) (4)

Conclusion:

The method is described in sufficient details in the revised SOP 1840, ver. 3 (Amendment 24) and is adequately validated as documented in the initial and supplemental validation reports MET 1279 and MET 1380 (Amendment 23). The changes in the (b) (4) procedure appear to ensure consistent and acceptable thrombin recovery values and showed improvement in method performance for (b) (4). ProFibrix will establish an (b) (4) for thrombin as discussed in the following section 4. The method is acceptable for its intended use for determination of *Thrombin* (b) (4).

The proposed specifications are:

(b) (4)

3. Thrombin (b) (4)

(b) (4)


(b) (4)

Reviewer's comments


A number of deficiencies were identified by FDA with the original method validation (Report MVR 122-02). IRs were sent to ProFibrix on 24 June 2014 and 22 October 2014. The responses were received in Amendment 14 (30 September 2014) and Amendment 20 (26 November 2014),

which also included an additional method validation report, MET 1359 and Study Report SR-FC-P120.


(b) (4)




(b) (4)




(b) (4)



(b) (4)



(b) (4)



(b) (4)

(b) (4)

Considering these issues, FDA recommended a “like-versus-like” approach, and ProFibrix committed to establish a new (b) (4) for thrombin for the *Thrombin* (b) (4) and *Thrombin* (b) (4), using a specific batch of (b) (4) as stated in Amendment 32 dated 17 April 2015. This (b) (4) thrombin (b) (4), and its (b) (4), will be calibrated in international units against the current (b) (4) and will be used for routine testing of commercial product. Alternatively, ProFibrix will use the (b) (4) directly as a (b) (4).

(b) (4)

(b)(4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

Method Improvement and Additional Method Validation

In addition to the review issues discussed above, the PLI of (b) (4) facility revealed recurrent OOS results with this assay that was the major objectionable observation (483 item #1). To address inspectional and review issues, the Applicant conducted a comprehensive investigation for the root cause and implemented a number of changes to the SOP:

- (b) (4)

The revised SOP, SOP 1810-04, was submitted in Amendment 24 received on 20 January 2015.

The method was re-validated (Validation Report MET 1369 was submitted in Amendment 23 on 31 December 2014). The validation was performed using Raplixa DP batch (b) (4) Thrombin Lot as a (b) (4) and (b) (4) as the (b) (4). Spray-dried fibrinogen batch (b) (4) trehalose batch (b) (4), and (b) (4) thrombin (b) (4) batch 04260011B were used in the accuracy study. The validation examined the linearity, range, precision, intermediate precision, accuracy, sample solution stability and robustness of the (b) (4) (b) (4) (Table 3). Specificity of the assay was not assessed as it was addressed in MVR-122-02 and was found acceptable.

Linearity and *range* of Raplixa DP were evaluated over the range of (b) (4) of the nominal thrombin content of (b) (4) (which translates to nominal sample concentration of (b) (4) and the concentration range of (b) (4). The range of the assay was established at (b) (4) of the nominal thrombin content (b) (4) at the time of validation), based on the linearity, accuracy and precision results. Based on FDA review of the manufacturing data, the specification range for *Thrombin Content* was further revised to (b) (4) and the nominal content to 699 IU/g.

Precision was measured by (b) (4) analyst performing (b) (4) measurements of DP Lot (b) (4) nominal thrombin concentration (b) (4) using (b) (4) thrombin standard. The %RSD was (b) (4) which met the acceptance criterion of (b) (4)

Intermediate precision was assessed by including results from a (b) (4) analyst who measured (b) (4) replicates of the (b) (4) lot, on a (b) (4) day. The %RSD of measurement for the (b) (4) analyst was (b) (4). The difference between the (b) (4) analyst was (b) (4) which was within the acceptance criterion of (b) (4).

For *accuracy*, triplicate samples of (b) (4) were (b) (4) into the DP (b) (4), and (b) (4) of the nominal concentration of (b) (4) and the recovery was measured in the assay using a (b) (4) thrombin lot calibrated against (b) (4). The % recovery ranged from (b) (4) which was within the acceptance range of (b) (4). However, it was necessary to apply the correction factor to these measured values to enable comparison with the results obtained using the (b) (4) thrombin standard.

Robustness studies supported sample solution stability for up to (b) (4) when stored at room temperature, and the temperature range of (b) (4) (b) (4).

(b) (4)

(b) (4)

Conclusion:

As outcome of the review and the PLI, the revision of the SOP 1810 has led to improved method performance for *repeatability* and *intermediate precision*, as demonstrated by Method Validation Report, MET 1369. *Linearity* and *accuracy* were demonstrated using simulated DP; and *the range* of the assay was established based on satisfactory linearity, accuracy and precision results and covers the proposed specification range for DP (b) (4). Thus, the method is suitable for its intended use.

Due to issues with the (b) (4) Thrombin standard identified during in-support testing by CBER and the potential of increased inaccuracy in assigning potency for the (b) (4) standards in the future with the use of correction factors, we requested that ProFibrix establishes, under a prospective protocol, a new (b) (4) for thrombin using a specific batch of (b) (4), and qualify (calibrate) it and its replacements, when needed, against the current (b) (4). Alternatively, ProFibrix can use the (b) (4) directly as a working standard in routine testing of the commercial product. ProFibrix committed to these studies in Amendment 32 dated 17 April 2015.

The proposed specifications for *Thrombin* (b) (4) are:

(b) (4)

4. (b) (4)

(b)(4)

(b) (4)

(b) (4)

Conclusion:

The (b) (4) method is described in sufficient detail in the SOP 1838-02, is adequately validated and was successfully transferred from (b) (4), and is suitable for its intended use. The proposed specifications are:

(b) (4)

5. (b) (4)

(b) (4)

An IR was sent to the Applicant on 30 May 2014 and the response was received on 28 August 2014 as part of Amendment 12. The Amendment included Validation Report MET-1360 with additional validation of specificity and linearity performed at (b) (4) using representative samples of Raplixa DP.

(b) (4)

(b) (4)

(b) (4)

ProFibrix stated that the conventional approach for accuracy validation, using (b) (4) with thrombin and fibrinogen, was not feasible for DP, as this contains additional proteins. Accuracy of the method was therefore inferred once linearity and specificity were established, as defined in ICH Q2 (R1). Although the Applicant has not provided any data or calculations to support this inference, we calculated the recovery from the linearity data and method description in the SOP. At the lowest and highest range limits (equivalent to the nominal concentrations of (b) (4), respectively), the measured results were (b) (4) mg/mL, which correspond to (b) (4) recovery. As this is within the allowable \pm (b) (4) range, we concluded that the accuracy of the method in the product matrix is acceptable.

The range of the method (previously set as (b) (4) standard) was revised for Raplixa DP to (b) (4) (corresponding to (b) (4) of nominal protein content of (b) (4) based on linearity and repeatability results using representative DP samples, and on the accuracy of the method within this range as shown by our calculations. This re-defined range is acceptable as it encompasses the DP specification range of (b) (4).

Robustness testing demonstrated that the (b) (4) method is sufficiently robust. The only factor which produced a significant effect on the measurements was the (b) (4).

Reproducibility of the validated method was assessed during technical method transfer by analysis of (b) (4) DP samples by (b) (4) analysts in the (b) (4) laboratories (b) (4) on (b) (4) (Transfer Report MET 1248). The %RSD for each set of (b) (4) measurements was (b) (4) (with acceptance limit of (b) (4)). Difference between sample means between (b) (4) results was (b) (4) for analysts (b) (4) and within the acceptable range of $\pm 10\%$. These results confirmed acceptable reproducibility of the method at (b) (4).

Conclusion:

The (b) (4) method is described in sufficient detail in SOP 1811 and is adequately validated for its intended purpose. The specification is set at (b) (4) (final specification, Amendment 24).

6. Moisture Content by (b) (4)

As both thrombin and fibrinogen are present in Raplixa DP, the absence of premature fibrin formation is critical for product efficacy. This is ensured through control of residual moisture content and fibrinogen status in DP.

The *Moisture Content* in spray-dried fibrinogen, spray-dried thrombin and Raplixa DP is determined using a quantitative (b) (4)

This study confirmed that the reproducibility of the validated method is acceptable as demonstrated by analysis of (b) (4) DP samples by (b) (4) analysts in the (b) (4) laboratories on (b) (4) days. The %RSD for each set of (b) (4) measurements was (b) (4) (with the acceptance limit of (b) (4)) the difference in the mean *Moisture Content* values generated at (b) (4) was (b) (4), respectively, and was within the allowable range of (b) (4)

The following deficiencies were identified with the original method validation: the assay acceptance criteria in SOP 1833 did not include the %RSD parameter for (b) (4) performed from each sample vial and acceptable variation between results of (b) (4) of the same sample; linearity and accuracy in the Report VR-549 were evaluated using (b) (4) but not the actual DP for which the assay is intended; besides, the range of the assay was calculated as (b) (4) and did not cover the upper specification limit of (b) (4). To address FDA concerns, an IR was sent to the Applicant on 30 May 2014, and the response was received on 28 August 2014 as part of Amendment 12.

ProFibrix clarified that during routine analysis, a (b) (4) is performed for each sample vial and, therefore, a %RSD criterion is not applicable. In this reviewer's opinion, the (b) (4) approach is justified by the satisfactory repeatability data ($n = (b) (4)$ analyst) from method validation (Report VR-549-01) and (b) (4) of the method (Report MET 1252-01) when the measurements of (b) (4) analyst and (b) (4) analysts were compared ($n = (b) (4)$): %RSD were (b) (4) for spray-dried fibrinogen; (b) (4) for spray-dried thrombin; and (b) (4) for (b) (4) DP; in addition, %RSD for precision of (b) (4) analysts were (b) (4) with all values being below the acceptance limit of (b) (4)

ProFibrix has performed additional method validation (Validation Report MET 1361-01) for *linearity* using (b) (4) different sample weights of representative DP samples containing (b) (4) of water (corresponding to (b) (4)), based on a nominal (b) (4) sample weight, and covering the DP specification of (b) (4) with each sample analyzed in (b) (4). The regression coefficient of the linearity graph was (b) (4) and met the acceptance criterion of (b) (4). Linearity data demonstrated adequate parallelism between the linear regression plots of DP and (b) (4) standard.

The Applicant also performed additional assessment of *accuracy* by (b) (4) standard into DP samples to achieve (b) (4), and the samples were analyzed in triplicates (Report MET 1361-01). The results generated from moisture content (b) (4) w/w level met the acceptance criterion of (b) (4) recovery. From the results for moisture content (b) (4) level, (b) (4) determinations at each level (b) (4)

(b) (4) failed to meet the accuracy acceptance criterion (b) (4). An investigation concluded that the samples containing large amount of water cause an unstable drift during analysis which results in samples being (b) (4). In order to

minimize the drift within the instrument in future analyses, a (b) (4) step was introduced prior to each sample analysis to ensure that the system is free of moisture and to allow more time for instrumental drift to stabilize. The results generated from the repeat analysis of the failed samples (b) (4) recovery) were within the acceptable range (b) (4). The implemented CAPA appear to be adequate and accuracy of the method can be considered confirmed.

Consequently, the *range* of the assay was re-defined to (b) (4) based on the new linearity and accuracy data in Report MET 1361-01 and original precision data and now covers the upper specification limit of (b) (4).

Conclusion:

The procedure for the (b) (4) method is described in sufficient detail; the method is adequately validated, and is acceptable for its intended use for the determination of *Moisture Content* in spray-dried intermediates and Raplixa DP. In the course of the review, the specification limit for *Residual Moisture Content* was (b) (4) from (b) (4) to reflect the manufacturing capability.

7. (b) (4)

(b)(4)

(b) (4)

(b) (4)

- The specification is set at (b) (4) band which corresponds to (b) (4) fibrin level in a sample. The specification is supported by the release and stability data and is adequately justified.

Conclusion:

The procedure for (b) (4) analysis of (b) (4) is described in sufficient detail in SOP 1929 ver. 02; the method is adequately validated and found acceptable for its intended use to monitor premature fibrinogen activation in Raplixa DP. The proposed specification is (b) (4)

9. (b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

10. (b) (4)

(b) (4)

(b) (4)

1. (b) (4)

This opinion was communicated to ProFibrix at the December 8, 2014 teleconference, and the Applicant requested withdrawal of this method as a lot release test in Amendment 22 dated 17 December 2014. The request was approved by CBER as documented in Dr. Wang's memo dated 14 January 2015.

11. Trehalose and Calcium Chloride

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

Conclusion:

Based on the nature of the manufacturing process, the provided data and the fact that other in-process control parameters act as indirect controls for trehalose and calcium, the DHRR and DBSQC reviewers deemed these in-process specifications redundant.

12. Other Tests

According to agreement reached at the 19 March 2014 internal meeting, the following tests were reviewed by DBSQC and therefore are not discussed in this memorandum:

- Appearance
- (b) (4)
- Sterility
- Pyrogenicity
- Endotoxin

The General Safety Test has been performed on DP throughout development and ProFibrix's intent to discontinue the GST was discussed at the IND stage (CRMTS # 8294). In the BLA, ProFibrix submitted the results of batch analyses demonstrating that the GST complied with the specification of 21 CFR 610.11 for all (b) (4) Phase 3/PPQ batches of Raplixa tested (Amendment 24). The Applicant submitted a request for waiver of the General Safety Test for the commercial product in section 3.2.P.5.6. The request was discussed internally and found to be sufficiently justified:

- both (b) (4) are licensed products with well-demonstrated safety profile;

- the manufacturing process for Raplixa DP is aseptic that minimizes the risk of introduction of extraneous toxic contaminant;
- sufficient in-process controls and release tests for safety are in place (Sterility, Pyrogenicity and Endotoxin);
- non-clinical studies for Raplixa did not reveal any toxicity concerns.

DHRR grants ProFibrix the waiver/exemption from the General Safety Test based on recent publication (Federal Register /Vol. 79, No. 163 / Friday, August 22, 2014 / Proposed Rules, pp. 49727-49731). The respective statement is included in the Approval Letter.

CONCLUSION

The Applicant has adequately resolved all issues identified with the validation of the analytical procedures in the course of the review and during the PLI of (b) (4) facility. As outcome of the review process, all test methods are sufficiently described in respective current SOPs, are adequately validated in accordance with ICH Guideline Q2R1, have been successfully transferred from (b) (4), and are found suitable by FDA to support quality control testing throughout manufacture, final product release and stability monitoring of Raplixa DP.

The results of in-support testing of the (b) (4) PPQ batches of Raplixa DP by the Laboratories of the DBSQC confirmed the suitability of the test methods for their intended use as release tests for the DP. All methods performed adequately satisfying all system suitability and assay validity criteria (except for the (b) (4) method due to the issue with (b) (4) for thrombin). The DBSQC results for the lots tested were within the proposed specifications and comparable to the results reported by ProFibrix.

Qualification of a (b) (4) for thrombin will be addressed as a Post-Marketing Commitment as confirmed by the Applicant in Amendment 32 dated 17 April 2015. This statement will be included in the Approval Letter.

1. ProFibrix will establish, following a prospectively defined protocol, its (b) (4) for thrombin for the *Thrombin* (b) (4) and *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) international units (b) (4)

ProFibrix will establish the protocol and will select, calibrate and qualify a (b) (4) for the appropriate assays.

ProFibrix will submit the full package to the FDA for review by 30 November 2015 as a Post-Marketing Study Commitment – Final Study Report.

I recommend **APPROVAL** of this BLA from the analytical methods perspective.