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To STN: #125640/0

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Product Human plasma-derived Fibrin Sealant

Subject Final/Addendum Review Memo for Quality Control Lot-release Test
Methods for Human plasma-derived Fibrin Sealant, VeraSeal Drug Product

Recommendation: Approval

Summary of Review

A new BLA was submitted for human plasma-derived Fibrin Sealant, VeraSeal Drug Product (STN 125640) by Instituto Grifols, S.A. This document constitutes the Final/Addendum review memo from LACBRP/DBSQC. The following analytical methods and their validations, which were used for the lot release testing of the drug product, were reviewed.

Fibronogen component

1. Determination of Fibrinogen (Clottable protein) by (b) (4) Method
2. Determination of Glutamic acid, Glycine, Arginine and Isoleucine by (b) (4)
3. Citrate Determination by (b) (4) Method
4. Determination of Chloride by (b) (4) method
5. Determination of Polysorbate 80 by (b) (4) method
6. Determination of Tri-n-Butyl Phosphate (TNBP) by (b) (4)
7. Sodium Determination by (b) (4)
8. Appearance of Frozen Product
9. Appearance of Solution after Thawing
10. pH

Thrombin component

11. Determination of Glycine by (b) (4)
12. (b) (4) Determination by (b) (4) Method
13. Determination of Chloride by (b) (4) method

14. Determination of Polysorbate 80 by (b) (4) method
15. Determination of Tri-n-Butyl Phosphate (TNBP) by (b) (4)
16. Sodium Determination by (b) (4)
17. Determination of Calcium by (b) (4)
18. Appearance of Frozen Product
19. Appearance of Solution after Thawing
20. pH

In the Primary Discipline Review memo (dated 20 September 2017) we concluded that except for the assays for the quantitation of TNBP in fibrinogen and thrombin products; and quantitation of glutamic acid, glycine, arginine and isoleucine in fibrinogen product, all other test methods listed above can be approved as quality control lot release test for fibrinogen and thrombin components of human plasma-derived Fibrin Sealant. This memo comprises of the review of outstanding information request related to the deficiencies in validation of the pending assays.

Conclusion:

The three methods reviewed in this memo can be approved for lot-release testing of the Fibrinogen and Thrombin drug products.

Background

Instituto Grifols, S.A. submitted a new BLA for their Veraseal drug product, which is a purified plasma-derived Fibrin Sealant (FS). Fibrin sealant is intended to be used as an adjunct to hemostasis for mild to moderate bleeding in adults (b) (4) undergoing surgery when control of bleeding by standard surgical techniques (such as suture, ligature, and cautery) is ineffective or impractical. The drug product consists of two components, thrombin and fibrinogen, which are assembled into a kit. The kit consists of two sterile syringes containing equal volumes of frozen solutions of human fibrinogen and thrombin, and a delivery device. The fibrin sealant Grifols is formulated for topical use, and is available in four presentations of 2 mL 4 mL, 6 mL and 10 mL.

In the Primary Discipline Review memo (dated 20 September 2017) we concluded that with the exception of following methods, all other proposed test methods can be approved as quality control lot release test for fibrinogen and thrombin components of human plasma-derived Fibrin Sealant.

- Determination of TNBP by (b) (4) for fibrinogen and Thrombin components
- Determination of Glutamic acid, Glycine, Arginine and Isoleucine by (b) (4) for Fibrinogen component

This memo constitutes review of the outstanding issues related to the validation of these assays.

Submitted Information Reviewed

This is an electronic submission. Information submitted and reviewed includes:

- 125640/0 — 1.2 Cover letter dated November 4, 2016
- 125640/0 — 2.3 Quality Overall Summary
- 125640/0 — 3.2.P.5.2 Analytical Procedures, Fibrinogen Component
- 125640/0 — 3.2.P.5.2 Analytical Procedures, Thrombin Component
- 125640/0 — 3.2.P.5.3 Validation of Analytical Procedures, Fibrinogen Component
- 125640/0 — 3.2.P.5.3 Validation of Analytical Procedures, Thrombin Component
- 125640/0.45 — 1.2 Cover Letter
- 125640/0.45 — 1.11.1 Quality Information Amendment: Response to FDA information request dated 7 September 2017, Received on 14 September 2017

Review Narrative

Fibrinogen and Thrombin Components

1. Determination of Tri-n-Butyl Phosphate (TNBP) by (b) (4)

TNBP is added together with Polysorbate 80 (Tween 80) during the fibrinogen and thrombin manufacturing process to inactivate lipid-enveloped viruses and is substantially removed by the subsequent (b) (4) steps. Thus, this is an assay for process-related impurity. The specification limits are (b) (4) for fibrinogen and thrombin components.

Method and Validation

The TNBP concentration in fibrinogen and thrombin components of fibrin sealant drug product is determined by a (b) (4) method as described in SOP IG-MA-000281A.

The method validation review, first and second IR's and review of the responses were included in the Primary Discipline Review memo (dated 20 September 2017).

Third Information request: Based on the review of the initial submission, and subsequent IR's on this assay, a third IR was sent to the sponsor on 7 September 2017. The response was received as Amendment 45 on 14 September 2017, which is reviewed below.

1. Regarding the Method validation reports for the determination of TNBP in fibrinogen product (Document IG_IVMA-000261_ING) and thrombin product (Document IG_IVMA-000237_ING): In your method validation for the TNBP assay, the range of the assay as based on linearity, accuracy and precision results is (b) (4) for fibrinogen product and (b) (4) for thrombin product. Since TNBP is present as an impurity in your product, it is critical to have an assay range that includes the upper specification limit of (b) (4). Please provide linearity and accuracy from

fibrinogen and thrombin samples to show that TNBP can be quantitated at the proposed upper specification limit of the assay.

Review of Response: Instituto Grifols conducted additional studies to assess linearity, accuracy and precision of the method using fibrinogen and thrombin drug products.

Validation using Fibrinogen product

For linearity, data from three independent (b) (4) runs were evaluated at TNBP concentrations ranging from (b) (4). A mean correlation coefficient (R) of (b) (4) was obtained, which met the pre-defined acceptance criteria for R to be (b) (4).

Accuracy was assessed at (b) (4) concentration levels of TNBP in the range of (b) (4). The pre-set acceptance criterion for recovery was (b) (4), and the actual recovery varied from (b) (4).

Repeatability and intermediate precision were estimated from (b) (4) concentration levels of TNBP covering the range of the assay. The RSD's for repeatability (obtained by testing each concentration three times within the same assay) varied from (b) (4). The RSD's for intermediate precision, obtained by testing each concentration three times in independent assays, were between (b) (4), and within the acceptable range of (b) (4).

Therefore, based on the submitted data for linearity, accuracy and precision, the LOQ or lowest reportable value is demonstrated to be (b) (4).

Validation using Thrombin product

For linearity, data from three independent (b) (4) runs were evaluated at TNBP concentrations ranging from (b) (4). A mean correlation coefficient (R) of (b) (4) was obtained, which met the pre-defined acceptance criteria for R to be (b) (4).

Accuracy was assessed at (b) (4) concentration levels of TNBP in the range of (b) (4). The pre-set acceptance criterion for recovery was (b) (4), and the actual recovery varied from (b) (4).

Repeatability and intermediate precision were estimated from (b) (4) concentration levels of TNBP covering the range of the assay. The RSD's for repeatability (obtained by testing each concentration three times within the same assay) varied from (b) (4). The RSD's for intermediate precision (obtained by testing each concentration three times in independent assays) varied from (b) (4), within the acceptable range of (b) (4).

Based on the submitted data, the LOQ or lowest reportable value at which linearity, accuracy and precision is demonstrated is (b) (4).

Conclusion: The methods for quantitation of TNBP in fibrinogen and thrombin products are validated appropriately, and are found to be suitable for their intended use. All outstanding issues in method validation were addressed appropriately.

2. Determination of Glutamic acid, Glycine, Arginine and Isoleucine by (b) (4)

Glutamic acid, arginine and isoleucine are excipients in fibrinogen component of fibrin sealant drug product. The specifications in fibrinogen are (b) (4) for glutamic acid, (b) (4) for arginine and (b) (4) for isoleucine. Glycine is a process derived impurity, and its specification is set at (b) (4) in the fibrinogen component of the drug product.

Method

The concentration of glutamic acid, glycine, arginine and isoleucine in fibrinogen component of fibrin sealant drug product is determined by (b) (4) after (b) (4) with (b) (4), following the procedure described in SOP, IG_MA-000358C_ING.

The method validation review, first and second IR's and review of the responses were covered in the Primary Discipline Review memo (dated 20 September 2017).

Third Information request: Based on the review of the initial submission, and subsequent IR's on this assay, a third IR was sent to the sponsor on 7 September 2017. The response was received as Amendment 45 on 14 September 2017, which is reviewed below.

1. We have the following questions/comments regarding the Method validation report, Document IG_IVMA-FGD1358C_ING: In your (b) (4) assay for the quantitation of amino acids, glycine is measured as an impurity. Therefore, during the study of validation characteristics, it is critical to include the data point at the defined specification limit of (b) (4). As mentioned in our information request dated 10 July 2017, please provide the requested data to permit complete review of your assay.

Review of Response: In response to CBER IR, the sponsor explained that a series of serial dilutions of the sample have been established to allow for the simultaneous determination of four amino acids. Glycine assayed by this method requires (b) (4) dilution because of the range of the method. Thus, the sample containing (b) (4) of glycine (which is the specification limit) will contain (b) (4) of glycine after dilution and at this concentration the sample will be within the quantifiable range of the assay, which is (b) (4). Since, the sponsor's evaluated range covers the set limit for glycine after dilution of the sample as specified in the test method, the response is acceptable.

Conclusion: The method has been adequately described and validated, and is acceptable as a lot-release test for the determination of amino acid content (glutamic acid, glycine, arginine and isoleucine) in fibrinogen drug product.