



From Ishrat Sultana, DBSQC/OCBQ
Grainne Tobin, DBSQC/OCBQ

To STN 125640/0

Through Lokesh Bhattacharyya, Chief, LACBRP, DBSQC/OCBQ
James Kenney, Acting Director, DBSQC/OCBQ

Product Fibrin Sealant (Human), VeraSeal

Sponsor Instituto Grifols, S.A

Subject Review Memo for Biological License Application for Quality Control Lot-Release Test Methods for the Drug Product for Fibrin Sealant (human)

Recommendation: Approval

Summary of Review

The Biological License application for Fibrin Sealant (human), STN 125640, was submitted by Instituto Grifols. This Review memo covers the following methods and validations for the lot release of the drug product:

1. Thrombin Determination by Coagulation Using the (b) (4)
2. (b) (4) Determination by (b) (4) in Fibrinogen Concentrates

The validation was carried out at the Instituto Grifols, S.A facility at Barcelona, Spain. The methods have been described and validated adequately and may be used for lot-release testing of Fibrin Sealant (human) drug product.

Background

Fibrin Sealant (human) (proprietary name: VeraSeal) is intend to support local hemostasis, to glue surfaces of injured tissues in order t0 obtain sealing of surfaces , to support sutures or to improve repair or healing by generating a cross-linked fibrin clot in a process that mimics the last stage of the human coagulation system. Human plasma-derived Fibrin Sealant drug product is composed of two syringes containing a sterile frozen solution of fibrinogen (component 1) and a sterile frozen solution of human thrombin with calcium chloride (component 2) assembled on a syringe holder. One applicator cannula is provided with the product. Both components are isolated from human plasma. The Fibrin Sealant solution contains 80 mg/mL of human fibrinogen and 500 IU/mL of human thrombin in separate syringes.

Submitted information reviewed:

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

125640/0 - 3.2.P.5.1 Specifications

- Specifications of the finished product- Fibrin Sealant, IG_ESP-00304_ING, version 1.0

125640/0 - 3.2.P.5.2 Analytical procedures

- (b) (4) determination by (b) (4) in Fibrinogen Concentrates, IG_MA-000185C_ING, version 6.0
- Thrombin evaluation by (b) (4), IG_MA-000475A_ING, version 11.0

125640/0 - 3.2.P.5.3 Validation of Analytical Procedures

- Validation for (b) (4) fibrinogen of (b) (4) determination by (b) (4) in Fibrinogen concentrates, IG_IVMA-FGDI185C_ING, version 2.0
- Validation for thrombin (sealant) of thrombin determination by (b) (4), IG_IVMA-000298_ING, version 2.0

125640/0 – 3.2.P.6 Reference Standards or Materials

- 1- Primary reference standards

125640/0.17 – 3.2.P.6 Reference Standards or Materials

- Thrombin preparation and standardisation of the secondary standard batch (b) (4) ((b) (4)), IG_IEST-000295_ING, version 1.0
- Thrombin preparation and standardisation of the secondary standard batch (b) (4) ((b) (4)), IG_IEST-000296_ING, version 1.0

125640/0.21 – 1.12.11 ANDA Basis for Submission Statement

- Responses to FDA Information request 23Mar17

125640/0.21 – 3.2.P.5.3 Validation of Analytical Procedures

- Routine assay example (b) (4)
- Intermediate precision assay (b) (4)

125640/0.21 – 3.2.P.5.6 Reference Standard or Materials

- (b) (4) (in fibrinogen concentrates), preparation and standardization of the (b) (4) secondary standard Lot (b) (4), IG_IEST-000519_ING, version 1.0

1. Thrombin Determination by Coagulation Using the (b) (4)

This clotting assay is based on the thrombin assay method described in the (b) (4)

(b) (4). It is used to measure the thrombin concentration of (b) (4) final drug product samples. The proposed specifications are (b) (4). The sponsor provided an analytical procedure, IG_MA-000475A_ING, version 11.0, and a validation report, IG_IVMA-000298_ING, version 2.0.

Method

(b) (4)

(b) (4)

First Information Request and Review

The following IRs were submitted to the sponsor on 23 March 2017. The response was received on 7 April 2017 as Amendment 21. The IR questions, the response from the sponsor and review of the responses are discussed below:

- a. Regarding Analytical Procedure IG_MA-000457A_ING: Thrombin Evaluation by Coagulation using (b) (4) :
 - i. In Section 4.1 of your SOP, you state that Thrombin secondary standard is used as both standard and control. If the same lot of the drug product is used as standard and control, it would amount to a circular reasoning. The control should be a different material at least from that of the drug product lot, which is different from the lot used as the standard. Please provide a detailed description of the standard and control used in this assay. If they are from the same lot of drug product, please provide your plan and timeline for qualification of a different lot of drug product to be used as control and submit the qualification data for review.

Review of Response: The sponsor clarified that the Thrombin secondary standards used as standard and control were derived from to (b) (4) different batches of drug product. Thrombin secondary standard used as standard, lot (b) (4), is derived from the raw material batch (b) (4), while thrombin secondary standard as control, lot (b) (4), is derived from the raw material batch (b) (4). This is satisfactory.

- ii. Please explain how your Reference Standard and Control and their values are qualified and assigned, respectively. Please provide representative sets of qualification data.

Review of Response: The sponsor submitted qualification reports for both the standard and control, detailing how each was prepared. (b) (4)

(b) (4)
(b) (4)
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(b) (4)
(b) (4) This is acceptable.

b. Regarding Method Validation Report IG_IVMA-000298_ING: Validation for Thrombin (Sealant) of Thrombin Determination by Coagulation Using the (b) (4)

(b) (4):

i. For linearity, you have measured the slopes and correlation coefficients from the (b) (4) for Thrombin, (b) (4). Please provide data demonstrating linearity and parallelism between your in-house standard and your drug product.

Review of Response: The sponsor provided linearity data for the standard and a representative drug product sample analyzed using the (b) (4) software. From this data, (b) (4)

(b) (4) for the standard and drug product, respectively. (b) (4)
(b) (4). This is adequate.

ii. Please provide data assessing the robustness of your method.

Review of Response: The robustness of the assay was examined by (b) (4)

(b) (4)
(b) (4)
(b) (4)
(b) (4)
(b) (4)
(b) (4)
(b) (4)
(b) (4) This is adequate.

Conclusions

The SOP and validation studies indicate that this method is suitable for use for lot-release testing.

2. (b) (4) **Determination by (b) (4)** (b) (4) **in Fibrinogen**

Instituto Grifols, S.A uses a (b) (4) method to determine the concentration of (b) (4) in Fibrin Sealant (human) drug product using a (b) (4) kit. The proposed lot release specifications for the drug product are (b) (4). The sponsor provided a Standard Operating Procedure, "(b) (4) determination by (b) (4)

(b) (4)

[Redacted]

[Redacted]

[Redacted]

First Information Request and Review

The following IRs were submitted on March, 23, 2017. The sponsor's response was received on April 07, 2017 as Amendment 21. The data provided by the sponsor and review of responses are provided below.

- a. Regarding Analytical Procedure IG_MA-000185C_ING: (b) (4) Determination by (b) (4) in Fibrinogen Concentrates:
 - i. Please provide a complete description of the secondary standard used in the assay, including how it is qualified. Please provide representative qualification data for the control.

Review of response: The sponsor provided a detailed description of the secondary standard used in the assay and the data in support of the qualification of (b) (4) as the secondary standard. The (b) (4) secondary standard, lot (b) (4), is (b) (4)

[Redacted] This is acceptable.

- b. Regarding Method Validation Report: IG_IVMA-FGDI185C_ING: Validation for (b) (4) Fibrinogen of (b) (4) Determination by (b) (4) in Fibrinogen Concentrates:

- i. You have studied linearity using the standard (b) (4) only. However, you have neither evaluated linearity of the drug product nor demonstrated parallelism between (b) (4) and the drug product. Please provide data on the linearity of the drug product and parallelism between concentration versus response plots of (b) (4) and the drug product.

Review of Response: The sponsor provided the data from an intermediate precision assay calculated by the statistical software, (b) (4)

(b) (4) between standard and drug product was (b) (4) which demonstrated parallelism.

- ii. Please provide robustness data with respect to variations in critical method parameters.

Review of Response: The sponsor provided data on robustness studies in a table form for three lots of drug product used as a control, which considered the parameters of

(b) (4)

(b) (4) This shows that using (b) (4) did not affect the measurement of the drug product.

- iii. Based on your validation data of accuracy in Table 4 on page 10 of your validation report (IG_IVMA-FGDI185C_ING), the final assay concentration range should be (b) (4), based on the result of your accuracy study. You have studied precision and linearity over a wide range, while accuracy over a narrow range. Therefore, the assay range should correspond with whichever yields the narrower range. However, in the summary of validation report on page 13, you indicated a wider assay range of (b) (4) instead. Please revise page 13 of your validation report to indicate that your assay range is (b) (4) and submit for review.

Review of Response: The sponsor again stated that the range of the assay was (b) (4), and not (b) (4), based on the accuracy data. They provided the calculations for how the theoretical quantity of each sample was determined, with the assumption that the theoretical quantity of the drug product into which the BRP standard is spiked has a concentration of (b) (4). Hence the range is (b) (4). This is adequate.

Conclusions

The SOP and validation studies provided show that this method is suitable for use for lot-release testing.