



Food & Drug Administration
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MEMORANDUM**DBSQC/OCBQ ANALYTICAL METHOD REVIEW MEMO**

To: The file STN 125833/0

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Product: FESILTY [Fibrinogen (Human) (BT524)]

Applicant: Grifols Therapeutics LLC

Subject: Analytical Methods for the Lot Release of (b) (4) Drug Product.

Recommendation: Approval

Executive Summary:

The following analytical methods used for lot release of FESILTY (Fibrinogen (Human) (BT524)) (b) (4) drug product (DP) from Grifols Therapeutics LLC, and the associated validations or qualifications, were reviewed:

- 1) pH – (b) (4) DP
- 2) Osmolality – DP
- 3) Total Protein – (b) (4) DP
- 4) Molecular Size Distribution – (b) (4) DP
- 5) Clarity and Opalescence – DP
- 6) Coloration of solution – DP
- 7) Residual Moisture – DP

Conclusion

The analytical methods and their validations and/or qualifications reviewed for FESILTY (b) (4) DP from Grifols Therapeutics LLC, were found to be adequate for their intended use in lot release testing.

Background

FESILTY (BT524), is a human fibrinogen indicated for 1) (b) (4) 2) treatment and prophylaxis of pediatric and

adult patients with congenital hypo- or afibrinogenemia with bleeding tendency. It is a combination of a heat-treated lyophilized and purified concentrated fibrinogen co-packaged with 50 mL vial of sterile WFI and a Nextaro v 5 µm 20/20 Transfer Device. The lyophilized part is reconstituted to give a single dose of 1 g human fibrinogen and one 50 mL sterile WFI for an intramuscular administration. One vial of drug product contains 1 g of human fibrinogen as active ingredient (DS). Excipients used include stabilizers (421.3 mg arginine hydrochloride, 25.5 mg of polysorbate 80, 73.5 mg sodium citrate dihydrate, and 567.5 mg trehalose dihydrate); electrolyte (292.2 mg sodium chloride); and diluent (water for injection, WFI). The specification of BT524 DP is 1 g/vial (b) (4) g/vial) of active fibrinogen.

Information Reviewed

Information in sections of the original submission and all responses to information requests and electronic mails that describe control of (b) (4) DP (3.2.S.4 and 3.2.P.5, respectively), including analytical procedures for DP, and validation of these analytical procedures, were reviewed.

Review Narrative


1. pH – (b) (4) DP






Introduction.

This procedure describes the determination of pH value in protein-containing solutions of fibrinogen (b) (4) DP. All tests are performed at Biotest (Dreieich) site's biochemistry laboratory in the quality control department. The current product specification is $6.5 \leq \text{pH} \leq 7.5$

Method


(b) (4)




Method verification**(b) (4)**




**Conclusion**


Determination of pH in in Fibrinogen (BT524) **(b) (4)** DP according to SOP-Q-00050 was verified and found suitable for its intended use.

2. Osmolality – DP**Introduction.**

Osmolality test on fibrinogen (BT524) DP solutions was performed at Biotest (Dreieich site, Quality control department) as per in-house method SOP-Q-00336 based on the compendial methods **(b) (4)**. The specification for osmolality is **(b) (4)**




Method**(b) (4)**


(b) (4)



Method Verification

(b) (4)

Conclusion:


Determination of osmolality in lot release Fibrinogen (BT524) DP samples according to SOP-Q-00438 was validated and found suitable for its intended use.

3. Total Protein – (b) (4) DP

The protein test is performed at Biotest (Dreieich) site's biochemistry laboratory in the quality control department. The release specifications for protein concentration determination in BT524 (b) (4) DP are (b) (4) (b) (4) SOP-Q-00438) and (b) (4) 20 g/L, SOP-Q-00438) respectively. The same method is used for both the (b) (4) DP. Since the DP has more excipients and a complex matrix, the sponsor used the DP as the worst-case scenario for the validation.







Method:

(b) (4)



1 page determined to be not releasable: (b)(4)

(b) (4)



4. Molecular Size Distribution – (b) (4) DP

Introduction.





This procedure describes the determination of molecular size distribution (MSD) in protein-containing solutions of fibrinogen (b) (4) DP. The MSD test is performed at Biotest (Dreieich) site's biochemistry laboratory in the quality control department. The specifications for molecular distribution of Fibrinogen (Human) (BT524) (b) (4) DP are:

(b) (4)

Monomers: $\geq 80\%$ release and shelf-life.

(b) (4)

(b) (4)





5. Clarity and Opalescence – DP

This procedure describes the determination of clarity and opalescence in protein-containing solutions of fibrinogen (b) (4) DP. All tests are performed at Biotest (Dreieich) site's biochemistry laboratory in the quality control department. The specification for DP clarity: Turbidity/degree of opalescence is (b) (4) .

Method

(b) (4)



(b) (4)

Conclusion:

The method for determination of clarity and opalescence in Fibrinogen (Human) (BT524) DP is suitable for lot release testing.

6. Coloration of solution – DP

Introduction.

This procedure describes the determination of coloration of protein-containing solutions of fibrinogen (BT524) DP. All tests are performed at Biotest (Dreieich) site's biochemistry laboratory in the quality control department. Specification for the coloration of DP solution is: Equal or less colored than reference solution (b) (4)

Method.

(b) (4)

7. Residual Moisture – DP.

Introduction.

This procedure describes the determination of residual moisture for fibrinogen (BT524) DP by (b) (4). All tests are performed at Biotest (Dreieich) site's biochemistry laboratory in the quality control department. The release specification

