



CBER REGULATORY REVIEW

01 July, 2014

To Administrative File: STN 125523/0

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Subject BLA: Review of Sterility, Pyrogen and Bacterial Endotoxin Test Qualifications
for Fibrocaps® (Human Fibrinogen and Human Thrombin) Fibrin Sealant.

Recommendation

Based on the scope of this review, I recommend approval of this Biologics License Application (BLA).

Conclusion

After a thorough review of this BLA and the response to CBER's Information Request (IR) (Amendment 125523/0.4- received on 08 April, 2014), this reviewer finds the sterility and (b) (4) bacterial endotoxin test (b) (4)-BET methods were qualified in accordance with USP (b) (4) and USP (b) (4), respectively, by demonstrating that the product matrix for Fibrocaps® is suitable for these intended test methods. In addition, this reviewer finds (b) (4) performed their rabbit pyrogenicity test method in accordance with USP (b) (4).

Background

Fibrocaps® (proposed proprietary name: Raplixa [Human Fibrinogen and Human Thrombin]) fibrin sealant is manufactured for ProFibrix BV in Leiden, Netherlands by (b) (4)

Fibrocaps® is indicated as an aid to surgical hemostasis for mild to moderate bleeding from small vessels when control of bleeding by standard surgical techniques is ineffective or impractical. Fibrocaps® is supplied as a pre-mixed, ready to use blend of human plasma-derived thrombin and fibrinogen presented in a powder format. All presentations (0.5g/vial, 1 g/vial and 2g/vial) contain the same concentration of drug product (79mg/g human fibrinogen and (b) (4) IU/g human thrombin per gram of powder). Other ingredients include; sodium chloride and sodium citrate (b) (4), trehalose, human albumin and L-arginine hydrochloride (b) (4) and calcium chloride (b) (4)

Fibrocaps® is used without reconstitution and can be applied directly onto the surgical bleeding site in one of three ways; 1) direct delivery from the vial, 2) by use of the Fibrospray device (sterile, single-use, dry powder spray device connected to an appropriate air supply) or 3) onto a dry or saline-moistened gelatin sponge. Regardless of the method of delivery, Fibrocaps® must be used in

combination with a gelatin sponge. Upon contact with aqueous fluids such as blood, the active thrombin component of Fibrocaps® triggers an immediate conversion of the fibrinogen component into insoluble fibrin polymers thereby promoting clot formation.

The DBSQC reviews BLAs and Supplements to ensure analytical methods are appropriate, properly validated and the product matrix is suitable for the intended test method. DBSQC also reviews release specifications for microbial and endotoxin testing and sterility to ensure they reflect process capability and meet regulatory compliance. These review activities support DBSQC's lot-release mission, which is the confirmatory testing of submitted product samples and review of manufacturers' lot-release protocols to ensure biological products are released according to licensed test methods and product specifications. Therefore, this review will focus on the qualification reports for the sterility, rabbit pyrogenicity and (b) (4) BET test methods to determine if the Fibrocaps® product matrix is suitable for these intended test methods.

Review

Sterility Test Qualification

(b) (4) performed their (b) (4) sterility test using the (b) (4) method by testing (b) (4) of Fibrocaps® drug product to demonstrate the drug product matrix does not inhibit bacterial and fungal growth. Of note, upon rehydration of the Fibrocaps® drug product, a clot is immediately formed due to the presence of thrombin. Therefore, to inhibit the thrombin activity and prevent clotting, (b) (4) to the addition of the drug product. The (b) (4) test was performed as follows:

(b) (4)

One protocol deviation occurred during the execution of this suitability qualification protocol. Due to an underweight issue noted with batch (b) (4) (Deviation GMP (b) (4)), the contents of (b) (4) rather than 10 vials of product ((b) (4)/vial presentation) were added to the respective growth media, to ensure the total weight of product tested reflected or exceeded the contents of (b) (4) correctly filled vials.

After (b) (4), all test media had turbidity comparable between the test sample and their respective (b) (4) control, while the (b) (4) showed no growth. The test was performed and compliant with USP (b) (4) and the test results indicate there is no product inhibition on microorganism growth; thus indicating the Fibrocaps® drug product matrix is suitable for testing using (b) (4) sterility test method.

Pyrogenicity Test

(b) (4) performed their pyrogenicity test using (b) (4) of their Fibrocaps® drug product to detect if the product induces a pyrogenic response in rabbits, as is indicated by a rise in body temperature. The pyrogenicity test is a compendial test that does not require suitability qualification testing; however, the method was reviewed to ensure it was performed in accordance with USP (b) (4).

Three rabbits were injected intravenously via the marginal ear vein with (b) (4) drug product ((b) (4)) at a dose of (b) (4) of body weight. The tested dosage represents the potential pyrogenic activity of the drug product with a safety factor of (b) (4) the human clinical dose.

The temperature of each rabbit was recorded every (b) (4) following injection. The maximum temperature rise (as compared to the initial temperature) was determined at the end of the (b) (4). The requirements of the test are met, as none of the rabbits displays a maximum rise in temperature (b) (4) above its initial body temperature. The test was performed and compliant with USP (b) (4).

Endotoxin Test Qualification

(b) (4), qualified their (b) (4)-BET test method using (b) (4) of their Fibrocaps drug product and (b) (4) to verify the product matrix is suitable for the intended test method.

A range of dilutions from (b) (4) were tested to determine a suitable product testing dilution that would not inhibit or enhance the known positive product control results in their (b) (4) BET method. A (b) (4) testing dilution demonstrated suitable (b) (4) and was selected as their sample testing dilution. The (b) (4) was calculated to be 1:17,500 as calculated from the: test specification (b) (4).

All bacterial endotoxin test parameters were within the test validity criteria – listed below - as specified in (b) (4) validation procedure and in USP (b) (4).

- (b) (4)

The bacterial endotoxin concentration results found during the (b) (4) respectively, which were within their release specification of (b) (4). Due to the nature and potential use of this product, CBER finds the release specification acceptable – even though it is well above their production process capability. That is, since the potential risk of bleeding out is greater than the potential risks associated with higher product endotoxin concentrations, when the product could be used in quantities associated with the saving of life.

Summary

After a thorough review of the information submitted in this BLA, this reviewer finds (b) (4) Fibrocaps® sample matrix is suitable for testing using their sterility and (b) (4) BET methods; these tests were qualified and performed in accordance with USP (b) (4) and USP (b) (4) respectively. In addition, this reviewer finds (b) (4) performed their rabbit pyrogenicity test method in accordance with USP (b) (4). Therefore, this reviewer finds these methods acceptable for their intended purpose and recommends their approval.