

## Tilghman, Tracy

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**From:** Tilghman, Tracy  
**Sent:** Tuesday, December 23, 2014 1:24 PM  
**To:** Linda Zuckerman (Linda.Zuckerman@THEMEDCO.com)  
**Subject:** Reference BL# 125523/0 - Information Request

**Importance:** High

### Reference BL#125523/0

Dear Dr. Zuckerman,

We are reviewing your January 31, 2014 original submission for Fibrin Sealant, Human Fibrinogen, Human Thrombin 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. We have reviewed your October 17, 2014 amendment in response to September 10, 2014 Information Request and have the following comments.

1. With reference to section 3.2.P.5.6 INV394 "US Specification Justification Report - Raplixa"

The following specifications are not sufficiently stringent based on the analysis of the manufacturing data provided, and the safety and efficacy for the extreme values of the specification ranges are not supported by clinical trials. Please revise/tighten the specification ranges/limits to be in line with the process capabilities.

For Drug Product:

- a. Fibrinogen potency. The suggested range is mean (b) (4)
- b. Fibrinogen content. The suggested range is mean (b) (4)
- c. Moisture content. The suggested value is (b) (4)
- d. Endotoxin. The suggested value is (b) (4) (considering that all data were below the method LOQ of (b) (4))

(b) (4)

We note that statistical analyses were performed on datasets including both the release and stability data. Although it appears, based on the submitted stability data, that specifications proposed are valid over the shelf life of the product, please verify it. Specifically, please provide the evidence/projection that Drug Product released with Thrombin Potency close to the lower specification limit will remain within specification at the end of shelf life. Optional: you may consider establishing an additional control for this parameter, e.g., an internal alert limit based on the analysis of release data only.

FDA reserves additional comments for Thrombin-related specification parameters depending on our review of the validation package and the specification assessment including the revised (b) (4) data package obtained using the revised (b) (4) method and Thrombin (b) (4) method which your company committed to submitted by January 20<sup>th</sup>, 2015 as part of response to Form FDA 483 item #1.

2. With reference to section 3.2.P.5.1 INV354 "Specification Justification Report – Fibrocaps Raw Materials"

The statistical approach used to establish the extended acceptance criteria ranges for Fibrinogen (b) (4) and Thrombin (b) (4) is statistically inappropriate. The confidence intervals calculated from the analysis of different lots of (b) (4) products do not carry a significant meaning, as they reflect along with analytical variability the expected lot-to-lot variability of (b) (4) material, and therefore cannot be applied to the (b) (4) CoA ranges which already are based on lot-to-lot and analytical variability on (b) (4) side. Taking into account the recovery data, we suggest the following specifications to be changed to:

(b) (4) difference of (b) (4) Recovery value from (b) (4) CoA value.

This specification may need to be revised through post-marketing commitment when more data will be available in the future.

**Please submit this information request as an amendment to this submission by January 12, 2015. If you are unable to respond by January 12<sup>th</sup>, please contact me at your earliest possible convenience.**

The review of this submission is ongoing and issues may be added, expanded upon, or modified as we continue to review this submission.

The action due date for this file is April 31, 2015.

If you have any questions, please contact me at (240) 402-8376.

Sincerely,

**LT Tracy Tilghman, MPH, CHES**

Lieutenant, United States Public Health Service

Regulatory Project Manager

U.S. Food & Drug Administration

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