

# Discipline Review Memo - RECOTHROM

**Date:** 25 September 2007  
**To:** Roman Drews, Ph.D. (HFM-392), Scientific Lead  
for Stn.125248.0-ZymoGenetics  
**From:** Eleanor Koo (HFM-340)  
**Subject:** Discipline review memo for ZymoGenetics Inc.  
Stn # 125248.0 (BLA)-Thrombin (Recombinant)  
(Human)  
**Through:** Timothy Lee, Ph.D., Acting Lab. Chief Laboratory of  
Hemostasis/DH/OBRR/CBER (HFM-392)  
**CC:** Mark Shields, RPM (HFM-380)

## **Background:**

Zymo Genetics Inc. (ZGI) has submitted an original Biologics License Application (BLA) for Recombinant human Thrombin (rhThrombin).

Recombinant human Thrombin (rhThrombin) is identical in amino acid sequence to endogenous human  $\alpha$ -thrombin. Recombinant human Thrombin is generated from a recombinant fragment of prothrombin called recombinant human prethrombin-1 (rh Prethrombin-1). The coded sequence for the rhPrethrombin-1 ----- truncated variant of the naturally occurring prothrombin.

Recombinant human Thrombin is indicated for use as a general adjunct to hemostasis when control of bleeding by conventional surgical techniques, including suture. Ligature and cautery is ineffective, insufficient or impractical. The product is indicated for topical use in conjunction with an absorbable gelatin sponge for hemostasis during surgery.

The commercial rhThrombin product is produced by changing its manufacturing process from ----- process to scale-up to commercial scale. The product has been extensively characterized by physicochemical methods; comparability of material from both processes has been demonstrated.

## **Additional long term stability data for qualification lots on 14 June 2007**

Received qualification lots (-----) with nine (9) months (-----), and six (6) months (-----) long term stability data at the recommended storage condition of 2-25°C and ----- . All test results met specification, and the drug product (Recombinant human Thrombin (rhThrombin)) is stable for up to 12 months at the recommended storage of 2-25°C.

## **ZyniGentics submitted updated stability as the following on 18 July 2007:**

- Reference standards (rThrombin and rPrethrombin-1)
- All ----- lots listed in the BLA (from pilot and commercial processes)
- All drug substance (BDS) lots listed in the BLA (from pilot and commercial processes)
- All drug product (DP) lots listed in the BLA (made from pilot and commercial process BDS)

## **Conclusion/recommendation:**

1. Real-time long term stability data for Commercial process Qualification lots ----- up to shelf life (Recommended 18 months) should be provided as they become available.

2. Please consult a statistician for statistical valuation of the stability data.
3. A shelf life of eighteen (18) is recommended.
4. This submission is approvable

**Summary of review:**

1. Container/Closure System for Bulk Intermediate drug Substance(3.2.S.6) and final drug Product (3.2.P.7)
2. Bulk Intermediate drug substance Stability data (3.2.S.7.3)
3. Final drug product Stability data (3.2.P.8.3)
4. Post-approval stability Protocol and stability commitment for Bulk Drug Substance (3.2.S.7.2) and final drug Product (3.2.P.8.2)

**Bulk drug substance (BDS) for rhThrombin:**

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**9**

**PAGES**

**Determined**

**To Be**



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6

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**Comments:**

**Long-term Stability data submitted by the firm (ZymoGenetics) On June 14, 2007:**

Received qualification lots ----- with nine (9) months -----, and six (6) months ----- long term stability data at the recommended storage condition of 2-25°C and -----

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Results: All test results met specification limit.

Recommendation: This drug product can be stored at the recommended storage condition and stable up to twelve months. A twelve (18) months shelf life can be assigned.

1. Please consult a statistician for statistical valuation of the stability data.
2. Please submission commercial process qualification lots (3) samples for potency testing.

Comment: Three commercial process qualification lots -----samples with diluents had been submitted and potency assay has done, they are within the specification limit.

The following table showed the assay results:

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**Reconstitution diluent and transfer devices:**

The recommended reconstitution diluent for the lyophilized 5000-International unit (IU) rhThrombin drug product is 0.9% sodium chloride injection, USP. Use of the recommended diluent results in a solution containing a nominal potency of 1000 IU/mL.

The commercial 5000-IU rhThrombin drug product is co-package with a 5-mL pre-felled normal saline syringe (-----), a ----- needle-free multidose vial access device (-----) and a 5mL LuerLok tip





