

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 α -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:

9

PAGES

Determined

To Be

[illegible]

Recombinant human Thrombin (rhThrombin) drug product is a sterile, lyophilized, and white to off-white solid and/or powder that contains no preservative and is reconstituted with 0.9% sodium chloride injection, USP. Upon reconstitution, rhThrombin drug product is a clear, colorless solution. It is intended for topical administration to bleeding surfaces. The quantitative composition for each vial is 5000-International unit (IU) of rhThrombin drug product.

[illegible]

6

PAGES

Determined

To Be

Not Releasable

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 -----

---	-----	-----
-----	-------	-------

[illegible]

(mg/mL) was observed after 24 hours of storage at 25°C, representing worst-case conditions; no changes in specific activity (U/mg a-thrombin) were observed. The use of surgical material other than absorbable gelatin sponges with rhThrombin is not recommended because potency may be affected.

Statistical assessment of stability data:

The purity graphs are generated by plotting all measured purity values (%) against time (months) at a given storage condition, while applying regression analysis and confidence intervals.

The 95% confidence interval (lines around the linear regression) represents the range of Y-values which encompass 95% of the sample points in normal statistical distribution.

As the regression line extends beyond real-time data points, it is considered a predicted estimate of the true mean at those future time points. The confidence interval reflects the prospective nature of this line by expanding as it extends through future time points, of which there is more uncertainty as to the true mean.

The results for the formal stability studies from the three lots -----
---- Commercial Process for Phase 3 clinical indicate that the rhThrombin drug product is stable to date (18 months) at the recommended storage condition of 2°C to 25°C.

Comment: Please consult a statistician for statistical assessment of stability data.

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