

6/22/2007 Fax - RECOTHROM

FACSIMILE TRANSMISSION RECORD

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To: **Mark Gauthier, Regulatory Affairs**

This Fax is regarding **STN 125248/0** that was submitted to the agency on **18-Dec-06**, designated as a **New BLA** for manufacture of Thrombin (Recombinant) indicated for use as a general adjunct to hemostasis during surgery when control of bleeding from oozing surfaces, capillaries and small venules, by standard surgical techniques is ineffective or impractical;.may be used in conjunction with an absorbable gelatin sponge USP...

Reviewers' Information Request

Chemistry, Manufacturing, and Controls

Regarding the post-production cell -----, please provide:

1. ---- images with clearly indicated -----
2. Results of genetic characterization studies that demonstrate the integrity of the expression ----- . The results should include, but not be limited to, images of ----- from ----- analysis, and the results should be compared to those obtained from the corresponding MCB.
3. Additional data demonstrating that observed differences in the ----- ---- between the MCB and post-production cell ---- result from the variability of the ----- -- method.

Regarding the production bioreactor:

1. Please clarify how you derived the minimum acceptable limits for ----- at the harvest stage. These proposed limits are not justified by results from conformance lot manufacture and scale-down validation study.
2. Please establish the limit for the maximum duration of the cell culture campaign as an in-process control parameter/specification. This limit can be expressed in doubling generation time or cell culture days. It should be justified by the duration of the conformance lot campaigns and genetic stability of the expression construct.

Regarding the -----:

1. As indicated in Table 51 (Page 48 of 51; 3.2.S.2.5), -----
----- were performed only as "additional testing during process validation study". Since purification of ----- is a critical step in the manufacture of -----, please include the referenced tests as routine in-process control testing for the manufacturing process. The necessity of these tests can be evaluated periodically when more data are available.
2. Please provide the current standard operating procedures for investigation of deviations in action limits

Regarding the ----- chromatography:

1. The validation runs performed at commercial and small scale resulted in yields of -----; however, the proposed action limit for the combined yield of ----- is -----.
Please provide justification for the proposed action limit.
2. The Acceptable Operating Range for the combined ----- chromatography load has been proposed as ----- . However, the critical parameters studies, based on validation runs, estimated the Acceptable Operating Range as ----- . Please describe how you derived the proposed load limit of -----.
3. Please establish an in-process control parameter for ----- yield expressed as -----.

Regarding process operational parameters:

1. Please explain the difference between the following terms: Acceptable Operating Range, Acceptance Criteria, and Action Limit in relation to the control of operation unit performance. Please describe also the difference in investigational procedures and resultant actions when the limits defined by these terms are breached.

Regarding Methods Validation:

1. Regarding validation of your ----- Activity assay:
 - a. For accuracy experiments:
 - i. You stated that assays 1-2 were performed from one set of preparations on day 1 and assays 3-6 were performed from a second set of preparations on day 2; yet, you chose to perform analyses on pooled values from assays 1-3 separately from assays 4-6. Please comment.

- ii. You claimed that ----- experiments were performed; however, you ----
----- rather than supplementing another -----
----- preparation that had a pre-determined concentration. Please comment.
 - b. For repeatability experiments:
 - i. Please clarify the origin of the duplicate values used for each concentration level.
 - ii. Please clarify the relationship of Table 2 values to Table 4 values.
 - c. For intermediate precision experiments:
 - i. Please clarify the relationship between Table 2/3 values and Table 5 values.
 - d. For non-product specificity experiments:
 - i. Please provide a summary of studies that supported the -----

-----.
 - e. For lower limit of detection and linearity/range experiments:
 - i. Please identify the reference standard used to generate standard curves.
 - f. Please submit the study report from validation of your assay with reference to the --
----- concentrates ----- . Please submit the study
report from calibration of your -----, -----,
with reference to the ----- concentrates.
 - g. Please validate your assay to demonstrate parallelism between reference curve
and sample ----- series.
 - h. Please describe control charting procedures you have implemented for monitoring
routine performance of the ----- Activity assay using a routine assay
control preparation (different from reference standard, -----).
 - i. Please validate your assay for determination of thrombin potency for release of
final drug product (i.e. please test final container product in validation experiments).
2. Please submit study reports from validation of analytical methods used to determine
excipient concentrations.

Regarding the Proposed Specification for Bulk Drug Substance (BDS):

1. Please establish acceptance ranges for -----.
2. Please establish an acceptance limit for -----, -----.
3. Please establish an acceptance range for -----since it is a critical process parameter that guides further manufacture.
4. Please retain your established acceptance limit for -----since reporting the removal of this ----- is critical to assurance of product safety.

Regarding the Proposed Release Specification for Final Drug Product (FDP):

1. Please establish a release specification that reflects testing performed on the FDP reconstituted according to instructions provided in the Full Prescribing Information i.e. 5 ml of 0.9% NaCl.
2. Please establish the release limit for residual moisture, -----.
3. Please establish a release range for thrombin potency that defines an upper and lower limit. The lower limit should be established such that release at the lower limit will assure compliance with the end of shelf life requirement.
4. Please re-establish the content uniformity specification with respect to thrombin potency.
5. Please establish a release range for specific activity relative to -----
-----.
6. Please establish a release range for the content of each excipient.
7. Please provide further justification for the acceptance criterion, ----- stated as part of the Appearance specification. Please provide evidence that a reconstituted final product that is ----- does not contain denatured protein precipitate.

8. Please re-state the purity specification, "-----" more accurately e.g. "-----".

9. Please submit the release specification for the 0.9% NaCl diluent.

Regarding manufacturing process validation:

1. Please confirm IQs and OQs were performed on the lyophilizer, dry heat oven, -----, and autoclave used in the production of rThrombin. Please provide dates of completion. Please provide a short description of each.

2. With reference to the Summary Report for the Lyophilizer Sterilization Validation Package, please provide the rationale for the placement of the TCs and BIs in the validation runs.

3. With reference to the Summary Report for the Steam Autoclave Validation Package,
 - a. Please provide the rationale for the placement of the TCs and BIs in both validation runs.
 - b. Please explain why --- TCs were used in the heat distribution studies for FR-VP-PQ-150-05 while ---- TCs were used in FR-VP-PQ-150-06.
 - c. Please explain how the D values for the BIs are confirmed or verified.

4. With reference to the Summary Report for the ----- Sterilization Validation Package,
 - a. Please provide the rationale for the placement of the TCs and BIs in the validation runs.

 - b. Please provide the rationale for the use of -----

-----.

5. With reference to the Summary Report for the Dry Heat Oven Validation Package, please explain how the locations of the thermocouples and BIs were determined for the validation.

6. In the Summary Report for the Lyophilization of Drug Product, the following statements are made, "Moisture testing is performed on ----- vials and reported as the average. This is considered acceptable; it is not unexpected that an occasional vial will have residual moisture content ----- which does not impact the quality of the drug product or the robustness of the lyophilization process and the uniformity of lyophilization throughout the entire chamber. This is further supported by ----- demonstrating acceptable stability of rhThrombin lyophilized drug product with moisture levels of -----."
- a. Please provide the rationale as to why it is acceptable to average the moisture results from the ----- vials as opposed to recording each result separately especially if one or more vials do not meet set release specifications.
 - b. Please provide the rationale as to why it is acceptable for a vial to have a moisture result above the moisture content specification of -----.
 - c. Please provide the data to show that a moisture content of ----- does not adversely affect the quality and stability of the product.
 - d. Was the expiration date based on any of the vials that had a moisture content of -- -----? If not, please explain why not.
 - e. Was temperature mapping performed to correlate product temperature to shelf temperature? If so, what were the results?
 - f. How was it determined which vials to sample during the validation?
 - g. Please provide a copy of Deviation 129/06.
7. With reference to the Summary Report for the Media Fill Validation Package, (Please reference Guidance for Industry for the Submission of Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products, Nov. 1994)
- a. Please provide specific details of the aseptic process media fills Batch numbers ---- ----- and ----- that were performed. The report summary only gave a general description of what criteria were considered during the description of a "worst case" fill such as number of people, duration of fill, etc. The report never indicated what actually happened during the fill.

- b. At what step does the media fill begin and end? Are all routine samples taken at each point? Is a batch record followed? Are weight checks and volume adjustments performed? What was the line speed? What was the fill volume? What was the duration of fill?
- c. What was the number of units actually filled?
- d. What was the number of units rejected and what was the cause? Please provide a list of what is considered a major or minor defect and what the alert and action levels are for each.
- e. Please provide a copy of the SOP for Visual Inspection.
- f. Are interventions or line stoppages incorporated into the media fill? If so, please give some examples of what the interventions were and duration of line stoppage.
- g. What were the ----- results?
- h. Were personnel monitored during the media fill? What were the results?
- i. Please describe the conditions under which the lyophilization cycle was simulated. What type of gas was used to break the vacuum?

8. Regarding Validation,

- a. Please indicate where the information for the validation of the stopper washer is located within the submission or provide a summary of the validation. If the stoppers are washed by the stopper manufacturer, please include information about how the depyrogenation of stoppers is verified.
- b. Please indicate where the information for the validation of the -----
----- is located within the submission or provide a summary of the validation.
- c. Please provide detailed information on the container/closure integrity testing including information on the sensitivity of the test or indicate where in the

submission this validation is located. The only information I can locate is a statement that a ----- test was performed. No other information can be located. Was a spark test performed?

- d. Please provide a summary of the validation of the ----- carts used for transporting the filled vials to the lyophilizer.

9. Regarding Production Records (BPR)

- a. The batch records are not complete. A number of steps state to attach specific data to the BPR. This has not been done. Please provide completed BPRs.
- b. Please clarify when the -----, Is it after the -----, please provide the rationale of how this is representative of the bulk material?
- c. What is the bulk material specification for -----? Where is this information recorded in the BPR? When is ----- started during the fill? I could not see where this was recorded in the BPR. Please indicate where this information is recorded or how batch monitoring is traced to the batch record.
- d. Are personnel monitored during the fill? Please indicate where in the BPR this is recorded or how this information can be traced to the batch record.
- e. Where is it recorded the cause of filled vial rejection either by production or QA/QC personnel?

10. Regarding Shipping,

- a. Please provide more detailed information on the shipping studies performed at all stages of manufacture and storage. What studies were performed and under what conditions? A statement in the BLA said that the shipping studies from ----- would be completed in March 2007. Has this information been submitted to the BLA? Please provide completed shipping studies for all stages to the BLA.

Clinical

- 1. Please submit a complete narrative on the subject 612-L-6461.

2. For subject 612-L-6331, the investigator assessed a possible relationship between the (blinded) study material and Grade 4 bilateral pulmonary emboli the day after surgery. Please submit your assessment as to the possible relationship with the product.
3. Please submit a summary table of adverse events that lists number of adverse events, rather than percentage of subjects with adverse events. The table should include all specific adverse events in the study, grouped by system organ class. The total number of adverse events for each system organ class and for the entire study should also be included in the table.
4. For subjects who developed peripheral edema in the test group, please submit the following information in a tabular format: Type of surgery, day when edema was recorded, cardiac and renal laboratory values, hospital stay and use of blood products.
5. You have summarized bleeding AEs in subjects with positive anti-product antibody results, showing that 6 out of 43 control subjects with antibodies to bovine thrombin also had bleeding AEs. However, most of these intersecting events would be expected by chance (43 antibody positive / 200 subjects x 24 bleeding AEs ~ 5). In any event, bleeding AEs occurred in these subjects starting on days 1, 2, 3, 5, and 8, so it would be difficult to relate development or increase in titer of antibodies to the AEs. The higher frequency of anti-product antibodies in the bovine thrombin group had no clinical manifestations and bleeding AEs in the bovine thrombin group could have appeared in antibody positive subjects by chance alone. *Please be advised that bleeding AEs in antibody-positive subjects do not appear to have occurred at a higher frequency than in antibody-negative subjects and that you may not advertise or promote any association of bleeding with antibody status.*
6. You have acknowledged that there could be different implications for repeat exposure depending on whether a subject developed no antibodies or low-titer antibodies, yet you do not propose to repeat the antibody assays to test for antibodies at titers lower than 1:50. Please explain how you propose to assess the potential risk of repeat exposure to recombinant Thrombin.
7. Please submit the case report forms of the subjects who developed antibodies in the test group.
8. Labeling: **Please note that additional labeling comments will be provided in a separate information request.**
 - a. Highlight sections:

- i. Indication and Usage section:
Please delete the words, "is a coagulation factor."
Please rewrite this section as follows: "As a general adjunct to hemostasis during surgery when control of bleeding from oozing surfaces, capillaries and small venules, by standard surgical techniques is ineffective or impractical.
Please also insert the following sentence as a new paragraph:
"May be used in conjunction with an Absorbable Gelatin Sponge, USP."
 - ii. Dosage and Administration section: Please bold the phrase "**For Topical Use Only**". Please add the following sentence after the above sentence: "Apply on the surface of bleeding tissue only."
 - iii. Contraindication section: Please rewrite this section as follows:
 - Do not inject directly into the circulatory system.
 - Do not use for the treatment of massive or brisk arterial bleeding.
 - iv. Warning and Precaution section: Please include the following statement:
"Potential risk of thrombosis if absorbed systemically."
 - v. Please add the section, "Use in Specific Populations"
- b. Full Prescribing Information:
- i. Indication and Usage section: Please change as recommended for the highlight section.
 - ii. Contraindication: Please change as recommended for the highlight section.
 - iii. Warning and Precaution section: Please change as recommended for the highlight section.
 - iv. Adverse Reactions section: Please follow the format as per *Guidance for Industry: Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products - Content and Format*. Please include a table highlighting the pre-specified events of heightened surveillance.

9. Statistical:

- a. Please provide the --- programs and two data sets (per-protocol and intend to treat) which produced the primary efficacy results reported in Table 3 on page 8 of 24, the integrated summary of efficacy report of the submission. The --- programs should include the estimation of incidence of hemostasis, standard error adjustment for the incidence of hemostasis, construction of the 95% confidence interval of the difference between the two treatments. The datasets should include the following variables: subject ID, incidence of hemostasis within 10 minutes, treatment, bleeding site type, surgery type, time to hemostasis, censored indication variable, length of stay in hospital. The datasets should be ready for analyses without further modifications.

END

Mark Shields

Regulatory Project Manager

FDA/CBER/DBA/OBRR/RPMB

Information provided by: Review Committee Members Date: 18-21 Jun-07

Approved by Tim Lee Date 22-Jun-07 Transmitted by M. Shields Date: 22-Jun-07