DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
1401 Rockville Pike
Rockville M D 20852-1448

Our STN: BL 125029/0

NOV 21 2001

Eli Lilly and Company
Attention: Gregory T. Brophy, Ph.D.
Director, U.S. Regulatory Affairs
Lilly Corporate Center
Indianapolis, IN 46285

Dear Dr. Brophy:

This letter hereby issues Department of Health and Human Services U.S. License No. 1611 to Eli Lilly and Company, Indianapolis, Indiana, in accordance with the provisions of Section 351(a) of the Public Health Service Act controlling the manufacture and sale of biological products. This license authorizes you to introduce or deliver for introduction into interstate commerce, those products for which your company has demonstrated compliance with establishment and product standards.

Under this license you are authorized to manufacture the product Drotrecogin alfa (activated). Drotrecogin alfa (activated) is indicated for the reduction of mortality in adult patients with severe sepsis (sepsis associated with acute organ dysfunction) who have a high risk of death (e.g., as determined by APACHE II).

Under this authorization, you are approved to manufacture Drotrecogin alfa (activated) drug substance at [redacted] Final formulated drug product will be manufactured, filled, labeled and packaged at [redacted] In accordance with approved labeling, your product will bear the proprietary name Xigris and will be marketed in 5 mg and 20 mg single-use vials.

The dating period for Drotrecogin alfa (activated) drug product shall be 18 months from the date of manufacture when stored at 2" to 8°C. The date of manufacture shall be defined as the date of final sterile filtration of the formulated drug product. The dating period for drug substance shall be [redacted] months when stored at [redacted] Results of ongoing stability studies should be submitted throughout the dating period, as they become available, including the results of stability studies from the first three production lots. The stability protocols in your license application are considered approved for the purpose of extending the expiration dating period of your drug substance and drug product as specified in 2 1 CFR 601.12.

You are not currently required to submit samples of future lots of Drotrecogin alfa (activated) to the Center for Biologics Evaluation and Research (CBER) for release by the Director,

CBER, under 21 CFR 610.2. FDA will continue to monitor compliance with 21 CFR 610.1 requiring assay and release of only those lots that meet release specification.

Any changes in the manufacturing, testing, packaging or labeling of Drotrecogin alfa (activated), or in the manufacturing facilities will require the submission of information to your biologics license application for our review and written approval consistent with 21 CFR 601.12.

As of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 FR 66632). We note that you have not fulfilled the requirements of 21 CFR 601.27. We are deferring submission of your pediatric studies until February 28, 2005, based on your commitment outlined in item 15 below.

We acknowledge your written commitments to provide additional information on ongoing studies and to conduct post-marketing studies as described in your letters of October 23, 2001, November 2, 2001, November 8, 2001, November 16, 2001, November 19, 2001, and November 20, 2001 as outlined below:

Chemistry, Manufacturing, and Controls

1. The drug substance and drug product specifications will be revised to include purity by SDS-PAGE analysis. This information will be submitted to the biologics license application (BLA) by September 1, 2002.

2. A ———— content specification for release of Drotrecogin alfa (activated) drug product, to assure glycosylation remains consistent, will be developed and submitted to the BLA by September 1, 2002.

3. Additional specificity studies regarding the APTT potency test will be submitted to the BLA by January 1, 2002.

4. A revised APTT method utilizing a standard curve comprised of more than two data points will be submitted to the BLA by September 1, 2002.

5. The drug substance release specifications will be re-evaluated and submitted to the BLA by May 1, 2002.

6. The drug product release specifications will be re-evaluated and submitted to the BLA by February 1, 2004.

7. An endotoxin assay with improved sensitivity ( ) for testing of drug product will be developed and validated. This assay will be established within the and submitted to the BLA by December 15, 2001.

8. A drug product control sample, representing the commercial drug product composition, will be established and characterized by December 1, 2001. This control sample will be used for the RP-HPLC identity/purity assay and the size-exclusion HPLC assay. Information regarding the drug product control sample will be submitted to the BLA by December 15, 2001.

9. The IP-RP-HPLC, RP-HPLC, and SE-HPLC purity methods for drug substance, as well as the RP-HPLC and SEC-HPLC methods for drug product will be revised to require evaluation of the main peak for split peaks or shoulders in comparison to the relevant reference standard or control sample. These methods will also be revised to include an evaluation of the solvent front (or void volume) to ensure that the response at the solvent front/void volume is not significantly elevated in comparison to that of the relevant reference standard or control sample. The revised methods will be implemented in the appropriate by February 1, 2002. The revised methods will be submitted to the BLA by March 1, 2002.

10 The Performance Qualification (PQ) at for the 20 mg presentation will be completed by November 30, 2001. The temperature mapping for the lyophilizer (equipment number -) will be completed by December 3 1, 2001. Information will be provided regarding the completion of the 20 mg PQ and the temperature mapping of the lyophilizer and will be submitted to the BLA by February 1, 2002.

11 The additional mixing study to support the mixing time for the bulk drug substance with the----- buffer will be completed by November 15, 2001. Information will be provided regarding the revised mixing time and will be submitted to the BLA by December 15, 2001.

12 -is implementing a global plan for the requalification of the HVAC and Environmental Monitoring Programs. The requalification of the HVAC and Environmental program for the ,where Drotrecogin alfa (activated) is produced, will be completed by December 31, 2001. Information regarding the requalification results will be submitted to the BLA by February 1, 2002.

Clinical

13. To submit data from an ongoing study to assess long-term survival outcome. The protocol for ———— entitled "Long-term follow-up of survivors from the PROWESS trial (an observational study)" was submitted to IND 5919 on July 2, 2001. Patient follow-up data will be collected by June 15, 2002 and a final study report will be submitted by November 15, 2002. Observed initial ICU-stay mortality rates and initial hospitalization mortality rates will be provided for Drotrecogin alfa (activated) and placebo patients. In addition, ———— estimates of 90-day, 180-day, and one-year survival for Drotrecogin alfa (activated) patients and placebo patients will be included.

14. To evaluate the efficacy and safety of Drotrecogin alfa (activated) in a study of approximately 11,350 adult patients with severe sepsis and a lower risk of death (e.g., APACHE II score of 24 or less). In addition, this trial will evaluate whether low-dose heparin has an effect on the mortality of Drotrecogin alfa (activated) treated patients in this patient population. The protocol will include appropriate neurological evaluation of patients to detect potential occult neurological events. The final protocol of this study will be submitted to CBER by May 15, 2002, a minimum of 5000 patients will be enrolled by December 1, 2003, patient accrual will be completed by March 1, 2005, and a final study report will be submitted to CBER by June 1, 2005.

15. To evaluate the efficacy and safety of Drotrecogin alfa (activated) in a study of approximately 500 pediatric patients with severe sepsis. The protocol will include appropriate neurological evaluation of patients to detect potential occult neurological events. The final protocol of this study will be submitted to CBER by May 15, 2002, patient accrual will be completed by November 1, 2004, and a final study report will be submitted to CBER by February 28, 2005.

16. To evaluate whether low-dose heparin has an effect on mortality in a study of approximately 2000 adult patients with severe sepsis who have a high risk of death and are receiving Drotrecogin alfa (activated). The protocol will include appropriate neurological evaluation of patients to detect potential occult neurological events. The final protocol of this study will be submitted to CBER by October 1, 2002, patient accrual will be completed by September 1, 2004, and a final study report will be submitted to CBER by December 1, 2004.

17. To develop and evaluate improved immunogenicity screening assay for detecting antibodies of all isotypes to Drotrecogin alfa (activated). The design (with validation plan) and the results of your evaluation and validation data for this improved screening assay will be submitted by November 30, 2001, and April 1, 2002, respectively.

18. To provide more complete validation data for the existing ——— immunogenicity neutralizing antibody assay by April 1, 2002.

19. To analyze, using the improved and validated immunogenicity screening assay, archived serum samples on patients from the phase 3 trial (———— ') with both baseline and post-baseline samples from both placebo and Drotrecogin alfa (activated) treatment groups. If antibodies to Drotrecogin alfa (activated) are detected, Lilly will submit data establishing whether these antibodies neutralize the anticoagulant (APTT) activity of activated protein C by the——— immunogenicity assay. The results, with revised labeling if applicable, will be submitted by August 1, 2002.

20. To monitor the immunogenicity response to Drotrecogin alfa (activated) treatment in patients with severe sepsis post-28 days in the current on-going open-label study ——— The addendum for this protocol will be submitted on December 1, 2001. The results of the immunogenicity response will be submitted as part of the final study report in June 2003.

21. To collect additional samples for immunogenicity testing from ongoing and future clinical studies (including the phase 4 study in patients with severe sepsis and a lower risk of death (e.g., APACHE II score of 24 or less)). This will include samples from the 6-8 week post-exposure window. The number of samples to be collected and analyzed will be determined in consultation with the Agency after reviewing the data from the re-analysis of the phase 3 trial (————) samples in August 2002.

Protocols should be submitted to your IND ——— with a cross-reference letter to the BLA.

We also acknowledge your agreement to conduct additional validation studies as described in your response to the Agency's pre-approval inspectional observations, including:

22. The ———— computer system validation for the Distributed Control System will be completed by April 30, 2002. You will submit confirmation that this validation was successfully completed in your BLA annual report; the data will be available for review during the next inspection.

23. Regarding the ———— " will be completed by October 3 1, 2001.

24. ———— Drotrecogin alfa (activated) during the formulation and filling operations will be completed after the ——— has been used———. times. The study will be completed by January 3 1, 2002.

25. A Validation Study will be completed by December 2 1, 2001 to document that the integrity of the glassware is not compromised by extended exposure in the hot zone.

For administrative convenience, we request that you provide the completed validation reports in your next annual report submitted under 2 1 CFR 601.12.

26. In the event that the Drug Product Solution requires re-filtration, you have agreed that the first two resulting final lots will be placed on stability and the data will be included in your annual report submitted under 21 CFR 601.12.

It is required that adverse experience reports be submitted in accordance with the adverse experience reporting requirements for licensed biological products (21 CFR 600.80) and that distribution reports be submitted as described (21 CFR 600.81). All adverse experience reports should be prominently identified according to 21 CFR 600.80 and be submitted to the Center for Biologics Evaluation and Research, HFM-210, Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852-1448.

You are required to submit reports of biological product deviations in accordance with 21 CFR 600.14. All manufacturing deviations, including those associated with processing, testing, packing, labeling, storage, holding and distribution, should be promptly identified and investigated. If the deviation involves a distributed product, may affect the safety, purity, or potency of the product, and meets the other criteria in the regulation, a report must be submitted on Form FDA-3486 to the Director, Office of Compliance and Biologics Quality, Center for Biologics Evaluation and Research, HFM-600, 1401 Rockville Pike, Rockville, MD 20852-1448.

Please submit all final printed labeling at the time of use and include implementation information on FDA Form 2567. Please provide a PDF-format electronic copy as well as original paper copies (ten for circulars and five for other labels). In addition, you may wish to submit three draft copies of the proposed introductory advertising and promotional labeling with an FDA Form 2567 or Form 2253 to the Center for Biologics Evaluation and Research, Advertising and Promotional Labeling Branch, HFM-602, 1401 Rockville Pike, Rockville, MD 20852-1448. Final printed advertising and promotional labeling should be submitted at the time of initial dissemination, accompanied by a FDA Form 2567 or Form 2253.

All promotional claims must be consistent with and not contrary to approved labeling. No comparative promotional claim or claim of superiority over other products should be made unless data to support such claims are submitted to and approved by the Center for Biologics Evaluation and Research.

Sincerely yours,

Steven A. Masiello
Director
Office of Compliance and
Biologics Quality
Center for Biologics
Evaluation and Research

Jay P. Siegel, M.D., FACP
Director
Office of Therapeutics
Research and Review
Center for Biologics
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