DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20852

Our STN: BL 125029/65

JUN 23 2005

Eli Lilly and Company
Attention: Peter Morrow, M.Sc.
Manager, U.S. Regulatory Affairs
Lilly Corporate Center
Indianapolis, IN 46285

Dear Mr. Morrow:

Your request to supplement your biologics license application (BLA) for Drotrecogin alfa (Activated), XIGRIS®, to update the Clinical Studies and Warnings sections of the package insert has been approved.

Post-marketing commitment (PMC) number 14 contained within the November 21, 2001, approval letter for STN 125029/0 states the following:

> 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.

In response to this commitment, we acknowledge that your supplement, STN 125029/65, contains clinical data from the patient population identified within PMC number 14. These data are derived from study F1K-MC-EVCL/EVCM entitled, "Efficacy and safety of Drotrecogin Alfa (Activated) in adult patients with early stage severe sepsis". The submitted study report provided follow-up clinical data comprehensive through 28 days after randomization. We note that protocol F1K-MC-EVCL/EVCM addendum number 3/4 (March 11, 2004) described the collection of one year mortality data for all subjects. Please be aware that fulfillment of PMC number 14 requires the submission of these one year follow-up clinical data.

Please use the following designators to label prominently all submissions, including supplements, relating to this postmarketing study commitment as appropriate:

- Postmarketing Study Final Report
- Postmarketing Study Correspondence
- Annual Report on Postmarketing Studies

For each postmarketing study subject to the reporting requirements of 21 CFR 601.70, you must describe the status in an annual report on postmarketing studies for this product. The status report for each study should include:

- information to identify and describe the postmarketing commitment,
- the original schedule for the commitment,
- the status of the commitment (i.e. pending, ongoing, delayed, terminated, or submitted),
- an explanation of the status including, for clinical studies, the patient accrual rate (i.e. number enrolled to date and the total planned enrollment), and
- a revised schedule if the study schedule has changed and an explanation of the basis for the revision.

As described in 21 CFR 601.70(e), we may publicly disclose information regarding this postmarketing study on our Web site (**http://www.fda.gov/cder/pmc/default.htm**). Please refer to the April 2001 Draft Guidance for Industry: Reports on the Status of Postmarketing Studies - Implementation of Section 130 of the Food and Drug Administration Modernization Act of 1997 (see **http://www.fda.gov/cber/gdlns/post040401.htm**) for further information.

Please submit all final printed labeling at the time of use and include implementation information on FDA Form 356h. Please provide a PDF-format electronic copy as well as original paper copies (ten for circulars and five for other labels).

Please refer to http://www.fda.gov/cder biologics/default.htm for important information regarding therapeutic biological products, including the address for submissions Effective Oct 4, 2004, the new address for all submissions to this application is:

CDER Therapeutic Biological Products Document Room
Center for Drug Evaluation and Research
Food and Drug Administration
12229 Wilkins Avenue
Rockville, Maryland 20852

This information will be included in your biologics license application file.

Sincerely,

Marc Walton, M.D., Ph.D.
Director
Division of Therapeutic Biological Internal Medicine Products
Office of Drug Evaluation VI
Center for Drug Evaluation and Research