DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

WRITTEN REQUEST – AMENDMENT #4

IND 40,061

Eli Lilly and Company
Attention: Colleen Mockbee, R.Ph.
Associate Director, U.S. Regulatory Affairs
Lilly Corporate Center
Indianapolis, IN 46285

Dear Ms. Mockbee:

Please refer to your correspondence dated December 14, 2006, requesting changes to FDA's October 5, 2001 Written Request for pediatric studies for Alimta® (pemetrexed). We also refer to our July 3, 2002 correspondence that re-issued the October 5, 2001 Written Request under the Best Pharmaceuticals for Children Act and our May 7, 2004 correspondence that amended the Written Request.

We have reviewed your proposed changes and are amending the Written Request. For convenience, the full text of the Written Request, as amended, follows. This Written Request supersedes the Written Request dated October 5, 2001.

Background:

The design of studies in pediatric oncologic drug development is discussed in detail in the guidance for industry, Pediatric Oncology Studies in Response to a Written Request.
http://www.fda.gov/cder/guidance/3745dft.pdf

Protocols for each of your studies should be submitted to the FDA for review prior to initiation of the studies. Each submission should review the overall development plan and justify the study designs.

- ***Type of studies:***

  Phase 1: A dose finding study, including pharmacokinetics, with doses determined for all appropriate age groups. The number of patients entered should be sufficient to achieve Phase 1 objectives, which may be in the range of 18-25.

  Phase 2: Enrollment of at least 10 pediatric patients in each of the following disease strata: osteosarcoma, Ewing sarcoma/peripheral PNET, (b) (4) neuroblastoma (b) (4) The study should be performed at facilities that have the experience, support, and the expertise to care for children with cancer.

- ***Indication(s) to be studied*** *(i.e., objective of each study):*

  Phase 1: Refractory solid tumors

  Phase 2: Refractory or relapsed pediatric patients with osteosarcoma, Ewing sarcoma/peripheral PNET, rhabdomysarcoma and neuroblastoma.

- ***Age group in which study(ies) will be performed:***

  Infants > 1 month of age to adolescents

- ***Study endpoints:***

  The Phase 1 study should have maximum tolerated dose (MTD) (or biologically effective dose = BED) as a primary endpoint with measurements of blood (and CSF if appropriate) concentrations, and clearance as secondary endpoints. A traditional or sparse sampling technique may be used to estimate the PK parameters and develop pharmacokinetic-pharmacodynamic relationship.

  The Phase 2 study should have a disease-specific surrogate or clinically relevant endpoint.

- ***Drug Information:***

  Dosage form: Age appropriate formulation
  Route of administration: Intravenous
  Regimen: As determined by Phase 1 study

- ***Drug specific safety concerns:***

  Myelosuppression, hearing loss, nephrotoxicity

- ***Statistical information, including power of study and statistical assessments:***

  Statistics appropriate to the phase of the study.

- ***Labeling that may result from the study(ies):***

  Appropriate sections of the label may be changed to incorporate the findings of the studies.

- ***Format of reports to be submitted:***

  Full study reports not previously submitted to the Agency addressing the issues outlined in this request with full analysis, assessment, and interpretation.

- ***Timeframe for submitting reports of the studies:***

  Reports of the above studies must be submitted to the Agency on or before July 2010. Please keep in mind that pediatric exclusivity attached to existing patient protection or exclusivity that has not expired at the time you submit your reports of the studies in response to this Written Request.

Reports of the studies that meet the terms of the Written Request dated October 5, 2001, and re-issued July 3, 2002, as amended by this letter, must be submitted to the Agency as part of a new drug application or supplement to an approved new drug application on or before (b) (4) 2010, in order to possibly qualify for pediatric exclusivity extension under Section 505A of the Act.

Submit protocols for the above studies to an investigational new drug application (IND) and clearly mark your submission, **"PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC EXCLUSIVITY STUDY"** in large font, bolded type at the beginning of the cover letter of the submission. Notify us as soon as possible if you wish to enter into a written agreement by submitting a proposed written agreement. Please clearly mark your submission, **"PROPOSED WRITTEN AGREEMENT FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission.

Submit reports of the studies as a supplement to an approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, clearly mark your submission **"SUBMISSION OF PEDIATRIC STUDY REPORTS – PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED"** in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. In addition, send a copy of the cover letter of your submission, via fax (301-594-0183) or messenger, to the Director, Office of Generic Drugs, HFD-600, Metro Park North II, 7500 Standish Place, Rockville, MD 20855-2773.

If you wish to discuss any amendments to this Written Request, submit proposed changes and the reasons for the proposed changes to your application. Clearly mark submissions of proposed changes to this request **"PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission. We will notify you in writing if we agree to any changes to this Written Request.

We hope you will fulfill this pediatric study request. We look forward to working with you on this matter in order to develop additional pediatric information that may produce health benefits to the pediatric population.

If you have any questions, call Patricia Garvey, Senior Regulatory Project Manager, at 301-796-1356.

Sincerely,

{See appended electronic signature page}

Karen D. Weiss, M.D.
Deputy Director
Office of Oncology Drug Products
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Karen Weiss

4/16/2007 03:06:06 PM