CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

18-936/SE5-064

APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 18-936/S-064

Eli Lilly and Company
Attention: Gregory T. Brophy, Ph.D.
Director, U.S. Regulatory Affairs
Lilly Corporate Center
Indianapolis, IN 46285-2643

Dear Dr. Brophy:

Please refer to your supplemental new drug application dated September 14, and received September 15, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Prozac (fluoxetine hydrochloride) pulvules.

We acknowledge receipt of your submissions dated October 4, 2001, and February 25, 2002. Your submission of October 4, 2001 constituted a complete response to our July 12, 2001 action letter.

This supplemental new drug application proposes the use of Prozac in the treatment of major depressive disorder (MDD) and obsessive compulsive disorder (OCD) in the pediatric population.

We have completed the review of this application, as amended, and it is approvable. Before the application may be approved, however, it will be necessary for you to submit the following information and respond to the following issues:

Labeling

Accompanying this letter (Attachment) is the Agency's counterproposal to the labeling submitted in your October 4, 2001 amendment. We have accepted many of your proposed changes, however, we have proposed alternative language in some sections. We have included bracketed comments to denote revisions to the labeling. Additionally, please note that the labeling may need to be subsequently revised based upon our receipt and further review of the ECG data requested later in this letter.

Pediatric ECG Data

We are still concerned that there may be a signal suggesting an increase in QTc interval duration in association with fluoxetine use. Therefore, we are requesting that you submit the following new information to further assist us in resolving the discrepancy in the three analyses of ECG data that you have provided:

1. Your "Justification of Cardiac Data" in the October 4, 2001 submission indicated that [redacted] measured ECG intervals according to a standardized process recommended by the CPMP. Please submit the standardized process that they followed, along with any changes to the procedure they may have made. You also assert that [redacted] did not follow a written procedure for QT measurement, although they measured QT intervals according to "generally accepted practice". Please request from the [redacted] group and from [redacted] recounting to the best of their ability of how they performed the "generally accepted practice" of reading QT intervals. For example, how many complexes were read, how were the complexes chosen, from which ECG leads were they chosen, etc. If they are not able to recall this particular evaluation, perhaps they could comment on how the "generally accepted practice" of reading QT intervals is conducted.

2. Please clarify whether or not the same ECG complexes were read for each patient by each subsequent analyzer of the ECGs.

3. Please identify the subgroup of patents whose measurement shifts were the basis for the differences in the three analyses and provide the raw ECG data for these patients.

4. Please provide a dataset with the raw data from each analysis lined up together (see table below for proposed arrangement).

	[redacted]		[redacted]		[redacted]	
Patient ID	Baseline	End of study	Baseline	End of study	Baseline	End of study
001						
002						
...						

5. Please provide a list from [redacted] of which patients (actual ID numbers, not just totals from each group) had sinus arrhythmia requiring 5 complexes (rather than 3) to be read, separated by treatment group. Please also include their criteria for defining the presence of sinus arrhythmia.

6. Please note that based on our review of the above requested data, we may request a subset of the actual ECG tracings.

Phase 4 Commitments

1. [redacted]

2. We note your agreement, in an e-mail dated March 11, 2002 from Sharon Hoog, of your firm, to Mr. Paul David, of this Agency, to conduct juvenile animal toxicology studies as a Phase 4 commitment. We additionally acknowledge your commitment to submit these reports to the Agency within 2 years from the date of the approval action for this supplement.

3. As addressed in the attached labeling, we have made your proposed changes regarding the finding of reduced alkaline phosphatase levels and speculation about longer-term effects of fluoxetine on growth. Nevertheless, we feel that the signal of an effect on growth from the shorter-term trial is of sufficient concern that we continue to ask you to commit to conducting a longer-term trial to address this issue.

If additional information relating to the safety or effectiveness of these drugs becomes available, revision of the labeling may be required.

Within 10 days after the date of this letter, you are required to amend the supplemental applications, notify us of your intent to file amendments, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the applications. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with these changes prior to approval of this supplemental application.

If you have any questions, call Paul David, R.Ph., Senior Regulatory Project Manager, at (301) 594-5530.

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Attachment

30 page(s) of revised draft labeling has been redacted from this portion of the review.

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

/s/

Russell Katz
3/19/02 04:25:36 PM