DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-148 **NDA APPROVAL**

Eli Lilly and Company
PO Box 6288
Indianapolis, IN 46206

Attention: Bryan Boggs, Pharm.D.
Manager, US Regulatory Affairs

Dear Dr. Boggs:

Please refer to your new drug application (NDA) dated August 14, 2007, received August 14, 2007, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Cymbalta (duloxetine hydrochloride) Delayed-Release Capsules.

We acknowledge receipt of your submissions dated September 20 and 30, October 3, November 15 and 16, 2007, and January 25, March 5 and 13, and May 28, 2008.

Reference is also made to your electronic communication dated June 10, 2008.

This new drug application provides for the use of Cymbalta (duloxetine hydrochloride) Delayed-Release Capsules for the management of fibromyalgia.

We have completed our review of this application, as amended, and it is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html that is identical to the enclosed labeling (text for the package insert, text for the Medication Guide). Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission, "SPL for approved NDA 22-148."

Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for ages 0 to 12 years for this application because necessary studies are impossible or highly impracticable. The population of pediatric fibromyalgia patients 12 years of age and younger is extremely small.

We are deferring submission of your pediatric study for ages 13 to 17 years for this application until June 2013 because this product is ready for approval for use in adults and the pediatric study has not been completed.

Your deferred pediatric study required under section 505B(a) of the FDCA is a required postmarketing study. The status of this postmarketing study must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the FDCA. This required study is listed below.

1. Deferred pediatric study under PREA for the management of fibromyalgia in pediatric patients ages 13 to 17.

   Final Report Submission: June 2013

Submit all final study reports to your NDA 21-427. Use the following designator to prominently label all submissions:

Required Pediatric Assessment

POSTMARKETING REQUIREMENTS UNDER 505(o)

Title IX, Subtitle A, Section 901 of the Food and Drug Administration Act of 2007 (FDAAA) amends the Federal Food, Drug, and Cosmetic Act (FDCA) to authorize FDA to require holders of approved drug and biologic product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute (section 505(o)(3)(A), 21 U.S.C. 355(o)(3)(A)). This provision took effect on March 25, 2008.

Since Cymbalta was approved in 2004 for the treatment of depression, we have become aware of adverse pregnancy outcomes in women taking Cymbalta during pregnancy. Now, with the approval of the fibromyalgia indication, the population will be overwhelmingly females of childbearing potential, and a study is necessary to assess this signal of a serious risk.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess the signal of a serious risk of adverse reactions in a fetus exposed to Cymbalta or to identify an unexpected serious risk to the nursing infants of women who are treated with Cymbalta.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) has not yet been established and is therefore not sufficient to assess these signals of a serious risk.

Therefore, based on appropriate scientific data, FDA has determined that you are required, pursuant to section 505(o)(3) of the FDCA, to conduct the following postmarketing study.

2. To develop and maintain a prospective, observational pregnancy exposure registry study conducted in the United States that compares the pregnancy and fetal outcomes of women exposed to Cymbalta during pregnancy to an unexposed control population. The registry will detect and record major and minor congenital anomalies, spontaneous abortions, stillbirths, elective terminations, and any serious adverse pregnancy outcomes. These events will be assessed among the enrolled women throughout the pregnancy. The events will also be assessed among infants through at least the first year of life. Annual interim reports will be submitted until FDA has acknowledged that sufficient data has been collected.

You will conduct this trial according to the following timetable:

Protocol Submission:	November 2008
Study Start Date:	May 2009
Final Report Submission:	Within six months of FDA notification that sufficient data has been collected.

Submit the protocol to your IND 63,615 with a cross-reference letter to NDA 21-427. Submit all final report(s) to your NDA 21-427. Use the following designators to prominently label all submissions, including supplements, relating to this postmarketing study as appropriate:

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

- **Required Postmarketing Protocol under 505(o)**
- **Required Postmarketing Final Report under 505(o)**
- **Required Postmarketing Correspondence under 505(o)**
- **Annual Status Report of Postmarketing Commitments**

You are required to report periodically to FDA on the status of these studies pursuant to sections 505(o)(3)(E)(ii) and 506B of the Act, as well as 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii). Under section 505(o)(3)(E)(ii), you are also required to periodically report to FDA on the status of any study or trial otherwise undertaken to investigate a safety issue associated with Cymbalta.

POSTMARKETING COMMITMENT

We acknowledge your written commitment dated June 10, 2008, to evaluate the efficacy of lower doses of Cymbalta.

3. To conduct a randomized, double-blind, placebo-controlled study of Cymbalta at lower doses of 20 – 30 mg per day in the management of fibromyalgia.

The timetable you submitted on June 10, 2008, states that you will conduct this trial according to the following schedule:

Protocol submission:	December 2008
Final Report Submission:	December 2011

Submit clinical protocols to your IND 63,615 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to NDA 21-427. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study.

All submissions, including supplements, relating to these postmarketing study commitments should be prominently labeled "**Postmarketing Study Commitment Protocol**", "**Postmarketing Study Commitment Final Report**", or "**Postmarketing Study Commitment Correspondence**."

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert(s), at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see www.fda.gov/cder/ddmac.

LETTERS TO HEALTH CARE PROFESSIONALS

If you issue a letter communicating important safety related information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit an electronic copy of the letter to both this NDA and to the following address:

MedWatch
Food and Drug Administration
Suite 12B05
5600 Fishers Lane
Rockville, MD 20857

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81). All 15-day alert reports, periodic (including quarterly) adverse drug experience reports, field alerts, annual reports, supplements, and other submissions should be addressed to the original **NDA 21-427** for this drug product, not to this NDA. In the future, do not make submissions to this NDA except for the final printed labeling requested above.

If you have any questions, call Parinda Jani, Chief, Project Management Staff, at (301) 796-1232.

Sincerely,

{See appended electronic signature page}

Bob Rappaport, M.D.
Director
Division of Anesthesia, Analgesia
and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and research

Enclosure

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

/s/

Bob Rappaport

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