DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-427

Eli Lilly and Co., Inc.
Attention: Gregory T. Brophy, Ph.D.
Lilly Corporate Center
Indianapolis, Indiana 46285

Dear Dr. Brophy:

Please refer to your new drug application (NDA) dated November 12, 2001, received November 13, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for CYMBALTA® (duloxetine hydrochloride) 20, 30, and 60 mg capsules.

We acknowledge receipt of your submissions dated December 22, 2003, April 8, 2004, May 13, 2004, June 4, 2004, June 14, 2004, July 1, 2004, July 7, 2004 and July 14, 2004. Your December 22, 2003 submission constituted a complete response to our September 29, 2003 action letter. Your June 4, 2004 submission constituted a major amendment submitted within three months of the review goal date, and our letter of June 22, 2004 extended the review goal date for this submission to September 23, 2004.

This new drug application provides for the use of CYMBALTA (duloxetine hydrochloride) Capsules for the treatment of major depressive disorder (MDD).

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

OCPB and CMC:
Approved Dissolution Specification and Expiration Date, Methods Validation
Approval of this application includes the following dissolution specification and method, to be used for all three approved strengths of duloxetine hydrochloride capsules:

Apparatus:	USP Apparatus I (Basket) at 100 RPM	
Media:	A: Gastric Challenge:	1000 mL of 0.1 N hydrochloric acid in deionized water at 37±0.5°±
	B: Medium 2:	1000 mL of 50 mM pH 6.8 Phosphate Buffer in deionized water at 37±0.5°±
Specifications:	(b)(4)----------	---------- ---------- ---------- ----------
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The approved expiration date for the drug product is 24 months.

We have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be identified.

Pediatric Research Equity Act (PREA) Requirements: Phase 4 Commitment: Studies Deferred
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.

We are waiving this requirement for children below the age of 7 years. We are deferring submission of your pediatric studies for ages 7 to 17 years (children and adolescents) until June 30, 2008 (see below). Your deferred pediatric studies required under Section 2 of the Pediatric Research Equity Act (PREA) are considered required postmarketing study commitments. The status of these postmarketing commitments shall be reported annually according to 21 CFR 314.81. The associated commitments are listed below.

1. *Deferred pediatric studies under PREA.*
   You are required to assess the safety and effectiveness of CYMBALTA as a treatment for major depressive disorder (MDD) in pediatric patients ages 7 to 17 (children and adolescents).

   Final Report Submission: June 30, 2008

Please submit study protocols to your IND for this product, with a cross-reference letter submitted to the NDA. Submit final study reports to this NDA. For administrative purposes, all submissions related to this pediatric postmarketing study commitment, whether submitted to the IND or the NDA, must be clearly designated "**Required Pediatric Study Commitments**".

Pediatric Exclusivity
Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the Guidance for Industry on Qualifying for Pediatric Exclusivity (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity, you should submit a "Proposed Pediatric Study Request" ***in addition to*** your plans for pediatric drug development described above. Please note that satisfaction of the requirements in Section 2 of PREA alone may not qualify you for pediatric exclusivity.

Additional Phase 4 Commitments (by Discipline)
We remind you of your additional postmarketing commitments, agreed upon in your submission dated December 22, 2003. These commitments are listed below.

2. *OCPB: Dissolution study.*
   As agreed, two *in vitro* dissolution experiments will be performed and the results submitted to
   (b)(4)----------

   (b)(4) (b)(4)----------(b)(4)----------as medium.
   For both experiments, please report the amount of ----------generated quantitatively, in addition to reporting it as a percentage of duloxetine.

   (b)(4)---------- ccept your previously submitted protocol, with the proviso that results for ----------will be reported as described above.

   Final Report Submission: On or before October 23, 2004.

3. *Educational Campaign to Educate Practitioners and Patients Concerning the Differences between CYMBALTA and SYMBYAX (olanzapine / fluoxetine hydrochloride)*.
   Your proposed trademark, CYMBALTA®, has been reviewed and is acceptable. You have agreed to assure continued differentiation in packaging between CYMBALTA and your approved drug SYMBYAX® (olanzapine / fluoxetine hydrochloride); this is an ongoing commitment, with no specific time limit. You have also agreed to institute an educational campaign that will educate practitioners and patients concerning the differences between CYMBALTA and SYMBYAX.

   Educational Campaign Materials Submission: On or before October 23, 2004.

4. *Clinical Safety: Clinical pharmacology study to evaluate the effect of duloxetine on the QT interval*.
   We are aware that two clinical pharmacology studies are currently underway or have recently been completed, and that the protocols for these investigations have already received detailed feedback from the Division of Reproductive and Urologic Drug Products (HFD-580) and the Division of Scientific Investigations.

   Final Study Report Submission: On or before December 31, 2004.

   Please submit the final study reports to the IND, clearly marked as a "**Postmarketing Study Final Report**". If the study reports are intended to support a change in labeling within this Division, please submit them to the NDA.

5. *Clinical Efficacy: Adult clinical study to address longer-term effectiveness of duloxetine in MDD.*
   You have agreed to submit the results of one adult clinical study of duloxetine in the longer-term treatment of MDD. Per our action letter of September 29, 2003, we note that you have an already ongoing study (not a continuation study) that is expected to meet the requirements of this commitment. We have already received and reviewed the protocol for this study.

   Final Report Submission: On or before June 30, 2006.

6. *Clinical Efficacy: Adult clinical study to address effects of duloxetine on female sexual function in depressed patients.*
   You have agreed to submit the results of one adult clinical study of the effects of duloxetine on female sexual function. This study must include an active control known to have deleterious effects on female sexual function.

   Final Report Submission: On or before June 30, 2008.

Please submit all final study reports other than those intended to support clinical efficacy claims, or changes in labeling, to your IND for this product, with a cross-reference letter submitted to this NDA. Please submit any final reports intended to support clinical efficacy claims or changes in labeling to this NDA. Please submit the educational campaign materials requested under point 3. above to this NDA.

In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary for each commitment in your annual report to this NDA. The status summary should include

- expected final report submission dates,
- any changes in plans since the last annual report,

- and, for clinical studies, the number of patients entered into each study.

All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled "**Postmarketing Study Protocol**", "**Postmarketing Study Final Report**", or "**Postmarketing Study Correspondence**." This includes IND cross-reference letters submitted to the NDA.

Labeling
The final printed labeling (FPL) must be identical to the enclosed agreed-upon labeling (text for the package insert) and submitted labeling (immediate container and carton labels submitted December 22, 2003). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "**FPL for approved NDA 21-427**." Approval of this submission by FDA is not required before the labeling is used.

Introductory Promotional Materials
In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division and two copies of both the promotional materials and the package insert(s) directly to:

Division of Drug Marketing, Advertising,
and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at www.fda.gov/medwatch/report/mmp.htm.

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81). In addition, we note your agreement to monitoring and reporting during the postmarketing period of liver-related Adverse Events, as outlined below:

- expedited reporting of all liver-related AEs received during the postmarketing period;
- quarterly summaries of all liver-related AEs along with estimates of drug usage for that specific quarter and an explanation of the method used to estimate drug usage;
- detailed follow-up information on reported cases of hepatotoxicity.

If you have any questions, please call Doris J. Bates, Ph.D., Regulatory Project Manager, at (301) 594-2850.

Sincerely,

{See appended electronic signature page}
Robert Temple, M.D.
Director
Office of New Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure: Agreed-upon labeling (clean copy)

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

/s/

Robert Temple
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