CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-427

Approval Letter(s)

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)----------	----------
	----------	----------

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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DEPARTMENT OF HEALTH & HUMAN SERVICES

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

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 HCl) Capsules, 20, 30, 40, and 60 mg. This NDA provides for the use of duloxetine in the treatment of adult major depressive disorder (MDD).

We also acknowledge receipt of your amendments dated:

February 26, 2002	March 12, 2002	March 15, 2002
March 29, 2002	April 4, 2002	April 24, 2002
June 7, 2002	August 19, 2002	August 29, 2002

We have completed the review of this application as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to address the following comments and requests.

Proposed Trademark CYMBALTA
As your firm has previously been informed (telephone conversation between Dr. D. Bates of this Division and Dr. S. Hoog of Lilly, August 9, 2002), your proposed proprietary name has been reviewed by the Office of Drug Safety / Division of Medication Errors and Technical Support (ODS/DMETS), which has no objection to the use of this trademark at this time.

Your firm was also informed that it is CDER policy that proposed proprietary names and their associated labels must be evaluated approximately 90 days prior to the anticipated approval of the NDA. Since the Agency is not yet prepared to approve your application, re-evaluation of your trademark will be necessary prior to final approval of the NDA.

Our telefax message of August 21, 2002 also conveyed summary comments from the ODS/DMETS review. These comments relate to the proposed labeling for the drug product. They are incorporated into this letter by reference, and should be addressed in your complete response.

Chemistry, Manufacturing and Controls (CMC): GMP Issues, Manufacturing Site; Approvability of Current Dosage Form

CYMBALTA (duloxetine) capsules are manufactured and quality controlled at the Lilly Technology Center, in Indianapolis, Indiana. During a GMP inspection of this manufacturing site in January and February, 2001, a number of deficiencies were noted and conveyed to the site's representative by the FDA inspector.

We are aware that Lilly is in the process of responding to these deficiencies. Satisfactory resolution of these deficiencies, including satisfactory completion of a preapproval site inspection for the manufacture of duloxetine capsules, is required before NDA 21-427 can be approved.

CMC: Environmental Assessment
We have completed our review of the Environmental Assessment information provided by your firm and have made a Finding of No Significant Impact for your application.

CMC: Other Issues
Drug Substance and Drug Product

1. [ ]

2. In the preparation [ ] Please explain the discrepancy.

3. Please explain [ ]

4. Please provide the certificates of analysis (CoAs) for all drug substance batches used in toxicology, clinical and stability studies.

5. We recommend tightening the specification [ ] % to % based upon batch analysis of toxicological and clinical trial lots.

6. We recommend tightening the specification [ ] % to % based upon batch analysis data for toxicological and clinical trial lots.

7. Please provide a detailed description of the procedures used in the manufacture of [ ]

8. Please provide the specifications (acceptance criteria / analytical methods) used for evaluating [ ]

9. Please provide [redacted]

10. Please provide certificates of analysis (CoAs) for each batch [redacted] used in the manufacture of duloxetine hydrochloride capsules.

11. Please explain how [redacted] is determined.

12. Please provide a detailed sampling plan for the production batch analyses. The sampling plan should include information on the number of samples selected for analysis per batch and the location of the samples selected.

13. Please submit updated drug product stability data.

In addition, we have made specific changes in the revised labeling appended to this letter. Please address these changes in your complete response.

Nonclinical Pharmacology and Toxicology

We have completed our review of the nonclinical information provided in your NDA. The following comment should be addressed prior to approval of your NDA.

- With regard to the two drug substance impurities, [redacted] for each of which a specification of not more than [redacted] has been proposed, we request the following additional information:
  - please indicate the amounts [redacted] present in lots of drug substance used for pivotal toxicology studies (i.e., genotoxicity, carcinogenicity, and reproduction studies).
  - please indicate the amounts [redacted] present in lots of drug substance used in the animal reproduction studies.
  - if the analytical data requested under the preceding bullet points do not adequately qualify these impurities per the ICH Q3A Guidance, we suggest that you lower the specification limit for each impurity to not more than 0.1%. If this cannot be accomplished, additional studies to qualify these impurities will be needed.

In addition, we have made specific changes in the revised labeling appended to this letter. Please address these changes in your complete response.

Clinical Pharmacology and Biopharmaceutics

1. Please adopt the following dissolution method and specifications for all four strengths of duloxetine hydrochloride capsules:

Apparatus:	USP Apparatus I (Basket) at 100 RPM
Media:	A: Gastric Challenge: 1000 mL of 0.1N hydrochloric acid in deionized water at 37±0.5°C
	B: Medium 2: 1000 mL of 50 mM pH 6.8 Phosphate

Specifications: For Medium A: Buffer in deionized water at 37±0.5°C [

For Medium B:]

2. Based on our review of the clinical pharmacology / biopharmaceutics section of your NDA, we have the following request:
Requested Postmarketing (Phase 4) Commitment. Due to the possibility of [ ] we request that you commit to performing the following two *in vitro* dissolution experiments to further test the [ ]
   a) [ ] medium
   b) [ ]

In addition, we have made specific changes in the revised labeling appended to this letter. Please address these changes in your complete response.

Clinical / Statistical / Clinical Safety (Safety Update)
We have completed our review of the clinical information provided in your NDA, and have the following requests for information:

1. We have identified six cases of syncope among patients in controlled studies of duloxetine. One case appears to have been mis-coded (111-2109) and should have been coded as dizziness. Patient 010-1919 experienced syncope in association with alcohol intake but no statement about the relative contribution was made (e.g. a blood alcohol level?). Patient 132-4201 experienced orthostasis due to poor oral intake. Please comment on the poverty of the oral intake and whether it was somehow connected with treatment or resulted from some other cause. Please provide further information about these cases, including any information available on prior symptoms or sequelae to these events.

2. We have also identified two patients, A09505 and E00301, who had abnormal liver chemistries identified as serious adverse events. Please provide more complete details on these cases, including information on concomitant medications, comorbid conditions, and more complete followup information. Labeling may need further revision based on whatever information can be obtained.

3. Please provide any new information on the regulatory status of duloxetine worldwide. We require a review of the status of all actions with regard to this drug, either taken or pending before foreign regulatory authorities. Approval actions can be noted, but we also ask that you describe in detail any and all actions taken that have been negative, supplying a full explanation of the views of all parties and the resolution of the matter. In addition, we ask that you provide us any current foreign labeling for duloxetine along with English translations when needed. It is

only necessary to provide information that is more recent than that provided in your original submission.

4. Also, in your response to this letter, please include a safety update as described in 21 CFR 314.50(d)(5)(vi)(b).
a) The safety update should include data from all non-clinical and clinical studies of the drug under consideration, regardless of indication, dosage form, or dose level.
b) Please describe in detail any significant changes or findings in the safety profile.
c) When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, please incorporate new safety data as follows:

- Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.
- Present tabulations of the new safety data combined with the original NDA data.
- Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the preceding bullet point.

d) For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.
e) Please present a retabulation of the reasons for premature study discontinuation by incorporating the dropouts from the newly completed studies. Describe any new trends or patterns identified.
f) Please provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, please provide narrative summaries for serious adverse events.
g) Please describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.
h) Prior to an approval action, we require an updated report on the world's archival literature pertaining to the safety of duloxetine. Please provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries. This report should include only literature not covered in your previous submissions. We will need your warrant that you have reviewed this literature systematically, and in detail, and that you have discovered no finding that would adversely affect conclusions about the safety of duloxetine. The report should also detail how the literature search was conducted, by whom (their credentials) and whether it relied on abstracts or full texts (including translations) of articles. The report should emphasize clinical data, but new findings in preclinical reports of potential significance should also be described. Should any report or finding be judged important, a copy (translated as required) should be submitted for our review.

5. Based on our review of the clinical section of your NDA, we have the following request:

Requested Postmarketing (Phase 4) Commitment. Major depressive disorder is a chronic condition requiring long-term treatment. Therefore, we ask that you commit to conducting, postapproval, a longer-term trial to address the longer-term effectiveness of duloxetine in this illness. We would be happy to discuss with you the design of such a trial.

In addition, we have made specific changes in the revised labeling which is appended to this letter. Please address these changes specifically in your complete response.

Labeling (Package Insert and Container Labeling)
In addition to responding to the points listed above, it will be necessary for you to submit draft labeling revised as shown in the attachment to this letter, including changes requested in our telefax of August 21, 2002.

We believe the attached draft labeling presents a fair summary of the information available on the benefits and risks of CYMBALTA (duloxetine) in the treatment of MDD.

Please use the proposed text verbatim, with the exception of revisions in response to comments from ODS/DMETS as cited above. You will see that we have proposed a number of changes to the draft labeling submitted in your November 12, 2001 submission, and explanations for these changes are provided in the bracketed comments embedded within the proposed text. Division staff are willing to discuss these proposed changes in detail and to meet with you to discuss any disagreements you might have with any part of the proposed labeling format or content.

Pediatric Final Rule and Pediatric Exclusivity
You have previously been advised that the Pediatric Final Rule (63 FR 66632) requires that 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 note FDA's prior agreements (December 16, 1999 and August 15, 2001) to deferral of this requirement pending approval of duloxetine for adult MDD.

We also acknowledge receipt of your Proposed Pediatric Study Request (PPSR), which was submitted to IND 38,838 on June 25, 2001. This PPSR was submitted in accordance with the requirements for Pediatric Exclusivity. We are in the process of reviewing your PPSR and it is our intent to issue a Written Request as separate correspondence.

Financial Disclosure Rule
Also, as you know, on February 2, 1999, the Financial Disclosure Rule, published in the Federal Register of February 2, 1998, became effective. We note that you have addressed the requirements of this rule in your initial submission. We have reviewed the information you have provided, and have found that you have satisfactorily addressed the requirements of this rule. Please note that this requirement may apply to future resubmissions and will also apply to pediatric studies. For further information about this requirement, you may contact Ms. Lee Ripper, Associate Director, Regulatory Affairs, Office of Drug Evaluation II, at (phone) 301-827-5921 or (fax) 301-480-6644.

Promotional Materials
In your complete response to this letter, please also submit three copies of the introductory promotional materials that you propose to use for this product. Please submit all material in draft or mock-up form rather than final printed format.

Please send one copy to this Division and two copies of both the promotional material and the package insert directly to:

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

Options Under 21 CFR 314.110

Within 10 (ten) days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action, FDA may proceed to withdraw this application as provided for under 21 CFR 314.65. Any amendment should respond to all of the comments and requests in this letter, including those incorporated by reference. We will not process a partial reply as a major amendment, nor will the review clock be reactivated, until all deficiencies have been addressed.

Opportunity for Informal Meeting Under 21 CFR 314.102(d)

Under 21 CFR 314.102(d), you may request an informal meeting or telephone conference with the Division of Neuropharmacological Drug Products, to discuss what further steps need to be taken before the application may be approved.

This drug product may not be legally marketed until you have been notified in writing that this application has been approved.

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 Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure (Revised Draft Labeling)
[Please note that the electronic signature page will be the last page of the document, following the enclosed labeling.]

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
9/13/02 05:29:43 PM