DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-520

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 4, 2002, received November 5, 2002, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for SYMBYAX (olanzapine and fluoxetine HCl) Capsules, 6mg/25mg, 6mg/50mg, 12mg/25mg, and 12mg/50mg. This NDA, which has been granted priority review status, provides for the use of the combination product, SYMBYAX, in the treatment of depressive episodes associated with bipolar disorder.

We acknowledge receipt of your submissions dated:

May 14, 2003	June 24, 2003	July 31, 2003
December 2, 2003	December 15, 2003	

Your June 24, 2003 submission constituted a Complete Response to our May 5, 2003 action letter.

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 enclosed agreed-upon labeling text.

Proposed Trademark SYMBYAX
We note the resubmission of your proposed trademark, SYMBYAX, for this drug product. It has been reviewed by the Office of Drug Safety / Division of Medical Errors and Technical Support, which has no objections to the proposed trademark.

Request for Phase 4 Commitment:
This section of the action letter lists only that Phase 4 commitment which we requested in our initial approvable letter *and* have elected to retain, as per agreement with your staff on December 23, 2003. Those commitments which we have re-evaluated and decided not to retain are discussed in the discipline-specific sections of this letter.

1. Nonclinical Pharmacology and Toxicology: We have reviewed your response to our request for a Phase 4 commitment to conduct a repeat prenatal/postnatal development study in rats. We retain our request that a repeat study be performed, as a Phase 4 commitment, with appropriately selected doses that will allow reliable assessment of postnatal developmental toxicity parameters and their dose-effect relationships and NOAEL (no adverse effect level).

As agreed, we would expect the study report to be submitted to the Division within three years of the signature date on this letter.

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1. Your proposed expiration date for the drug product, 24 months, is acceptable.
2. Methods validation has been completed and is acceptable.
3. We note that the Eli Lilly(b)(4)----------(b)(4)----------), which was found to be unacceptable by the FDA's Office of Compliance, has been withdrawn from this application. All facilities involved in the manufacture and control of the drug substance and drug product have now been found acceptable by the Office of Compliance.
4. Please note that a satisfactory inspection (and prior Agency approval) will be needed to add the previously withdrawn(b)(4)-------- -site or any new alternate site (that would perform the corresponding functions) to NDA 21-520. However, the presently listed sites are acceptable.
5. As noted in our previous action letter, your request for a Categorical Exclusion from the requirement to perform a full Environmental Assessment for this application has been granted.

Nonclinical Pharmacology and Toxicology

1. We have reviewed your response concerning the need to conduct a repeat prenatal/postnatal development study in rats, addressing the high postnatal mortality seen with the high-dose combination of olanzapine and fluoxetine, and the developmental disturbances (e.g., testicular degeneration) observed postnatally in the reproductive systems of F_1 males at the low-dose combination. As noted above, we are retaining our request for a Phase 4 commitment to conduct this study.
2. We have reviewed your response concerning the need to address the evaluation (b)(4)---(b)(4)----as a Phase 4 commitment. We are withdrawing our req----------this ----------

Clinical Pharmacology and Biopharmaceutics

1. We have reviewed your response to our request that you(bodify your dissolution specifications. We agree with your proposed Q value of)(% dissolved at 30 minutes. Therefore, please adopt the following dissolution metho4)-nd specifications for all strengths of olanzapine/fluoxetine hydrochloride capsules:

Apparatus:	USP Apparatus 2 (Paddle) at 50 RPM
Medium:	900 mL of 0.1N hydrochloric acid at 37±0.5°C
Specifications:	(b **%** dissolved at 3**0 minutes**.

2. We have reviewed your response to our request for a postmarketing (Phase 4) commitment to conduct a drug interaction study with the highest strength of olanzapine and fluoxetine HCl capsules and a potent CYP1A2 inhibitor. Based on our review, and on the enclosed agreed-upon labeling, we withdraw our request for this commitment.

Division of Scientific Investigations
Our field investigator has now completed the inspection of all sites involved in the biopharmaceutics studies of olanzapine and fluoxetine HCl capsules. The overall inspection was satisfactory.

Clinical / Statistical / Clinical Safety
We have completed our review of your response to our requests, including our request that you justify the absence of a fluoxetine-only treatment arm. Your response is satisfactory.

Labeling (Package Insert and Container Labeling)
The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert and the Patient Package Insert) and to the immediate container and carton labels as submitted in your Complete Response of June 24, 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, please designate this submission **"FPL for Approved NDA 21-520".** Approval of this submission by FDA is not required before the labeling is used.

Promotional Materials
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

MedWatch-to-Manufacturer Program
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).

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}

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

Enclosure (Approved Agreed-Upon Labeling)
[The electronic signature page will follow the labeling.]

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

12/24/03 02:50:32 PM