CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-520

ADMINISTRATIVE DOCUMENTS

ITEM 14: PATENT CERTIFICATION

NDA 21-520
SYMBIAX
(olanzapine-fluoxetine combination)

Eli Lilly and Company (Lilly) claims a three year period of exclusivity for the use of Olanzapine-Fluoxetine Combination in the treatment of depressive episodes associated with bipolar disorder, as provided by 21 C.F.R. 314.108(b)(4).

Clinical trial conducted which is essential to approval of this NDA is identified as F1D-MC-HGGY.

As required by 21 C.F.R. 314.50(j)(4), Lilly certifies that to the best of Lilly's knowledge:

1. the above clinical investigation included in this application meets the definition of "new clinical investigation" as set forth in 21 C.F.R. 314.108(a);

2. the above clinical investigation is "essential to approval" of this application. Lilly, through its employees, electronically searched the Scientific literature as of April 30, 2002 via the Medicine database cluster on STN and World Patents Index, and has not discovered any published studies or publicly available reports for which Lilly is seeking approval. In Lilly's opinion and to the best of Lilly's knowledge, there are no published studies or publicly available reports to provide a sufficient basis for the approval of the conditions for which Lilly is seeking approval without reference to the new clinical investigation in this application;

3. the above clinical investigation was conducted by Lilly. Lilly was the sponsor named in the Form FDA-1571 of IND number 28-705 under which the new clinical investigation that is essential to the approval of this application was conducted.

Gregory T. Brophy, Ph.D.
Director, US Regulatory Affairs

8/15/02
Date

ITEM 13: PATENT INFORMATION

NDA 21-520
Symbiax
(olanzapine-fluoxetine combination)

The undersigned declares that the following patents cover the formulation, composition, and/or method of use of the Olanzapine-Fluoxetine Combination. This product is the subject of this application for which approval is being sought:

Patent Number	Expiration Date	Claim Type
5,229,382	April 23, 2011	Compound, formulation
5,945,416	March 24, 2017	Formulation

The above patents are all owned by or exclusively licensed by Eli Lilly and Company, Indianapolis, Indiana.

Gregory T. Brophy, Ph.D.
Director, US Regulatory Affairs

8/15/02
Date

APPEARS THIS WAY
ON ORIGINAL

EXCLUSIVITY SUMMARY for NDA # 21-520 SUPPL # ---

Trade Name SYMBYAX Generic Name olanzapine/fluoxetine HCl
Applicant Name Eli Lilly & Co., Inc. HFD- 120
Approval Date Dec. 24, 2003

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

   a) Is it an original NDA? YES/_X_/ NO /___/

   b) Is it an effectiveness supplement? YES /___/ NO /___/

      If yes, what type(SE1, SE2, etc.)?

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

      YES /_X_/ NO /___/

      If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

      If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES /_X_/ NO /___/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

THREE (3)

e) Has pediatric exclusivity been granted for this Active Moiety? YES /___/ NO /_X_/

Note: pediatric exclusivity has been granted for fluoxetine alone, but not for olanzapine alone or for the combination of olanzapine and fluoxetine.

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC) Switches should be answered No - Please indicate as such).

YES /___/ NO /_X_/

If yes, NDA # _____ Drug Name

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_X_/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product. (Not applicable.)

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA #

NDA #

NDA #

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /_X_/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # 20-592: ZYPREXA (olanzapine)

NDA # 18-936: PROZAC (fluoxetine)

NDA # 18-936 / SE1-058, SE1-067: SARAFEM (fluoxetine)

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: <u>THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS</u>

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /_X_/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications

(i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /_X_/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /_X_/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /_X_/

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /_X_/

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # F1D-MC-HGGY(A)

Investigation #2, Study # F1D-MC-HGGY(B)

Investigation #3, Study #

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /_X_/

Investigation #2 YES /___/ NO /_X_/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the

NDA in which each was relied upon:

NDA # _____ Study #
NDA # _____ Study #
NDA # _____ Study #

(b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /_X_/

Investigation #2 YES /___/ NO /_X_/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study #

NDA # _____ Study #

NDA # _____ Study #

(c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #1, Study # HGGY(A)

Investigation #2, Study # HGGY(B)

Investigation #__, Study #

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial

support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1	HGGY (A)
IND # 28,705 YES /_X_/	NO /___/ Explain:
Investigation #2	HGGY (B)
IND # 28,705 YES /_X_/	NO /___/ Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study? Not applicable

Investigation #1	
YES /___/ Explain _____	NO /___/ Explain _____
_____	_____
_____	_____
Investigation #2	
YES /___/ Explain _____	NO /___/ Explain _____
_____	_____
_____	_____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /_X_/

If yes, explain: _____

_____

_____

(see electronic signature page for signature and date)
Doris J. Bates Date
Regulatory Health Project Manager

(see electronic signature page for signature and date)
Signature of Office or Division Director Date

cc:
Archival NDA
HFD- /Division File
HFD- /RPM
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

APPEARS THIS WAY
ON ORIGINAL

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

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

/s/

Doris Bates
12/24/03 02:38:27 PM

Russell Katz
12/24/03 02:56:05 PM

APPEARS THIS WAY
ON ORIGINAL

PEDIATRIC PAGE

(Complete for all APPROVED original applications and efficacy supplements)

Although the Pediatric Rule is no longer in effect a Pediatric Page should be filled out as if it were still in effect to document what the Division would have done under the Rule. Therefore, if the Division would have deferred and/or waived specific age ranges for the application under review, this information should be captured on this Pediatric Page. Furthermore, if any pediatric studies were completed for this application, then that information should be captured as well.

NDA/BLA # : 21-520 [SYMBYAX (olanzapine and fluoxetine HCl) Capsules]

Supplement Type (e.g. SE5): Original NDA

Stamp Date: November 5, 2002 **Action Date:** see signature page (DFS)

HFD 120 **Trade and generic names/dosage form:** see above

Applicant: Eli Lilly & Co., Inc. **Therapeutic Class:** Antimanic (Bipolar Depression)

Indication(s) previously approved: None for the combination entity

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): one

Indication #1: Depressive episodes associated with bipolar disorder

Is there a full waiver for this indication (check one)?

☐ **Yes: Please proceed to Section A.**

☒ **No: Please check all that apply:** ____ **Partial Waiver** ☑ **Deferred** ____ **Completed**
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

☐ **Products in this class for this indication have been studied/labeled for pediatric population**
☐ **Disease/condition does not exist in children**
☐ **Too few children with disease to study**
☐ **There are safety concerns**
☐ **Other:** _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min	**kg**	**mo.**	**yr.**	**Tanner Stage**	
Max	**kg**	**mo.**	**yr.**	**Tanner Stage**	

Reason(s) for partial waiver:

☐ **Products in this class for this indication have been studied/labeled for pediatric population**
☐ **Disease/condition does not exist in children**

☐Too few children with disease to study
☐There are safety concerns
☐Adult studies ready for approval
☐Formulation needed
☐Other:_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred: Pediatric patients age 10-17 years.

Min _____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____
Max_____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____

Reason(s) for deferral:

☐ **Products in this class for this indication have been studied/labeled for pediatric population**
☐ **Disease/condition does not exist in children**
☐ **Too few children with disease to study**
☐ **There are safety concerns**
☒ **Adult studies ready for approval**
☐ **Formulation needed**
☐ **Other:**___

Date studies are due (mm/dd/yy): **Jan. 1, 2014**

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____
Max_____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Doris J. Bates, Ph.D.
Regulatory Project Manager
cc: NDA
HFD-960/ Grace Carmouze
(revised 10-14-03)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

Attachment A Not Required: Single Indication NDA.

REQUEST FOR DEFERRAL OF PEDIATRIC STUDIES

NDA Number: 21-520
Sponsor: Eli Lilly and Company
Indication: Depressive Episodes Associated with Bipolar Disorder

Because the pivotal studies with SYMBIAX in adults with bipolar depression were only recently completed, no clinical studies with the olanzapine/fluoxetine combination (LY900000) in a pediatric population have not been conducted. Lilly plans to submit a pediatric clinical study proposal for the Agency's feedback prior to initiating any clinical study.

Please refer to the Draft Guidance "Recommendations for Complying With the Pediatric Rule (21 CFR 314.55(a) and 601.27(a)", Section III. B., the Sponsors minutes from the Olanzapine plus Fluoxetine for Treatment-resistant Depression meeting on August 18, 1999, question 10, and the FDA Pre-NDA meeting minutes from the Bipolar Depression meeting on April 30, 2002, question 9.

Collectively, these represent and document agreement between Lilly and HFD-120 that a deferral of studies in the pediatric population has been granted.

Lilly commits to consider the study and study design of pediatric studies in Depressive Episodes associated with Bipolar Disorder after completion of the review of the efficacy and safety of the olanzapine/fluoxetine combination for treatment of Major Depressive Disorder in the adult population.

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

/s/

Doris Bates
12/24/03 02:34:48 PM

APPEARS THIS WAY
ON ORIGINAL

Debarment Certification

NDA Application No.: 21-520

Drug Name: **Symbiax (olanzapine/fluoxetine combination)**

Pursuant to the provisions of 21 U.S.C. 335a(k)(1), Eli Lilly and Company, through Gregory T. Brophy, Ph.D., hereby certifies that it did not and will not use in any capacity the services of any person debarred under Section (a) or (b) [21 U.S.C. 335a(a) or (b)] of the Generic Drug Enforcement Act of 1992, in connection with the above referenced application.

ELI LILLY AND COMPANY

By: _____
Gregory T. Brophy, Ph.D.
Director, U.S. Regulatory Affairs

8/15/02
Date

APPEARS THIS WAY
ON ORIGINAL

7/8/03 SYMBYAX (olanzapine/fluoxetine)

NDA 21-520

Review Team Roster

Clinical: Team Leader: Tom Laughren / Paul Andreason
Reviewer: Paul A.
Clinical Consult Reviewer:
Drug Abuse Reviewer:

Clin Safety: Team Leader: Judy
Reviewer: Tarek Hammad
ODS Consult Reviewer:

Pharm/Tox: Team Leader: Barry
Reviewer: Sonya Tabacova
Carcinogenicity Consult Reviewer:

Biopharm: Team Leader: Ray / Ramana
Reviewer: Sally Yasuda
Pharmacometrics Consult Reviewer: Meiyu Shen

Biometrics: Team Leader: Kun
Reviewer: Shiddul Siddiqui

CMC: Team Leader: Tom Oliver
Reviewer: Li-Shan Hsieh

Trademark review:
DMETS reviewer: Charlie Hoppes

DSI:
Clinical DSI contact: Ni Khin, Brenda Friend
Biopharm DSI Contact: C. Viswanathan, M. Yau, Mike Skelly

DDMAC: CSO Contact: Lisa Stockbridge
Reviewer: Sunny Saini

Symbyax - Response Meetg. 7-8-03

Sally Paul A. Tarek Judy Mc Rusty

CMC - complete & they can do 2 mos
P/T - complete & they can do 2 mo.

Biopharm - complete & they can do 2 mos.
DH issue discussed (pivotal BE)
No stats, they weren't asked to be Lore.

Tradename - like Cymbalta. (Entreve)

Clin safety - 6 mos. 40 narratives
not bookmarked 400 pp.
not sorted
we will have to ask
for stuff soon.

Question 7 is the major point

But also the bleeding abn.
in labeling. Lots of stuff

APPEARS THIS WAY
ON ORIGINAL

Document Type	Submission Description	Authors	Discipline	Submission Name	Content Type	Object Type	Drug Name	Generic Name
Review		Sally Yasuda	BIOPHARMACEUTICS	N 021520 N 000 04-Nov-2002	Word 6.0 (MacOS), 6.0-7.0 (Windows)	Amf Review	SYMBIAX (OLANZAPINE) CAPSULES	OLANZAPINE
Review	Abuse Potential Assessmen	Katherine Bonson	PHARMACOLOGIST	N 021520 N 000 04-Nov-2002	Word 6.0 (MacOS), 6.0-7.0 (Windows)	Amf Review	SYMBIAX (OLANZAPINE) CAPSULES	OLANZAPINE
Review	Symbyax-tradename accept	Linda Kim-Jung	PHARMACIST	N 021520 N 000 04-Nov-2002	Word 6.0 (MacOS), 6.0-7.0 (Windows)	Amf Review	SYMBIAX (OLANZAPINE) CAPSULES	OLANZAPINE
Review		Michael Skelly	PHARMACOLOGIST	N 021520 N 000 04-Nov-2002	Word 6.0 (MacOS), 6.0-7.0 (Windows)	Amf Review	SYMBIAX (OLANZAPINE) CAPSULES	OLANZAPINE
NDA Letters	AE letter and labeling fo	Doris Bates	CSO	N 021520 N 000 04-Nov-2002	Acrobat PDF	Amf Review	SYMBIAX (OLANZAPINE) CAPSULES	OLANZAPINE
Memo to File		Russell Katz	MEDICAL OFFICER	N 021520 N 000 04-Nov-2002	Acrobat PDF	Amf Review	SYMBIAX (OLANZAPINE) CAPSULES	OLANZAPINE
NDA Letters	AE letter and labeling fo			N 021520 N 000 C 21-Nov-2002	Acrobat PDF	Amf Review	SYMBIAX (OLANZAPINE) CAPSULES	OLANZAPINE
NDA Letters	AE letter and labeling fo			N 021520 N 000 C 04-Dec-2002	Acrobat PDF	Amf Review	SYMBIAX (OLANZAPINE) CAPSULES	OLANZAPINE
NDA Letters	AE letter and			N 021520 N 000 C 09-	Acrobat PDF	Amf Review	SYMBIAX (OLANZAPIN	OLANZAPINE

	labeling fo			Dec-2002			E) CAPSULES	
NDA Letters	AE letter and labeling fo			N 021520 N 000 C 16-Dec-2002	Acrobat PDF	Amf Review	SYMBIAX (OLANZAPINE) CAPSULES	OLANZAPINE
NDA Letters	AE letter and labeling fo			N 021520 N 000 SU 18-Dec-2002	Acrobat PDF	Amf Review	SYMBIAX (OLANZAPINE) CAPSULES	OLANZAPINE
Review	Abuse Potential Assessmen			N 021520 N 000 BP 18-Dec-2002	Word 6.0 (MacOS), 6.0-7.0 (Windows)	Amf Review	SYMBIAX (OLANZAPINE) CAPSULES	OLANZAPINE
NDA Letters	AE letter and labeling fo			N 021520 N 000 BP 18-Dec-2002	Acrobat PDF	Amf Review	SYMBIAX (OLANZAPINE) CAPSULES	OLANZAPINE
Memo to File		Russell Katz	MEDICAL OFFICER	N 021520 N 000 FG 04-Nov-2002	Word 6.0 (MacOS), 6.0-7.0 (Windows)	Amf Review	SYMBIAX (OLANZAPINE) CAPSULES	OLANZAPINE
NDA Letters	AE letter and labeling fo			N 021520 N 000 BL 27-Feb-2003	Acrobat PDF	Amf Review	SYMBIAX (OLANZAPINE) CAPSULES	OLANZAPINE
NDA Letters	AE letter and labeling fo			N 021520 N 000 BZ 27-Jan-2003	Acrobat PDF	Amf Review	SYMBIAX (OLANZAPINE) CAPSULES	OLANZAPINE
NDA Letters	AE letter and labeling fo			N 021520 N 000 BB 03-Feb-2003	Acrobat PDF	Amf Review	SYMBIAX (OLANZAPINE) CAPSULES	OLANZAPINE
NDA Letters	AE letter and labeling			N 021520 N 000 C 02-Apr-2003	Acrobat PDF	Amf Review	SYMBIAX (OLANZAPINE)	OLANZAPINE

	fo						CAPSULES	
NDA Letters	AE letter and labeling fo			N 021520 N 000 BM 11-Apr-2003	Acrobat PDF	Amf Review	SYMBIAX (OLANZAPINE) CAPSULES	OLANZAPINE
NDA Letters	AE letter and labeling fo			N 021520 N 000 C 22-Apr-2003	Acrobat PDF	Amf Review	SYMBIAX (OLANZAPINE) CAPSULES	OLANZAPINE
Review		Sally Yasuda	BIOPHARMACEUTICS	N 021520 N 000 AZ 24-Jun-2003	Word 6.0 (MacOS), 6.0-7.0 (Windows)	Amf Review	SYMBIAX (OLANZAPINE) CAPSULES	OLANZAPINE
Review		Li-Shan Hsieh	CHEMIST	N 021520 N 000 AZ 24-Jun-2003	Word 6.0 (MacOS), 6.0-7.0 (Windows)	Amf Review	SYMBIAX (OLANZAPINE) CAPSULES	OLANZAPINE
Forms	request for second review	Doris Bates	CSO	N 021520 N 000 AZ 24-Jun-2003	Acrobat PDF	Amf Review	SYMBIAX (OLANZAPINE) CAPSULES	OLANZAPINE
Review	ODS/DSRCS PPI Review	Jeanine Best	CSO	N 021520 N 000 AZ 24-Jun-2003	Word 6.0 (MacOS), 6.0-7.0 (Windows)	Amf Review	SYMBIAX (OLANZAPINE) CAPSULES	OLANZAPINE
NDA Telecons	July 16, 2003 request for	Doris Bates	CSO	N 021520 N 000 AZ 24-Jun-2003	Acrobat PDF	Amf Review	SYMBIAX (OLANZAPINE) CAPSULES	OLANZAPINE
Meeting Minutes	resubmissi on filing meeti	Doris Bates	CSO	N 021520 N 000 AZ 24-Jun-2003	Acrobat PDF	Amf Review	SYMBIAX (OLANZAPINE) CAPSULES	OLANZAPINE
NDA Letters	Ack Class 2 complete resp	Doris Bates	CSO	N 021520 N 000 AZ 24-Jun-2003	Acrobat PDF	Amf Review	SYMBIAX (OLANZAPINE) CAPSULES	OLANZAPINE

Forms	SYMBYAX resub bpharm cons	Doris Bates	CSO	N 021520 N 000 AZ 24-Jun-2003	Acrobat PDF	Amf Review	SYMBIAX (OLANZAPINE) CAPSULES	OLANZAPINE
Forms	N 21-520 resubmission CSS	Doris Bates	CSO	N 021520 N 000 AZ 24-Jun-2003	Acrobat PDF	Amf Review	SYMBIAX (OLANZAPINE) CAPSULES	OLANZAPINE
Forms	Includes a proposed PPI f	Doris Bates	CSO	N 021520 N 000 AZ 24-Jun-2003	Acrobat PDF	Amf Review	SYMBIAX (OLANZAPINE) CAPSULES	OLANZAPINE

Table of Contents

NDA 21-520

SYMBYAX™ (olanzapine / fluoxetine hydrochloride) Capsules

—, 6/25, 6/50, 12/25, and 12/50 mg/mg (mg equivalent olanzapine/mg equivalent fluoxetine)

Applicant's Complete Response to May 5, 2003 Approvable Letter

Approval Package

Table of Contents

NDA 21-520

SYMBYAX™ (olanzapine / fluoxetine) Capsules

—— , 6/25, 6/50, 12/25, and 12/50 mg/mg (mg equivalent olanzapine/mg equivalent fluoxetine)

Applicant's Complete Response to May 5, 2003 Approvable Letter

Approval Package

NDA 21-520 Symbyax Amendment Labeling Table Of Contents		
Description	**Review copy volume number**	**Archive copy folder/file name**
Labeling Table of Contents		\Labeling\Labeltoc.pdf
Labeling Text		\Labeling\Labltext
Proposed Labeling Text Clean (Word Version)		\Labeling\Labltext\Proposed_Clean_Word
Proposed Labeling Text Clean		\Labeling\Labltext\Proposed_Clean
Proposed Labeling Text (Word Version)		\Labeling\Labltext\Proposed_Word
Proposed Labeling Text		\Labeling\Labltext\Proposed
Proposed Labeling Text (Annotated Version)		\Labeling\Labltext\Proposed_Annotated
Proposed Patient Labeling Text (Word Version)		\Labeling\Labltext\Proposed_PPI_Word
Proposed Patient Labeling Text		\Labeling\Labltext\Proposed_PPI
Annotated Label Cross-References to NDA 21-520		\Labeling\Labltext\Cross_Reference
[		]
Blister 6-25 mg ID100		\Labeling\Blister_6-25mg_ID100.pdf
Blister 6-50 mg ID100		\Labeling\Blister_6-50mg_ID100.pdf
Blister 12-25 mg ID100		\Labeling\Blister_12-25mg_ID100.pdf
Blister 12-50 mg ID100		\Labeling\Blister_12-50mg_ID100.pdf
[		]
Carton 6-25 mg 1000ct		\Labeling\Carton_6-25mg_1000.pdf
Carton 6-50 mg 1000ct		\Labeling\Carton_6-50mg_1000.pdf
Carton 12-25 mg 1000ct		\Labeling\Carton_12-25mg_1000.pdf
Carton 12-50 mg 1000ct		\Labeling\Carton_12-50mg_1000.pdf
[		]

Container 6-25 mg 30ct		\Labeling\Contain_6-25mg_30.pdf
Container 6-25 mg 100ct		\Labeling\Contain_6-25mg_100.pdf
Container 6-25 mg 1000ct		\Labeling\Contain_6-25mg_1000.pdf
Container 6-25 mg ID100		\Labeling\Contain_6-25mg_ID100.pdf
Container 6-50 mg 30ct		\Labeling\Contain_6-50mg_30.pdf
Container 6-50 mg 100ct		\Labeling\Contain_6-50mg_100.pdf
Container 6-50 mg 1000ct		\Labeling\Contain_6-50mg_1000.pdf
Container 6-50 mg ID100		\Labeling\Contain_6-50mg_ID100.pdf
Container 12-25 mg 30ct		\Labeling\Contain_12-25mg_30.pdf
Container 12-25 mg 100ct		\Labeling\Contain_12-25mg_100.pdf
Container 12-25 mg 1000ct		\Labeling\Contain_12-25mg_1000.pdf
Container 12-25 mg ID100		\Labeling\Contain_12-25mg_ID100.pdf
Container 12-50 mg 30ct		\Labeling\Contain_12-50mg_30.pdf
Container 12-50 mg 100ct		\Labeling\Contain_12-50mg_100.pdf
Container 12-50 mg 1000ct		\Labeling\Contain_12-50mg_1000.pdf
Container 12-50 mg ID100		\Labeling\Contain_12-50mg_ID100.pdf

Draft Labeling

Office of Drug Safety

MEMO

To: Russell Katz, M.D.
Director, Division of Neuropharmacological Drug Products
HFD-120

From: Scott Dallas, R.Ph.
Safety Evaluator, Division of Medication Errors and Technical Support
HFD-420

Through: Carol Holquist, R.Ph.
Deputy Director, Division of Medication Errors and Technical Support
HFD-420

CC: Doris Bates, Ph.D.
Project Manager, Division of Neuropharmacological Drug Products
HFD-120

Date: December 15, 2003

Re: ODS Consult 03-0112-2;
Symbyax (Olanzapine and Fluoxetine Hydrochloride Capsules)
6 mg/25 mg, 6 mg/50 mg, 12 mg/25 mg, and 12 mg/50 mg;
NDA 21-520

This memorandum is in response to a December 2, 2003 request from your Division for a re-review of the proprietary name, Symbyax and the revised labels and labeling.

The Division of Medication Errors and Technical Support (DMETS) has not identified any additional proprietary or established names that have the potential for confusion with Symbyax since we conducted our initial review dated April 23, 2003, and our first re-review dated July 11, 2003, that would render the name objectionable. Therefore, we have no objections to the use of this proprietary name. We also note that the sponsor has adequately addressed all of DMETS label and labeling comments included in the April 23, 2003 review.

The Division of Drug Marketing, Advertising, and Communications (DDMAC) finds the proposed name, Symbyax, acceptable from a promotional perspective.

The Division of Medication Errors and Technical Support (DMETS) considers this a final name review. However, if the approval of the NDA is delayed beyond 90 days from the date of this review, the name must be re-evaluated. A re-review of the name before NDA approval will rule out any objections based upon approvals of other proprietary/established names from this date forward.

If you have any questions or need clarification, please contact the project manager, Sammie Beam at 301-827-3242.

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

/s/

Scott Dallas
12/15/03 02:49:21 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
12/15/03 03:13:40 PM
DRUG SAFETY OFFICE REVIEWER

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*: Director, Division of Medication Errors and Technical Support (ODS/DMETS), HFD-420, PKLN Rm. 6-34			FROM: Dr. Doris Bates for Drs. P. Andreason and T. Oliver	
DATE November 28, 2003	IND NO.	NDA NO. 21520	TYPE OF DOCUMENT resubmitted NDA (trademark re-review)	DATE OF DOCUMENT June 24, 2003
NAME OF DRUG SYMBYAX (olanzapine and fluoxetine hydrochloride)	PRIORITY CONSIDERATION NDA 4P		CLASSIFICATION OF DRUG bipolar depression	DESIRED COMPLETION DATE: December 15, 2003 for a deadline of December 19, 2003 (see below)
NAME OF FIRM: Eli Lilly and Company, Inc.				

REASON FOR REQUEST

I. GENERAL

☐ NEW PROTOCOL	☐ PRE--NDA MEETING	☐ RESPONSE TO DEFICIENCY LETTER
☐ PROGRESS REPORT	☐ END OF PHASE II MEETING	☐ FINAL PRINTED LABELING
☐ NEW CORRESPONDENCE	☐ RESUBMISSION	☐ LABELING REVISION
☐ DRUG ADVERTISING	☐ SAFETY/EFFICACY	☐ ORIGINAL NEW CORRESPONDENCE
☐ ADVERSE REACTION REPORT	☐ PAPER NDA	☐ FORMULATIVE REVIEW
☐ MANUFACTURING CHANGE/ADDITION	☐ CONTROL SUPPLEMENT	☒ OTHER *(SPECIFY BELOW)*:
☐ MEETING PLANNED BY		

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

☐ DISSOLUTION	☐ DEFICIENCY LETTER RESPONSE
☐ BIOAVAILABILTY STUDIES	☐ PROTOCOL-BIOPHARMACEUTICS
☐ PHASE IV STUDIES	☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL	☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES	☐ SUMMARY OF ADVERSE EXPERIENCE
☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)	☐ POISON RISK ANALYSIS
☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP	

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL	☐ PRECLINICAL

Please see next page for comments and special instructions.

APPEARS THIS WAY
ON ORIGINAL

COMMENTS/SPECIAL INSTRUCTIONS:

Attached to the hard and electronic copies of this form is a copy of the most recent DMETS review of the proposed trademark SYMBYAX for the olanzapine/fluoxetine combination product. A consult was sent upon initial receipt of the firm's class 2 resubmission (June 26, 2003 sending date) and the review was received on July 25, 2003:

We are requesting re-review of the trademark proposal because the July 25, 2003 date of the initial response was more than 3 months prior to the December 25, 2003 due date. However, because of planned absences in the Division during the week of December 25, we are requesting feedback by December 15, 2003 in order to meet A December 19, 2003 action due date.

Because most of the evaluation work was done in depth for the July 25, 2003 review, and because of the tight time frame for this request, we are happy to accept an e-mail response for this request and will enter it in DFS for the record.

Please note that the package provided in June, 2003 included the following items:

1. FDA's approvable letter
2. Lilly proposed package insert (clean)
3. FDA proposed package insert with FDA and Lilly annotations
4. Lilly annotated proposed package insert (WORD printout)
5. Lilly proposed Patient Package Insert (WORD printout)
6. List of links to annotated Package Insert (for use with EDR copy of files)
7. All container, carton, and blister labeling, ordered by increasing dosage strength and by container size (blisters, then 30s, 100s, 100-Identidose, 1000s, 2000s)
8. Copy of the trademark consult review received for the NDA (OK at that time)
9. the EDR URL for this NDA resubmission is \\Cdsesub1\n21520\N_000\2003-06-24

Full size, full color mockups of the proposed container and carton labeling were also attached.

PLEASE ALSO NOTE: Lilly also has an antidepressant NDA still pending (N 21-427, AE actions September 13, 2002; and September 25, 2003) for the NCE duloxetine. The proposed trademark for this drug is CYMBALTA. An initial NDA trademark consult was submitted and initial NDA trademark review found no objections to the proposed trademark. Re-review for the 2003 action date found the proposed trademark still acceptable. The firm has not yet responded to our September 2003 letter, but they do propose to retain the CYMBALTA trademark when they respond.

Please contact Dr. Bates at 594-5536 or via e-mail at batesd if any additional information or clarification is needed.

SIGNATURE OF REQUESTER electronic signature on next page	METHOD OF DELIVERY (Check one) ☒ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

2 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: July 22, 2003

TO: Russell Katz, M.D., Director
Division of Neuropharmacological Drug Products
HFD-120

VIA: Doris Bates, Regulatory Health Project Manager
Division of Neuropharmacological Drug Products
HFD-120

FROM: Jeanine Best, M.S.N., R.N., P.N.P.
Patient Product Information Specialist
Division of Surveillance, Research, and Communication Support
HFD-410

THROUGH: Toni Piazza-Hepp, Pharm. D., Acting Director
Division of Surveillance, Research, and Communication Support
HFD-410

SUBJECT: ODS/DSRCS Review of Patient Labeling for Symbyax™
(olanzapine and fluoxetine HCl capsules), NDA 21-520

The attached patient labeling (clean copy) represents the revised risk communication materials for Symbyax™ (olanzapine and fluoxetine HCl capsules), NDA 21-520. We have simplified the wording, made it consistent with the PI, removed other unnecessary information (the purpose of patient information leaflets is to enhance appropriate use and provide important risk information about medications), and put it in the format that we are recommending for all patient information. Our proposed changes are known through research and experience to improve risk communication to a broad audience of varying educational backgrounds.

Comments to the review division are bolded, underlined and italicized. We can provide a marked-up and clean copy of the revised document in Word if requested by the review division. Please call us if you have any questions.

6 page(s) of draft labeling has been removed 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/

Jeanine Best
7/22/03 09:03:39 AM
CSO

Toni Piazza Hepp
7/22/03 01:43:44 PM
DRUG SAFETY OFFICE REVIEWER

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE
(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: August 31, 2005
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Eli Lilly and Company	December 15, 2003
TELEPHONE NO *(Include Area Code)*	FACSIMILE *(FAX)* Number *(Include Area Code)*
317-276-2000	317-276-1652
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued)*: Lilly Corporate Center, Indianapolis, IN 46285	AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* NDA 21-520

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY	CODE NAME *(If any)*
Olanzapine	Symbyax™	

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*	DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
	Capsules	O/F mg ~~=~~ ,6/25,12/25,6/50,12/50	Oral

(PROPOSED) INDICATION(S) FOR USE:
Depressive Episodes Associated with Bipolar Disorder

APPLICATION INFORMATION

APPLICATION TYPE *(check one)* ■ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) ☐ BIOLOGICS LICENSE APPLICATION (21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ■ 505 (b)(1) ☐ 505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug _____ Holder of Approved Application _____

TYPE OF SUBMISSION *(check one)* ☐ ORIGINAL APPLICATION ☐ AMENDMENT TO APENDING APPLICATION ☐ RESUBMISSION ☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ■ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION: Response to FDA Questions

PROPOSED MARKETING STATUS *(check one)* ■ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 THIS APPLICATION IS ☐ PAPER ☐ PAPER AND ELECTRONIC ■ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

NA

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

This application contains the following items: *(Check all that apply)*	
☐	1. Index
☐	2. Labeling *(check one)* ☐ Draft Labeling ☐ Final Printed Labeling
☐	3. Summary (21 CFR 314.50 (c))
☐	4. Chemistry section
☐	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
☐	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
☐	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
☐	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
☐	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
☐	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
■	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
☐	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
☐	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
☐	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
☐	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
☐	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
☐	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
☐	15. Establishment description (21 CFR Part 600, if applicable)
☐	16. Debarment certification (FD&C Act 306 (k)(1))
☐	17. Field copy certification (21 CFR 314.50 (l)(3))
☐	18. User Fee Cover Sheet (Form FDA 3397)
☐	19. Financial Information (21 CFR Part 54)
☐	20. OTHER *(Specify)*

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE:
Patrick Burns	Patrick R. Burns, PharmD., Regulatory Research Scientist, U.S. Regulatory Affairs	12/15/03

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
Lilly Corporate Center, Indianapolis, IN 46285	(317) 277-3554

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CDER, HFD-99
1401 Rockville Pike

Food and Drug Administration
CDER (HFD-94)
12229 Wilkins Avenue
Rockville, MD 20852

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Office of Drug Safety

MEMO

To: Russell Katz, M.D.
Director, Division of Neuropharmacological Drug Products
HFD-120

From: Linda Y. Kim, R.Ph.
Safety Evaluator, Division of Medication Errors and Technical Support, Office of Drug Safety
HFD-420

Through: Denise P. Toyer, Pharm.D.
Team Leader, Division of Medication Errors and Technical Support, Office of Drug Safety
HFD-420

Carol A. Holquist, R.Ph.
Deputy Director, Division of Medication Errors and Technical Support, Office of Drug Safety
HFD-420

CC: Doris Bates
Project Manager, Division of Neuropharmacological Drug Products
HFD-120

Date: July 11, 2003

Re: ODS Consult 03-0112-1, Symbyax (Olanzapine and Fluoxetine Hydrochloride Capsules) [redacted], 6 mg/25 mg, 6 mg/50 mg, 12 mg/25 mg, and 12 mg/50 mg; NDA 21-520.

<u>NOTE</u>: This review contains proprietary and confidential information that should not be released to the public. These names are pending approval.

This memorandum is in response to a June 26, 2003 request from your Division for a final review of the proprietary name, Symbyax. The label, carton and insert labeling were provided for review and comment. The proposed proprietary name was found acceptable by DMETS on April 23, 2003 (ODS Consult 03-0112). We note that the sponsor has adequately addressed all of DMETS' label and labeling comments included in the April 23, 2003 review.

Since that review, DMETS has identified three additional proprietary names: [redacted]** and Cymbalta*** as having potential sound-alike confusion with Symbyax and Symlin*** as having potential look-alike confusion with Symbyax.

——— was reviewed by DMETS on May 7, 2002 and found unacceptable from a safety perspective. The sponsor plans to use an alternate proprietary name, Aloxi. Therefore, ——— will not be discussed in this review.

Symlin is the proposed proprietary name for Pramlintide Acetate which is indicated as adjunctive therapy to insulin to improve glycemic and metabolic control in people with type 1 and 2 diabetes mellitus. Symlin is not approved or marketed in the United States at this time. Symlin was reviewed by DMETS (ODS Consult 00-0230) on March 5, 2001 and was found acceptable. The status of the proprietary name is still pending at the Division level. Although Symbyax and Symlin share the first three letters, "SYM", the remaining portions of the name, "yax" vs. "lin", are different both phonetically and orthographically. [redacted]

Symlin is also supplied as a 0.6 mg/mL sterile injection in 5 mL vials for use with a syringe. Although there is a possibility that Symlin and Symbyax may be launched into the marketplace within close proximity to each other, the potential for confusion is minimal. The two products have different dosage forms, strengths, and route of administration. Additionally, since both products are available in different strengths, a prescriber would have to write the strength of the product when prescribing, further differentiating Symbyax from Symlin.

Cymbalta is the proposed proprietary name for duloxetine hydrochloride capsules, indicated to treat major depression. Cymbalta is not approved or marketed in the United States at this time. Cymbalta was reviewed by DMETS (ODS Consult 01-0167-1) on June 20, 2003 and was found acceptable. The status of the proprietary name is still pending at the Division level. Although Symbyax and Cymbalta share the same beginning sounds, "Symb" vs. "Cymb", the remaining portions of the name, "yax" vs. "alta", are different both phonetically and orthographically. Symbyax is a combination product (olanzapine/fluoxetine) indicated for the treatment of depressive episodes with bipolar disorder and will be available in multiple strengths (———, 6 mg/25 mg, 6 mg/50 mg, 12 mg/25 mg, and 12 mg/50 mg). Cymbalta is a single ingredient (duloxetine) drug product indicated for major depressive disorder and will be available in strengths of 20 mg, 30 mg, ——— and 60 mg. The dosage strengths do not overlap, however, both will be available as oral capsules for once daily administration. Additionally, Symbyax and Cymbalta are sponsored by the same manufacturer, Eli Lilly, and may be launched into the marketplace within close proximity to each other. Confusion may be further compounded as a result of similarities in the established names (fluOXETINE vs. dulOXETINE). Therefore, DMETS recommends that efforts be made to differentiate the packaging in hopes of minimizing the likelihood of possible confusion. In addition, DMETS would like to recommend that some educational measures be taken to emphasize the differences between these two medications at the time of approval.

In summary, DMETS has no objection to the use of the proprietary name, Symbyax. We consider this a final review. If the approval of the NDA is delayed beyond 90 days from the date of this review, the name must be re-evaluated. A re-review of the name before NDA approval will rule out any objections based upon approvals of other proprietary and/or established names from this date forward.

We would be willing to meet with the Division for further discussion if needed. If you have any questions or need clarification, please contact Sammie Beam at 301-827-3242.

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

/s/

Linda Kim-Jung
7/25/03 09:53:04 AM
PHARMACIST

Carol Holquist
7/25/03 10:13:29 AM
PHARMACIST

APPEARS THIS WAY
ON ORIGINAL

2 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	**REQUEST FOR CONSULTATION**

O *(Division/Office)*: Director, Division of Medication Errors and Technical Support (ODS/DMETS), HFD-420, PKLN Rm. 6-34			FROM: Dr. Doris Bates for Drs. P. Andreason and T. Oliver	
DATE June 26, 2003	IND NO.	NDA NO. 21520	TYPE OF DOCUMENT resubmitted NDA (trademark review, PPI Review)	DATE OF DOCUMENT June 24, 2003
NAME OF DRUG SYMBYAX (olanzapine and fluoxetine hydrochloride)	PRIORITY CONSIDERATION NDA 4P		CLASSIFICATION OF DRUG bipolar depression	DESIRED COMPLETION DATE: July 30, 2003 for a deadline of August 25, 2003 (if Class 1: see below)

NAME OF FIRM: Eli Lilly and Company, Inc.

REASON FOR REQUEST

I. GENERAL

☐ NEW PROTOCOL	☐ PRE--NDA MEETING	☐ RESPONSE TO DEFICIENCY LETTER
☐ PROGRESS REPORT	☐ END OF PHASE II MEETING	☐ FINAL PRINTED LABELING
☐ NEW CORRESPONDENCE	☐ RESUBMISSION	☐ LABELING REVISION
☐ DRUG ADVERTISING	☐ SAFETY/EFFICACY	☐ ORIGINAL NEW CORRESPONDENCE
☐ ADVERSE REACTION REPORT	☐ PAPER NDA	☐ FORMULATIVE REVIEW
☐ MANUFACTURING CHANGE/ADDITION	☐ CONTROL SUPPLEMENT	☒ OTHER *(SPECIFY BELOW)*:
☐ MEETING PLANNED BY		

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

☐ DISSOLUTION	☐ DEFICIENCY LETTER RESPONSE
☐ BIOAVAILABILTY STUDIES	☐ PROTOCOL-BIOPHARMACEUTICS
☐ PHASE IV STUDIES	☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL	☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES	☐ SUMMARY OF ADVERSE EXPERIENCE
☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)	☐ POISON RISK ANALYSIS
☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP	

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL	☐ PRECLINICAL

Please see next page for comments and special instructions.

COMMENTS/SPECIAL INSTRUCTIONS:

Attached to the hard copy of this form is comprehensive documentation for re-review of the proposed trademark SYMBYAX, including the following materials:

1. FDA's approvable letter
2. Lilly proposed package insert (clean)
3. FDA proposed package insert with FDA and Lilly annotations
4. Lilly annotated proposed package insert (WORD printout)
5. Lilly proposed Patient Package Insert (WORD printout)
6. List of links to annotated Package Insert (for use with EDR copy of files)
7. All container, carton, and blister labeling, ordered by increasing dosage strength and by container size (blisters, then 30s, 100s, 100-Identidose, 1000s, 2000s)
8. Copy of the trademark consult review received for the NDA (OK at that time)
9. the EDR URL for this NDA resubmission is \\Cdsesub1\n21520\N_000\2003-06-24

Full size, full color mockups of the proposed container and carton labeling are attached.

PLEASE NOTE: Lilly also has an antidepressant NDA pending (N 21-427, AE action September 13, 2002; resubmitted, with Class 2 deadline September 25, 2003) for the NCE duloxetine. The proposed trademark for this drug is CYMBALTA. An initial NDA trademark consult was submitted and initial NDA trademark review found no objections to the proposed trademark. A second trademark review has also been requested for this trademark.

Please contact Dr. Bates at 594-5536 or via e-mail at batesd if any additional information or clarification is needed.

SIGNATURE OF REQUESTER electronic signature on next page	METHOD OF DELIVERY (Check one) ☒ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

APPEARS THIS WAY
ON ORIGINAL

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

/s/

Doris Bates
6/27/03 05:45:21 PM
Resubmission received June 25; two month deadline is August 25; six month deadline is Christmas. I am currently assuming the two month deadline and asking for input by July 30, 2003 if possible

10 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling