CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-148

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Duloxetine

21-427

ITEM 13: PATENT INFORMATION

The following patents cover the above referenced product, claiming the drug substance, the drug product, and/or a method of use. This product is currently approved under Section 505 of the Federal Food, Drug, and Cosmetic Act (FFDCA).

Patent Number	Expiration Date
5,023,269	June 11, 2013
5,508,276	July 18, 2014
6,596,756	September 10, 2019

The above patents are all owned or exclusively licensed by Eli Lilly and Company, Indianapolis, Indiana. Attached is an FDA Form 3542a for patent 6,596,756.

Department of Health and Human Services
Food and Drug Administration

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

Form Approved: OMB No. 0910-0513
Expiration Date: 07/31/06
See OMB Statement on Page 3.

NDA NUMBER
21-427

NAME OF APPLICANT / NDA HOLDER
Eli Lilly and Company

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)
Cymbalta®

ACTIVE INGREDIENT(S)	STRENGTH(S)
Duloxetine Hydrochloride	20mg, 30mg, and 60mg

DOSAGE FORM
Capsules delayed release pellets, oral

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4).
Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
6,596,756	07/22/2003	09/10/2019

d. Name of Patent Owner	Address *(of Patent Owner)*	
	P.O. Box 6288	
	City/State	
Eli Lilly and Company	Indianapolis, IN	
	ZIP Code	FAX Number *(if available)*
	46206-6288	317-276-3861
	Telephone Number	E-Mail Address *(if available)*
	317-276-2958	patents@lilly.com

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)	Address *(of agent or representative named in 1.e.)*	
	P.O. Box 6288	
	City/State	
	Indianapolis, IN	
	ZIP Code	FAX Number *(if available)*
	46206-6288	317-276-3861
General Patent Counsel, Eli Lilly and Company	Telephone Number	E-Mail Address *(if available)*
	317-276-2958	patents@lilly.com

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☐ Yes X No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☐ No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1	Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.2	Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.3	If the answer to question **2.2** is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4	Specify the polymorphic form(s) claimed by the patent for which you have the test results described in **2.3**.		
2.5	Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☒ No
2.6	Does the patent claim only an intermediate?	☐ Yes	☒ No
2.7	If the patent referenced in **2.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

3. Drug Product (Composition/Formulation)

3.1	Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
3.2	Does the patent claim only an intermediate?	☐ Yes	☒ No
3.3	If the patent referenced in **3.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1	Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
4.2	Patent Claim Number *(as listed in the patent)* 1	Does the patent claim referenced in **4.2** claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes ☐ No	
4.2a	If the answer to **4.2** is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* Method of treating fibromyalgia	
4.2	Patent Claim Number *(as listed in the patent)* 2	Does the patent claim referenced in **4.2** claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes ☐ No	
4.2a	If the answer to **4.2** is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* Method of treating fibromyalgia	

5. No Relevant Patents	
For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.	☐ Yes

6. Declaration Certification

6.1 ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide information below)*

Date Signed: August 9, 2007

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☐ NDA Applicant/Holder	☒ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name: Angela J. Grayson	
Address: P.O. Box 6288	City/State: Indianapolis, IN
ZIP Code: 46206-6288	Telephone Number: 317-433-2538
FAX Number *(if available)*: 317-276-3861	E-Mail Address *(if available)*: patents@lilly.com

EXCLUSIVITY SUMMARY

NDA # 22-148 SUPPL # HFD # 170

Trade Name Cymbalta Delayed-Release Capsules

Generic Name duloxetine HCl

Applicant Name Eli Lilly

Approval Date, If Known 6-13-08

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy 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 a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(1)

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 ☒ 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 ☒ NO ☐

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

3 years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

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

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (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.

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# 21-427

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 ☐ NO ☐

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

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

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 ☒ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

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.

(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 ☒ 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 8:

(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 ☐ 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 ☒

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 ☒

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:

HMCA, HMCJ

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

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 ☒

Investigation #2 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:

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 ☒

Investigation #2 YES ☐ NO ☒

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

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"):

HMCA, HMCJ

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		!
		!
IND # 63,615	YES ☐	! NO ☐
		! Explain:

Investigation #2		!
		!
IND # 63,615	YES ☐	! 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?

Investigation #1	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! 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 ☒

If yes, explain:

==========

Name of person completing form: Parinda Jani
Title: Chief, project Management Staff
Date: June 12, 2008

Name of Office/Division Director signing form: Bob Rappaport, M.D.
Title: Director, Division of Anesthesia, Analgesia and Rheumatology Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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

/s/

Bob Rappaport
6/13/2008 06:59:53 PM

ITEM 14: CLAIMED EXCLUSIVITY

Eli Lilly and Company (Lilly) claims a three-year period of exclusivity for Cymbalta in the treatment of fibromyalgia as provided in 21 C.F.R. § 314.108(b)(5) and 21 U.S.C. §§ 355(c)(3)(E)(iv) and 355(j)(5)(F)(iv). The present supplemental application contains reports of new clinical investigations (other than bioavailability studies) that were conducted or sponsored by Lilly, and that are essential to the approval of this supplemental application, as follows:

1. "New Clinical Investigation": To the best of Lilly's knowledge and belief, each of the clinical investigations included in this supplemental application meets the definition of a "new clinical investigation" set forth in 21 C.F.R. § 314.108(a);
2. "Essential to Approval": Lilly has thoroughly searched the scientific literature for all published studies and publicly available reports of clinical investigations relevant to the approval being requested in this supplement. No such studies or publicly available reports were identified. Therefore the clinical investigations contained in this application are essential to approval as defined in 21 C.F.R. § 314.108(a).
3. "Conducted or Sponsored By Lilly": Lilly was the sponsor named in the Form FDA-1571 for an investigational new drug application, IND No. - 38,838, under which the new clinical investigation(s) that are essential to the approval of its application were conducted.

PEDIATRIC PAGE
(Complete for all filed original applications and efficacy supplements)

DA/BLA#: 22-148 Supplement Number: _____ NDA Supplement Type (e.g. SE5): _____

Division Name: DAARP PDUFA Goal Date: 6-14-08 Stamp Date: 8/14/2007

Proprietary Name: Cymbalta

Established/Generic Name: duloxetine HCl

Dosage Form: Capsules

Applicant/Sponsor: Eli Lilly

Indication(s) *previously approved* (please complete this question for supplements and Type 6 NDAs only):
(1) Major Depressive Disorder
(2) General Anxiety Disorder
(3) Neuropathic Pain
(4) _____

Q1: Is this application in response to a PREA PMC? Yes ☐ Continue

No ☒ Please proceed to Question 2.

If Yes, NDA/BLA#: _____ Supplement #:_____ PMC #:_____

Does the division agree that this is a complete response to the PMC?

☐ Yes. **Skip to signature block.**

☐ No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

Q2: Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW ☐ active ingredient(s); ☒ indication(s); ☐ dosage form; ☐ dosing regimen; or ☐ route of administration?*

(b) ☐ No. PREA does not apply. **Skip to signature block.**

**** Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.***

Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s): 1
(Attach a completed Pediatric Page for each indication in current application.)

Indication: management of fibromyalgia

Q3: Does this indication have orphan designation?

☐ Yes. PREA does not apply. **Skip to signature block.**

☒ No. Please proceed to the next question.

Q4: Is there a full waiver for all pediatric age groups for this indication (check one)?

☐ Yes: (Complete Section A.)

☒ No: Please check all that apply:

☒ Partial Waiver for selected pediatric subpopulations (Complete Sections B)

☒ Deferred for the remaining pediatric subpopulations (Complete Sections C)

☐ Completed for some or all pediatric subpopulations (Complete Sections D)

☐ Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)

☐ Extrapolation in One or More Pediatric Age Groups (Complete Section F)

(Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL OR AT 301-796-0700.

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (**check, and attach a brief justification**)

- ☐ Necessary studies would be impossible or highly impracticable because:
  - ☐ Disease/condition does not exist in children
  - ☐ Too few children with disease/condition to study
  - ☐ Other (e.g., patients geographically dispersed): _____
- ☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- ☐ Evidence strongly suggests that product would be ineffective or unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

☐ Justification attached.

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

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

				Reason (see below for further detail):			
		minimum	maximum	Not feasible#	Not meaningful therapeutic benefit*	Ineffective or unsafe†	Formulation failed$^{\Delta}$
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☒	Other	0 yr. 0 mo.	12 yr. __ mo.	☒	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☒ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☒ No; ☐ Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

Not feasible:

- ☐ Necessary studies would be impossible or highly impracticable because:
- ☒ Disease/condition does not exist in children
- ☒ Too few children with disease/condition to study
- ☐ Other (e.g., patients geographically dispersed): _____

* Not meaningful therapeutic benefit:

- ☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- ☐ Evidence strongly suggests that product would be ineffective or unsafe in this/these pediatric population(s) (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL OR AT 301-796-0700.

Δ Formulation failed:

☐ Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. *(Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)*

☐ Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and F and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Sections D and F and complete the PeRC Pediatric Assessment form); and/or (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Sections E and F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for remaining pediatric subpopulations). Complete Section F on Extrapolation.

Check pediatric subpopulation for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				**Reason for Deferral**			**Applicant Certification †**	
opulation		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Yes	No
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐	☐
☒	Other	13 yr. __ mo.	17 yr. __ mo.	☒	☐	☐	X	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐	☐
☐	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐	☐	☐	☐
	Date studies are due (mm/dd/yy): 06/30/2013							

Are the indicated age ranges (above) based on weight (kg)? ☒ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☒ No; ☐ Yes.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL OR AT 301-796-0700.

If all of the pediatric subpopulations have been covered through the partial waivers and deferrals, proceed to Section F. For those pediatric subpopulations for which studies have been completed, proceed to Sections D and F and complete the PeRC Pediatric Assessment form. For those pediatric subpopulations for which additional studies are not needed because the drug is appropriately labeled in one or more pediatric subpopulations, proceed to Sections E and F.

Section D: Completed Studies (for some or all pediatric subpopulations). Complete Section F on Extrapolation.

Pediatric subpopulation(s) in which studies have been completed (check below):					
Population		minimum	maximum	PeRC Pediatric Assessment form attached?.	
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes ☐	No ☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: For those pediatric subpopulations for which additional studies are not needed because the drug is appropriately labeled in one or more pediatric subpopulations, proceed to Sections E and F. If there are no further pediatric subpopulations to cover based on the partial waivers, deferrals and completed studies, go to Section F.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations): (Complete section F)

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:			
Population		minimum	maximum
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

If studies are not needed because efficacy is being extrapolated from other adult and/or pediatric studies, proceed to Section F. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the target pediatric subpopulation needing studies. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

(Revised: 4/2008)

NOTE: If you have no other indications for this application, you may delete the attachments from this document.

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

/s/

Parinda Jani
6/13/2008 08:54:39 AM

REQUEST FOR DEFERRAL OF PEDIATRIC STUDIES

NDA: 22-148

Sponsor: Eli Lilly and Company

Indication: Fibromyalgia (FM)

Lilly has not conducted clinical studies with LY248686 in the fibromyalgia pediatric population. 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, and the FDA meeting minutes from March 13, 2007 FM pre-NDA meeting.

In accordance with 21 CFR 314.55(b)(2), and agreed upon by the Division at the pre-NDA meeting, Lilly requests for a deferral of pediatric studies in adolescents until after the approval of the adult fibromyalgia indication. These adult studies are completed and ready for approval.

Lilly requests a Partial Waiver for pediatric age groups including neonates, infants and children due to the low prevalence of this condition in these pediatric populations.

REQUEST FOR PARTIAL WAIVER OF PEDIATRIC STUDIES

NDA: 22-148

Sponsor: Eli Lilly and Company

Indication: Fibromyalgia (FM)

Lilly has not conducted clinical studies with LY248686 in the fibromyalgia pediatric population. 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, and the FDA meeting minutes from March 13, 2007 FM pre-NDA meeting.

In accordance with 21 CFR 314.55(3)(ii), Lilly requests for a partial waiver of pediatric studies to include the age groups represented by neonates, infants and children. Lilly has submitted a deferral request for adolescents until after the approval of the adult fibromyalgia indication.

Lilly requests a Waiver for pediatric age groups including neonates, infants and children due to the low prevalence of this condition in these pediatric populations. A diagnosis if fibromyalgia in patients under 16 years of age is so rare that it would be highly impractical or impossible to conduct clinical studies in patients of these ages.

Debarment Certification

NDA Application No.: 22-148

Drug Name: Cymbalta™(Duloxetine Hydrochloride)

Pursuant to the provisions of 21 U.S.C. 335a(k)(1), Eli Lilly and Company, through Bryan Boggs, 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: _____

Bryan Boggs, Pharm.D., Manager
U.S. Regulatory Affairs

August 13, 2007

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF SURVEILLANCE AND EPIDEMIOLOGY

DATE: 11 June 2008

FROM: John R. Senior, M.D., Associate Director for Science, Office of Surveillance and Epidemiology (OSE)

TO: Bob Rappaport, M.D., Director, Division of Anesthesia, Analgesia, and Rheumatology Products (DAARP)
Celia Winchell, M.D., Medical Team Leader, DAARP

VIA: Mark Avigan, M.D., Director, Division of Adverse Events Analysis 1
Gerald Dal Pan, M.D., Director, OSE

SUBJECT: Consultation regarding the question of duloxetine dose-induced hepatotoxicity

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Documents reviewed:

1) Consultation request from DAARP dated 10 June 2008, assigned OSE #2008-961, with request for immediate response by 11 June
2) Memorandum dated 2 May 2008 from Dr. Celia Winchell concerning cross-disciplinary team leader review of type 6 NDA 22-148 for treatment of fibromyalgia
3) Copies of Lilly's response for revised labeling of 9 June, MedGuide for patients, and Note to Reviewers, forwarded 10 June 2008

Duloxetine hydrochloride, a serotonin and norepinephrine reuptake inhibitor (SNRI), brand name CYMBALTA®Lilly, was approved (NDA 21-427) for treatment of major depressive disorder on 3 August 2004, and for treatment of diabetic neuropathic pain (NDA 21-733) 3 September 2004. It

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The request for this consultation comes from DAARP under urgent circumstances derived from labeling discussions currently underway. The issue at hand concerns an additional indication, ———of fibromyalgia (NDA 22-148, submitted 14 August 2007) for which the sponsor asks ——————————————— The data that were reviewed did not show that the higher dose was appreciably more effective than the 60 mg-dose, and DAARP was concerned that the risk of hepatotoxicity might be greater. The hepatologist at Lilly, Dr. Arie Regev, argued that the hepatotoxicity risk of duloxetine had been shown to be rare and idiosyncratic in the post-marketing experience with CYMBALTA since 2004, and stated that "idiosyncratic reactions are not dose-related." This statement was presumably based on the Often-cited classification by the late Hyman Zimmerman in his classic 1999 textl of hepatotoxic drugs into two major types: 1) intrinsic, predictable, true toxicants that cause clearly dose-related and high incidence liver injuries that are experimentally and rapidly\ reproducible in animals,

and 2) "idiosyncratic" reactions that are usually uncommon or rare, not clearly dose-related or reproducible in animals, and may have long latency periods from exposure to evidence of injury. The consultation request from DAARP asks me to address that controversial issue.

Comment: Briefly, this issue has come increasingly to the forefront of hepatology research recently, and is in fact mentioned in the current June 2008 issue of HEPATOLOGY in an article2 by Lammert et al. who found evidence that idiosyncratic drug-related hepatotoxicity was more common for drugs administered at daily doses of more than 50 mg than for those given at 10-50 mg/day, and far more than those for which the daily dose was less than 10 mg. The editors of HEPATOLOGY had asked me to review that article before publication, and based on some of my remarks had then requested that I write an editorial about the article that they published in the same issue.[3] In addition, one of the authors of the article, Dr. Naga Chalasani, is especially interested in the question of duloxetine-induced liver injury, and has collected cases in his experience at Indiana University Medical Center, one of the selected site for the drug-induced liver injury network (DILIN) supported by the National Institutes of Health (NIH). At a recent conference in March 2008, he mentioned[4] that he had 2 cases of his own and knew of 3 others that had been reported to the DILIN of relatively clean, unconfounded cases of duloxetine hepatotoxicity. He also mentioned in the recent HEPATOLOGY paper[2] an unpublished case of a woman with no history of alcohol abuse or known liver disease who had been taking 30 mg/day of duloxetine for many weeks without any adverse effects, but had "pronounced hepatotoxicity" very soon after increasing the dose to 60 mg/day. There is only one case of serious liver injury in the peer-reviewed published literature, reported[5] in 2006, interestingly also after increasing the dose from 30 to 60 mg/day. A very recent review[6] "white-washed" the problem, but I have not had a chance as yet to examine their data or methods of analysis.

Your e-mail message of today (11 June) says that the labeling negotiations with Lilly yesterday lead to their accepting Marc Stone's recommendations on the hepatotoxicity warnings, ——————————————————————————————— This very brief consultation response is sent today, as you had requested, but the short time period did not allow for more thorough discussion. I did send a message to Dr. Naga Chalasani yesterday, and he will be sending more information about the cases he knows of and how to obtain more details about them.

Recommendations:

- You have done an efficient and excellent job of countering the sponsor's specious arguments and have held the line on reasonable labeling. Please keep me informed of further developments.
- I shall forward to you additional information on the cases sent by Dr. Chalsani, and perhaps those reported to the DILIN group,as they become available.

John R. Senior, M.D.

cc: OSE #2008-961
M. Avigan, OSE/ DAEA 1
G. Dal Pan, OSE
C. Winchell, DAARP
B. Rappaport, DAARP

REFERENCES

1. Zimmerman, HJ. Hepatotoxicity: The Adverse Effects of Drugs and Other Chemicals on the Liver. Lippincott Williams & Wilkins, Philadelphia, 1999. Page 122-136.

2. Lammert C, Einarsson S, Saha C, Niklasson A, Bjornsson E, Chalasania N. Relationship between daily doses of oral medications and idiosyncratic drug-induced liver injury; search for signals. Hepatology 2008; 47(6):2003-9. [PMID 18454504]

3. Senior JR. What is idiosyncratic hepatotoxicity? What is it not? Hepatology 2008; 47(6): 1813-5. [PMID 18508312]

4. Chalasani N. Discussion of presentation by W. Lee, 27 March 2008. www.fda.gov/cder/livertox/presentations2008/32-d3aNPQ.pdf

5. Hanje AJ, Pell LJ, Votolato NA, Frankel WL, Kirkpatrick RB. Case report: fulminant hepatic failure involving duloxetine hydrochloride. Clin Gastroenterol Hepatol. 2006; 4(7):912-7. [PMID 16797245]

6. McIntyre RS, Panjwani ZD, Nguyen HT, Woldeyohannes HO, Alsuwaidan M, Soczynska JK, Louenco MT, Konarski JZ, Kennedy SH. The hepatic safety profile of duloxetine; a review. Expert Opin Drug Metab Toxicol 2008; 4(3):281-5. [PMID 18363543]

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

/s/

John Senior
6/13/2008 08:19:49 AM
MEDICAL OFFICER
Entered into DFS 13 June 2008

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]			
BLA # NDA # 22-148	BLA STN# NDA Supplement #	If NDA, Efficacy Supplement Type	
Proprietary Name: Cymbalta Established Name: duloxetine hydrochloride Dosage Form: Capsules		Applicant: Eli Lilly	
RPM: Parinda Jani		Division: HFD-170	Phone # (301) 796-1232

NDAs:
NDA Application Type: X 505(b)(1) ☐ 505(b)(2)
Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2)

(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)

505(b)(2) Original NDAs and 505(b)(2) NDA supplements:
Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)):

Provide a brief explanation of how this product is different from the listed drug.

☐ If no listed drug, check here and explain:

Prior to approval, review and confirm the information previously provided in Appendix B to the Regulatory Filing Review by re-checking the Orange Book for any new patents and pediatric exclusivity. If there are any changes in patents or exclusivity, notify the OND ADRA immediately and complete a new Appendix B of the Regulatory Filing Review.

☐ No changes ☐ Updated
Date of check:

If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.

On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.

❖ User Fee Goal Date ❖ Action Goal Date (if different)	6-14-2008 6-13-2008
❖ Actions	
• Proposed action	X AP ☐ TA ☐ AE ☐ NA ☐ CR
• Previous actions *(specify type and date for each action taken)*	X None
❖ Advertising *(approvals only)* Note: If accelerated approval (21 CFR 314.510/601.41), advertising must have been submitted and reviewed *(indicate dates of reviews)*	XRequested in AP letter ☐ Received and reviewed

[1] The **Application Information** section is (only) a checklist. The **Contents of Action Package** section (beginning on page 5) lists the documents to be filed in the Action Package.

❖ Application Characteristics

Review priority: X Standard ☐ Priority
Chemical classification (new NDAs only):

NDAs, BLAs and Supplements:
☐ Fast Track
☐ Rolling Review

☐ Orphan drug designation

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

NDAs and NDA Supplements:
☐ OTC drug

Other:

Other comments:

❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	☐ Yes X No
• This application is on the AIP	☐ Yes ☐ No
• If yes, exception for review granted *(file Center Director's memo in* Administrative Documents *section)*	☐ Yes
• If yes, OC clearance for approval *(file communication in* Administrative Documents *section)*	☐ Yes ☐ Not an AP action
❖ Date reviewed by PeRC (required for approvals only) If PeRC review not necessary, explain: ☐	May 28, 2008
❖ BLAs only: RMS-BLA Product Information Sheet for TBP has been completed and forwarded to OBPS/DRM (approvals only)	☐ Yes, date
❖ Public communications (approvals only)	
• Office of Executive Programs (OEP) liaison has been notified of action	☐ Yes X No
• Press Office notified of action	☐ Yes X No
• Indicate what types (if any) of information dissemination are anticipated	XNone ☐ HHS Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other

❖ Exclusivity	
• NDAs only: Exclusivity Summary (approvals only) *(file Summary in* Administrative Documents *section)*	X Included
• Is approval of this application blocked by any type of exclusivity?	X No ☐ Yes
• NDAs and BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	X No ☐ Yes If, yes, NDA/BLA # and date exclusivity expires:
• NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application)? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	X No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	X No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	X No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? *(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)*	X No ☐ Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs and NDA supplements only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.	X Verified ☐ Not applicable because drug is an old antibiotic.
• Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) ☐ Verified 21 CFR 314.50(i)(1) ☐ (ii) ☐ (iii)
• [505(b)(2) applications] If the application includes a **paragraph III** certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	☐ No paragraph III certification Date patent will expire
• [505(b)(2) applications] For **each paragraph IV** certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (*Summary Reviews*)).*	☐ N/A (no paragraph IV certification) ☐ Verified

- [505(b)(2) applications] **For each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

  Answer the following questions for **each** paragraph IV certification:

  (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? ☐ Yes ☐ No

  (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))).

  *If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).*

  (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).*

  *If "**No**," continue with question (3).*

  (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? ☐ Yes ☐ No

  (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))).

  *If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*

  (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).*

  *If "**No**," continue with question (5).*

  (5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? ☐ Yes ☐ No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). *If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).* *If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.*	
CONTENTS OF ACTION PACKAGE	
❖ Copy of this Action Package Checklist	X
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list.	X
❖ Documentation of consent/non-consent by officers/employees	X
Decisional Memos	
Office Director Decisional Memo *(indicate date for each review)*	
❖ Division Director Summary Review *(indicate date for each review)*	X 6-13-2008
❖ Cross-Discipline Team Leader Review *(indicate date for each review)*	X 5-2-2008, 6-12-2008
Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	X Action(s) and date(s)
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)	
• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)	
• Original applicant-proposed labeling • Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	X
❖ Patient Package Insert *(write submission/communication date at upper right of first page of PPI)*	
• Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling)	
• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)	
• Original applicant-proposed labeling	

• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	
❖ Medication Guide *(write submission/communication date at upper right of first page of MedGuide)*	
• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)	
• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)	
• Original applicant-proposed labeling	X
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date at upper right of first page of each submission)*	N/A Type 6 NDA
• Most-recent division proposal for (only if generated after latest applicant submission)	
• Most recent applicant-proposed labeling	
❖ Labeling reviews and any minutes of internal labeling meetings *(indicate dates of reviews and meetings)*	X RPM ☐ DMEDP ☐ DRISK ☐ DDMAC ☐ SEALD ☐ Other reviews ☐ Memos of Mtgs
Administrative Documents	
❖ Administrative Reviews (RPM Filing Review/Memo of Filing Meeting; ADRA) *(indicate date of each review)*	X
❖ NDA and NDA supplement approvals only: Exclusivity Summary *(signed by Division Director)*	X Included
• AIP-related documents • Center Director's Exception for Review memo • If approval action, OC clearance for approval	
❖ Pediatric Page *(a new Pediatric Page for each review cycle)*	X Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent. *(Include certification.)*	X Verified, statement is acceptable
❖ Postmarketing Commitment (PMC) Studies	☐ None
• Outgoing Agency request for postmarketing commitments *(if located elsewhere in package, state where located)*	X
• Incoming submission documenting commitment	X
❖ Postmarketing Requirement (PMR) Studies	☐ None
• Outgoing communications *(if located elsewhere in package, state where located)*	X
• Incoming submissions/communications	X
❖ Outgoing communications (letters (except previous action letters), emails, faxes, telecons)	X
❖ Internal memoranda, telecons, etc.	X
❖ Minutes of Meetings	
• Pre-Approval Safety Conference *(indicate date; approvals only)*	X Not applicable
• Regulatory Briefing	X No mtg
• Pre-NDA/BLA meeting *(indicate date)*	March 13, 2007 ☐ No mtg
• EOP2 meeting *(indicate date)*	July 28, 2004 ☐ No mtg

• Other (e.g., EOP2a, CMC pilot programs)	
Advisory Committee Meetings	X No AC meeting
• Date(s) of Meetings	
• 48-hour alert or minutes, if available	
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	
CMC/Quality Information	
❖ ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	X None
❖ PAL/BUD Review(s) *(indicate date for each review)*	05-20-2008 X None
❖ CMC/product quality review(s) *(indicate date for each review)*	X None
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date for each review)*	X None
❖ BLAs: Product subject to lot release (APs only)	☐ Yes ☐ No
❖ Environmental Assessment (check one) (original and supplemental applications)	
• ☐ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	
• ☐ Review & FONSI *(indicate date of review)*	5-13-2008
• ☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ NDAs: Microbiology reviews (sterility & apyrogenicity) *(indicate date of each review)*	☐ Not a parenteral product
❖ Facilities Review/Inspection	
❖ NDAs: Facilities inspections (include EER printout) N/A	Date completed: ☐ Acceptable ☐ Withhold recommendation
❖ BLAs: Facility-Related Documents • Facility review *(indicate date(s))* • Compliance Status Check (approvals only, both original and all supplemental applications (except CBEs)) *(indicate date completed, must be within 60 days prior to AP)*	☐ Requested ☐ Accepted ☐ Hold
❖ NDAs: Methods Validation	☐ Completed ☐ Requested ☐ Not yet requested X Not needed
Nonclinical Information	
❖ ADP/T Review(s) *(indicate date for each review)*	☐ None
❖ Supervisory Review(s) *(indicate date for each review)*	☐ None
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	10-3-07 X None
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☐ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	X No carc
❖ ECAC/CAC report/memo of meeting	Included in P/T review, page
❖ Nonclinical inspection review summary (DSI)	☐ None requested

Clinical Information	
❖ Clinical Team Leader Review(s) *(indicate date for each review)*	5-2-08
❖ Clinical review(s) *(indicate date for each review)*	4-25-08
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR ❖ If no financial disclosure information was required, review/memo explaining why not	Clinical Page-14
❖ Clinical reviews from other review disciplines/divisions/Centers *(indicate date of each review)*	
❖ Clinical microbiology reviews(s) *(indicate date of each review)*	X Not needed
❖ Safety update review(s) *(indicate location/date if incorporated into another review)*	
❖ REMS review(s) (including those by OSE) *(indicate location/date if incorporated into another review)*	
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date of each review)*	X Not needed
❖ DSI Inspection Review Summary(ies) *(include copies of DSI letters to investigators)*	☐ None requested
• Clinical Studies	X
• Bioequivalence Studies	
• Clinical Pharmacology Studies	
Biostatistics	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☐ None
❖ Statistical Team Leader Review(s) *(indicate date for each review)*	☐ None
❖ Statistical Review(s) *(indicate date for each review)*	5-1-08 ☐ None
Clinical Pharmacology	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☐ None
❖ Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☐ None
❖ Clinical Pharmacology review(s) *(indicate date for each review)*	4-16-08 ☐ None

Appendix A to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

(1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.

(2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.

(3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations(see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).

(2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.

(3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).

(2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.

(3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's ADRA or the OND ADRA.

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/s/

Parinda Jani
6/13/2008 05:43:36 PM

Division of Anesthesia, Analgesia, and Rheumatology Products

REGULATORY PROJECT MANAGER REVIEW

Application Number: NDA 22-148
Name of Drug: Cymbalta (duloxetine HCl) Delayed-Release Capsules
Applicant: Eli Lilly

Material Reviewed:

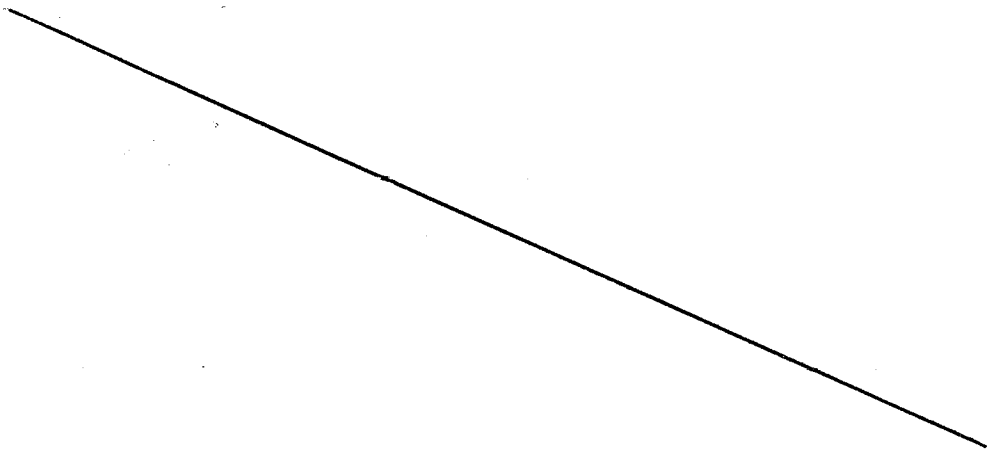
Submission Date(s): August 14, 2007 (original) and June 10, 2008
Receipt Date(s): August 14, 2007 and June 10, 2008
Reviews Completed: Parinda Jani, CPMS

Background and Summary: NDA 22-148 is a Type 6 NDA to expand the indication for Cymbalta for the management of fibromyalgia. NDA 21-427 for Cymbalta is already approved for the treatment of Major Depressive Disorder (MDD), General Anxiety Disorder (GAD), and Diabetic Peripheral Neuropathic Pain (DPNP).

The revised label submitted on June 10, 2008, was compared to the one approved by DPP on November 28, 2007 (NDA 21-427/S-015 and S-017). In addition, a Supplement Request letter was sent to the sponsor on June 4, 2008, to revise and strengthen the Hepatotoxicy (5.2) subsection of WARNINGS AND PRECAUTIONS section. The sponsor agreed to incorporate the proposed language in their final proposed labeling.

Review

Please note that the sponsor's proposed omissions are indicated by strikeovers, inclusions by underlined text



9 Page(s) Withheld

✓ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Administrative- 1

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/s/

Parinda Jani
6/13/2008 04:44:50 PM
CSO

From: Bryan E Boggs [mailto:BOGGS_BRYAN_E@LILLY.COM]
Sent: Wednesday, June 11, 2008 3:16 PM
To: Jani, Parinda
Subject: RE: Lilly NDA 22-148

Hi Parinda,

Lilly accepts this change.

Regards,
Bryan

"Jani, Parinda" <parinda.jani@fda.hhs.gov>

06/11/2008 02:34 PM

To "Bryan E Boggs" <BOGGS_BRYAN_E@LILLY.COM>
cc
Subject RE: Lilly NDA 22-148

Hi Bryan:

We would like you to revise the statement in the Clinical Trials section as follows:

Pain reduction was observed in patients both with and without comorbid MDD. However, the degree of pain reduction may be greater in patients with comorbid MDD.

Let me know, if we need further discussion.

Thanks

Parinda

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/s/

Parinda Jani
6/13/2008 08:43:53 AM
CSO

Jani, Parinda

From: Jani, Parinda
Sent: Thursday, June 05, 2008 10:50 PM
To: Dent, Ricardo; Winchell, Celia J; Hertz, Sharon H
Cc: Rappaport, Bob A
Subject: FW: proposed revisions to CYmbalta label

Attachments: proposedFDA version.6-5-08.pdf

FYI

I will DFS this on Monday, too tired to do it now. Please let me know what PMC you want. I can forward it to Lilly tomorrow.

From: Jani, Parinda
Sent: Thursday, June 05, 2008 10:47 PM
To: 'Bryan E Boggs'
Subject: proposed revisions to CYmbalta label

proposedFDA version.6-5-08.pdf...

Hi Bryan:

ached is a marked-up version of the proposed labeling changes. We will be happy to discuss the changes with you lier next week.

Regards,

Parinda

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/s/

Parinda Jani
6/11/2008 10:22:53 AM
CSO

Jani, Parinda

From: Jani, Parinda
Sent: Monday, June 09, 2008 5:30 PM
To: 'Bryan E Boggs'
Subject: FW: Sponsor Request 06-09-08.doc

Attachments: Sponsor Request 06-09-08.doc

Hi Bryan:

As discussed:

1. Tables/graphs from Dr. Buenconsejo's statistical review.

Sponsor Request 06-09-08.doc (...

2. In addition, under Highlights of prescribing information:

WARNINGS AND PRECAUTIONS

Instead, include all the terms from Section 5.6: dizziness, nausea, headache, fatigue, paresthesia, vomiting, irritability, nightmares, insomnia, diarrhea, anxiety, hyperhidrosis and vertigo.

3. The MHT recommends that you develop and maintain a prospective, observational pregnancy exposure registry conducted in the United States that compares the pregnancy and fetal outcomes of women exposed to duloxetine (for any indication) during pregnancy to an unexposed control population.

The registry should be conducted as a post-marketing requirement (PMR under FDAAA). The outcomes of the registry should include major and minor congenital anomalies, spontaneous abortions, stillbirths, elective terminations, and other serious adverse pregnancy outcomes. These outcomes should be assessed throughout pregnancy. Infant outcomes should be assessed through at least the first year of life. The MHT would be happy to review the draft pregnancy registry protocol.

guidance on how to establish a pregnancy exposure registry, review the Guidance for Industry on Establishing Pregnancy Exposure Registries available at http://www.fda.gov/cder/guidance/3626fnl.htm.

4. In addition, as Dr. Winchell stated, we would like you to evaluate efficacy of Cymbalta at a lower dose,

i.e. 20 - 30 mg/day for the treatment of fibromyalgia. Please send your proposal in the following format.

Conduct a randomized, double-blind, placebo-controlled study of Cymbalta at a dose of 20 – 30 mg p day in the treatment of fibromyalgia.

Protocol submission:	XXX
Study Start	xxxxxx
Final report	XXX

5. Also, please include the MEDGUIDE with your submission. Eventhough there are no changes, it is part of the label.

Let me know if you need further clarification, I will be available by BB.

Regards,

Parinda

For the 20 mg QD (Study HMCJ):

Table 17: Brief Pain Inventory Average Pain Score Mean Change from Baseline to Endpoint at Endpoint: All Randomized Patients in the 3-Month Therapy Phase Placebo-Controlled Studies: F1J-MC-HMBO, F1J-MC-HMCA, and F1J-MC-HMCJ

Study	Treatment Group	BPI Average Pain Score (BOCF)			BPI Average Pain Score (LOCF/BOCF)	
		Baseline	LSMean Change	p-value	LSMean Change	p-value
HMBO*	Placebo	6.11	-0.7		-0.6	
	Duloxetine 60 mg BID	6.13	-1.2	0.067	-1.2	0.049
HMCA	Placebo	6.52	-0.9		-1.0	
	Duloxetine 60 mg QD	6.37	-2.1	<0.001†	-2.2	<0.001†
	Duloxetine 60 mg BID	6.37	-1.8	0.001	-2.1	<0.001
HMCJ	Placebo	6.58	-1.1		-1.2	
	Duloxetine 20 mg QD	6.77	-1.6	0.135†	-1.9	0.039†
	Duloxetine 60 mg QD	6.49	-1.6	0.065	-1.8	0.036
	Duloxetine 120 mg QD	6.59	-1.7	0.036	-1.8	0.038

†unadjusted p-value.

Figure 5: Overall Response Profile for Study HMCJ at 3 months

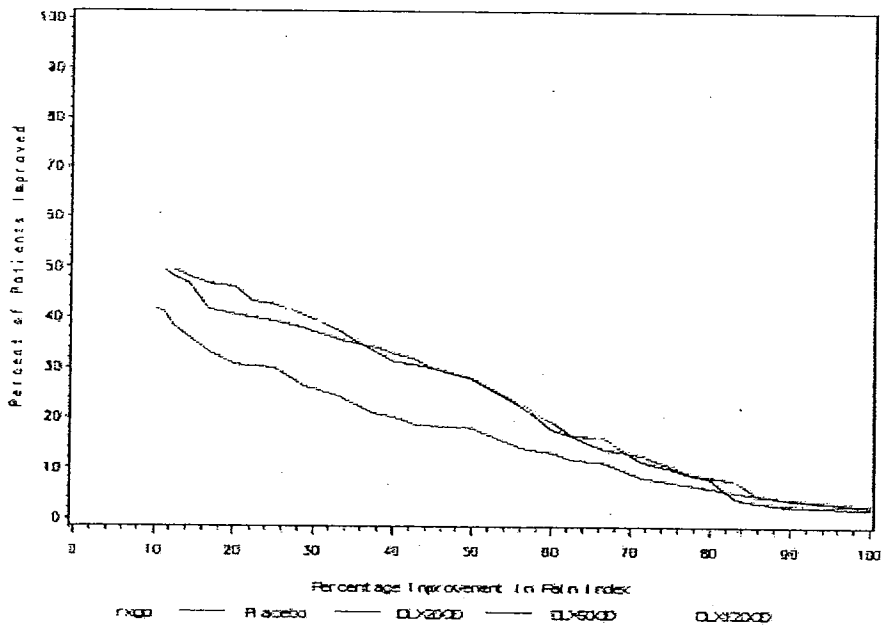


Table 20: Responder Analysis of Brief Pain Inventory Average Pain Score at Endpoint: All Randomized Patients in the 3-Month Therapy Phase Placebo-Controlled Studies: F1J-MC-HMCA, and F1J-MC-HMCJ

		≥ 30% Improvement in Pain			≥ 50% Improvement in Pain	
Study	Treatment Group	N	n(%)	p-value	n(%)	p-value
HMCA	Placebo	120	24 (20%)		18 (15%)	
	Duloxetine 60 mg QD	118	54 (46%)	<0.001	42 (36%)	<0.001
	Duloxetine 60 mg BID	116	45 (39%)	0.002	36 (31%)	0.003
HMCJ	Placebo	144	37 (26%)		26 (18%)	
	Duloxetine 20 mg QD	79	28 (35%)	0.126	22 (28%)	0.089
	Duloxetine 60 mg QD	150	56 (37%)	0.032	42 (28%)	0.043
	Duloxetine 120 mg QD	147	57 (39%)	0.017	44 (30%)	0.018

Table 25: Responder Profile at Endpoint based on responder analysis at three months: All Randomized Patients in the 6-Month Therapy Phase Placebo-Controlled Study: F1J-MC-HMCJ

	Responders at 3 months			NonResponders at 3 months	
Treatment Group	N	Remained Responders at 6 months	Became non-responders at 6 months	N	Became responders at 6 months
Placebo	37	27 (73%)	10 (27%)	107	10 (9%)
Duloxetine 20/60 mg QD	28	22 (79%)	6 (21%)	51	8 (16%)
Duloxetine 60 mg QD	56	34 (61%)	22 (39%)	94	8 (9%)
Duloxetine 120 mg QD	57	35 (61%)	22 (39%)	90	12 (13%)

For the MDD Status:

Table 41: Endpoint Mean Pain Score Analysis: All Randomized Patients in the 3-Month Therapy Phase Placebo-Controlled Studies by Major Depressive Disorder Status: F1J-MC-HMCA and F1J-MC-HMCJ

		No MDD			With MDD		
Study	Treatment Group	N	Baseline	LSMean Change *	N	Baseline	LSMean change *
			BOCF				
HMCA	Placebo	88	6.3	-1.0	32	7.2	-0.7
	Duloxetine 60 mg QD	89	6.3	-1.9	29	6.7	-2.8
	Duloxetine 60 mg BID	84	6.2	-1.6	32	6.8	-2.5
HMCJ	Placebo	109	6.4	-1.1	35	7.0	-1.4
	Duloxetine 20 mg QD	57	6.6	-1.4	22	7.2	-2.0
	Duloxetine 60 mg QD	115	6.4	-1.5	35	6.7	-2.1
	Duloxetine 120 mg QD	113	6.3	-1.6	34	6.6	-2.1
			LOCF/BOCF				
HMCA	Placebo	88	6.3	-1.1	32	7.2	-0.9
	Duloxetine 60 mg QD	89	6.3	-1.9	29	6.7	-3.0
	Duloxetine 60 mg BID	84	6.2	-1.8	32	6.8	-3.1
HMCJ	Placebo	109	6.4	-1.2	35	7.0	-1.3
	Duloxetine 20 mg QD	57	6.6	-1.6	22	7.2	-2.5
	Duloxetine 60 mg QD	115	6.4	-1.6	35	6.7	-2.4
	Duloxetine 120 mg QD	113	6.3	-1.6	34	6.6	-2.2

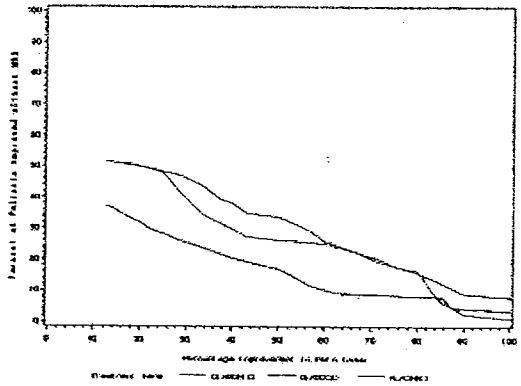
*ANCOVA model including treatment and pooled center as fixed effects, and baseline pain score as covariate

Table 42: Responder Analysis of Brief Pain Inventory Average Pain Score at Endpoint: All Randomized Patients in the 3-Month Therapy Phase Placebo-Controlled Studies: F1J-MC-HMCA and F1J-MC-HMCJ

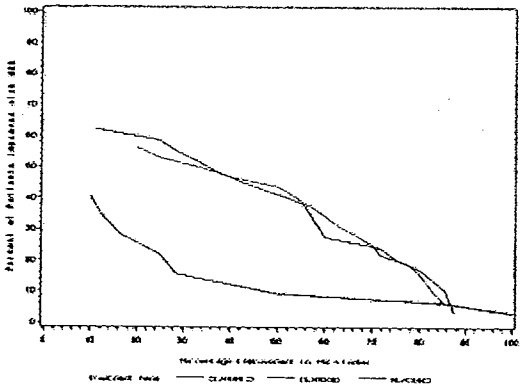
Study		Treatment Group	N	≥ 30% Improvement in Pain n(%)	≥ 50% Improvement in Pain n(%)
HMCA					
	Without MDD	Placebo	88	21 (24%)	15 (17%)
		Duloxetine 60 mg QD	89	39 (44%)	30 (34%)
		Duloxetine 60 mg BID	84	29 (35%)	22 (26%)
	With MDD	Placebo	32	3 (9%)	3 (9%)
		Duloxetine 60 mg QD	29	15 (52%)	12 (41%)
		Duloxetine 60 mg BID	32	16 (50%)	14 (44%)
HMCJ					
	Without MDD	Placebo	109	30 (28%)	22 (20%)
		Duloxetine 20 mg QD	57	19 (33%)	14 (25%)
		Duloxetine 60 mg QD	115	41 (36%)	33 (29%)
		Duloxetine 120 mg QD	113	43 (38%)	34 (30%)
	With MDD	Placebo	35	7 (20%)	4 (11%)
		Duloxetine 20 mg QD	22	9 (41%)	8 (36%)
		Duloxetine 60 mg QD	35	15 (43%)	9 (26%)
		Duloxetine 120 mg QD	34	14 (41%)	10 (29%)

Figure 15: Responder Profiles for HMCA

Without MDD



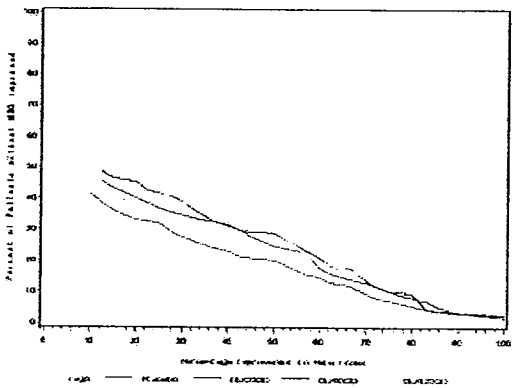
With MDD



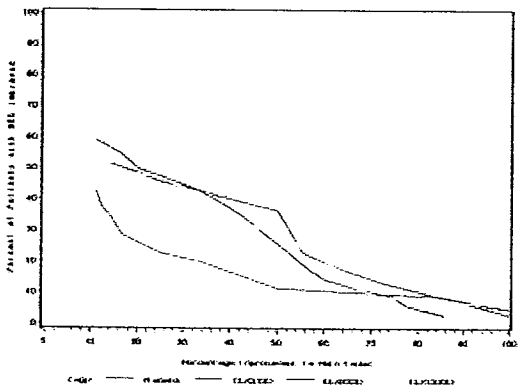
Red: DLX60BID, Blue: DLX60QD, Black: Placebo

Figure 16: Responder Profiles for HMCJ

Without MDD



With MDD



Red: Placebo, Blue: DLX20QD, Black: DLX60QD, Yellow: DLX120QD

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/s/

Parinda Jani
6/11/2008 10:17:43 AM
CSO

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

REQUEST FOR CONSULTATION

TO *(Office/Division)*: Dr. John Senior, OSE	FROM *(Name, Office/Division, and Phone Number of Requestor)*: Parinda Jani Division of Anesthesia, ANalgesia, and Rheumatology Products

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
06-10-08		22-148	Type 6 NDA	August 14, 2007

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Cymbalta	P	6S	6-11-08

NAME OF FIRM: Lilly

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- OTOCOL REVIEW
- HER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: Cymbalta (dyuloxetine) is approved for the treatment of Major Depressive Disorder, General Anxiety Disorder, and Neuropathic Pain. Cymbalta is currently under review for the Fibromyalgia. Cymbalta has been shown to be effective as a treatment for fibromyalgia at doses of 60 mg/day and 120 mg/day; however, no incremental benefit has been shown for the 120 mg/dose. Although few adverse events appeared to be clearly more common at the 120 mg/day dose compared to the 60 mg/day dose, the Division believes that the hepatic effects of duloxetine are sufficient grounds to clearly communicate to prescribers that there is no reason to titrate the dose above 60 mg/day.

Specifically, Lilly states that the hepatic effects of duloxetine are idiosyncratic, and not dose-related.

Please comment on whether the hepatic effects of duloxetine are dose-dependent, and justify discouraging up-titration of the dose beyond the minimum effective dose.

The proposed label in in the EDR
\\Cdsesub1\evsprod\NDA022148\0005\m1\us\us-regional.xml
Copy of the CDTL memo by Dr. Winchell is attached.

If you have any questions call Parinda Jani at (301) 796-1232

SIGNATURE OF REQUESTOR	METHOD OF DELIVERY (Check one) ☐ DFS ☐ EMAIL ☐ MAIL ☐ HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

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Parinda Jani
6/10/2008 11:22:30 AM

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

REQUEST FOR CONSULTATION

...ffice/Division): Office of Maternal Health

FROM (*Name, Office/Division, and Phone Number of Requestor*): Parinda Jani
Division of Anesthesia, ANalgesia, and Rheumatology Products

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
05-20-08		22-148	Type 6 NDA	August 14, 2007

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Cymbalta	P	6S	6-2-08

NAME OF FIRM: Lilly

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ ONTROLLED STUDIES
- ☐ .OTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: Cymbalta (dyuloxetine) is approved for the treatment of Major Depressive Disorder, General Anxiety Disorder, and Neuropathic Pain. Cymbalta is currently under review for the of Fibromyalgia, a condition which occurs in women of child-bearing age. Please provide advice on the need for, and nature of, a post-marketing pregnancy registry study"

The proposed label in in the EDR
\\Cdsesub1\evsprod\NDA022148\0005\m1\us\us-regional.xml
...y of the CDTL memo by Dr. Winchell is attached.

If you have any questions call Parinda Jani at (301) 796-1232

SIGNATURE OF REQUESTOR	METHOD OF DELIVERY (Check one)

	☐ DFS ☐ EMAIL ☐ MAIL ☐ HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

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

/s/

Parinda Jani
5/20/2008 01:01:44 PM

NDA REGULATORY FILING REVIEW

(Including Memo of Filing Meeting)

NDA # 22-148 Supplement # Efficacy Supplement Type SE-

Proprietary Name: Cymbalta
Established Name: duloxetine hydrochloride Capsules
Strengths: 20, 30, — and 60 mg

Applicant: Eli Lilly and Company
Agent for Applicant (if applicable):

Date of Application: August 14, 2007
Date of Receipt: August 14, 2007
Date clock started after UN:
Date of Filing Meeting: September 26, 2007
Filing Date: October 13, 2007
Action Goal Date (optional): User Fee Goal Date: June 14, 2008

Indication(s) requested: For the ——— of fibromyalgia

Type of Original NDA: (type 6 NDA) (b)(1) X (b)(2)
AND (if applicable)
Type of Supplement: (b)(1) (b)(2)

NOTE:

(1) If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application or efficacy supplement is a (b)(2), complete Appendix B.

Review Classification: S X P ☐
Resubmission after withdrawal? ☐ Resubmission after refuse to file? ☐
Chemical Classification: (1,2,3 etc.) 1
Other (orphan, OTC, etc.)

Form 3397 (User Fee Cover Sheet) submitted: YES X NO ☐

User Fee Status: Paid X Exempt (orphan, government) ☐
Waived (e.g., small business, public health) ☐

NOTE: *If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required by contacting the User Fee staff in the Office of Regulatory Policy. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application. Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the User Fee staff.*

- Is there any 5-year or 3-year exclusivity on this active moiety in any approved (b)(1) or (b)(2) application? YES X NO ☐

If yes, explain: (b)(1) exclusivity. Eli Lilly has this drug approved for: Major Depressive Disorder, Diabetic Peripheral Neuropathic Pain, and Generalized Anxiety Disorder

Note: If the drug under review is a 505(b)(2), this issue will be addressed in detail in appendix B.

- Does another drug have orphan drug exclusivity for the same indication? YES ☐ NO X

- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?

YES ☐ NO X

If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES ☐ NO X
If yes, explain:

- If yes, has OC/DMPQ been notified of the submission? YES ☐ NO ☐

- Does the submission contain an accurate comprehensive index? YES X NO ☐
If no, explain:

- Was form 356h included with an authorized signature? YES X NO ☐
If foreign applicant, both the applicant and the U.S. agent must sign.

- Submission complete as required under 21 CFR 314.50? YES X NO ☐
If no, explain:

- Answer 1, 2, or 3 below (do not include electronic content of labeling as an partial electronic submission).

1. This application is a paper NDA YES ☐

2. This application is an eNDA or combined paper + eNDA YES ☐
This application is: All electronic ☐ Combined paper + eNDA ☐
This application is in: NDA format ☐ CTD format ☐
Combined NDA and CTD formats ☐

Does the eNDA, follow the guidance?
(http://www.fda.gov/cder/guidance/2353fnl.pdf) YES ☐ NO ☐

If an eNDA, all forms and certifications must be in paper and require a signature.

If combined paper + eNDA, which parts of the application were submitted in electronic format?

Additional comments:

3. This application is an eCTD NDA. YES X
If an eCTD NDA, all forms and certifications must either be in paper and signed or be electronically signed.

Additional comments:

- Patent information submitted on form FDA 3542a? YES X NO ☐

- Exclusivity requested? YES, X 3 Years NO ☐
NOTE: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.

- Correctly worded Debarment Certification included with authorized signature? YES X[NO ☐
If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

NOTE: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge . . . ."

- Are the required pediatric assessment studies and/or deferral/partial waiver/full waiver of pediatric studies (or request for deferral/partial waiver/full waiver of pediatric studies) included?
YES X NO ☐

- If the submission contains a request for deferral, partial waiver, or full waiver of studies, does the application contain the certification required under FD&C Act sections 505B(a)(3)(B) and (4)(A) and (B)?
YES X NO ☐

- Is this submission a partial or complete response to a pediatric Written Request? YES ☐ NO X

If yes, contact PMHT in the OND-IO

- Financial Disclosure forms included with authorized signature? YES X NO ☐
(Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an agent.)
NOTE: *Financial disclosure is required for bioequivalence studies that are the basis for approval.*

- Field Copy Certification (that it is a true copy of the CMC technical section) YES X NO ☐

- PDUFA and Action Goal dates correct in tracking system? YES X NO ☐
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.

- List referenced IND numbers: 63,615

- Are the trade, established/proper, and applicant names correct in COMIS? YES X NO ☐
If no, have the Document Room make the corrections.

- End-of-Phase 2 Meeting(s)? Date(s) July 28, 2004 NO ☐
If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) April 13, 2007 NO ☐
If yes, distribute minutes before filing meeting.

- Any SPA agreements? Date(s) _____ NO X
  If yes, distribute letter and/or relevant minutes before filing meeting.

Project Management

- If Rx, was electronic Content of Labeling submitted in SPL format? YES X NO ☐
  If no, request in 74-day letter.

- If Rx, for all new NDAs/efficacy supplements submitted on or after 6/30/06:
  Was the PI submitted in PLR format? YES X NO ☐

  If no, explain. Was a waiver or deferral requested before the application was received or in the submission? If before, what is the status of the request:

- If Rx, all labeling (PI, PPI, MedGuide, carton and immediate container labels) has been consulted to DDMAC? YES X NO ☐

- If Rx, trade name (and all labeling) consulted to OSE/DMETS? YES ☐ NO X

- If Rx, MedGuide and/or PPI (plus PI) consulted to ODE/DSRCS?
  N/A X YES ☐ NO ☐

- Risk Management Plan consulted to OSE/IO? N/A X YES ☐ NO ☐

- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling submitted? NA X YES ☐ NO ☐

If Rx-to-OTC Switch or OTC application:

- Proprietary name, all OTC labeling/packaging, and current approved PI consulted to OSE/DMETS? YES ☐ NO ☐

- If the application was received by a clinical review division, has DNPCE been notified of the OTC switch application? Or, if received by DNPCE, has the clinical review division been notified? YES ☐ NO ☐

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff?
  YES ☐ NO X

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES ☐ NO X
  If no, did applicant submit a complete environmental assessment? YES X NO ☐
  If EA submitted, consulted to EA officer, OPS? YES X NO ☐
- Establishment Evaluation Request (EER) submitted to DMPQ? YES X NO ☐

- If a parenteral product, consulted to Microbiology Team? YES ☐ NO ☐

ATTACHMENT

MEMO OF FILING MEETING

DATE: September 26, 2007

NDA #: 22-148

DRUG NAMES: Cymbalta

APPLICANT: Eli Lilly and Company

BACKGROUND: This is a Type-6 NDA. The product is approved under NDA 21-427/for Major Depressive Disorder and General Anxiety Disorder (HFD-130), and NDA 21-733 (HFD-170) for Diabetic Peripheral Neuropathic Pain. This indication in this NDA is for the ——— of Fibromyalgia.

ATTENDEES: Ricardo Dent, Celia Winchell, Sharon Hertz, Bob Rappaport, Joan Buenconsejo, Dionne Price, Srikanth Nallani, Suresh Doddapaneni, Kathleen Young, Ramesh Raghvachari

ASSIGNED REVIEWERS (including those not present at filing meeting) :

Discipline/Organization	**Reviewer**
Medical:	Ricardo Dent
Secondary Medical:	Celia Winchell
Statistical:	Joan Buenconsejo
Pharmacology:	Kathleen Young
Statistical Pharmacology:	N/A
Chemistry:	Ramesh Raghvachari
Environmental Assessment (if needed):	Rannan
Biopharmaceutical:	Srikanth Nallani
Microbiology, sterility:	N/A
Microbiology, clinical (for antimicrobial products only):	N/A
DSI:	Sherbet Samuels
OPS:	
Regulatory Project Management:	Parinda Jani
Other Consults:	

Per reviewers, are all parts in English or English translation? YES X NO ☐
If no, explain:

CLINICAL FILE X REFUSE TO FILE ☐

- Clinical site audit(s) needed? YES X NO ☐
  If no, explain:
- Advisory Committee Meeting needed? YES, date if known _____ NO X

- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?

N/A X YES ☐ NO ☐

CLINICAL MICROBIOLOGY	N/A	X	FILE	☐	REFUSE TO FILE	☐
STATISTICS	N/A	☐	FILE	X	REFUSE TO FILE	☐
BIOPHARMACEUTICS			FILE	X	REFUSE TO FILE	☐

- Biopharm. study site audits(s) needed? ☐ YES ☐ NO X

PHARMACOLOGY/TOX	N/A	X	FILE	☐	REFUSE TO FILE	☐

- GLP audit needed? YES ☐ NO ☐

CHEMISTRY			FILE	X	REFUSE TO FILE	☐

- Establishment(s) ready for inspection? YES X NO ☐
- Sterile product? YES ☐ NO X
  If yes, was microbiology consulted for validation of sterilization? YES ☐ NO ☐

ELECTRONIC SUBMISSION:
Any comments:

REGULATORY CONCLUSIONS/DEFICIENCIES:
(Refer to 21 CFR 314.101(d) for filing requirements.)

☐ The application is unsuitable for filing. Explain why:

☐ The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.

- ☐ No filing issues have been identified.
- X Filing issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

1. ☐ Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into COMIS.
2. ☐ If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.
3. ☐ If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
4. ☐ If filed, complete the Pediatric Page at this time. (If paper version, enter into DFS.)
5. ☐ Convey document filing issues/no filing issues to applicant by Day 74.

Parinda Jani
Regulatory Project Manager
Version 6/14/2006

Appendix A to NDA Regulatory Filing Review

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

(1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
(2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations(see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),

(2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.

(3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the

original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),

(2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or

(3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's Office of Regulatory Policy representative.

Appendix B to NDA Regulatory Filing Review
Questions for 505(b)(2) Applications

1. Does the application reference a listed drug (approved drug)? YES ☐ NO ☐

*If "**No**," skip to question 3.*

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s):

3. Is this application for a drug that is an "old" antibiotic (as described in the draft guidance implementing the 1997 FDAMA provisions? (Certain antibiotics are not entitled to Hatch-Waxman patent listing and exclusivity benefits.)

YES ☐ NO ☐

*If "**Yes**," skip to question 7.*

4. Is this application for a recombinant or biologically-derived product?

YES ☐ NO ☐

*If "**Yes** "contact your ODE's Office of Regulatory Policy representative.*

5. The purpose of the questions below (questions 5 to 6) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

   (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved?

   YES ☐ NO ☐

   (***Pharmaceutical equivalents*** are drug products in identical dosage forms that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and** **(3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))

*If "**No**," to (a) skip to question 6. Otherwise, answer part (b and (c)).*

   (b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval? YES ☐ NO ☐

   (c) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)? YES ☐ NO ☐

*If "**Yes**," (c), list the pharmaceutical equivalent(s) and proceed to question 6.*

*If "**No**," to (c) list the pharmaceutical equivalent and contact your ODE's Office of Regulatory Policy representative.*
Pharmaceutical equivalent(s):

6. (a) Is there a pharmaceutical alternative(s) already approved? YES ☐ NO ☐

(***Pharmaceutical alternatives*** are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

*If "**No**," to (a) skip to question 7. Otherwise, answer part (b and (c)).*

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval? YES ☐ NO ☐

(c) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? YES ☐ NO ☐

*If "**Yes**," to (c), proceed to question 7.*

***NOTE:** If there is more than one pharmaceutical alternative approved, consult your ODE's Office of Regulatory Policy representative to determine if the appropriate pharmaceutical alternatives are referenced.*

*If "**No**," to (c), list the pharmaceutical alternative(s) and contact your ODE's Office of Regulatory Policy representative. Proceed to question 7.*

Pharmaceutical alternative(s):

7. (a) Does the application rely on published literature necessary to support the proposed approval of the drug product (i.e. is the published literature necessary for the approval)? YES ☐ NO ☐

*If "**No**," skip to question 8. Otherwise, answer part (b).*

(b) Does any of the published literature cited reference a specific (e.g. brand name) product? Note that if yes, the applicant will be required to submit patent certification for the product, see question 12.

8. Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution").

9. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA may refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)). YES ☐ NO ☐

10. Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application may be refused for filing under 21 CFR 314.101(d)(9)). YES ☐ NO ☐

11. Is the application for a duplicate of a listed drug whose only difference is YES ☐ NO ☐

that the rate at which the product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application may be refused for filing under 21 CFR 314.101(d)(9).

12. Are there certifications for each of the patents listed in the Orange Book for the listed drug(s) referenced by the applicant (see question #2)? (This is different from the patent declaration submitted on form FDA 3542 and 3542a.) YES ☐ NO ☐

13. Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

☐ Not applicable (e.g., solely based on published literature. See question # 7

☐ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)
Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)
Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)
Patent number(s):

NOTE: *IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must* ***subsequently*** *submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]. The applicant must also submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]. OND will contact you to verify that this documentation was received.*

☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).
Patent number(s):

☐ Written statement from patent owner that it consents to an immediate effective date upon approval of the application.
Patent number(s):

☐ 21 CFR 314.50(i)(1)(ii): No relevant patents.

☐ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)
Patent number(s):

14. Did the applicant:

- Identify which parts of the application rely on the finding of safety and effectiveness for a listed drug or published literature describing a listed drug or both? For example, pharm/tox section of application relies on finding of preclinical safety for a listed drug.

  YES ☐ NO ☐

  *If "**Yes**," what is the listed drug product(s) and which sections of the 505(b)(2) application rely on the finding of safety and effectiveness or on published literature about that listed drug*
  Was this listed drug product(s) referenced by the applicant? (see question # 2)

  YES ☐ NO ☐

- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug(s)?

  N/A ☐ YES ☐ NO ☐

15. (a) Is there unexpired exclusivity on this listed drug (for example, 5 year, 3 year, orphan or pediatric exclusivity)? Note: this information is available in the Orange Book.

YES ☐ NO ☐

If "**Yes**," please list:

Application No.	Product No.	Exclusivity Code	Exclusivity Expiration

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

/s/

Parinda Jani
4/18/2008 01:42:08 PM
CSO

M E M O R A N D U M

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

CLINICAL INSPECTION SUMMARY

DATE: March 14, 2008

TO: Lisa Malandro, Regulatory Project Manager
Ricardo E. Dent, Medical Officer

FROM: Sherbet Samuels, R.N., M.P.H.
Good Clinical Practice Branch I
Division of Scientific Investigations

THROUGH: Constance Lewin, M.D., Ph.D.
Branch Chief, Good Clinical Practice Branch I
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA #: 22-148

APPLICANT: Eli Lilly and Company

DRUG: Cymbalta (duloxetine hydrochloride)

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATIONS: ——— of fibromyalgia

CONSULTATION REQUEST DATE: 11/29/07

DIVISION ACTION GOAL DATE: June 9, 2008

PDUFA DATE: June 13, 2008

I. BACKGROUND:

Duloxetine is a serotonin and norepinephrine reuptake inhibitor (SNRI) approved in the United States and marketed by Eli Lilly for treatment of major depressive disorder (MDD), diabetic peripheral neuropathic pain (DPNP), and generalized anxiety disorder (GAD). The sponsor, Eli Lilly and Company, submitted a new drug application for marketing approval of Cymbalta

for ——— of fibromyalgia. Drs. Leslie Arnold, Timothy Smith, Jeffrey Gitt, Richard Weinstein, James Knutson, and Patricia Buchanan were selected for inspection due to enrollment of a large number of subjects, large number of protocol violations, and high treatment responders at their sites. In addition, ——————— was inspected because ——reported an equity interest of greater than $500,000 in Eli Lilly. The goals of the inspections were to assess adherence to FDA regulatory requirements; specifically, investigator oversight, protocol compliance, accuracy of primary efficacy endpoint data, and protection of subjects' rights, safety, and welfare.

In February 2008, the sponsor notified DSI that they became aware of a programming error in preparing site specific audit materials for adverse events. The sponsor informed DSI that the error stemmed from programming mistakes and there were no issues with the underlying data sets. The sponsor representative (Mr. Bryan Boggs) stated that he is confident that the SAS transport files provided within the sNDA submission are unaffected by this programming error.

The protocols inspected include:

F1J-MC-HMBO (a) entitled "Duloxetine versus Placebo in the Treatment of Fibromyalgia Patients with or without Major Depressive Disorder"
F1J-MC-HMCA entitled "Duloxetine Versus Placebo in the Treatment of Fibromyalgia Patients With or Without Major Depressive Disorder"
F1J-MC-HMCJ entitled "Dose Response Study of Duloxetine Versus Placebo in the Treatment of Fibromyalgia Syndrome"

II. RESULTS (by Site):

Name of CI, IRB, or Sponsor City, State or Country	Indication: Protocol #:	Insp. Date	Final Classification
Leslie Arnold, M.D. 231 Albert Sabin Way Cincinnati, OH 45267-0559	F1J-MC-HMBO(a) F1J-MC-HMCA F1J-MC-HMCJ	February 2-March 3, 2008	Pending
Jeffrey Gitt, M.D. 13832 N. 32nd Street, Suite #150 Phoenix, AZ 85032	F1J-MC-HMCA F1J-MC-HMCJ	January 23-February 18, 2008	Pending
Richard Weinstein, M.D. 2255 Ygnacio Valley Road, Suite K-1 Walnut Creek, CA 94598	F1J-MC-HMBO(a) F1J-MC-HMCA F1J-MC-HMCJ	January 23-February 15, 2008	Pending
James Knutson, M.D. 10200 N.E. 132nd Street Kirkland, WA 98034	F1J-MC-HMCJ	January 14-29, 2008	Pending

Timothy Smith, M.D. 1585 Woodlake Drive Chesterfield, MO 63017	F1J-MC-HMCA F1J-MC-HMCJ	February 7-14, 2008	Pending
Patricia Buchanan, M.D. 890 River Road Eugene, OR 97404	F1J-MC-HMCA F1J-MC-HMCJ	March 3-14, 2008	Pending

Key to Classifications
NAI = No deviation from regulations.
VAI-No Response Requested= Deviations(s) from regulations.
VAI-R = Response Requested = Deviation(s) from regulations.
OAI = Significant deviations from regulations.
Pending = Preliminary classification based on information in 483; EIR has not been received from the field and/or complete review of EIR is pending.

Note: Although the division action goal date is not until June 9, 2008, the CIS is being submitted at this time, while receipt of all EIRs is still pending, at the request of the review division. Observations noted below for each clinical investigator are based on the Form FDA 483 and communications with the field investigator. An addendum to this clinical inspection summary will be forwarded to the review division should there be a change in the final classification or additional observations of clinical and regulatory significance are discovered after reviewing the establishment inspection reports (EIRs).

1. Leslie Arnold, M.D.
   231 Albert Sabin Way
   Cincinnati, OH 45267-0559

   a. **What was inspected**: For protocol F1J-MC-HMCA, 59 subjects were screened, 22 subjects were enrolled, and 12 subjects completed the study. Primary efficacy data for all subjects were reviewed. An in-depth review of 11 subjects' records was performed. For protocol F1J-MC-HMCJ, 37 subjects were screened, 22 subjects were enrolled, and 14 subjects completed the study. Primary efficacy data for all subjects were reviewed. An in-depth review of 10 subjects' records was performed.

      For protocol F1J-MC-HMBO(a), 51 subjects were screened, 17 subjects were enrolled, and 13 subjects completed the study. Primary efficacy data for all subjects were reviewed. An in-depth review of 8 subjects' records was performed. The records reviewed for each study included case report forms, source documents, adverse events, concomitant medicines, laboratory records, test article accountability, and Sponsor and IRB correspondences.

   b. **General observations/commentary**:

   - For protocol F1J-MC-HMCA, several record keeping deficiencies and protocol violations were noted:

- A tension headache was noted on the CRF's and source document for Subject 1107 on 12/12-16/02. It was rated as mild and possibly related to the study medicine. This adverse event was not included on the data listings provided by the sponsor.
- Numerous visits for subjects 1107, 1122, 1145, and 1149 did not occur within the protocol specified timeframes.
- During the screening process there is an exclusionary level of C-reactive protein of 0.287 mg/dl. If one tested above the exclusionary level, the protocol permitted re-testing prior to baseline at visit 2 provided the site obtain advance approval from the sponsor. Subject 1122 had a C-reactive protein level of 1.7 mg/dl at screening and was enrolled. However, an approval letter from the sponsor allowing the subject's admittance into the trial was not on site.
- Subjects were allowed to take up to 10 mg acetaminophen per day. The inspection was unable to determine how much acetaminophen subjects 1117 and 1122 were taking each day.

- For protocol F1J-MC-HMCJ the inspection found that numerous visits for subjects 1001, 1003, 1007, 1009, 1017, 1018, 1022, 1026, 1028, and 1036 did not occur within the protocol specified timeframes. The inspection also found that the informed consent document used in this trial was revised four times. The IRB required re-consenting of subjects, due to significant changes to the risks and side effects. Subjects 1105, 1109, and 1124 visited the site twice before they were re-consented using the revised informed consent document.
- For protocol F1J-MC-HMBO, the inspection found that numerous visits for subjects 1111, 1113, 1123, 1127, 1133, and 1143 did not occur within the protocol specified timeframes. Required laboratory tests needed at specific visits were not conducted for subjects 1133 and 1143. There was inconsistency noted with a few of the efficacy end points. Specifically, for subject 1123, the FIQ score at visit 8 was calculated as 33.4 and was rated 34; however, at visit 9, the FIQ score was calculated as 23.4, but was rated as 23.

c. **Assessment of data integrity**: Data from this site appear acceptable.

2. Jeffrey Gitt, M.D.
13832 N. 32nd Street, Suite #150
Phoenix, AZ 85032

a. **What was inspected**: For protocol F1J-MC-HMCA, 84 subjects were screened, 33 subjects were enrolled, and 12 subjects completed the study. Primary efficacy data for all subjects were reviewed. For protocol F1J-MC-HMCJ, 69 subjects were screened, 29 subjects were enrolled, and 10 subjects completed the study. Primary efficacy data for all subjects were reviewed.

c. **General observations/commentary**:

- For protocol F1J-MC-HMCA, subject 2379 did not meet the inclusion criteria for laboratory results for C-Reactive Protein. A non-certified rater performed the Hamilton Depression Rating Scale and Tender Point Pain

Threshold for subject 2360 at visit 5. There were discrepancies in drug accountability records for quantity dispensed, received, or retuned for subjects 2302, 2329, and 2357. Subjects 2352 and 2358 did not sign the most current IRB approved version of the informed consent document. For subject 2352, the clinical investigator did not circle yes or no in the diagnostic boxes for Antisocial Personality Disorder. For subjects 2369 and 2378 the clinical investigator did not circle yes or no in the diagnostic boxes for alcohol abuse and dependence.

- For Protocol F1J-MC-HMCJ, subject 2047 was not eligible for the study due to dysthmia and subject 2060 stopped taking fluoxetine less than the protocol required 30 days prior to being enrolled in the study. The clinical investigator did not circle yes or no in the diagnostic box for B. dysthymia for subject 3067.

c. **Assessment of data integrity:** Data from this site appear acceptable.

3. Richard Weinstein, M.D.
2255 Ygnacio Valley Road, Suite K-1
Walnut Creek, CA 94598

a. **What was inspected**: For protocol F1J-MC-HMCA, 69 subjects were screened, 30 subjects were enrolled, and 17 subjects completed the study. An in-depth review of 15 subjects' records was performed. For protocol F1J-MC-HMCJ, 50 subjects were screened, 22 subjects were enrolled, and 19 subjects completed the study. An in-depth review of 22 subjects' records was performed. For protocol F1J-MC-HMBO(a), 77 subjects were screened, 25 subjects were enrolled, and 17 subjects completed the study. An in-depth review of 13 subjects' records was performed.

d. **General observations/commentary**:

- For protocol F1J-MC-HMCJ—Source documents of ECG tracing and clinical laboratory reports were not maintained for the following subjects: 1222 (ECG Tracing at visit 1), 1227 Clinical Laboratory Results at visit 10, 1228, laboratory results at visit 11, and 1232 laboratoy results at visit 10. Adverse events for the following subjects were not reported to the sponsor:
  Subject 1211- Upper respiratory infection
  Subject 1215- Nausea, increased pain, increased fatique, depression, and hot flashes
  Subject 1221-Upper respiratory infection, hot flashes, chin laceration from fall, insomnia, and influenza
  Subject 1223-Upper respiratory infection, worsening constipation, restless sleep, decreased sex drive, and decreased concentration.
  Subject 1227-Pruritus, seasonal allergies, and right knee pain
  Subject 1228-Worsening headache and facial rash

Subject 1233-Upper respiratory infection, sinus infection nausea, abdominal discomfort, fatigue, malaise, and headache.
Subject 1236-Kidney stone, hypertension, and decreased hearing in left ear.

- For protocol F1-MC-HMBO(a) adverse events of nausea and skin itching, for subject 2843, were not reported to the sponsor
- For protocol F1J-MC-HMCA, protocol required assessments were not completed for the following three subjects: 1402, physical exam at early termination visit, 1419, Mean Tender Point Pain Threshold at visit 2, and subject 1423, MINI interview at visit 1.

c. **Assessment of data integrity**: Data from this site appear acceptable.

4. James Knutson, M.D.
10200 N.E. 132nd Street
Kirkland, WA 98034

a. **What was inspected**: For protocol F1J-MC-HMCJ, 94 subjects were screened. Of the 94 subjects screened, 49 were enrolled and 13 completed the study. Primary endpoint data were verified for 49 subjects. An in-depth review of 23 subjects' records was conducted.

e. **General observations/commentary**:

- The inspection found that adverse events for the following three subjects were not reported to the sponsor: For subject 4528, increased insomnia and increased pain in the leg reported by the subject at visit 3, early termination; for subject 4550, mid-back and left knee pain reported at visit 3 and headache reported at visit 5; for subject 4570, urinary tract infection reported at visit 5.

- The inspection found the following protocol violations:
  - At visit 6, subject 4535 marked "2" on question #9 of the Beck Depression Inventory ("I would like to kill myself"): The protocol defines this as a serious adverse event (SAE) and requires the subject to be discontinued from the study. This subject was allowed to continue in the study for nearly two more months, until the sponsor requested that the subject be discontinued and the event be reported as an SAE.
  - Visit 1 screening labs for subject 4577 revealed a high level of antinuclear antibody (ANA) at 1:640, meeting the protocol's exclusion criteria for ANA (equal to or more than 1:320). This subject was randomized into the study in violation of the protocol.
  - The protocol requires subjects to undergo a washout period of disallowed medications prior to visit 2. The protocol specified a seven day wash-out period for antidepressants and a 30-day washout period for fluoxetine. The washout periods were not adhered to for the following subjects: Subject 4521 stopped taking Zoloft on 11/2/05 and returned for visit 2 on 11/5/05; subject 4528 stopped taking Amitriptyline and Celexa on 11/25/05 and returned for visit 2 on 11/28/05; subject 4558 stopped taking Effexor on 2/15/06 and returned for visit 2 on 2/16/06, and

study drug was started on 2/18/06; and subject 4550 stopped taking Prozac on 1/20/05 and returned for visit 2 on 1/27/05.
- Patient's Global Impressions of Improvement scale data were not obtained for subject 4515 at visit 3.

- The inspection found that Dr. Knutson did not maintain adequate and accurate records. Specifically,
  - For Brief Pain Inventory (BPI): For subject 4572 visit5, data for questions #1, #3, and #4 were incorrectly transcribed on to the case report form from the subject's source document found in the study file. The subject recorded "8", "5", and "3", respectively, but "4", "3", and "4" were transcribed on to the case report form. For subject #4586 visit 15, for question #3, the subject recorded "4" on the source document in the study file; however "5" was transcribed on to the case report form. For subject 4587, visit-14, data was transcribed on to the case report form, but visit-13 was the final visit for this subject.
  - For Patient Global Impression - Improvement (PGI-I): For subject 4511 visit 4, this source document data was missing from the subject's study file, but the score of "2" was recorded on to the case report form. For subject 4587, visit 14 data was transcribed on to the case report form, but visit 13 was the final visit for this subject. Preliminary communications with the field investigator suggests that this was a transcription error.

c. **Assessment of data integrity**: Data from this site appear acceptable.

5. Timothy Smith, M.D.
1585 Woodlake Drive
Chesterfield, MO 63017

a. **What was inspected**: For protocol F1J-MC-HMCA, 81 subjects were enrolled and 12 subjects completed the study. An in-depth review of 28 subjects' records was conducted. For protocol F1J-MC-HMCJ, 7 subjects were enrolled and three completed the study. All subject records were reviewed.

b. **General observations/commentary**: No significant regulator violations were noted.

c. **Assessment of data integrity**: Data from this site appear acceptable.

6. Patricia Buchanan, M.D.
890 River Road
Eugene, OR 97404

a. **What was inspected**: For protocol F1J-MC-HMCA, 89 subjects were screened, 32 subjects were enrolled, and 24 subjects completed the study. Primary efficacy endpoint data was reviewed for all subjects. An in-depth review of 19 subjects' records was performed. For protocol F1J-MC-HMCJ, 46 subjects were screened, 24 subjects were enrolled, and 10 subjects completed

the study. Primary endpoint data for 17 subjects were reviewed. An in-depth review of 12 subjects' records was performed.

b. **General observations/commentary**:

- For protocol HMCA, no significant violations were noted.
- For protocol HMCJ, underreporting of adverse events were observed. For example:
  Subject #2202 - Depressed for 5 days.
  Subject #2204 - Viral cold
  Subject #2216 - Depression worsened.
  Subject #2218 – Fell, contusion on right side of chest, and skinned right knee.
  Subject #2220 – Edema and vomiting.
  Subject #2222 - Shortness of breath, excessive face sweating, dry Mouth, tiredness, intermittent headache, and viral cold.
  Subject #2227 - Pass kidney stone.
  Subject #2228 - Severe chest pain.
  Subject #2235 - Urge to urinate and vomiting.
- For protocol HMCJ, protocol violations were observed. For example:
  Subject #2202 - Pre-existing conditions, restless leg syndrome, and concomitant medication use of valtrex, were not reported to the sponsor
  Subject #2210 - Visit-6 effectiveness data (BPI and PGI-I) were not obtained from the subject.
  Subject #2213 - Did not complete a 7-day washout period from antidepressant effexor. The last dose of effexor was taken on 10/12/05 and the subject was randomized on 10/14/05.
  Subject #2228 - Use of concomitant medication, nitroglycerin, was not reported to the sponsor.
  Subject #2235 - Use of concomitant medication, ciprofloxacin and flagyl, were not reported to the sponsor.

c. **Assessment of data integrity**: Data from this site appear acceptable.

IV. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Inspection of Dr. Smith found no significant regulatory violations. Inspections of Dr. Arnold, Gitt, Weinstein, and Knutson found protocol violations and record keeping deficiencies. Inspection of Dr. Buchanan found protocol violations. The data from these sites appear acceptable in support of the respective indications. As previously mentioned, the observations noted above are based on the Form FDA 483 and communications with the field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIRs.

{See appended electronic signature page}

Sherbet Samuels, R.N., M.P.H.
Good Clinical Practice Branch I
Division of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Constance Lewin, M.D., M.P.H.
Branch Chief, Good Clinical Practice Branch I
Division of Scientific Investigations
Office of Compliance

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

/s/

Sherbert Samuels
3/26/2008 07:38:21 PM
CSO

Constance Lewin
3/27/2008 10:11:18 AM
MEDICAL OFFICER

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

REQUEST FOR CONSULTATION

TO *(Office/Division)*: OPS, Staff (HFD-354)
Attn: Bai Nguyen (301-796-1531)
)21 RM3523

FROM *(Name, Office/Division, and Phone Number of Requestor)*: Teshara G. Bouie, ONDQA, Division of Post-Marketing Assessment, 301-796-1649

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
February 19, 2008		22-148	Type 6 NDA	August 14, 2007

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Cymbalta			May 14, 2008

NAME OF FIRM: Eli Lilly and Co.

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
-)THER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: This is a type 6 NDA for the ——— of fibromyalgia. Please review the Environmental Assessment. This submission can be found in the EDR. The goal date is June 14, 2008.

SIGNATURE OF REQUESTOR	METHOD OF DELIVERY (Check one)
Teshara G. Bouie	☒ DFS ☐ EMAIL ☐ MAIL ☐ HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/

Teshara Bouie
2/19/2008 04:15:04 PM

Stradley, Sara

From: Stradley, Sara
Sent: Wednesday, February 13, 2008 2:58 PM
To: 'BOGGS_BRYAN_E@LILLY.COM'
Cc: Jani, Parinda; Stradley, Sara
Subject: NDA 22-148---information request

Attachments: Information Request_2 12 08.doc

Bryan

I am covering NDA 22-148 while Parinda Jani is on leave. We have a few information requests (see attached document). Please respond to these inquires as soon as possible. Parinda will be back in the office on Feb 21. Thanks

Information
:equest_2 12 08.do.

Sara E. Stradley, MS
Chief, Project Management Staff
Division of Anesthesia, Analgesia and Rheumatology Products
Office of Drug Evaluation II
Office of New Drugs
Center for Drug Evaluation and Research
phone # 301-796-1298
mail: Sara.Stradley@fda.hhs.gov

1. Regarding the analysis of duloxetine drug exposure, we refer to the total number of patients that were randomized to and received each study dose. Table 2.7.4.4, Page 20, 2.7.4 Summary-Clin-Safety (see table below), states that there were a total of 29 patients who received DLX20QD, however, the clinical study synopsis of Study F1J-MC-HMCJ states that there were 79 patients randomized to DLX20QD and 49 patients completed 3-months at this dose. Clarify the reason(s) for this discrepancy and provide us with an updated table. If, there are similar discrepancies in other sections of your adverse event descriptions, identify and clarify those as well.

Table 2.7.4.4.
Study Drug Exposure by Dose
All Randomized Patients
Primary Placebo-Controlled Analyses Set

	Placebo	DLX20QD	DLX30QD	DLX60QD	DLX60BID	DLX120QD	DLXTOT
Variable	(N=535)	(N=29)	(N=37)	(N=369)	(N=220)	(N=221)	(N=876)
Duration of Exposure (Days)							
No. Patient	535	29	37	369	220	221	876
Mean	105.11	59.79	6.62	118.86	60.59	168.87	110.15
STD	68.43	43.26	18.83	73.03	33.01	49.25	72.51
Maximum	224.00	138.00	116.00	237.00	96.00	224.00	237.00
Median	85.00	77.00	3.00	91.00	83.00	189.00	87.00
Minimum	0.00	0.00	0.00	1.00	0.00	14.00	0.00
Patient years	153.96	4.75	0.67	120.08	36.49	102.18	264.17
Duration of Exposure n (%)							
No. Patient	535	29	37	369	220	221	876
0	4 (0.7)	1 (3.4)	7 (18.9)	0 (0)	2 (0.9)	0 (0)	10 (1.1)
>0	531 (99.3)	28 (96.6)	30 (81.1)	369 (100.0	218 (99.1)	221 (100.0)	866 (98.9)
>=7	513 (95.9)	27 (93.1)	6 (16.2)	349 (94.6)	202 (91.8)	221 (100.0)	805 (91.9)
>=14	494 (92.3)	22 (75.9)	2 (5.4)	331 (89.7)	184 (83.6)	221 (100.0)	760 (86.8)
>=30	444 (83.0)	18 (62.1)	1 (2.7)	307 (83.2)	159 (72.3)	215 (97.3)	700 (79.9)
>=60	375 (70.1)	16 (55.2)	1 (2.7)	276 (74.8)	139 (63.2)	208 (94.1)	640 (73.1)
>=90	225 (42.1)	7 (24.1)	1 (2.7)	191 (51.8)	16 (7.3)	194 (87.8)	409 (46.7)
>=120	195 (36.4)	1 (3.4)	0 (0)	172 (46.6)	0 (0)	181 (81.9)	354 (40.4)
>=183	172 (32.1)	0 (0)	0 (0)	150 (40.7)	0 (0)	161 (72.9)	311 (35.5)
>=365	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

N = Number of patients within each treatment group based upon patients maximum dose received.
Patient years calculated as total exposure days/365.25.

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On Original

2. Provide updated tables of Treatment-Emergent Adverse Events in Placebo-Controlled Trials, by assigned dose and for dose at time of event (in a separate table). Create one table sorting TEAEs by SOC and HLGT in one table and by PT and HLT in separate tables.

Treatment-Emergent Adverse Events (Placebo-Controlled Trials)													
SOC	**HLGT**	**DLX 120QD**	**N=221**	**DLX 60BID**	**N=220**	**DLX 60QD**	**N=369**	**DLX 30QD**	**N=37**	**DLX 20QD**	**N=29**	**PBO**	**N=535**
Cardiac disorders													
Eye disorders													
Etc.													

3. Provide a table of Serious Adverse Events by Decreasing Frequency for all fibromyalgia patients treated with duloxetine (placebo-controlled and open-label) similar to the table you provided in the clinical study report of Study HMCJ (Table 12.7):

Table 12.7.
Serious Adverse Events by Decreasing Frequency
All Randomized Patients
3-Month Therapy Phase

Preferred Term	Treatment	N	n	Percent
PATIENTS WITH >=1 SERIOUS ADVERSE EVENT	1) PLACEBO	144	7	4.9
	2) DLX20QD	79	1	1.3
	3) DLX60QD	150	2	1.3
	4) DLX120QD	147	8	5.4
Asthma	1) PLACEBO	144	1	0.7
	2) DLX20QD	79	0	0.0
	3) DLX60QD	150	1	0.7
	4) DLX120QD	147	0	0.0
Suicidal ideation	1) PLACEBO	144	1	0.7
	2) DLX20QD	79	0	0.0
	3) DLX60QD	150	0	0.0
	4) DLX120QD	147	1	0.7
Etc.				

MedDRA Version: 9.1
N = Number of randomized patients, n = Number of patients with serious adverse event.
*Frequencies are analyzed using Fisher's exact test.

4. Submit your categorical exclusion. If you have submitted it, please provide its location in your application.

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

/s/

Sara Stradley
2/13/2008 03:23:39 PM
CSO

DSI CONSULT: Request for Clinical Inspections

Date:

To: Constance Lewin, M.D., M.P.H, Branch Chief, GCP1, HFD-46
Joe Salewski., Branch Chief (Acting), GCP2, HFD-47
Name of DSI Primary Reviewer (if known)

Through: Ricardo E. Dent, M.D., Medical Officer, DAARP, HFD-170
Celia Winchell, M.D., Team Leader, DAARP, HFD-170

From: Lisa Malandro, Regulatory Health Project Manager, DAARP, HFD-170

Subject: **Request for Clinical Site Inspections**

I. General Information

Application#: NDA 22-148
Sponsor/Sponsor contact information (to include phone/email):
Bryan Boggs, Pharm.D.
US Regulatory Affairs
Eli Lilly and Company
Office: 317-276-6685 FAX: 317-276-1652
Cell: 317-681-4997 bboggs@lilly.com
Drug: Cymbalta (duloxetine hydrochloride)
NME: No
Standard or Priority: Standard
Study Population < 18 years of age: No
Pediatric exclusivity: No

PDUFA: June 13, 2008
Action Goal Date: June 9, 2008
Inspection Summary Goal Date: March 14, 2008

II. Background Information

This supplemental application is an application for an indication of of fibromyalgia.

Duloxetine is a serotonin and norepinephrine reuptake inhibitor (SNRI) approved in the United States and marketed by Eli Lilly for treatment of major depressive disorder (MDD), diabetic peripheral neuropathic pain (DPNP), and generalized anxiety disorder (GAD). Serotonin and norepinephrine are thought to mediate analgesic mechanisms in the brain and spinal cord. Fibromyalgia is a syndrome characterized by chronic diffuse musculoskeletal pain, disordered sleep

and fatigue that is commonly associated with nonspecific complaints such as cognitive difficulties, depression, and headaches. The etiology of fibromyalgia has not been identified, but is thought to be related to aberrancies in the central nervous system.

The studies submitted to support the safety and efficacy of duloxetine for treatment of fibromyalgia include the following protocols: FJ1-MC-HMBO (HMBO), F1J-MC-HMCA (HMCA), F1J-MC-HMCJ (HMCJ), F1J-MC-HMEH (HMEH), and F1J-MC-HMEF (HMEF). Studies HMBO, HMCA, and HMCJ are double-blind, parallel-group, placebo-controlled studies of 3 month duration, whereas HMEF is a similar study of 6-month duration. HMEH is an open-label, 1-year extension study.

III. Protocol/Site Identification

Site # (Name,Address, Phone number, email, fax#)	Protocol #	Number of Subjects	Indication
Site #100, 101 Leslie Arnold, M.D. 231 Albert Sabin Way Cincinnati, OH 45267-0559 513-475-8110	**F1J-MC-HMBO(a)** F1J-MC-HMCA F1J-MC-HMCJ	61	Treatment of fibromyalgia
Site #110, 113 Jeffrey Gitt, M.D. 13832 N. 32nd Street, Suite #150 Phoenix, AZ 85032 602-482-2116	**F1J-MC-HMCA** F1J-MC-HMCJ	62	Treatment of fibromyalgia
Site #102, 104, 118 Richard Weinstein, M.D. 2255 Ygnacio Valley Road, Suite K-1 Walnut Creek, CA 94598 925-930-7267	F1J-MC-HMBO(a) **F1J-MC-HMCA** F1J-MC-HMCJ	77	Treatment of fibromyalgia
Site #135 James Knutson, M.D. 10200 N.E. 132nd Street Kirklan, WA 98034 425-443-9551	**F1J-MC-HMCJ**	49	Treatment of fibromyalgia
Site #120, 121 Timothy Smith, M.D. 1585 Woodlake Drive Chesterfield, MO 63017 314-251-8890	F1J-MC-HMCA **F1J-MC-HMCJ**		Treatment of fibromyalgia

Alternative Site			
Site # (Name,Address, Phone number, email, fax#)	**Protocol #**	**Number of Subjects**	**Indication**
Site #112, 120 Patricia Buchanan, M.D. 890 River Road Eugene, OR 97404 541-688-0674	**F1J-MC-HMCA** F1J-MC-HMCJ	56	Treatment of fibromyalgia

IV. Site Selection/Rationale

The above sites are requested due to their large proportion of study participants and number of protocol violations. In addition, ——————— reported an equity interest of > $500,000 in Eli Lilly.

Domestic Inspections:

Reasons for inspections (please check all that apply):

_x_ Enrollment of large numbers of study subjects
_x_ High treatment responders (specify):
____ Significant primary efficacy results pertinent to decision-making
____ There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
_x_ Other (specify): Large number of protocol violations

Note: International inspection requests or requests for five or more inspections require sign-off by the OND Division Director and forwarding through the Director, DSI.

Should you require any additional information, please contact Lisa Malandro at Ph: 301-796-1251 or Ricardo Dent, MD at Ph: 301-796-2248.

Concurrence: (as needed)

_____ Medical Team Leader
_____ Medical Reviewer
_____NA_____ Director, Division Director (for foreign inspection requests only)

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/s/

Celia Winchell
11/29/2007 03:47:42 PM

Malandro, Lisa

From: Malandro, Lisa
Sent: Tuesday, September 18, 2007 10:58 AM
To: 'Bryan E Boggs'
Cc: Malandro, Lisa
Subject: INFORMATION REQUEST: NDA 22-148 Cymbalta-Fibro

Hi Bryan,
The review team is having difficulty opening the file "ISS READ ME." Can you tell me what information is located in the file (we're hoping that it's something that defines the different ISS datasets for us)? Is it possible to email me a copy of the file for their immediate use and then have it resubmitted?
Thanks,
Lisa

Lisa Malandro, MBA
Regulatory Health Project Manager
Division of Anesthesia, Analgesia and Rheumatology Products; HFD-170
301-796-1251
fax-301-796-9722

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/s/

Lisa Malandro
10/16/2007 03:51:20 PM
CSO

Malandro, Lisa

From: Malandro, Lisa
Sent: Friday, September 07, 2007 2:15 PM
To: 'Bryan E Boggs'
Cc: Malandro, Lisa
Subject: INFORMATION REQUEST: NDA 22-148 Cymbalta

Hi Bryan,
The Medical Officer has requested the following:

Please provide a description and analysis of safety data from worldwide commercial marketing experience with Cymbalta.

Please provide response via an amendment to the application. If you have any questions, please do not hesitate to contact me.
Lisa

Lisa Malandro, MBA
Regulatory Health Project Manager
Division of Anesthesia, Analgesia and Rheumatology Products; HFD-170
301-796-1251
fax-301-796-9722

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/s/

Lisa Malandro
10/16/2007 03:49:24 PM
CSO

Malandro, Lisa

From: Malandro, Lisa
Sent: Tuesday, September 25, 2007 3:19 PM
To: 'Bryan E Boggs'
Cc: Malandro, Lisa
Subject: Reply: INFORMATION REQUEST: NDA 22-148 Cymbalta SAS Program Request

Bryan,

At this time, we do not have sufficient usable information to complete our filing review. In order to complete this review we must receive the following information by October 1, 2007:

1 . The safety datasets (events, vital signs, labs, etc) should be resubmitted broken out by indication. If a file for a particular indication is too large it should be broken into appropriately sized portions that we can reassemble. The new datasets should include flags for the 5 categories (fibromyalgia placebo-controlled, fibromyalgia short-term, etc) such that we can easily identify them.

2. A dataset that gives us all of the adverse events that occurred during a study or within 30 days after treatment discontinuation so that an analysis of treatment-emergent events can be completed. Pre-existing conditions such as are included in the dataset "events" should NOT be included in this dataset. We have noted that there are over 29,000 events for which the field defining whether an event was pre-existing , treatment event, or post-treatment event has been left blank.

3. We have noted that within the events occurring in the fibromyalgia studies, the current datasets lack the flag for serious (yes/no) in over 1,400 events. You should review the CRFs and include this information in the new datasets.

The Division is requesting this information because the datasets as currently submitted are too large and cumbersome for our reviewers to work with during the course of the review cycle.

Thank you,
Lisa

From: Bryan E Boggs [mailto:BOGGS_BRYAN_E@LILLY.COM]
Sent: Tuesday, September 25, 2007 10:27 AM
To: Malandro, Lisa
Subject: Re: INFORMATION REQUEST: NDA 22-148 Cymbalta SAS Program Request

Hi Lisa,

I'm talking to my statistician to see if this can be made clearer. Did you receive the new

SAS program Q207SPLT.SAS? or is it that it is not yet uploaded in the eCTD backbone? We are available today if needed. Would it be of benefit to get on the line (tcon) with our statisticians to have a technical discussion regarding the use of these programs? Again, we are also willing to send someone there at short notice to help with the datasets.

Regards,
Bryan

"Malandro, Lisa" <lisa.malandro@fda.hhs.gov>

09/25/2007 09:54 AM

To "Bryan E Boggs" <BOGGS_BRYAN_E@LILLY.COM>
cc
Subject INFORMATION REQUEST: NDA 22-148 Cymbalta S.

HI Bryan,
Our statistical reviewer is looking for the SAS program Q207SPLT.SAS which is referenced as being submitted to the Agency in your recent communication. The reviewer is having difficulty creating the "FMS controlled and open-label dataset" because the definition provided in Table 2 is unclear.

Thanks,
Lisa

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/s/

Lisa Malandro
10/16/2007 03:52:38 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 22-148

Eli Lilly and Company
PO Box 6288
Indianapolis, IN 46206

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

Dear Dr. Boggs:

Please refer to your new drug application (NDA) dated August 14, 2007, received August 14, 2007, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for CYMBALTA (LY248686, duloxetine hydrochloride) 20, 30, — and 60 mg.

We also refer to your submissions dated September 20 and 30, and October 3, 2007.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application is considered filed 60 days after the date we received your application in accordance with 21 CFR 314.101(a). The review classification for this application is **Standard**. Therefore, the user fee goal date is June 14, 2007.

At this time, we are notifying you that, we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

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 that you have not fulfilled the requirements. We acknowledge receipt of your request for a (1) waiver of pediatric studies for this application for neonates, infants and children (patients under the age of 16) and (2) deferral of pediatric studies for this application for adolescents (16 and older).

If you have any questions, contact Lisa Malandro, MBA, Regulatory Health Project Manager, at (301) 796-1251.

Sincerely,

{See appended electronic signature page}

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

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/s/

Bob Rappaport
10/15/2007 02:40:35 PM

Form Approved: OMB No. 0910 - 0297 Expiration Date: January 31, 2010 See instructions for OMB Statement, below.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

PRESCRIPTION DRUG USER FEE COVERSHEET

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: http://www.fda.gov/cder/pdufa/default.htm

1. APPLICANT'S NAME AND ADDRESS

ELI LILLY AND CO
Belinda Schluchter
LILLY CORPORATE CENTER DROP CODE 2546
INDIANAPOLIS IN 46285
US

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER

22148

2. TELEPHONE NUMBER
317-6511322

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?

[X] YES [ ] NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.
IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW:

[X] THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION

[ ] THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

3. PRODUCT NAME
Cymbalta (duloxetine)

6. USER FEE I.D. NUMBER
PD3007561

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

[ ] A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory)

[ ] A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE

[ ] THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food,Drug, and Cosmetic Act

[ ] THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? [ ] YES [X] NO

OMB Statement:
Public reporting burden for this collection of information is estimated to average 30 minutes 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
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CDER, HFD-94
12420 Parklawn Drive, Room 3046
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.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
Gregory T. Brophy, PhD	Director, USRA	8/8/2007

9. USER FEE PAYMENT AMOUNT FOR THIS APPLICATION
$448,100.00

Form FDA 3397 (03/07)

Close Print Cover sheet