

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
022516Orig1s000

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # **022516**

SUPPL #

HFD # **170**

Trade Name **Cymbalta**

Generic Name **duloxetine hydrochloride**

Applicant Name **Eli Lilly and Company**

Approval Date, If Known **November 4, 2010**

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), This is a type 6 NDA that will be rolled over into the parent NDA 021427 upon approval.

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?

Three 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 Cymbalta

NDA# 21-733 (Type 6) Cymbalta

NDA# 22-148 (Type 6) Cymbalta

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:

Studies:

HMGC

HMEN

HMEP

HMFG

HMEO

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"):

Studies:

- HMGC
- HMEN
- HMEP
- HMFG
- HMEO

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 #1-5 !
 !
 IND # 63,615 YES ! NO
 ! Explain:

Investigation # !
 !
 IND # YES ! NO
 ! Explain:

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

/s/

AYANNA S AUGUSTUS
11/04/2010

BOB A RAPPAPORT
11/04/2010

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 022516 BLA #	NDA Supplement # BLA STN #	If NDA, Efficacy Supplement Type:
Proprietary Name: Cymbalta Established/Proper Name: duloxetine hydrochloride Dosage Form: capsules		Applicant: Eli Lilly and Company Agent for Applicant (if applicable):
RPM: Ayanna Augustus		Division: Division of Anesthesia and Analgesia Products
<p>NDA: NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>(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 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)</p>		<p>505(b)(2) Original NDAs and 505(b)(2) NDA supplements: Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p>If no listed drug, explain.</p> <p><input type="checkbox"/> This application relies on literature. <input type="checkbox"/> This application relies on a final OTC monograph. <input type="checkbox"/> Other (explain)</p> <p><u>Two months prior to each action, review the information in the 505(b)(2) Assessment and submit the draft to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u></p> <p><u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u></p> <p><input type="checkbox"/> No changes <input type="checkbox"/> Updated Date of check:</p> <p>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.</p>
❖ Actions		
<ul style="list-style-type: none"> • Proposed action • User Fee Goal Date is <u>March 15, 2010</u> 		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> • Previous actions (<i>specify type and date for each action taken</i>) 		<input checked="" type="checkbox"/> None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____		<input type="checkbox"/> Received

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

❖ Application Characteristics ²	
<p>Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only): 6</p> <p><input type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch <input type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch <input type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC</p> <p>NDAs: Subpart H BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Accelerated approval (21 CFR 601.41) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) <input type="checkbox"/> Restricted distribution (21 CFR 601.42)</p> <p>Subpart I Subpart H <input type="checkbox"/> Approval based on animal studies <input type="checkbox"/> Approval based on animal studies</p> <p><input type="checkbox"/> Submitted in response to a PMR <input type="checkbox"/> Submitted in response to a PMC <input type="checkbox"/> Submitted in response to a Pediatric Written Request</p> <p>Comments:</p>	
❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	<input type="checkbox"/> Yes, dates
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications (<i>approvals only</i>)	
• Office of Executive Programs (OEP) liaison has been notified of action	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Press Office notified of action (by OEP)	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Indicate what types (if any) of information dissemination are anticipated	<input type="checkbox"/> None <input checked="" type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other

² Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
<ul style="list-style-type: none"> Is approval of this application blocked by any type of exclusivity? 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> NDA and BLAs: Is there existing orphan drug exclusivity for the “same” drug or biologic for the proposed indication(s)? <i>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.</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(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.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> 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. 	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> 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) <input type="checkbox"/> Verified 21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> [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). 	<input type="checkbox"/> No paragraph III certification Date patent will expire
<ul style="list-style-type: none"> [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). <i>(If the application does not include any paragraph IV certifications, mark “N/A” and skip to the next section below (Summary Reviews)).</i> 	<input type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> 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 the rest of the patent questions.

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).

<p>(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?</p> <p>(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).</p> <p><i>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).</i></p> <p><i>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.</i></p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>
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CONTENTS OF ACTION PACKAGE

❖ Copy of this Action Package Checklist ³	November 4, 2010
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included
Action Letters	
❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Action(s) and date(s) Approval, November 4, 2010
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
<ul style="list-style-type: none"> • Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	October 14, 2010
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	May 15, 2009
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	

³ Fill in blanks with dates of reviews, letters, etc.
Version: 7/8/10

❖ Medication Guide/Patient Package Insert/Instructions for Use (<i>write submission/communication date at upper right of first page of each piece</i>)	<input checked="" type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> None
<ul style="list-style-type: none"> Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	
<ul style="list-style-type: none"> Original applicant-proposed labeling 	May 15, 2009
<ul style="list-style-type: none"> Example of class labeling, if applicable 	November 19, 2009
❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>)	
<ul style="list-style-type: none"> Most-recent draft labeling 	
❖ Proprietary Name <ul style="list-style-type: none"> Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) Review(s) (<i>indicate date(s)</i>) 	
❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>)	<input checked="" type="checkbox"/> RPM November 4, 2010 <input type="checkbox"/> DMEPA <input type="checkbox"/> DRISK <input checked="" type="checkbox"/> DDMAC February 24, 2010 <input type="checkbox"/> CSS <input type="checkbox"/> Other reviews
Administrative / Regulatory Documents	
❖ Administrative Reviews (<i>e.g., RPM Filing Review⁴/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>)	November 20, 2009
❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte	<input type="checkbox"/> Not a (b)(2)
❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment (<i>indicate date</i>)	<input type="checkbox"/> Not a (b)(2)
❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)	<input checked="" type="checkbox"/> Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
<ul style="list-style-type: none"> Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> This application is on the AIP <ul style="list-style-type: none"> If yes, Center Director's Exception for Review memo (<i>indicate date</i>) If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action
❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> Date reviewed by PeRC <u>February 17, 2010 and October 13, 2010</u> If PeRC review not necessary, explain: _____ Pediatric Record(<i>approvals only, must be reviewed by PERC before finalized</i>) 	<input checked="" type="checkbox"/> 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 (<i>include certification</i>)	<input checked="" type="checkbox"/> Verified, statement is acceptable
❖ Outgoing communications (<i>letters (except action letters), emails, faxes, telecons</i>)	6/5/09, 7/17/09, 9/25/09, 9/30/09, 12/4/09, 12/11/09, 1/28/10, 2/4/09, 5/18/10, 7/29/10, 9/22/10, 9/27/10, 9/28/10, 10/8/10, 10/12/10,

⁴ Filing reviews for scientific disciplines should be filed behind the respective discipline tab.
Version: 7/8/10

	10/13/10, 10/14/10, 10/15/10, 11/4/10
❖ Internal memoranda, telecons, etc.	
❖ Minutes of Meetings	
• Regulatory Briefing (<i>indicate date of mtg</i>)	<input checked="" type="checkbox"/> No mtg
• If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)	<input checked="" type="checkbox"/> N/A or no mtg
• Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)	<input type="checkbox"/> No mtg November 16, 2007
• EOP2 meeting (<i>indicate date of mtg</i>)	<input type="checkbox"/> No mtg October 7, 2005
• Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>)	Type C, March 31, 2006
❖ Advisory Committee Meeting(s)	<input type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	August 19, 2010
• 48-hour alert or minutes, if available (<i>do not include transcript</i>)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Division Director Summary Review (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None November 4, 2010
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None October 13, 2010
PMR/PMC Development Templates (<i>indicate total number</i>)	<input checked="" type="checkbox"/> None
Clinical Information⁵	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	CDTL Memo October 13, 2010
• Clinical review(s) (<i>indicate date for each review</i>)	February 2, 2010
• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not (<i>indicate date of review/memo</i>)	See clinical review
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> Not applicable
❖ Risk Management <ul style="list-style-type: none"> • REMS Documents and Supporting Statement (<i>indicate date(s) of submission(s)</i>) • REMS Memo(s) and letter(s) (<i>indicate date(s)</i>) • Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>) 	May 15, 2009 <input type="checkbox"/> None OSE/DRISK February 19, 2009
❖ DSI Clinical Inspection Review Summary(ies) (<i>include copies of DSI letters to investigators</i>)	<input type="checkbox"/> None requested 10/23/09, 1/22/10, 1/27/10, 2/18/10, 3/29/10

⁵ Filing reviews should be filed with the discipline reviews.
Version: 7/8/10

Clinical Microbiology		<input checked="" type="checkbox"/> None
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)		<input type="checkbox"/> None
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)		<input type="checkbox"/> None
Biostatistics		<input type="checkbox"/> None
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)		<input checked="" type="checkbox"/> None
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)		<input type="checkbox"/> None February 23, 2010
Statistical Review(s) (<i>indicate date for each review</i>)		<input type="checkbox"/> None February 23, 2010
Clinical Pharmacology		<input checked="" type="checkbox"/> None
❖ Clinical Pharmacology Division Director Review(s) (<i>indicate date for each review</i>)		<input type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) (<i>indicate date for each review</i>)		<input type="checkbox"/> None
Clinical Pharmacology review(s) (<i>indicate date for each review</i>)		<input type="checkbox"/> None
❖ DSI Clinical Pharmacology Inspection Review Summary (<i>include copies of DSI letters</i>)		<input type="checkbox"/> None
Nonclinical		<input checked="" type="checkbox"/> None
❖ Pharmacology/Toxicology Discipline Reviews		
• ADP/T Review(s) (<i>indicate date for each review</i>)		<input type="checkbox"/> None
• Supervisory Review(s) (<i>indicate date for each review</i>)		<input type="checkbox"/> None
• Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)		<input type="checkbox"/> None
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)		<input type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)		<input type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting		<input type="checkbox"/> None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary (<i>include copies of DSI letters</i>)		<input type="checkbox"/> None requested
Product Quality		<input type="checkbox"/> None
❖ Product Quality Discipline Reviews		
• ONDQA/OBP Division Director Review(s) (<i>indicate date for each review</i>)		<input checked="" type="checkbox"/> None
• Branch Chief/Team Leader Review(s) (<i>indicate date for each review</i>)		<input type="checkbox"/> None March 15, 2010
• Product quality review(s) including ONDQA biopharmaceutics reviews (<i>indicate date for each review</i>)		<input checked="" type="checkbox"/> None
❖ Microbiology Reviews		<input checked="" type="checkbox"/> Not needed
<input type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) (<i>indicate date of each review</i>)		
<input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (DMPQ/MAPCB/BMT) (<i>indicate date of each review</i>)		
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer (<i>indicate date of each review</i>)		<input checked="" type="checkbox"/> None

❖ Environmental Assessment (check one) (original and supplemental applications)	
<input type="checkbox"/> Categorical Exclusion (<i>indicate review date</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>)	
<input type="checkbox"/> Review & FONSI (<i>indicate date of review</i>)	
<input checked="" type="checkbox"/> Review & Environmental Impact Statement (<i>indicate date of each review</i>)	November 2, 2009
❖ Facilities Review/Inspection	
<input checked="" type="checkbox"/> NDAs: Facilities inspections (include EER printout) (<i>date completed must be within 2 years of action date</i>) (<i>only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites⁶</i>)	Date completed: March 15, 2010 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER (<i>date of most recent TB-EER must be within 30 days of action date</i>) (<i>original and supplemental BLAs</i>)	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation (<i>check box only, do not include documents</i>)	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed (per review)

⁶ I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Appendix 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.

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/s/

AYANNA S AUGUSTUS
11/05/2010

Augustus, Ayanna

From: Jani, Parinda
Sent: Thursday, November 04, 2010 5:56 PM
To: 'Matt Kuntz'; Augustus, Ayanna
Subject: RE: Cymbalta

Thanks, we will be taking an action within a few minutes, so stay tuned.....

From: Matt Kuntz [mailto:KUNTZ_MATT@LILLY.COM]
Sent: Thursday, November 04, 2010 5:55 PM
To: Augustus, Ayanna; Jani, Parinda
Subject: RE: Cymbalta

Hello Parinda and Ayanna,
Thanks for the call! Per our discussion this afternoon, Lilly agrees to the following revision to the **Highlights of Prescribing Information** for Cymbalta:

-----INDICATIONS AND USAGE-----

Chronic Musculoskeletal Pain, [REDACTED]
[REDACTED]-(1.5).

(b) (4)

If possible, could you send me a Word copy of the final, approved labeling?

Do you know if FDA intends to issue a press release? If so, do you think it will be this evening?

Thanks,
Matt

Matt Kuntz, RPh, MBA, RAC
Global Regulatory Affairs - US
Eli Lilly and Company
Office 317.433.1766
Mobile 317.625.5151

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/s/

AYANNA S AUGUSTUS
11/05/2010

Augustus, Ayanna

From: Greeley, George
Sent: Wednesday, October 20, 2010 1:34 PM
To: Augustus, Ayanna
Cc: Salis, Olga
Subject: NDA 22-516 Cymbalta

Importance: High

Attachments: 1_Pediatric_Record.pdf

Hi Ayanna,

The Cymbalta (duloxetine hydrochloride) full waiver was reviewed by the PeRC PREA Subcommittee on October 13, 2010.

The Division recommended a full waiver because there are too few children with disease/condition to study.

The PeRC agreed with the Division to grant a full waiver for this product. The pediatric record is attached as proof of the PeRC's review for Cymbalta.



1_Pediatric_Record
.pdf (54 KB)...

Thank you.

George Greeley
Regulatory Health Project Manager
Pediatric and Maternal Health Staff
FDA/CDER/OND
10903 New Hampshire Avenue
Bldg. 22, Room 6467
Silver Spring, MD 20993-0002
Phone: 301.796.4025
Email: george.greeley@fda.hhs.gov

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/s/

AYANNA S AUGUSTUS
10/20/2010

Augustus, Ayanna

From: Augustus, Ayanna
Sent: Friday, October 15, 2010 5:36 PM
To: 'KUNTZ_MATT@LILLY.COM'
Subject: Cymbalta/MedGuide

Hi Matt,

Please send me a word copy of the last approved medication guide for cymbalta.

Thanks,
Ayanna

Ayanna Augustus, Ph.D.
Regulatory Project Manager
Division of Anesthesia and Analgesia Products
Center for Drug Evaluation and Research
Food and Drug Administration
Bldg. 22, Room 3219
10903 New Hampshire Ave
Silver Spring, MD 20993
301-796-3980 (phone)
301-796-9717 (fax)

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/s/

AYANNA S AUGUSTUS
10/15/2010

Augustus, Ayanna

From: Augustus, Ayanna
Sent: Tuesday, October 12, 2010 8:31 PM
To: 'Matt Kuntz'
Subject: RE: Cymbalta/container labels
Importance: High
Attachments: proposed label 10 05 10.doc

Hi Matt,

Attached is the revised label for Cymbalta which has been reviewed by Dr. Rappaport. Please review and provide a label in clean and tracked changes. In addition, time has been set side on the Division calendar to discuss the labeling on Thursday, October 14th at 9 AM. Please confirm Lilly's availability for labeling discussion at that time and provide a call-in number as well.

Regards,
Ayanna

From: Matt Kuntz [mailto:KUNTZ_MATT@LILLY.COM]
Sent: Friday, October 08, 2010 4:21 PM
To: Augustus, Ayanna
Subject: Re: Cymbalta/container labels

Hi Ayanna,
It looks as though container labels were included with an amendment dated 11 January 2010 (NDA 22-516 sequence # 0006). Please let me know if you don't find these or would like me to send them.

Any update regarding the pediatric waiver request or Dr. Rappaport's review of labeling?

Have a great weekend!
Many thanks,
Matt

Matt Kuntz, RPh, MBA, RAC
Global Regulatory Affairs - US
Eli Lilly and Company
Office 317.433.1766
Mobile 317.625.5151

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"Augustus, Ayanna" <Ayanna.Augustus@fda.hhs.gov>

To

10/15/2010

10/08/2010 03:50 PM

'Matt Kuntz' <KUNTZ_MATT@LILLY.COM>

cc

Subject Cymbalta/container labels

Hi Matt,

I noticed that the NDA submission does not contain a copy of the currently approved carton/container labels for Cymbalta nor was I able to find a reference to them. Please submit a copy of the labels to the NDA as soon as possible.

Regards,
Ayanna

*Ayanna Augustus, Ph.D.
Regulatory Project Manager
Division of Anesthesia and Analgesia Products
Center for Drug Evaluation and Research
Food and Drug Administration
Bldg. 22, Room 3219
10903 New Hampshire Ave
Silver Spring, MD 20993
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301-796-9717 (fax)*

10/15/2010

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/s/

AYANNA S AUGUSTUS
10/15/2010

Augustus, Ayanna

Subject: RE: NDA 22-516 Cymbalta - continuous responder graphs

From: Matt Kuntz [mailto:KUNTZ_MATT@LILLY.COM]
Sent: Thursday, September 23, 2010 4:35 PM
To: Augustus, Ayanna
Subject: RE: NDA 22-516 Cymbalta - continuous responder graphs

Hi Ayanna,
This is very helpful. Many thanks for the follow-up. I'll keep you updated on the timing for our response.
Best regards,
Matt

Matt Kuntz, RPh, MBA, RAC
Global Regulatory Affairs - US
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Office 317.433.1766
Mobile 317.625.5151

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"Augustus, Ayanna" <Ayanna.Augustus@fda.hhs.gov>

To 'Matt Kuntz' <KUNTZ_MATT@LILLY.COM>

cc

09/23/2010 04:19 PM

Subject RE: NDA 22-516 Cymbalta - continuous responder graphs

Hi Matt,

Obviously, a tcon with the stats group isn't going to happen today. The statistician has indicated that you should use the diary data in order to get the information for each week. There should be 12 graphs per study (one graph for each week).

If it will not be possible to provide the graphs by week based on BPI than provide graphs based on Diary measures.

Let me know if you have additional questions.

Ayanna

10/15/2010

From: Matt Kuntz [mailto:KUNTZ_MATT@LILLY.COM]
Sent: Thursday, September 23, 2010 9:28 AM
To: Augustus, Ayanna
Subject: RE: NDA 22-516 Cymbalta - continuous responder graphs

Hi Ayanna,

Our stats group is preparing a total of 10 graphs based on the three positive studies with BPI as primary:
3 for OA study HMFG - BPI collected at week 4,7,13
3 for CLBP study HMEN - BPI collected at week 4,7,13
4 for CLBP study HMGC - BPI collected at week 3,6,9,12

Please confirm this will satisfy the request or let me know if we need to modify the output. If we've interpreted the request correctly and no revisions are needed, we should be able to provide these by COB tomorrow.

Thanks,
Matt

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Matt Kuntz/AM/LLY

09/22/2010 06:39 PM
To "Augustus, Ayanna" <Ayanna.Augustus@fda.hhs.gov>
cc
Subject RE: NDA 22-516 Cymbalta - continuous responder graphs [Link](#)

Hi Ayanna,
Thanks for the prompt reply. I've forwarded this to our stats group and will let you know if there are any additional questions.
Matt

Matt Kuntz, RPh, MBA, RAC
Global Regulatory Affairs - US
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Office 317.433.1766
Mobile 317.625.5151

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recipient, please contact the sender by reply e-mail and destroy all copies of the original message.

"Augustus, Ayanna" <Ayanna.Augustus@fda.hhs.gov>

09/22/2010 05:26 PM

To 'Matt Kuntz' <KUNTZ_MATT@LILLY.COM>

cc

Subject RE: NDA 22-516 Cymbalta - continuous responder graphs

Hi Matt,

I've populated the Division's responses to the questions below in red. If possible, please provide graphs by COB, Friday, September 24th.

Thanks,
Ayanna

From: Matt Kuntz [mailto:KUNTZ_MATT@LILLY.COM]
Sent: Wednesday, September 22, 2010 4:12 PM
To: Augustus, Ayanna
Subject: RE: NDA 22-516 Cymbalta - continuous responder graphs

Hi Ayanna,
I've gotten the following three questions back from our Stats Group. Clarification on these points as soon as possible would be greatly appreciated.

1) Given that the request is for graphs by week, does the Agency want these graphs based on Diary measures or based on the in office BPI?

Based on the in office BPI.

2) By continuous responder graphs, does the Agency want a table similar to those provided within the current draft labeling, but with a separate graph for each week? **Yes, separate graphs for each week**

3) For each of these responder graphs, should patients who drop out be considered nonresponders at every week after they drop out or should we count patients who drop out prior to study completion as nonresponders at all weeks, even those occurring prior to study drop out? **The latter. All patients that drop out should be nonresponders at all weeks.**

As much as we would like to, we may not be able to provide the graphs requested by noon tomorrow because of the underlying complexity and the need for validation of all the programs to ensure they are accurate. I'll keep you posted.

I'll send you the tcon info and Lilly attendees in a separate email.

Thanks

Matt

Matt Kuntz, RPh, MBA, RAC

10/15/2010

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"Augustus, Ayanna" <Ayanna.Augustus@fda.hhs.gov>

09/22/2010 03:16 PM

To 'Matt Kuntz' <KUNTZ_MATT@LILLY.COM>
cc
Subject RE: NDA 22-516 Cymbalta - next steps following the AC meeting

Hi Matt,

Please provide continuous responder graphs for each week for CLBP and OA with the y-axis ranging from 1-100%. Please provide this data by noon, tomorrow or sooner if possible.

Also, please provide a call-in number for tomorrow's meeting and a list of Lilly attendees.

Thanks,
Ayanna

From: Matt Kuntz [mailto:KUNTZ_MATT@LILLY.COM]
Sent: Monday, September 20, 2010 9:44 AM
To: Augustus, Ayanna
Subject: RE: NDA 22-516 Cymbalta - next steps following the AC meeting

Hi Ayanna.
Do you think the review team will provide any comments back on our 9/13/10 proposed labeling prior to the teleconference this Thursday?

Could you provide the expected FDA participant names? I'll provide a teleconference number and Lilly participants later this week.

Thanks,
Matt

Matt Kuntz, RPh, MBA, RAC
Global Regulatory Affairs - US
Eli Lilly and Company
Office 317.433.1766
Mobile 317.625.5151

10/15/2010

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"Augustus, Ayanna" <Ayanna.Augustus@fda.hhs.gov>

09/14/2010 01:02 PM

To 'Matt Kuntz' <KUNTZ_MATT@LILLY.COM>

cc

Subject RE: NDA 22-516 Cymbalta - next steps following the AC meeting

10/15/2010

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/s/

AYANNA S AUGUSTUS
10/15/2010

Augustus, Ayanna

Subject: RE: Cymbalta/container labels

From: Matt Kuntz [mailto:KUNTZ_MATT@LILLY.COM]
Sent: Thursday, October 14, 2010 9:30 AM
To: Augustus, Ayanna
Subject: RE: Cymbalta/container labels

Hi Ayanna,

Thanks for the call this morning. It was very helpful to confirm our understanding of review status. Please don't hesitate to let me know if anything is needed from us.

Best,
Matt

Matt Kuntz, RPh, MBA, RAC
Global Regulatory Affairs - US
Eli Lilly and Company
Office 317.433.1766
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"Augustus, Ayanna" <Ayanna.Augustus@fda.hhs.gov>

To 'Matt Kuntz' <KUNTZ_MATT@LILLY.COM>

cc

Subject RE: Cymbalta/container labels

10/14/2010 09:04 AM

Hi Matt,
We'll call in in about 10 minutes or so

From: Matt Kuntz [mailto:KUNTZ_MATT@LILLY.COM]
Sent: Thursday, October 14, 2010 8:37 AM
To: Augustus, Ayanna
Cc: 'Matt Kuntz'
Subject: RE: Cymbalta/container labels

Hi Ayanna,

While we don't have any specific labeling comments to discuss, we would be interested in understanding whether there are any remaining review items, and if not when an action is likely to occur. A very brief teleconference would be appreciated. Please let me know if we could still have a short tcon.

Thanks,

10/15/2010

Matt

Matt Kuntz, RPh, MBA, RAC
Global Regulatory Affairs - US
Eli Lilly and Company
Office 317.433.1766
Mobile 317.625.5151

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"Augustus, Ayanna" <Ayanna.Augustus@fda.hhs.gov>

10/14/2010 08:22 AM

To: 'Matt Kuntz' <KUNTZ_MATT@LILLY.COM>
cc
Subject: RE: Cymbalta/container labels

Hi Matt,

Since there are only two minor revisions to the label I'm wondering if a tcon is still needed. Let me know if Lilly has any specific comments on the label that you'd like to discuss.

Thanks,
Ayanna

From: Matt Kuntz [mailto:KUNTZ_MATT@LILLY.COM]
Sent: Wednesday, October 13, 2010 5:09 PM
To: Augustus, Ayanna
Subject: RE: Cymbalta/container labels

Thanks Ayanna.

Please find attached the clean/track changes labeling.

We made two minor revisions (track changes version):
Line 1118: Studies in Chronic Pain Due to Osteoarthritis

Line 1066: Added a new sentence "Randomization was stratified by the patients' baseline NSAIDs-use status." prior to the existing sentence: "Subgroup analyses did not indicate that there were differences in treatment outcomes as a function of NSAIDs use." in order to inform why this subgroup data is being described. This suggested additional sentence comes from the OA section.

I look forward to speaking with you tomorrow morning.
Regards,

10/15/2010

Matt

Matt Kuntz, RPh, MBA, RAC
Global Regulatory Affairs - US
Eli Lilly and Company
Office 317.433.1766
Mobile 317.625.5151

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"Augustus, Ayanna" <Ayanna.Augustus@fda.hhs.gov>

10/13/2010 03:12 PM

To 'Matt Kuntz' <KUNTZ_MATT@LILLY.COM>
cc
Subject RE: Cymbalta/container labels

10/15/2010

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AYANNA S AUGUSTUS
10/15/2010

Augustus, Ayanna

From: Augustus, Ayanna
Sent: Tuesday, September 28, 2010 11:39 AM
To: 'Matt Kuntz'
Subject: RE: NDA 22-516 Cymbalta - pediatric plan
Importance: High

Hi Matt,

The Division is going to need the revised pediatric plan/waiver request by **Friday 10:00 AM** rather than a week from today as discussed during this morning's tcon. Lilly's revised plan/waiver request will need to be reviewed by the Pediatric Review Committee which as you can imagine will need to occur *very* soon.

Please let your team know that this will need to be formally submitted to the NDA by Friday morning.

Just to reiterate, if Lilly provides a revised plan, please be sure to provide dates for the following timeline:

Final protocol submission date
Study completion date
Final study report submission date

If Lilly request a waiver, justification for the request. Let me know if you have any additional questions.

Thanks!!
Ayanna

From: Matt Kuntz [mailto:KUNTZ_MATT@LILLY.COM]
Sent: Monday, September 27, 2010 3:08 PM
To: Augustus, Ayanna
Subject: RE: NDA 22-516 Cymbalta - pediatric plan

Hi Ayanna.
I'm confirming for the tcon tomorrow at 10:30 to discuss the pediatric plan.

Here is the call-in number for tomorrow.

Toll Free: 866-213-2145
International: 609-454-9913
Access Code: **4282830**
Host: Matt

Lilly Participants:
Vladimir Skljarevski, Medical Fellow, Cymbalta
Smriti Iyengar, Sr. Research Scientist, Cymbalta
Brady Cunningham, Senior Advisor- Project Management

10/15/2010

Robin Wojcieszek, Sr. Director, Global Regulatory Affairs - US
Matt Kuntz, Manager, Global Regulatory Affairs - US

There may be a couple other Lilly participants, but I have not been able to confirm their availability at this point.

Thanks,
Matt

Matt Kuntz, RPh, MBA, RAC
Global Regulatory Affairs - US
Eli Lilly and Company
Office 317.433.1766
Mobile 317.625.5151

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Matt Kuntz/AM/LLY

To "Augustus, Ayanna" <Ayanna.Augustus@fda.hhs.gov>

cc

09/27/2010 12:50 PM

Subject RE: NDA 22-516 Cymbalta - pediatric plan [Link](#)

Hi Ayanna. I'll get back to you as soon as possible.

Thanks,
Matt

Matt Kuntz, RPh, MBA, RAC
Global Regulatory Affairs - US
Eli Lilly and Company
Office 317.433.1766
Mobile 317.625.5151

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"Augustus, Ayanna" <Ayanna.Augustus@fda.hhs.gov>

To 'Matt Kuntz' <KUNTZ_MATT@LILLY.COM>

cc

09/27/2010 11:52 AM

Subject RE: NDA 22-516 Cymbalta - pediatric plan

Hi Matt,

10/15/2010

In light of the revised indication of chronic musculoskeletal pain, the Division would like to schedule a brief tcon for tomorrow, 9/28, at 10:30 AM to discuss the pediatric plan for this NDA. [REDACTED] (b) (4)

[REDACTED] The pediatric plan will need to be revised to address the indication of chronic musculoskeletal pain.

Please confirm that 10:30 AM works for Lilly and provide a call-in number and list of attendees for this meeting.

Regards,
Ayanna

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/s/

AYANNA S AUGUSTUS
10/15/2010

Augustus, Ayanna

From: Augustus, Ayanna
Sent: Thursday, July 29, 2010 12:25 PM
To: 'Matt Kuntz'
Subject: RE: NDA 22-516 Cymbalta

Hi Matt,

Regarding the pediatric (b) (4) study for chronic pain, please provide the date by which the Division will receive the final study protocol, and the trial completion date by COB, Wednesday, August 4, 2010. Also, formally submit this to the NDA.

Thanks,
Ayanna

From: Matt Kuntz [mailto:KUNTZ_MATT@LILLY.COM]
Sent: Friday, July 23, 2010 12:13 PM
To: Augustus, Ayanna
Subject: RE: NDA 22-516 Cymbalta

Hi Ayanna,
I'm sorry for not getting a response back yesterday.

We'd prefer to wait until we've had an opportunity to review the FDA briefing document and make any adjustments to our core slides. This should help ensure the draft core presentation we send is reasonably stable. Based on a July 30th receipt, I think we can get our draft slides to you by Aug 9th, if not sooner.

Do you think this will provide enough time for the FDA presenters to react accordingly with their own slide development?

Best regards,
Matt

Matt Kuntz, RPh, MBA, RAC
Global Regulatory Affairs – US
Eli Lilly and Company
Office 317.433.1766
Mobile 317.625.5151

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22516	ORIG-1	ELI LILLY AND CO	CYMBALTA

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/s/

AYANNA S AUGUSTUS
07/29/2010

Augustus, Ayanna

From: Augustus, Ayanna
Sent: Tuesday, May 18, 2010 5:14 PM
To: 'Bryan E Boggs'
Subject: RE: Cymbalta
Attachments: 22516cymbalta working label 051210 shh.doc

Hi Bryan,

Our general practice is to provide the sponsor with the AC agenda which outlines the topics that will be discussed during the meeting. As was mentioned during the April 14th tcon between the Division and Lilly, the Agency intends to present the safety and efficacy data in the NDA as well as the current data on the hepatotoxicity issue.

We also generally request that sponsors provide a copy of any draft presentations and a draft background package as this will help minimize overlap between the Agency and sponsor presentations so any draft copies you have to share at this time are appreciated.

The Division is still working on the meeting agenda so I don't have one to share at this time. Please keep in mind that the AC meeting date is tentative and not made official until the FR notice is published. Therefore, please do not issue any press releases about the meeting until the notice has been published.

Attached you will find a copy of the current draft label. Please note that there are several comments throughout the label that will need to be addressed, which I've also noted below:

1. Section 5.2, Revise the rate of ALT>3 times upper limit of normal for Cymbalta and placebo-treated patients to include the percentage of patients with both normal and abnormal baseline LFTs.
2. In section 6.1 Provide data to support the proposed changes to the exposure numbers for the placebo-controlled data for MDD and GAD as these numbers are inconsistent with the exposure numbers in the label approved on 11/19/09.
3. In section 6.2 in the DPNP section, provide an explanation for the new numbers.
4. In section 6.2 in the Chronic Low Back Pain section, include numbers from HMCG study.

Please provide a revised label in by COB, Friday, May, 28th. Please accept all changes for which there is agreement between Lilly and the Division. Any changes that require additional discussion or review should be visible in track changes mode. Please email me if you have any questions.

Regards,
Ayanna

From: Bryan E Boggs [mailto:BOGGS_BRYAN_E@LILLY.COM]
Sent: Tuesday, May 18, 2010 6:46 AM
To: Augustus, Ayanna

7/8/2010

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22516	ORIG-1	ELI LILLY AND CO	CYMBALTA

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/s/

AYANNA S AUGUSTUS
07/08/2010

Augustus, Ayanna

From: Greeley, George
Sent: Tuesday, March 23, 2010 9:35 AM
To: Augustus, Ayanna
Cc: Stowe, Ginneh D.
Subject: NDA 22-516 Cymbalta

Importance: High

Hi Ayanna,

The Cymbalta (duloxetine hydrochloride) partial waiver and deferral and plan was reviewed by the PeRC on February 17, 2010.

The Division recommended a partial waiver in patients 0-6 years because there are too few children with disease/condition to study and a deferral in patients 7-16 years of age because the product is ready for approval in adults.

The PeRC agreed with the Division to grant a partial waiver and deferral for this product.

Thank you.

George Greeley
Regulatory Health Project Manager
Pediatric and Maternal Health Staff
FDA/CDER/OND
10903 New Hampshire Avenue
Bldg. 22, Room 6467
Silver Spring, MD 20993-0002
Phone: 301.796.4025
Email: george.greeley@fda.hhs.gov

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22516	ORIG-1	ELI LILLY AND CO	CYMBALTA

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/s/

AYANNA S AUGUSTUS
06/29/2010

REQUEST FOR CONSULTATION

TO (Office/Division): OSE, Abolade Adeolu, RPM

FROM (Name, Office/Division, and Phone Number of Requestor): DAARP,
Ayanna Augustus, RPM

DATE 6/7/10	IND NO.	NDA NO. 22516	TYPE OF DOCUMENT Type 6 NDA	DATE OF DOCUMENT 5/15/09
NAME OF DRUG Cymbalta (duloxetine hydrochloride)		PRIORITY CONSIDERATION priority	CLASSIFICATION OF DRUG analgesia	DESIRED COMPLETION DATE 7/7/10

NAME OF FIRM: Eli Lilly and Co.

REASON FOR REQUEST

I. GENERAL

<input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION <input type="checkbox"/> MEETING PLANNED BY	<input type="checkbox"/> PRE-NDA MEETING <input type="checkbox"/> END-OF-PHASE 2a MEETING <input type="checkbox"/> END-OF-PHASE 2 MEETING <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> SAFETY / EFFICACY <input type="checkbox"/> PAPER NDA <input type="checkbox"/> CONTROL SUPPLEMENT	<input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> FINAL PRINTED LABELING <input type="checkbox"/> LABELING REVISION <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> FORMULATIVE REVIEW <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): Summary review for Advisory Committee background package
--	---	--

II. BIOMETRICS

<input type="checkbox"/> PRIORITY P NDA REVIEW <input type="checkbox"/> END-OF-PHASE 2 MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):	<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):
---	--

III. BIOPHARMACEUTICS

<input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE 4 STUDIES	<input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST
--	--

IV. DRUG SAFETY

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

V. SCIENTIFIC INVESTIGATIONS

<input type="checkbox"/> CLINICAL	<input type="checkbox"/> NONCLINICAL
-----------------------------------	--------------------------------------

COMMENTS / SPECIAL INSTRUCTIONS: Cymbalta (duloxetine) is approved for the treatment of Major Depressive Disorder, Generalized Anxiety Disorder (NDA 21427-parent NDA in the Division of Psychiatry Products), Neuropathic pain and Fibromyalgia. NDA 22-516 for Cymbalta for the indication of treatment of chronic pain is being presented to the Anesthetic and Life Support Drugs Advisory Committee on **August 19, 2010** to discuss the overall risk benefit of approving this medication for the broad indication of chronic pain. An important aspect of the discussion will be the safety profile of Cymbalta, specifically the associated hepatotoxicity. We request that you provide a summary document of the safety profile for duloxetine, including data regarding hepatotoxicity for the background package to be distributed to members of the advisory committee. Please submit the summary to Ayanna Augustus by **July 7, 2010**. Ellen Fields (6-1209) is the CDTL for this application.

Please contact Ayanna Augustus if you have any additional questions (6-3980)

SIGNATURE OF REQUESTOR Ayanna Augustus, RPM	METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> DARRTS <input type="checkbox"/> EMAIL <input type="checkbox"/> MAIL <input type="checkbox"/> HAND
--	---

PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER
--	---

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22516	ORIG-1	ELI LILLY AND CO	CYMBALTA

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/s/

AYANNA S AUGUSTUS
06/07/2010

REQUEST FOR CONSULTATION

TO (Office/Division): Division of Psychiatry Products, Paul David, CPMS; Steve Hardeman, CPMS

FROM (Name, Office/Division, and Phone Number of Requestor): DAARP, Ayanna Augustus, RPM

DATE 6/7/10	IND NO.	NDA NO. 22516	TYPE OF DOCUMENT Type 6 NDA	DATE OF DOCUMENT 5/15/09
NAME OF DRUG Cymbalta (duloxetine hydrochloride)		PRIORITY CONSIDERATION priority	CLASSIFICATION OF DRUG analgesia	DESIRED COMPLETION DATE 7/7/10

NAME OF FIRM: Eli Lilly and Co.

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> SAFETY / EFFICACY | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): Summary review for Advisory Committee background package |
| <input type="checkbox"/> MEETING PLANNED BY | <input type="checkbox"/> CONTROL SUPPLEMENT | |

II. BIOMETRICS

- | | |
|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW | <input type="checkbox"/> CHEMISTRY REVIEW |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY |
| <input type="checkbox"/> CONTROLLED STUDIES | <input type="checkbox"/> BIOPHARMACEUTICS |
| <input type="checkbox"/> PROTOCOL REVIEW | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): | |

III. BIOPHARMACEUTICS

- | | |
|--|--|
| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG SAFETY

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

V. SCIENTIFIC INVESTIGATIONS

- | | |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS / SPECIAL INSTRUCTIONS: NDA 22516 for Cymbalta (duloxetine) for the indication of treatment of chronic pain is being presented to the Anesthetic and Life Support Drugs Advisory Committee on August 19, 2010 to discuss the overall risk benefit of approving this medication for the broad indication of chronic pain. An important aspect of the discussion will be the safety profile of Cymbalta, specifically the associated hepatotoxicity. We request that you provide a summary document of the hepatotoxicity analysis performed by your division for the background package to be distributed to members of the advisory committee. Please submit the summary to Ayanna Augustus by **July 7, 2010**. Ellen Fields (6-1209) is the CDTL for this application.

Please contact Ayanna Augustus if you have any additional questions (6-3980)

SIGNATURE OF REQUESTOR Ayanna Augustus, RPM	METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> DARRTS <input type="checkbox"/> EMAIL <input type="checkbox"/> MAIL <input type="checkbox"/> HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22516	ORIG-1	ELI LILLY AND CO	CYMBALTA

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/s/

AYANNA S AUGUSTUS
06/07/2010

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

DRUG USE REQUEST FORM
for OFFICE of SURVEILLANCE and EPIDEMIOLOGY
PLEASE SUBMIT REQUESTS TO: CDER OSE CONSULTS (OSECONSULTS@CDER.FDA.GOV)

PART 1 - Requestor Information

4-WEEK TURNAROUND ON ALL DATA REQUESTS EXCEPT IN EXTRAORDINARY CASES.

Requestor's Name:	Ellen Fields	Today's Date:	2010-05-27
Office/Division:	OND/DAAP	Desired Completion Date:	2010-08-02
Phone number:	301-796-1209	Drug name(s):	Cymbalta (duloxetine HCl)
Email Address:	ellen.fields@fda.hhs.gov	Drug Classification:	Antidepressant
Existing RCM #		NDA#	22-516
		IND#	
		ANDA#	
		BLA#	

PART 2 - Purpose of Drug Use Data

Please select appropriate choice (s):

- AC Meeting/Sponsor Meeting
 Safety Review
 Trade Name Review
 Pediatric Drug Use Analysis (eg, BPCA, PdIT)
 Other:
 Publication/Manuscript/Presentation/Research

PART 3 - Background and Reason for Request

Please provide a DETAILED background of the issue(s) surrounding the drug use request and the question you are trying to answer.

Background: We are currently reviewing NDA 22-516 for duloxetine for the treatment of chronic pain. An advisory committee meeting is planned for August 19, 2010 to discuss the risk/benefit of approving this drug for a larger patient population given its safety profile, specifically some liver toxicity. It is currently approved for the treatment of major depressive disorder, generalized anxiety disorder, diabetic peripheral neuropathy, and fibromyalgia (NDAs 21-427, 21-733, 22-148).

For comparison purposes, we need data regarding the use of cymbalta for both on and off label indications. We request drug use data by indication and also by type of prescriber, as well as overall prescribing data to present at the AC, so we can estimate how much, approving this drug for chronic pain, will actually increase the patient population. Please let me know if you have any questions.

PART 4 - Specifics (time period of analysis, demographics such as age bands)

Please select appropriate choice(s):

**Analysis may take longer than 4 weeks*

<input type="radio"/> Duration of Use analysis*	Study Period:
<input type="radio"/> Concurrency analysis*	Display Time from (Year) 2005 to (Year) 2010
<input type="radio"/> Data to display gender breakdown	<input type="radio"/> monthly increments
<input type="radio"/> Data to display age bands:	<input checked="" type="radio"/> yearly increments
Age bands to include: <input type="text"/>	<input type="radio"/> Other indications, prescribers

PART 5 - CLEARANCE (Required if data are to be shared outside of FDA or with non-FDA Persons)

CLEARANCE PROCESS TAKES 48 ADDITIONAL HOURS

Drug Use Data are proprietary and obtained by FDA under contract. Therefore, these data cannot be released to the public/non-FDA personnel without contractor approval obtained through the FDA/CDER Office of Surveillance and Epidemiology.

CLEARANCE NEEDED?

- YES NO

For information on clearance procedures and forms, go to:
<http://inside.fda.gov/CDER/OfficeofSurveillanceandEpidemiology/>

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
----- NDA-22516	----- ORIG-1	----- ELI LILLY AND CO	----- CYMBALTA

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/s/

AYANNA S AUGUSTUS
06/03/2010

Augustus, Ayanna

To: Augustus, Ayanna

Subject: RE: FW: NDA 21427 - Type A Meeting Granted

From: Augustus, Ayanna

Sent: Thursday, February 04, 2010 2:16 PM

To: 'Bryan E Boggs'

Cc: Kevin C Sheehan

Subject: RE: FW: NDA 21427 - Type A Meeting Granted

Hi Bryan,

The revised pediatric plan emailed on 1/15/10 was never formally sent via Gateway. Please try submitting it again.

In addition, please indicate the date Lilly plans to submit the final protocol for the (b) (4) pediatric study. Please provide a response by COB, Monday, February 8, 2010.

Regards,
Ayanna

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22516	ORIG-1	ELI LILLY AND CO	CYMBALTA

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/s/

AYANNA S AUGUSTUS
02/10/2010

Augustus, Ayanna

From: Augustus, Ayanna
Sent: Thursday, January 28, 2010 3:19 PM
To: 'Bryan E Boggs'
Subject: RE: NDA 22-516

Hi Bryan,

The Agency is currently reviewing the REMS proposal for NDA 22516. Although Cymbalta has an approved Medication Guide, it does not have an approved REMS. Please submit to the parent NDA, 21427 the identical REMS proposal submitted to the chronic pain NDA.

In addition, please submit your latest version of Cymbalta labeling annotated with explanations for all changes in active links. Please submit this labeling by Monday, February 1st.

Regards,
Ayanna

From: Bryan E Boggs [mailto:BOGGS_BRYAN_E@LILLY.COM]
Sent: Thursday, January 28, 2010 8:42 AM
To: Augustus, Ayanna
Subject: NDA 22-516

Hi Ayanna,

I am sure you will let me know if there is anything else you need from Lilly for this NDA. After today's reviewers meeting, would you let me know if timelines have changed (specifically PMCs and labeling requests by February 22)? Thanks.

Kind regards,
Bryan

Bryan Boggs, Pharm.D.
Global Regulatory Affairs - US
Eli Lilly & Company
Office: 317-276-6685 FAX: 317-276-1652
Mobile: 317-681-4997 bboggs@lilly.com

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22516	ORIG-1	ELI LILLY AND CO	CYMBALTA

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/s/

AYANNA S AUGUSTUS
02/10/2010

Augustus, Ayanna

From: Bryan E Boggs [BOGGS_BRYAN_E@LILLY.COM]
Sent: Friday, December 11, 2009 12:31 PM
To: Augustus, Ayanna
Subject: Re: NDA 22516/Cymbalta/Pediatric Plan

Hi Ayanna,

The team met today and discussed the Division's proposed pediatric plan for chronic pain in children and adolescents. Lilly understands the need for pediatric data in chronic pain and are committed in providing an appropriate plan that we would be able to implement within a reasonable time period. After careful preliminary consideration, we believe there are several pieces to the proposed plan below that will not be feasible in this population. We acknowledge the need to include children and will take that into consideration. We also understand the desire for a randomized, double-blind, placebo-controlled trial. We will also consider this within our updated plan.

We don't believe a study, such as proposed by the FDA below in CLBP is feasible within a reasonable timeframe based on the estimated children and adolescents with this condition. We will not be able to provide a proposal back by December 18, 2009 as requested and ask that the Division consider our revised pediatric chronic pain plan to be submitted no later than January 15, 2010. We realize the Division's internal review timelines and your January final review meeting, however, we want to provide to you a plan that is well researched and previewed both internally and externally on clinical need and feasibility. So we ask the Division to accept a response date to this request of on or before January 15, 2010.

Kind regards,
 Bryan

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

"Augustus, Ayanna" <Ayanna.Augustus@fda.hhs.gov>

To <BOGGS_BRYAN_E@LILLY.COM>

cc

Subject NDA 22516/Cymbalta/Pediatric Plan

12/10/2009 02:02 PM

Dear Byran,

The clinical reviewer for this NDA has the following comments regarding the pediatric plan :

We have reviewed your proposed pediatric plan and found it unacceptable.

(b) (4)

12/18/2009

(b) (4)

(b) (4)

. You are required to attempt to formulate an age appropriate formulation for younger patients if necessary. As part of the pediatric plan, you must submit the type(s) of studies you plan to carry out, along with the following dates: protocol submission, study start, study completion, and submission of final study report to the Agency.

Please submit the revised pediatric plan to the Agency by December 18, 2009.

Regards,
Ayanna

Ayanna Augustus, Ph.D.
Regulatory Project Manager
Division of Anesthesia, Analgesia,
and Rheumatology Products
Center for Drug Evaluation and Research
Food and Drug Administration
Bldg. 22, Rm 3219
10903 New Hampshire Ave
Silver Spring, MD 20993
301-796-3980 (phone)
301-796-9717 (fax)

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22516	ORIG-1	ELI LILLY AND CO	CYMBALTA

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/s/

AYANNA S AUGUSTUS
12/18/2009

Augustus, Ayanna

To: Bryan E Boggs**Subject:** RE: NDA 022516/Cymbalta/Information Request**From:** Bryan E Boggs [mailto:BOGGS_BRYAN_E@LILLY.COM]**Sent:** Friday, December 04, 2009 3:14 PM**To:** Augustus, Ayanna**Subject:** RE: NDA 022516/Cymbalta/Information Request

Hi Ayanna,

Attached is a response to your reviewers request on the FM discontinuation number change. I have also sent this as a formal response through eCTD to NDA 21-427. Please let me know if there are further questions.

Regards,
Bryan

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

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"Augustus, Ayanna" <Ayanna.Augustus@fda.hhs.gov>

To "Bryan E Boggs" <BOGGS_BRYAN_E@LILLY.COM>

cc

12/02/2009 01:52 PM

Subject RE: NDA 022516/Cymbalta/Information Request

Hi Bryan,

I hope you had a wonderful Thanksgiving holiday. Please indicate when the Division might receive a response to the information request sent to you on Monday, November 23rd (please see attachment).

Regards,
Ayanna

----- Message from "Augustus, Ayanna" <Ayanna.Augustus@fda.hhs.gov> on Mon, 23 Nov 2009 15:54:23 -0500 -----

To: "Bryan E Boggs" <BOGGS_BRYAN_E@LILLY.COM>

12/18/2009

Subject: RE: NDA 022516/Cymbalta/Information Request

Hi Bryan,

Please send the outline of the background package as well as a copy of your slides on Dec 10th to me via email.

Regarding the updated labeling, please submit your revised labeling which should include the approved changes along with your proposed changes to address the chronic pain indication you are seeking. Please send updated labeling in tracked changes mode and a clean copy as WORD documents.

The Division is working with DPP on the review of the PAS submitted for Cymbalta (NDA 21427 SLR-033) which provides for changes to the fibromyalgia sections of the label. The clinical reviewer has the following comment and request for clarification:

In the prior approval supplement (PAS) submitted September 22, 2009, you request a change in the number of FM patients treated with duloxetine who discontinued treatment due to an adverse reaction (b) (4) and the accompanying percentage (b) (4). Your rationale is that the number (b) (4) reflects what was listed in the Integrated Summary of Safety (Section 5.3.5.3) submitted with the initial application 22-148.

When we opened the initial application for NDA 22-148 (August 14, 2007), Table 2.7.4.6 from the ISS Tables, page 27 has the number (b) (4) for duloxetine patients who discontinued due to adverse event. Following revisions of the comments on the Case Report Forms, this number changed to (b) (4) (Table 2.7.4.7 from the ISS Tables, page 28).

Explain why (b) (4) is the number that reflects what was in the ISS submitted with the initial application 22-148."

Please provide a response by COB, Tuesday December 1, 2009

Regards,

Ayanna

Phone: 317 276 2000

04 December 2009

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Psychiatry Products

RESPONSE TO FDA REQUEST FOR INFORMATION

Re: NDA 21-427; LY248686 Cymbalta[®] (Duloxetine Hydrochloride); eCTD Sequence No. 0081

Dear Dr. Laughren,

Reference is made to the Prior Approval Supplement submitted on 22 September 2009 to the Division of Psychiatry products (sequence 0072). Reference is also made to an FDA email sent to Bryan Boggs (Lilly) from Ayanna Augustus (FDA's project manager for the Division of Anesthesia, Analgesia and Rheumatology Products) on 23 November 2009 requesting additional information. Lilly's response to the Division's information request is provided below. This response was also emailed separately to Ayanna Augustus.

FDA Request: *"In the prior approval supplement (PAS) submitted September 22, 2009, you request a change in the number of FM patients treated with duloxetine who discontinued treatment due to an adverse reaction from (b) (4) and the accompanying percentage from (b) (4). Your rationale is that the number (b) (4) reflects what was listed in the Integrated Summary of Safety (Section 5.3.5.3) submitted with the initial application 22-148.*

When we opened the initial application for NDA 22-148 (August 14, 2007), Table 2.7.4.6 from the ISS Tables, page 27 has the number (b) (4) for duloxetine patients who discontinued due to adverse event. Following revisions of the comments on the Case Report Forms, this number changed to (b) (4) (Table 2.7.4.7 from the ISS Tables, page 28).

Explain why (b) (4) is the number that reflects what was in the ISS submitted with the initial application 22-148."

Lilly Response: *The rationale stated in the original PAS submitted to FDA for Cymbalta (NDA 21427 SLR-033) for changing the number of FM patients treated with duloxetine who discontinued treatment due to an adverse reaction from (b) (4) contained an incorrect reference. The number of (b) (4) FM patients discontinued due to an adverse event is based upon table APP.5.2 in NDA 22-516 (page 4128, Section 5.3.5.3) instead of NDA 22-148.*

The reason for the number change from (b) (4) in NDA 22-148 to (b) (4) in NDA 22-516 is due to the fact that a different database for study HMCJ was used for those 2 submissions. For NDA 22-148, data from an interim lock (for the acute, placebo-controlled study period only) was used, and patient HMCJ-112-2203 was recorded as discontinued due to "subject decision" in that interim database. Study HMCJ had an extension phase and final data locked occurred after the original FM submission (22-148). In the final database, the disposition reason for patient HMCJ-112-2203 was changed to "discontinued due to adverse events" (DCAE). For NDA 22-516, data from that HMCJ final lock was used, and this patient "HMCJ-112-2203" was added to the count of DCAE resulting (b) (4) patients discontinued due to adverse event from FM studies in NDA 22-516.

This submission is being sent via the FDA WebTrader Gateway. The submission was prepared on a virus protected workstation and all files were automatically scanned upon submission to the FDA. Lilly workstations are protected by the up-to-date version of the Symantec AntiVirus software. For eCTD technical questions concerning the format of the electronic submissions, please contact Amy Holloway at 317-276-9813 or holloway_amy_jo@lilly.com.

Please call me at (317) 276-6685 if you require further information or have any questions. Alternatively, you may contact Dr. Gregory T. Brophy, Senior Director, US Regulatory Affairs, at (317) 277-3799.

Sincerely,
ELI LILLY AND COMPANY

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

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
----- NDA-22516	----- ORIG-1	----- ELI LILLY AND CO	----- CYMBALTA

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/s/

AYANNA S AUGUSTUS
12/18/2009

REQUEST FOR DDMAC LABELING REVIEW CONSULTATION

****Please send immediately following the Filing/Planning meeting****

TO: CDER-DDMAC-RPM	FROM: (Name/Title, Office/Division/Phone number of requestor) Ayanna Augustus, Project Manager, DAARP (6-3890)
------------------------------	--

REQUEST DATE 11/25/08	IND NO.	NDA/BLA NO. 22516	TYPE OF DOCUMENTS (PLEASE CHECK OFF BELOW)
---------------------------------	---------	-----------------------------	---

NAME OF DRUG Cymbalta	PRIORITY CONSIDERATION standard	CLASSIFICATION OF DRUG Analgesic	DESIRED COMPLETION DATE January 18, 2010
---------------------------------	---	--	--

NAME OF FIRM: Eli Lilly and Company	PDUFA Date: March 15, 2010
---	-----------------------------------

TYPE OF LABEL TO REVIEW

TYPE OF LABELING: (Check all that apply) <input checked="" type="checkbox"/> PACKAGE INSERT (PI) <input type="checkbox"/> PATIENT PACKAGE INSERT (PPI) <input type="checkbox"/> CARTON/CONTAINER LABELING <input checked="" type="checkbox"/> MEDICATION GUIDE <input type="checkbox"/> INSTRUCTIONS FOR USE(IFU)	TYPE OF APPLICATION/SUBMISSION <input type="checkbox"/> ORIGINAL NDA/BLA <input type="checkbox"/> IND <input checked="" type="checkbox"/> EFFICACY SUPPLEMENT/Type 6 NDA <input type="checkbox"/> SAFETY SUPPLEMENT <input type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> PLR CONVERSION	REASON FOR LABELING CONSULT <input checked="" type="checkbox"/> INITIAL PROPOSED LABELING <input type="checkbox"/> LABELING REVISION
--	---	---

EDR link to submission: This product is approved for multiple indications in DPP and DAARP. The PI and Medication Guide contains new information to reflect the proposed chronic pain indication. Anjelina Pokrovnichka is the clinical reviewer for this NDA. <\\CDSESUB1\EVSPROD\NDA022516\022516.enx>

Please Note: There is no need to send labeling at this time. DDMAC reviews substantially complete labeling, which has already been marked up by the CDER Review Team. The DDMAC reviewer will contact you at a later date to obtain the substantially complete labeling for review.

COMMENTS/SPECIAL INSTRUCTIONS:

Mid-Cycle Meeting: October 15, 2009

Labeling Meetings: January 5, 18, 27 and February 2

Wrap-Up Meeting: January 15, 2010

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> DAARTS <input type="checkbox"/> HAND
SIGNATURE OF RECEIVER	

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22516	ORIG-1	ELI LILLY AND CO	CYMBALTA

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/s/

AYANNA S AUGUSTUS
11/25/2009

Augustus, Ayanna

From: Augustus, Ayanna
Sent: Wednesday, September 30, 2009 4:45 PM
To: 'Bryan E Boggs'
Subject: RE: NDA 022516/Cymbalta/Information Request

Hi Bryan,

The clinical reviewer has the following response to your proposed approaches to address our information requests:

1. For all the analyses requested, patients with abnormal baseline LFT's values should be defined as patients who had >1xULN liver function test values. Do not include patients with values <1xULN.
2. Markedly abnormal values for ALT and AST should be presented as >3xULN, >5xULN, and >10xULN.
3. For the extension phase of HMEN trial, in addition to the analysis that you are proposing, submit a separate analysis in which the 60mg and 120mg dose groups (regardless of what was their treatment assignment during the acute phase) are compared.

Regards,
 Ayanna

From: Bryan E Boggs [mailto:BOGGS_BRYAN_E@LILLY.COM]
Sent: Wednesday, September 30, 2009 1:50 PM
To: Augustus, Ayanna
Subject: Re: NDA 022516/Cymbalta/Information Request

Hi Ayanna,

Just to add additional clarity, I have added two sentences in [blue](#) from my previous message. Otherwise, this is the same as what I just sent to you.

Regards,
 Bryan

Bryan E Boggs/AM/LLY

09/30/2009 01:43 PM

To "Augustus, Ayanna" <Ayanna.Augustus@fda.hhs.gov>
 cc
 Subject Re: NDA 022516/Cymbalta/Information Request [Link](#)

Hi Ayanna,

We are currently working on providing the analyses requested in your e-mail from September 25. Our approach

10/1/2009

to each of the requests are outlined below in **RED**. The Division's original requests are in normal black text.

I am sending this to you so that the reviewers have a chance to comment on the expected analyses before we submit the results on October 7th. In the meantime, our team is working to provide a response as outlined below.

Kind regards,
Bryan

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

Confidentiality Notice - this e-mail message from Eli Lilly and Company (including all attachments) is for the sole use of the intended recipients(s) and may contain confidential and privileged information. Any unauthorized review, use, disclosure, copying or distribution is strictly prohibited. If you are not the intended recipient, please contact me by reply e-mail and destroy all copies of the original message.

1. We request that you submit a separate pooled analysis (HMEO, HMEN, HMEP, and HMFG trials) of hepatic safety presented, by treatment group and duloxetine dose for the first 7 weeks and for the weeks 8 to 13, that includes *only randomized subjects with abnormal baseline LFT's values*. Similar to the presentation approach in your August 14, 2009 submission, you can separate the hepatic-related analyses into four different sections:

- Pooled analysis of hepatic-related adverse events.

[Lilly Approach] Patients with abnormal baseline LFT's values will be defined as patients with abnormally high (>1X ULN) or low (<1X ULN) values for any of the hepatic labs including ALT, AST, Total Bilirubin, ALKPH and GGT at any time during baseline visits.

- Pooled analysis of liver function tests, including mean change from baseline, shift analysis from baseline to abnormal (high and low), and markedly abnormal values.

[Lilly Approach] For the Mean change from baseline to endpoint/maximum, Lilly will create two separate tables: a) one for patients with abnormally high baseline values (i.e, the last nonmissing value at baseline is high); and b) one for patients with abnormally low baseline values (i.e, the last nonmissing value at baseline is low).

For the shift analysis from baseline to abnormal (either high or low), patients with abnormal high or low values at any baseline visits will be included in this analysis. Lilly will create the tables based on the mock up table below.

Lab	Direction	Placebo N n %	DLX20QD N n %	DLX60QD N n %	DLX120QD N n %	DLX Total N n %
XXX	Low -Lower					
	Low-Low					
	Low- Normal					
	Low-High					

High -Low
High-Normal
High -High
High-Higher

To assess "markedly abnormal values", Lilly will use two approaches: a) For ALT and AST, a definition commonly used for to assess a clinically significant high as >3XULN will be used, patients with abnormal high (>1XULN) values at any baseline visits will be included in this analysis. b) For all hepatic labs including ALT and AST, Lilly will also conduct treatment emergent potentially clinically significant (PCS) high analysis for all hepatic labs, patients with abnormal high or low values at any baseline visits will be included in this analysis.

- Pooled analysis of discontinuation due to hepatic-related adverse event or elevations in LFTs.

[Lilly Approach] Patients with abnormal baseline LFT's values will be defined as patients with abnormally high or low values for any of the hepatic labs including ALT, AST, Total Bilirubin, ALKPH and GGT at any time during baseline visits.

- Pooled analysis for laboratory values overtime for subjects with increase in ALT/AST and bilirubin values. Indicate whether treatment was discontinued or not and time of discontinuation related to obtaining lab tests.

[Lilly Approach] A previously submitted listing, "Table APP.2. Listing of Patients with Abnormal ALT, AST, or Bilirubin Values at Anytime During Postbaseline Visits" actually includes all patients with normal or abnormal baseline values. For this response, Lilly will create a report that is the same as Table APP.2, except that this new table will only include patients with abnormal high or low baseline values.

Below is the first page from Table APP.2 contained in the August 14, 2009 regulatory Response.



2. In addition, for the extension phase of the HMEN trial, submit the analyses described above presented by dose (duloxetine 60mg and duloxetine 120mg) at the time of the event. For these analyses, include both subjects who had normal and abnormal liver function tests at randomization.

[Lilly Approach] For all these analyses, Lilly will categorize patients into four dose groups: a) PLA_DLX60QD for patients who are on Placebo at acute phase and stayed on 60QD across the whole extension phase; b) PLA_DLX60/120QD for patients who are on Placebo at acute phase and titrated up to 120QD at any time during the extension phase; c) DLX_DLX60QD for patients who are on DLX at acute phase and stayed on 60QD across the whole extension phase; d) DLX_DLX60/120QD for patients who are on DLX at acute phase and started with 120QD or titrated up to 120QD at any time during the extension phase. In addition, PLA_DLX60QD and DLX_DLX60QD will be combined as DLX60QD group; PLA_DLX60/120QD and DLX_DLX60/120QD will also be combined as DLX60/120QD group.

Lilly believes this is the appropriate way to analyze the dose relationship due to the following reasons:
a) Since dose titration is determined based on efficacy and safety considerations, direct comparison of

DLX60QD and DLX120QD dose groups at the time of an event is prone to selection bias since patients are not randomized to 60QD or 120QD; b) comparing patients stayed on 60mg vs patients started or titrated up to 120mg is close to clinical practice; and c) The treatment group at acute phase need to be taken into consideration when analyzing extension phase data.

For all these analyses, Lilly will use either the entire acute phase or the end of acute phase as our baseline as follows. For the mean change analysis, the last nonmissing values at acute phase will be used as baseline; for categorical analysis, the whole entire acute phase (visit 3- 5) will be used as baseline to define TEAEs and Treatment emergent abnormal hepatic labs.

"Augustus, Ayanna" <Ayanna.Augustus@fda.hhs.gov>

To <BOGGS_BRYAN_E@LILLY.COM>

cc

09/25/2009 12:43 PM

Subject NDA 022516/Cymbalta/Information Request

Hi Bryan,

The clinical reviewer has the following information request.

The hepatic safety analysis submitted on August 14, 2009 included only subjects with normal baseline liver function tests (LFTs) values.

We request that you submit a separate pooled analysis (HMEO, HMEN, HMEP, and HMFG trials) of hepatic safety presented, by treatment group and duloxetine dose for the first 7 weeks and for the weeks 8 to 13, that includes *only randomized subjects with abnormal baseline LFT's values*. Similar to the presentation approach in your August 14, 2009 submission, you can separate the hepatic-related analyses into four different sections:

- Pooled analysis of hepatic-related adverse events.
- Pooled analysis of liver function tests, including mean change from baseline, shift analysis from baseline to abnormal (high and low), and markedly abnormal values.
- Pooled analysis of discontinuations due to hepatic-related adverse event or elevations in LFTs.
- Pooled analysis for laboratory values overtime for subjects with increase in ALT/AST and bilirubin values. Indicate whether treatment was discontinued or not and time of discontinuation related to obtaining lab tests.

In addition, for the extension phase of the HMEN trial, submit the analyses described above presented by dose (duloxetine 60mg and duloxetine 120mg) at the time of the event. For these analyses, include both subjects who had normal and abnormal liver function tests at randomization.

Please provide a response by COB, Wednesday, October 7, 2009.

Regards,

10/1/2009

Ayanna

Ayanna Augustus, Ph.D.

*Regulatory Project Manager
Division of Anesthesia, Analgesia,
and Rheumatology Products
Center for Drug Evaluation and Research
Food and Drug Administration
Bldg. 22, Room 3219
10903 New Hampshire Ave
Silver Spring, MD 20993
301-796-3980 (phone)
301-796-9717 (fax)*

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
----- NDA-22516	----- ORIG-1	----- ELI LILLY AND CO	----- CYMBALTA

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/s/

AYANNA S AUGUSTUS
10/01/2009

Augustus, Ayanna

From: Augustus, Ayanna
Sent: Friday, September 25, 2009 12:43 PM
To: 'BOGGS_BRYAN_E@LILLY.COM'
Subject: NDA 022516/Cymbalta/Information Request

Importance: High

Hi Bryan,

The clinical reviewer has the following information request.

The hepatic safety analysis submitted on August 14, 2009 included only subjects with normal baseline liver function tests (LFTs) values.

We request that you submit a separate pooled analysis (HMEO, HMEN, HMEP, and HMFG trials) of hepatic safety presented, by treatment group and duloxetine dose for the first 7 weeks and for the weeks 8 to 13, that includes *only randomized subjects with abnormal baseline LFT's values*. Similar to the presentation approach in your August 14, 2009 submission, you can separate the hepatic-related analyses into four different sections:

- Pooled analysis of hepatic-related adverse events.
- Pooled analysis of liver function tests, including mean change from baseline, shift analysis from baseline to abnormal (high and low), and markedly abnormal values.
- Pooled analysis of discontinuations due to hepatic-related adverse event or elevations in LFTs.
- Pooled analysis for laboratory values overtime for subjects with increase in ALT/AST and bilirubin values. Indicate whether treatment was discontinued or not and time of discontinuation related to obtaining lab tests.

In addition, for the extension phase of the HMEN trial, submit the analyses described above presented by dose (duloxetine 60mg and duloxetine 120mg) at the time of the event. For these analyses, include both subjects who had normal and abnormal liver function tests at randomization.

Please provide a response by COB, Wednesday, October 7, 2009.

Regards,
Ayanna

Ayanna Augustus, Ph.D.
Regulatory Project Manager
Division of Anesthesia, Analgesia,
and Rheumatology Products
Center for Drug Evaluation and Research
Food and Drug Administration
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10903 New Hampshire Ave
Silver Spring, MD 20993
301-796-3980 (phone)
301-796-9717 (fax)

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
----- NDA-22516	----- ORIG-1	----- ELI LILLY AND CO	----- CYMBALTA

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AYANNA S AUGUSTUS
09/25/2009

Augustus, Ayanna

From: Pokrovnichka, Anjelina
Sent: Thursday, July 23, 2009 11:23 AM
To: Augustus, Ayanna
Subject: FW: Cymbalta.

[Can you send this request to the sponsor please.](#)

From: Fields, Ellen
Sent: Thursday, July 23, 2009 6:31 AM
To: Pokrovnichka, Anjelina
Subject: Re: Cymbalta.

Yes
Ellen

From: Pokrovnichka, Anjelina
To: Fields, Ellen
Sent: Wed Jul 22 17:14:23 2009
Subject: Cymbalta.

Can we ask the sponsor the following:

"For trial HMEN, the discontinuation by dose analysis results, in particular discontinuations due to lack of efficacy during the last 6 weeks, presented in Table 2.7.4.21 (CSS, page 68) are different from the results from the same analysis submitted for NDA 22-333 (9/11/08 amendment, Tables 24 and 25, pp. 170-171).

Please explain."

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
----- NDA 22516	----- ORIG 1	----- ELI LILLY AND CO	----- CYMBALTA

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/s/

AYANNA S AUGUSTUS
07/30/2009

Augustus, Ayanna

From: Pokrovnichka, Anjelina
Sent: Monday, July 20, 2009 5:16 PM
To: Augustus, Ayanna
Cc: Fields, Ellen
Subject: Cymbalta.

Hi Ayanna,
Can you please send the sponsor the question below.
Anjelina

From: Fields, Ellen
Sent: Monday, July 20, 2009 5:07 PM
To: Pokrovnichka, Anjelina
Subject: RE: Cymbalta.

sure

Ellen

From: Pokrovnichka, Anjelina
Sent: Monday, July 20, 2009 5:06 PM
To: Fields, Ellen
Subject: Cymbalta.

Can we ask the sponsor the following question:

"The Financial Disclosure provided in Module 1 of the eCTD application (1.3.4), does not list the investigators for HMFG, similar to what you have for HMEN, HMEO and HMEP. Nevertheless, a financial disclosure form is included for [REDACTED]^{(b) (4)}, sub investigator of Dr. Harvey Resnick for Study HMFG. The list description of the Investigators site for HMFG (Module 5, 5.3.5.1.7) does not include Dr. Harvey Resnick.

Please clarify."

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
----- NDA 22516	----- ORIG 1	----- ELI LILLY AND CO	----- CYMBALTA

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/s/

AYANNA S AUGUSTUS
07/27/2009



NDA 22-516

FILING COMMUNICATION

Eli Lilly and Company
Lilly Corporate Center
Indianapolis, IN 46285

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

Dear Dr. Boggs:

Please refer to your new drug application (NDA) dated May 15, 2009, received May 15, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Cymbalta (duloxetine hydrochloride), 20, 30, and 60 mg Capsules.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is March 15, 2010.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by February 22, 2010.

During our filing review of your application, we identified the following potential review issues. Submit a response to these issues within 30 days of the date of this letter.

1. Submit revised exposure analysis for the primary chronic pain trials that describes drug exposure by duloxetine dose group (e.g. 20mg QD, 60mg QD, 120 mg QD, and any duloxetine dose). Present data in a table formatted as shown below and summarized in a text:

Table : Exposure to duloxetine by dose received – HMEN, HMEP, HMFG and HMEO

Exposure duration (days)	DLX 20mg QD	DLX 60mg QD	DLX 120mg QD	Any DLX dose
	N=	N=	N=	N=
	n (%)			
Mean				
Minimum				
Maximum				
Median				
0-7				
8-14				
15-30				
31-60				
61-90				
91-120				
≥ 121				

2. For HMEN, HMFG, and HMEP trials, provide pooled analysis for subject disposition, presented by treatment group and duloxetine dose received (placebo, DLX 60mg QD, and DLX 120mg QD) for the first 7 weeks and for the weeks 8 to 13.
3. For the primary chronic pain analysis set (CP), including the HMEO, HMEN, HMEP, and HMFG trials, provide pooled analysis for adverse events (serious, events of interest, common and other significant adverse events) presented by treatment group and duloxetine dose received (i.e. placebo, duloxetine 20mg, duloxetine 60mg, and duloxetine 120mg) for the first 7 weeks and for the weeks 8 to 13. **Data should be presented in tables and summarized in a text.**
4. For the primary chronic pain analysis set (CP), including the HMEO, HMEN, HMEP, and HMFG trials, provide pooled analysis for laboratory data (chemistry, liver function, including analysis for AST, and hematology), vital signs, and ECG presented by treatment group (placebo, duloxetine 20mg, 60mg, and 120mg QD) for the first 7 weeks and the last 6 weeks of the treatment period. Include mean change from baseline, shift analysis from baseline to abnormal (high and low), markedly abnormal values and discontinuations due to abnormal laboratory, vital signs, and ECG parameters. **Data should be presented in tables and summarized in a text.**
5. Submit pooled analysis (HMEO, HMEN, HMEP, and HMFG trials) of hepatic safety presented by treatment group and duloxetine dose (placebo, duloxetine 20mg, 60mg, and 120mg QD) for the first 7 weeks and for the weeks 8 to 13. Include analysis of changes in aspartateaminotransferase (AST) values in this section. In order to assess reversibility of abnormal liver function overtime, in addition to the overall duloxetine exposure

integrated analyses set, provide available laboratory values over time for subjects with abnormal ALT/AST and bilirubin values for the primary chronic pain analysis set (CP). Indicate whether treatment was discontinued or not and time of discontinuation related to obtaining lab tests.

6. For HMEN and HMFG trials, conduct efficacy analysis for the comparison of duloxetine 60mg only dose versus placebo at Week 13, using BOCF and mBOCF imputation strategies and continuous responder analyses (BOCF).

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

If you have not already done so, you must submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/oc/datacouncil/spl.html>. The content of labeling must be in the Prescribing Information (physician labeling rule) format.

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Pediatric studies conducted under the terms of section 505B of the Federal Food, Drug and Cosmetic Act (the Act) may also qualify for pediatric exclusivity under the terms of section 505A of the Act. If you wish to qualify for pediatric exclusivity, please consult the Division of Division of Anesthesia, Analgesia, and Rheumatology Products. Please note that satisfaction of the requirements in section 505B of the Act alone may not qualify you for pediatric exclusivity under 505A of the Act.

We acknowledge receipt of your request for a full waiver of pediatric studies in patients with osteoarthritis for this application. Once we have reviewed your request, we will notify you if the full waiver request is denied and a pediatric drug development plan is required.

We acknowledge receipt of your request for a partial waiver of pediatric studies for ages birth to 7 years for this application. Once we have reviewed your request, we will notify you if the partial waiver request is denied.

We acknowledge receipt of your request for a partial deferral of pediatric studies for ages 8 to 18 years for this application. Once we have reviewed your request, we will notify you if the partial deferral request is denied.

If you have any questions, contact Ayanna Augustus, Regulatory Project Manager, at ayanna.augustus@fda.hhs.gov or (301) 796-3980.

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
7/17/2009 04:21:33 PM

REQUEST FOR CONSULTATION

TO (Office/Division): Raanan Bloom, OPS/PARS, (301)796-2185

FROM (Name, Office/Division, and Phone Number of Requestor): Don Henry
Project Manager, ONDQA, 301-796-4227 on behalf of
Danae Christodoulou

DATE
July 9, 2009

IND NO.

NDA NO.
22-516

TYPE OF DOCUMENT
NDA submission

DATE OF DOCUMENT
May 15, 2009

NAME OF DRUG
duloxetine HCl (Cymbalta)

PRIORITY CONSIDERATION
standard

CLASSIFICATION OF DRUG
analgesic (DAARP)

DESIRED COMPLETION DATE
October 31, 2009

NAME OF FIRM: Eli Lilly

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> SAFETY / EFFICACY | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY | <input type="checkbox"/> CONTROL SUPPLEMENT | |

II. BIOMETRICS

- | | |
|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW | <input type="checkbox"/> CHEMISTRY REVIEW |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY |
| <input type="checkbox"/> CONTROLLED STUDIES | <input type="checkbox"/> BIOPHARMACEUTICS |
| <input type="checkbox"/> PROTOCOL REVIEW | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): | |

III. BIOPHARMACEUTICS

- | | |
|--|--|
| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG SAFETY

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

V. SCIENTIFIC INVESTIGATIONS

- | | |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS / SPECIAL INSTRUCTIONS: A review of the environmental assessment is requested. This is an electronic submission (M1).

SIGNATURE OF REQUESTOR
{See appended electronic signature page }

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 page is the manifestation of the electronic signature.**

/s/

Ali Al-Hakim

7/10/2009 03:48:52 PM

REQUEST FOR CONSULTATION

TO (Office/Division): OSE/DRISK/Chris Wheeler, RPM

FROM (Name, Office/Division, and Phone Number of Requestor): Division of Anesthesia, Analgesia, and Rheumatology Products/Ayanna Augustus, RPM

DATE
6/26/09

IND NO.

NDA NO.
22-516

TYPE OF DOCUMENT
New NDA

DATE OF DOCUMENT
5/15/09

NAME OF DRUG
Cymbalta

PRIORITY CONSIDERATION
Standard

CLASSIFICATION OF DRUG
pain

DESIRED COMPLETION DATE
1/8/10

NAME OF FIRM: Eli Lilly & Co.

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|---|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> RESUBMISSION | <input checked="" type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> SAFETY / EFFICACY | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY | <input type="checkbox"/> CONTROL SUPPLEMENT | |

II. BIOMETRICS

- | | |
|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW | <input type="checkbox"/> CHEMISTRY REVIEW |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY |
| <input type="checkbox"/> CONTROLLED STUDIES | <input type="checkbox"/> BIOPHARMACEUTICS |
| <input type="checkbox"/> PROTOCOL REVIEW | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): | |

III. BIOPHARMACEUTICS

- | | |
|--|--|
| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG SAFETY

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

V. SCIENTIFIC INVESTIGATIONS

- | | |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
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COMMENTS / SPECIAL INSTRUCTIONS: Please review and provide feedback on the sponsor's proposed REMS. The submission is located in the EDR \\CDSESUB1\EVSPROD\NDA022516\0000. Anjelina Pokrovnichka is the clinical reviewer for this submission, Ellen Fields is the CDTL. Please contact Ayanna Augustus (6-3980) if you need additional information.

SIGNATURE OF REQUESTOR
Ayanna Augustus

METHOD OF DELIVERY (Check one)
 DFS EMAIL MAIL HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

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/s/

Ayanna Augustus
6/26/2009 04:21:10 PM



NDA 22-516

NDA ACKNOWLEDGMENT

Eli Lilly and Company
Lilly Corporate Center
Indianapolis, IN 46285

Attention: Bryan Boggs, PharmD
Manager, US Regulatory Affairs

Dear Dr Boggs:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Cymbalta (LY248686, duloxetine hydrochloride)

Date of Application: May 15, 2009

Date of Receipt: May 15, 2009

Our Reference Number: 22-516

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on July 14, 2009 in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/oc/datacouncil/spl.html>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anesthesia, Analgesia and Rheumatology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/cder/ddms/binders.htm>.

If you have any questions, call Tanya Clayton, Regulatory Project Manager, at (301) 796-0871.

Sincerely,

{See appended electronic signature page}

Tanya Clayton
Regulatory Health Project Manager
Division of Anesthesia, Analgesia and
Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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this page is the manifestation of the electronic signature.**

/s/

Tanya Clayton
6/5/2009 12:49:24 PM