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Supplemental Expert Report
May 2015
Cymbalta Discontinuation Litigation

ASSIGNMENT

In September 2014, I provided an initial report reflecting my opinions on the adequacy of the product labeling for Eli Lilly and Company's ("Lilly") antidepressant drug, Cymbalta (duloxetine hydrochloride). In preparing that report, I reviewed materials provided to me by Plaintiffs' counsel in the Cymbalta withdrawal litigation. That September 2014 report, and the materials reviewed in preparing it, form part of the basis of this Supplemental Expert Report and are fully incorporated herein by reference.

Since the completion of that September 2014 report, at counsel's request, I have continued to review additional materials they have provided to me, including: the reports and sworn testimony of Lilly's regulatory expert, Dr. Karen Becker, internal Lilly documents (many of which I understand were not produced in discovery until after completion of my first report); documents reflecting the interactions between Lilly and the Food & Drug Administration (FDA) specifically regarding the discussion of "discontinuation syndrome" in the U.S. Package Insert; and the sworn testimony of certain Lilly employees. These additional materials provide further support for my opinions. This Supplemental Expert Report expounds on the opinions set forth in my September 2014 report and the sworn testimony I have already provided in this litigation. I reserve the right to continue to review materials as they are provided to me and, if warranted, add to or modify my existing opinions.

After reviewing these additional materials, my ultimate opinion remains: to a reasonable degree of professional certainty and based on 40 years of experience at FDA and consulting for the pharmaceutical industry, I have concluded that product label information presented to physicians about Cymbalta is misleading and inadequate to inform prescribers and patients about the risks of discontinuation.

OPINIONS

I. False or misleading labeling

According to the Food Drug and Cosmetic Act (FDCA); the term; "labeling means all labels and all other written, printed or graphic matter" accompanying the product (Section 201(m)). The FDCA specifies that a drug shall be deemed to be misbranded if "its labeling is

false or misleading in any particular" (Section 353 (a)). It is illegal to misbrand any drug released into interstate commerce [FD&C Act, sec. 301(b); 21 U.S.C. 331(b)].

The FDAC (section 201 (n)) states:

"If an article is alleged to be misbranded because the labeling or advertising is misleading, then in determining whether the labeling or advertising is misleading there shall be taken into account (among other things) not only representations made or suggested by statement, word, design, device, or any combination thereof, but also the extent to which the labeling or advertising *fails to reveal facts material in the light of such representations* or material with respect to consequences which may result from the use of the article to which the labeling or advertising relates under the conditions of use prescribed in the labeling or advertising thereof or under such conditions of use as are customary or usual."

Therefore, all of the important information necessary to make a labeling claim (i.e., a statement about the risks or benefits of the product) must be sufficiently complete (i.e., all of the "material facts" disclosed) so that reasonable members of the audience correctly understand the statements made and the consequences of use of the product.

The consideration of what constitutes "misleading" labeling has been most fully discussed by FDA in relation to reviewing advertisements and promotional labeling. A FDA Guidance [Presenting Risk Information in Prescription Drug and Medical Device Promotion, May 2009] notes four important aspects of how FDA determines whether labeling or advertising information is considered false or misleading that have implications for Cymbalta labeling. First, the Guidance states that:

"when FDA evaluates the risk communication in a promotional piece, FDA looks not just at specific risk-related statements, but at the *net impression* – i.e., the message communicated by all elements of the piece as a whole. The purpose of the evaluation is to determine whether the piece ***as a whole*** conveys an accurate and non-misleading impression of the benefits and risks of the promoted product." Thus, FDA maintains that "[a] promotional communication that conveys a deceptive net impression of the product could be misleading, even if specific individual claims or presentations are not misleading."

Second, the FDA's analysis of labeling or advertising is based upon whether the impressions gained from the piece are likely to mislead a "reasonable consumer." The *reasonable consumer standard* used by FDA in evaluating promotional materials is adopted from the Federal Trade Commission (FTC). According to the FTC, promotional communications are examined from the perspective of a "consumer acting reasonably in the circumstances." If the material is directed primarily to a particular audience, the FTC examines reasonableness from the perspective of that audience. Similarly, when applying the reasonable consumer standard, FDA, "takes into account the different levels of expertise of lay consumers and healthcare

professionals. Due to their training and experience, healthcare professionals develop a level of knowledge related to scientific concepts and medical conditions and products that lay consumers do not possess. FDA takes this difference in knowledge and experience into account when assessing promotional materials directed at healthcare professionals versus those directed at lay audiences." However, FDA notes that "research has shown that experts [in this case, healthcare professionals] are subject to the same cognitive biases and processing limitations as non-experts."

Third, is consideration of the extent to which an audience is misled. Not all members of an audience (or even a majority of the audience) have to be misled for a piece to be considered misleading. A labeling piece is considered misleading even if only a percentage of the audience is deceived by its message. There can be multiple interpretations of a claim (i.e., labeling statement) that are all considered reasonable. In fact, the FTC maintains that a statement can be considered deceptive even if it is a "secondary" interpretation and the primary interpretation is accurate (see FTC policy statement at footnote 21). The FDA also maintains that there can be more than one interpretation of a claim and (quoting the FTC policy) "when a seller's representation conveys more than one meaning to reasonable consumers, one of which is false, the seller is liable for the misleading interpretation."

Fourth, the Guidance, and regulations upon which it is based, describe the types of promotional material that constitute false or misleading claims. Among the concepts underlying FDA law and regulations is the idea that drug companies have a requirement to provide an accurate and thorough description of the risks of the medicines they market in a balanced fashion. Section 502(n) of the FDC Act requires companies to present a "true statement" of information in brief summary relating to side effects, contraindications, and effectiveness. FDA regulations specify that an advertisement does not satisfy the requirement of providing a "true statement" of information if (among other reasons):

(i) It is false or misleading with respect to side effects, contraindications, or effectiveness; or

(ii) It fails to present a fair balance between information relating to side effects and contraindications, or

(iii) It fails to reveal facts "material in the light of its representations or material with respect to consequences that may result from the use of the drug as recommended or suggested" in the promotional material (21 CFR 202.1(e)(5) (i, ii, iii).

Thus, a company's failure to disclose important, material facts can prevent physicians from accurately comprehending the risk statements being made and constitute false or misleading information.

II. Application to Cymbalta Labeling

FDA approved Cymbalta for the treatment of major depressive disorder in August, 2004. The original label for the product mentioned discontinuation effects in several sections of the label, discussing it most fully in a precaution entitled: "Discontinuation of treatment with Cymbalta." It read as follows:

> "Discontinuation of Treatment with Cymbalta – Discontinuation symptoms have been systematically evaluated in patients taking Cymbalta. Following abrupt discontinuation in placebo-controlled clinical trials of up to 9-weeks duration, the following symptoms occurred at a rate **greater than or equal to 2%** (bold emphasis added) and at a significantly higher rate in duloxetine-treated patients compared to those discontinuing from placebo: dizziness; nausea; headache; paresthesia, vomiting; irritability; and nightmare.
>
> During the marketing of other SSRIs and SNRIs (Serotonin and Norepinephrine Reuptake Inhibitors), there have been spontaneous reports of adverse events occurring upon discontinuation of these drugs, particularly when abrupt, including the following: dysphoric mood, irritability, agitation, dizziness, sensory disturbances (e.g., paresthesias such as electric shock sensations), anxiety, confusion, headache, lethargy, emotional lability, insomnia, hypomania, tinnitus, and seizures. Although these events are generally self-limiting, some have been reported to be severe.
>
> Patients should be monitored for these symptoms when discontinuing treatment with Cymbalta. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose but at a more gradual rate (see DOSAGE and ADMINISTRATION)."

As mentioned above, there were several additional sections in the product label where discontinuation symptoms and treatment (gradual reduction of dose) were discussed. In addition, the wording of this section was revised several times over the years including changing the rate for side effect listing from 2% to 1%. However, the basic structure and content of this warning/precaution remained the same.

It is commonly understood that *risk* is defined as the combination of the *probability of occurrence of harm* and the *severity* of that harm [Guidance for Industry, Q9 Quality Risk Management, June 2006]. FDA's process of risk assessment is premised on the notion that, in order for a physician to competently assess risks and benefits of a product, the drug manufacturer must enable the physician to identify and characterize the nature, frequency, and severity of the risks. [Guidance for Industry Premarketing Risk Assessment March 2005]. The Cymbalta

product label lists a series of individual symptoms associated with product discontinuation. The severity is further discussed indirectly as it characterizes the side effects of other SSRI/SNRI drugs by stating that these effects are generally self-limiting. The description also states that "some" of these other drug's effects have "been reported to be severe." The only description of the frequency of discontinuation effects is the statement that describes that the symptoms "occurred at a rate greater than or equal to 2%".

Lilly's expert, Dr. Karen Becker, states that the frequency description of the "rate greater than or equal to 2%" represents the rate at which individual symptoms occurred (not the rate at which any patient experienced a discontinuation side effect). She opines that a "reasonable medical professional" would not be misled by "such common language" in this label (page 14 Becker report). To conclude that the label is not misleading, Dr. Becker's assertion that a "reasonable medical professional" would not be misled necessarily implies that "no reasonable doctor" would interpret this phraseology to apply to the number of patients that experience discontinuation effects.

The only support that Dr. Becker appears to garner for her position is that the language used in the label in this section is similar to the language used to describe the frequency of adverse drug reactions in that section of the label. Prescription drug product labels commonly display the adverse reactions occurring above a certain frequency threshold, listing individual side effects occurring above that threshold. Dr. Becker assumes that a "reasonable" doctor would apply that logic to discerning the meaning of the phrase used to describe the frequency of discontinuation effects found in the warning/precaution section of the label.

However, the rate (greater than or equal to 2%) that Lilly provides for discontinuation symptoms does not adequately specify that it applies to individual "adverse reactions" rather than patients (i.e., the rate of discontinuation syndrome). There are two reasons underlying my interpretation of the phraseology.

First, Dr. Becker assumes that physicians will view the signs and symptoms described as discontinuation effects as they would adverse effects listed in the Adverse Reactions section of the product label. Clearly, in the "Adverse Reactions" section of the Cymbalta label individual adverse events that occur above a certain incidence threshold are listed in a series of tables. The individual adverse reactions are displayed along with numbers showing the percentage of patients experiencing that adverse reaction. This additional context conveys that the percentage displayed is associated with an individual adverse reaction. However, in the "Discontinuation of Treatment" section of the Warnings/Precautions, the individuals signs and symptoms are lumped in a single list and only one percentage value (i.e., greater than or equal to 2%) is mentioned. Further, this listing of effects is described as "symptoms" (i.e., the following symptoms occurred) not as "adverse reactions."

In fact, the term "symptoms" is used consistently throughout the Cymbalta label to describe the effects. I counted ten times that the Cymbalta label described these effects. In eight of these instances the term "symptoms" is used and two times the phrase "adverse reactions" is used). The term "adverse reactions" is used when describing the effects of other SSRIs/SNRIs and in the Adverse Reactions section when describing post-marketing effects. In the section entitled, "Use in Special Populations," possible effects in newborns are described as due possibly to "a drug discontinuation syndrome."

Second, Lilly maintains that physicians are very familiar with antidepressant discontinuation syndrome (Knowles Deposition at page 203). Indeed, some physicians may be knowledgeable of the occurrence of these discontinuation effects, and that product labeling for antidepressants has conveyed the possibility of discontinuation syndrome for some years. However, to make an informed prescribing decision, a physician must be able to correctly assess the risks and benefits of the drug, including discontinuation effects. As such, it is incumbent on manufacturers to warn physicians about not only the occurrence of such a risk, but importantly, the severity and frequency of occurrence. It is not enough to know that discontinuation effects can occur. A physician must be informed by the company about what happens if they occur (severity of reaction), how often they occur (probability of occurrence) and what to do to prevent or treat the patient if they occur (prevention/treatment). It merely describes the most common adverse effects and states that dosage should be tapered when discontinuing the medicine. Again, there may be physicians who know about the use and effects of Cymbalta and other antidepressants and who might also understand that patients experience discontinuation effects more frequently than 1% or 2% of the time. However, Lilly's wording of the discontinuation syndrome risk is not adequate to inform those physicians who do not have that independent knowledge.

Studies find that some doctors, especially generalists, are not that familiar with discontinuation effects. In a survey conducted by Young and Currie (1997), 50 psychiatrists and 53 GPs responded to the questionnaire. Of the respondents, 36 (72%) of the psychiatrists but only 16 (30%) of the GPs were aware that patients may experience antidepressant discontinuation events. However, this survey was conducted in the late 1990's in Ireland. A more recent internet study conducted by Lilly market research (2006) of 305 primary care physicians found that 41% stated that they were not very (35%) or not at all (6%) aware of the discontinuation side effects of Cymbalta. Therefore, a sizeable proportion of primary care physicians admit that they are not very familiar with its discontinuation effects. These physicians would be most vulnerable to receiving a misleading message from the Cymbalta label. Research surveys indicate that most antidepressant prescribing is conducted by general practitioners. Based on data from a survey conducted between 2001 and 2003, Mojtabai and Olfson (2008), found that approximately 1 in 10 adults (10.5%) were treated with an antidepressant in the previous year, usually prescribed by a general medical provider (73.6%).

Thus, about three-fourths of the people receiving antidepressant prescriptions are being treated by general practitioners, 40% of which are likely to state they are not very familiar with discontinuation effects.

Along with misleading information about the frequency of discontinuation effects, there is also misleading information presented about the duration (and therefore, severity) of these discontinuation effects. The original label mentioned: dizziness; nausea; headache; paresthesia, vomiting; irritability; and nightmare. Most of these effects can vary in severity depending on the intensity and duration of the effects (from mild and transient to intense and prolonged). Other than listing individual symptoms, the label for Cymbalta describes the effects of other SSRI/SNRI drugs as follows: "Although these events are generally self-limiting, some have been reported to be severe." Perahia et al (2005), found about half of the symptoms lasted over two weeks. This statement in the label that these effects are "generally self-limiting" is not confirmed by this study. Failure to clarify the duration of effects from the Cymbalta studies constitutes the failure to reveal "material facts" that would prevent a reader from becoming misled by the information presented in the label.

III. Use of a "threshold" to discuss discontinuation effects

Dr. Becker also maintains that the use of the 2% (and later 1%) figure represents a "frequency threshold" for reporting safety information. She states that it was "appropriate, reasonable and consistent with the regulations" to report discontinuation effects in this manner. She refers to FDA regulations and a FDA Guidance [Guidance for Industry Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products — Content and Format, January 2006] indicating the use of a threshold when reporting safety data. This implies that the method used to report the symptoms of discontinuation of Cymbalta in its label is appropriate and consistent with FDA rules and Guidance for discussion of discontinuation effects.

However, the use of a threshold refers to the reporting in the Adverse Reactions section of the label, not the reporting in the Warnings/Precautions section. The Cymbalta product label mentions discontinuation effects in several places, however, it is most fully presented in the warnings/precautions section of their label and the misleading information is presented primarily in this section. The specific regulations cited by Dr. Becker refer to the reporting of data in the Adverse Reactions section of the product label (CFR 201.57(c)(7)). This section of the label describes the overall adverse reaction profile of the drug based on the entire safety database. Dr. Becker correctly states that it is appropriate to use a frequency cutoff as a basis for selecting which Adverse Reactions to present in this section of the label. However, when reporting Adverse Reactions, it is also appropriate to specify the rate of individual adverse reactions listed

in the label. The FDA Guidance on Adverse Reactions cited by Dr. Becker supports the use of a frequency cutoff. The Guidance states that:

> "The presentation of adverse reactions identified from clinical trials is the major component of the ADVERSE REACTIONS section. The ADVERSE REACTIONS section must include a listing of all such reactions that occurred at or above a specified rate that is appropriate to the drug's safety database."

However, the Guidance goes on to state that "to the extent information is available and relevant, additional detail about the nature, frequency, severity, duration, dose-response, and demographic characteristics of those adverse reactions with significant clinical implications" should be included. Indeed, in the Adverse Reactions section of the Cymbalta label, not only is a frequency cutoff used, but this section contains several tables in which the rate of individual reactions is specified. As described in my original report, the listing of rates for each of the individual adverse effects adds additional context and clarifies that the frequency cutoff applies to individual adverse reactions and does not apply to a rate for the occurrence of a syndrome or cluster of symptoms.

The warning/precautions section of the label is misleading, not because Lilly used a frequency cutoff, but because of the "failure to reveal material facts" to prevent misleading the audience. By specifying the frequency of individual discontinuation symptoms, Lilly could have avoided leading a reasonable medical professional from interpreting the "threshold" number presented to apply to discontinuation syndrome. By comparison, the discussion of discontinuation effects in the product label for Paxil CR (paroxetine hydrochloride) Controlled-Release Tablets uses a frequency cutoff. However, that label also reports the rate of individual adverse events compared to the placebo rate as follows:

"the following adverse events were reported at an incidence of 2% or greater for PAXIL CR and were at least twice that reported for placebo: Dizziness (11.9% versus 1.3%), nausea (5.4% versus 2.7%), nervousness (2.4% versus 1.1%)"

This method of reporting discontinuation adverse events prevents a reader from drawing a misleading impression that the overall incidence rate (2% or greater) is a rate for a cluster of symptoms but rather a threshold for individual symptom reporting.

Rather than rely on the FDA Guidance for reporting Adverse Reactions, the correct FDA Guidance to apply for the reporting of information in the warnings/precautions section would be the FDA Guidance on how information should be presented in this section and related sections of the label of the label [Guidance for Industry: Warnings and Precautions, Contraindications, and Box Warning Sections of Labeling for Human Prescription Drugs and Biological Products —

Content and Format, October, 2011]. This Guidance states that the information that should be supplied in this section of the label should provide a "succinct description of each topic selected for inclusion." According to this Guidance, the information provided in the warnings/precautions section should include:

- A succinct description of the adverse reaction and outcome
- **A numerical estimate of risk or adverse reaction rate** [emphasis added]
- Know risk factors for the adverse reaction
- Steps to decrease the likelihood, duration or severity of the reaction
- How to treat or manage the reaction.

The use of a cutoff rate does not provide "a numerical estimate of the risk or adverse reaction rate." Specifying a cutoff (1% or 2%) does not leave the reader with the understanding that 44% of the patients in clinical trials suffered a discontinuation effect (Perahia, et al, 2005). When describing how to present information about risk, FDA makes it clear that nonspecific terms that lack a commonly understood meaning (e.g., rare, infrequent, frequent), should be avoided because they may be misleading. FDA suggests that ranges may be helpful in specifying the drug's safety profile (e.g., less than 1/100 or less than 1/500) [Guidance for Industry Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products — Content and Format, January 2006].

Lilly does specify a range in this section of the Cymbalta label (1% or greater). This use of a rate stands the FDA suggestion on its head. Rather than informing the reader that the adverse effects occurred below a certain level (e.g., less than 1%) the rate presented informs the reader that the effect occurred above a minimal level (i.e., 1% or more of the time). This could mean 1%, 2%, 5%, 50% or, 100% of the time and be factually correct. However, by presenting rates in this fashion, the label presents a vague and nonspecific descriptor of frequency. A reader would likely assume that the rate presented would approach the 1% level (why else use the 1% descriptor). This results in misleading the audience.

IV. Changes Being Effected (CBE)

Manufacturers are required to keep product labels up to date to reflect new information that is learned about a drug. Each time FDA reviews a drug for new efficacy information (e.g., a new use for the medicine), the entire label is reviewed to update and improve or strengthen the communication of safety information [FDA, Guidance for Industry; Labeling for Human Prescription Drug and Biological Products – Implementing the PLR Content and Format Requirements, February 2013].

There are three ways in which companies may modify a product label after initial approval [Guidance for Industry: Changes to an Approved NDA or ANDA April 2004].

First, any "major" change such as a new indication must be submitted to FDA via a "Prior Approval Supplement." These are changes that FDA must approve before the label to the drug can be changed.

Second, "moderate" changes in labeling can be accomplished by a "changes being effected" supplement. This is a supplemental application that the company submits to FDA concurrent with distribution of the changed label. FDA will then review the CBE supplement and inform the company whether it accepts the change or if the company must modify the information in a subsequent version of the label.

Third, "minor" changes (such as editorial modifications) can be made in the drug's annual report.

FDA regulations (314.70(c)(6)(iii)) and the Guidance detail the types of changes that can be made via a CBE supplement. Among the types of modifications that can be made to a product label via a CBE is information that:

(1) adds or strengthens a contraindication, warning, precaution, or adverse reaction,
(2) adds or strengthens a statement about drug abuse, dependence, psychological effect, or overdose,
(3) adds or strengthens an instruction about dosage and administration that is intended to increase the safe use of the drug product, or
(4) deletes false, misleading, or unsupported indications for use or claims for effectiveness.

In addition, a change that normally requires a supplement submission and approval prior to distribution of the drug product can be submitted as a CBE if FDA specifically requests a CBE submission. On occasion, the FDA may ask companies to submit a CBE application when there is a specific warning that FDA wants to add to the product label. This may be the case when FDA believes that the warning applies to a broad class of drugs and FDA wants consistency in the label warning. However, even in these instances, FDA will consider modification to the proposed language if the company disagrees with the FDA-specified wording (see class labeling below).

The evidence shows that, over the years, Lilly employed all three of these types of methods to make changes to parts of the "discontinuation syndrome" warning section of the Cymbalta label. (see Becker exhibit). In total, Dr. Becker details eleven (11) such modifications following FDA's initial approval of the drug. Six of the 11 modifications to the

"Discontinuation" warning/precaution were made when Lilly submitted a prior approval supplement for an additional a new indication and one of the modifications was due to review of a prior approval supplement when Lilly submitted a comprehensive Medication Guide. Thus, seven modifications accomplished via prior approval supplements. Three of the modifications were changes based on new safety analyses that modified the listed symptoms or directions based on additional studies undertaken. These were accomplished via a CBE supplement. One change involved the addition of a discontinuation symptom that was submitted in the annual report.

However, Dr. Becker's chronology does not indicate that Lilly changed the wording of this discontinuation warning section to clarify that 44% of the people who discontinue Cymbalta suffer from discontinuation effects. There is no record that Lilly ever attempted to change the label to include the 44% incidence rate. Lilly could have used pre-approval, CBE or annual reports—as it did on a number of occasions—to strengthen or clarify thelanguage, providing physicians with accurate information about the extent of discontinuation effects.

V. Class Labeling

The term "class labeling" is used in a variety of ways to connote that drugs within a distinct pharmacologic class have identical or similar wording in their product labels. Historically, FDA has on occasion, required manufacturers of all drugs within a pharmacologic class to use identical wording to convey safety information. Sometimes, these warnings are mandated by FDA regulation and all labels within that drug class must have the same exact wording to be in compliance with the regulations. However, most often, these "identical class label warnings" are not required by regulation but accomplished by FDA request in letters to NDA application holders. The Food and Drug Administration Amendments Act of 2007 (FDAAA) added a new Section (505(o)(4)) to the Federal Food, Drug, and Cosmetic Act providing authority for FDA to require sponsors to amend the approved labeling for products in response to new safety information. In these cases, the labeling of all members of a drug class can be asked to include identical statements. However, manufacturers who receive letters requesting such class labeling changes can disagree with FDA-proposed language and propose their own versions of the labeling language. A FDA Guidance [Guidance for Industry Safety Labeling Changes —Implementation of Section 505(o)(4) of the FD&C Act, July 2013] provides mechanisms for FDA and the manufacturers to resolve differing opinions about appropriate label language. In general, even if FDA seeks to institute class labeling language, FDA will accept different wording for drug labels within a class if there "is a well-justified, scientific rationale to support different wording" [Guidance for Industry Safety Labeling Changes —Implementation of Section 505(o)(4) of the FD&C Act, July 2013]. Having specific data showing differences among a class member will likely support such different wording.

The term "class labeling" is also used more informally to connote occasions when FDA and/or manufacturers seek to use existing labeling for drugs in the same class as a "template" for language in the new labels being drafted. If FDA reviewers conclude that all drugs within a class have the same effect (i.e., a "class effect"), the FDA may seek to have those drugs convey the same information. This would mitigate against drug manufacturers differentiating among competing products on the basis of idiosyncrasies in the manner in which the drug label is composed rather than on the basis of scientific information. However, if the manufacturer has specific information that describes the action of their drug they can add to, modify, or strengthen proposed "class labeling" language.

Review of the "Discontinuation" section of the Cymbalta label compared to other drugs in the class demonstrates both similarities and differences among members of the SSRI/SNRI class of drugs.

As discussed above, there are three paragraphs in the Discontinuation section of the Cymbalta warning/precaution. The first paragraph describes data specific to Cymbalta. The second paragraph describes discontinuation effects found in similar drugs within the class. The third paragraph describes treatment recommendations.

Other drugs within this class vary in whether they present two, three or four paragraphs of information in the discontinuation warning/precaution section. Some drugs have only the second and third paragraphs (e.g., Zoloft (Sertraline HCI); Lexapro (escitalopram oxalate); Celexa (citalopram hydrobromide)). The labeling information in these paragraphs is similar to other drugs in the class in describing the spontaneous adverse events seen in these drugs and in providing treatment advice. Other drugs have three paragraphs (Effexor (venlafaxine hydrochloride) or four paragraphs (PAXIL CR (paroxetine hydrochloride)) that contains more specific information about their product. The Effexor label mentions 23 symptoms related to discontinuation but does not provide any information about the frequency with which they occur. As described above, the Paxil label section provides information about the frequency of individual adverse events (it does not call them "symptoms") and provides a 2% threshold. Thus, although there is some common language in the class product labels, it is clear that the language is merely a "template," not a hard and fast verbatim requirement. Antidepressant manufacturers clearly retain the ability to seek to add information even if there is a class template.

Another important example is Lilly's own earlier-marketed antidepressant, Prozac (fluoxetine hydrochloride). The Prozac label contains a single paragraph in the warnings/precautions section about discontinuation effects. The paragraph describes discontinuation effects that have occurred with Prozac and other SSRI/SNRI drugs and provides advice about tapering off the drug when stopping treatment. The Prozac label also states, "Plasma fluoxetine and norfluoxetine concentration decrease gradually at the conclusion of

therapy which may minimize the risk of discontinuation symptoms with this drug." Thus, for this antidepressant, Lilly added information to the class template that suggested a lower risk of discontinuation symptoms specific to Prozac and its chemical make-up. There is no such information about blood levels or half-life of the drug included in the Cymbalta label. The inclusion of this language in the Prozac label shows that Lilly was aware of meaningful differences between and among drugs in the class in the degree to which they are associated with discontinuation syndrome/effects. However, Lilly's Cymbalta label fails to convey the incidence rate of discontinuation syndrome specific to that drug.

VI. Medical Letters – Unsolicited Spontaneous Requests

FDA has long maintained that pharmaceutical companies can fully communicate scientific information about their products, even if the information covers uses that are not included in the product label, as long as the companies do not make promotional claims about the product (CFR Section 312.7(a)). To provide scientific information about the product, companies may fully answer requests from health professionals as long as the requests are "unsolicited." Unsolicited requests are initiated by physicians or other persons and are completely independent of the actions of the manufacturer [Guidance for Industry, Responding to Unsolicited Requests for Off-Label Information About Prescription Drugs and Medical Devices, December 2011]. FDA has long taken the position that firms can respond to unsolicited requests for information about FDA-regulated medical products by providing truthful, balanced, non-misleading, and non promotional scientific or medical information that is responsive to the specific request, even if responding to the request requires a firm to provide information on unapproved indications or conditions of use.

To assure that the information meets FDA standards for scientific exchange, companies prepare "Medical Letters" that can be mailed to physicians who ask certain questions. Lilly has prepared such letters that respond to such unsolicited requests where physicians ask specifically ask about Cymbalta's discontinuation/withdrawal effects ((Helgeson Declaration). According to this declaration, in September 2006, the Medical Information Letter on Cymbalta Discontinuation effects incorporated data from the Perahia et al (2005) study indicating a 44% rate of discontinuation effects.

Starting in March, 2009, the Medical Letter distributed in response to an unsolicited question about discontinuation effects contained the introductory statement that "Information on the discontinuation-emergent adverse events … included in this letter may contain information that does not completely match the current US prescribing information for Cymbalta." Thus, Lilly appears to acknowledge that the information distributed was different than the information that appeared in the label. This differs from some statements made by Dr. Karen Becker that the information presented in the Perahia et al (2005) study was the same as the information that was

presented in the product label. In Dr. Becker's rebuttal report and deposition (page 177-178), she states: "the US package insert is not inconsistent with the European label." "They just reflect different ways of communicating the same essential message…." [the European labeling cites the 44% figure but the US label does not].

It should be noted that although the Medical Letter information was freely available to doctors, the doctor had to specifically request such information without any prompting from Lilly (i.e., a spontaneous unsolicited request). It is estimated that in 2010 there were 146,000 practicing primary care physicians in the U.S that treated adult patients. Adult treating-primary care physicians consist of family physicians, general practitioners, general internists and geriatricians. Of the nearly 956 million visits that Americans made to office-based physicians in 2008, 51.3% were to primary care physicians (AHRQ, 2014). In addition, there was an estimated 32,000 psychiatrists active in patient care (AAMC, 2014). Thus, there were approximately 178,000 doctors that might consider prescribing Cymbalta (this does not include other specialties that might consider prescribing, such as neurologists and rheumatologists). From September 2006 to September 2013, Lilly sent its medical information letter on Cymbalta discontinuation symptoms to 1,072 health care professionals (March 19, 2015 letter from Lilly's counsel to Plaintiff's counsel). (It is unclear if the "medical professionals" included only physicians or other health-related professions.) Thus, about one-half of one percent of the target market for Cymbalta received a medical letter regarding discontinuation effects over all the years Cymbalta has been marketed. Assuming the Medical Letters were all sent to physicians in the target market, that means that less than 1% of physicians who might prescribe Cymbalta (1,072/178,000 = 0.6%) received the Medical Letter indicating that 44% of patients suffered discontinuation effects.

VII. Market Research Studies

Prior to and during the marketing of Cymbalta in the United States, Lilly conducted market research studies of physicians, "payers" and sometimes consumers to gain a better understanding of how to "position" and promote Cymbalta.

Physician understanding of a variety of Cymbalta's attributes, including discontinuation effects, was a topic of some of this research. Lilly was interested not only in how Cymbalta was perceived by physicians, but how it was perceived relative to competing antidepressant medicines.

In 1999, Lilly conducted 20 qualitative interviews with neurologists, psychiatrists and primary care physicians. They also conducted 29 "validation interviews" via telephone and 22 in person interviews in Hamburg Germany at a medical conference. In the findings, the report noted that product safety was one of the issues noted by physicians. The research team removed a statement from the description of Cymbalta that it was "five times more potent than Effexor"

because physicians perceived Cymbalta as potentially dangerous. They added a statement regarding safety and tolerability, claiming that Cymbalta was similar to SSRIs and superior to prescription analgesics.

This research also found that primary care physicians, more than other physicians, were strongly interested in the benefits Cymbalta might bring to a wide range of patients as it might be easier for them to convince depressed-pain patients to take this medication for their condition.

In a May 2002 study using 77 in-depth interviews of psychiatrists and primary care physicians (PCPs) Lilly studied how to create "selling stories." They found psychiatrists generally had more knowledge of antidepressants and were more aware of Effexor and its benefits and limitations. To distinguish Cymbalta from other SNRIs, tolerability and safety were important messages. Doctors were concerned about Effexors's side effects during use and on discontinuation. PCPs saw Cymbalta as an improvement over Effexor (more/quicker symptom relief with fewer side effects). They were uncomfortable with Effexor due to its side effects on starting and need for tapering patients. Psychiatrists viewed Cymbalta as more effective and broadly useful than Effexor. The psychiatrists were disappointed with Effexor due to its nausea, withdrawal symptoms and remission rates. Some physicians (psychiatrists and PCPs) had questions about Cymbalta's withdrawal symptoms in comparison to Effexor. The research team recommended distinguishing Cymbalta from Effexor in regards to tolerability and safety.

A July 2002 Canadian study of 85 GPs and 41 Psychiatrists sought to determine the potential for Cymbalta in the market and the key "drivers" of Cymbalta use. At that time the majority of respondents were aware of Paxil and Effexor (about 95% of the study population) but not aware of Cymbalta (2%). When examining what physicians viewed as the major advantages of Cymbalta (after reading a description of the medicine), 37% viewed product safety as a main advantage (with 4% stating that there was low/no discontinuation reaction with Cymbalta); whereas 11% viewed discontinuation reactions as a concern with Cymbalta. The researchers constructed a "discrete choice model" seeking to determine what factors would lead a doctor to prescribe Cymbalta rather another antidepressant. After formulary coverage and price, product safety was the most important factor influencing product choice.

In August 2002, Lilly conducted a pricing study to determine the relative importance of drug cost, as well as other attributes that might justify Cymbalta's price. There were 24 psychiatrists and 23 PCPs studied in focus group interviews. They found that both physician groups lacked knowledge of drug costs, were uncomfortable in drug cost discussions and that price was not a driving factor in antidepressant prescribing decisions. The study found that only three factors could justify premium pricing of Cymbalta relative to Effexor XR: (1) faster onset of action, (2) greater efficacy at lower dose and (3) a significant decrease in the rate and severity of withdrawal or discontinuation syndrome. Physicians did not view price as influencing the clinical value of a product.

In June 2004, Lilly conducted a Patient Segmentation Study. The study was conducted in Turkey among 292 physicians (101 GPs, 97 Neurologists and 94 Psychiatrists). Among the factors found most important in influencing doctors' selection of an antidepressant was avoiding dependency and withdrawal issues. This factor was rated the highest among 13 attributes presented.

In a January, 2006 study, Lilly interviewed 305 PCPs in an online study to test physician knowledge and reaction to several promotional "themes" or product claims (these were presented in slides show to respondents). One of the themes tested was that Cymbalta had minimal adverse effects with one particular slide presentation regarding Cymbalta having minimal discontinuation side effects. While 47% of the doctors believed that the theme of minimal discontinuation side effects were communicated extremely or very well, 41% stated that they were not very (35%), or not at all (6%) familiar with this information.

The results of these studies informed Lilly, even before the launch of Cymbalta in the United States, that certain physicians prescribing antidepressant had concerns about discontinuation symptoms. The studies informed Lilly that the appearance of low discontinuation side effects would be an attribute that could distinguish Cymbalta from competing antidepressants, particularly Effexor. Some doctors viewed product safety as an important issue influencing prescribing and that low discontinuation effects could justify a high selling price.

Some of this thinking appears to have influenced Lilly sales force training. In a March 2003 "self-instructional" manual designate for training Lilly representatives, the strengths and weaknesses of various competing antidepressants is discussed. Among the weaknesses noted for Effexor is "discontinuation-emergent side effects are very bothersome." The short half-life of Effexor is cited as the reason for these discontinuation-emergent side effects.

CONCLUSION

Lilly's United States Cymbalta label is false and misleading as to the risk of discontinuation syndrome posed by the drug. Lilly had the ability to change and strengthen the Cymbalta label, and indeed, undertook other changes to that very section of the label on a number of occasions over the lifespan of Cymbalta. Neither FDA Guidance on "frequency" cutoffs nor template "class labeling" for antidepressants prevented Lilly from modifying the Cymbalta label. There is no evidence that Lilly ever engaged FDA to add the Perahia incidence rate. Nor is there evidence to suggest that the FDA would have denied or blocked such a request. The Medical Letters containing the Perahia incidence rate that Lilly alleges to have sent to less than 1% of its target physician audience were not an adequate "fix" to the effects of the false and misleading labeling.

All of the opinions stated in this Supplemental Expert Report are based upon my additional review of materials and my education, experience, and background at FDA and in industry, and have been arrived at to a reasonable degree of professional certainty.

I declare, under penalty of perjury that the information conveyed herein is true and correct to the best of my knowledge, information and belief.

5/14/15
Date

Louis A Morris
Louis A. Morris, Ph. D.

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Additional Material Reviewed:

March 19, 2015 letter from Lilly's counsel to Plaintiffs' counsel

Lilly Market Research:

1999 Executive Summary Message Development	CYM-02785859
2002 Duloxetine CELA	CYM-02783656
2002 Discrete Choice Study	CYM-02783884
2002 Cymbalta Discrete Choice Model	CYM-02783967
2002 US Strategic Pricing Study	CYM-02786215
2004 Patient Segmentation Study	CYM-02784114
2006 Data Impact Test with PCPs	CYM-02784272

Training Material:

2003 The Market and Competition for Cymbalta	CYM 01866789

Reports and Transcripts/Depositions

Dr. Karen Becker
Dr. Stephen Knowles

Material Reviewed but not cited:

Reports and Transcripts/Depositions

Sworn testimony of Lilly employees and exhibits (Perahia, Hoog, Mescher, Phillips, and Knowles)

Becker: "Cymbalta Medication Guide Changes Timeline" (and supporting documents)

Becker: "Cymbalta Labeling Changes Chronology" (and supporting documents)

Cymbalta U.S. product labeling, 2004-current

Cymbalta foreign product labeling, various years

Other antidepressant product labeling, various years

Code of Federal Regulations (CFR), Title 21

FDA Guidances

Reports of Dr. Joseph Glenmullen (on behalf of Plaintiff)

Declaration of Sarah L. Hegelson re: Medical Letters (and supporting exhibits)

Various internal Lilly documents:

9/17/06 Email Carol H. Stephens to Michael Detlke CYM-02363882 – 02363885
11/11/02 Pierre V. Tran Email re: Comments on SUI Clinical Expert Report - CYM-01813088 – 01813089
7/2/03 David Perahia Email re: An Obscure Question – CYM-01873414 – 01873416
-10 November 2006 Summary of the Minutes of the Cymbalta National Advisory Board CYM-01797201 – 01797204
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7/2/03 Email David Perahia re: An Obscure question CYM-01873414 – 01873416