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October 16, 2007

By Facsimile [301-796-9877]
and First-Class Mail

Thomas Abrams, RPh, MBA
Director
Division of Drug Marketing, Advertising, and Communications
10903 New Hampshire Ave.
Bldg 22 Rm 1400
Silver Spring, MD 20993-0002

Re: NDA # 21-733
CYMBALTA® (duloxetine hydrochloride) Delayed-release Capsules
MACMIS # 14550

Dear Mr. Abrams:

On September 21, 2007, the Division of Drug Marketing, Advertising, and Communications (DDMAC) sent an untitled letter to Eli Lilly and Company (Lilly) alleging that a professional mailer (mailer) for CYMBALTA® (duloxetine hydrochloride) Delayed-release Capsules was false or misleading and therefore misbranded the drug in violation of section 502(a) and 201(n) of the Federal Food, Drug, and Cosmetic Act (FDCA), 21 U.S.C. §§ 352(a) and 321(n), and FDA implementing regulations. According to DDMAC, this mailer is unlawful because it overstates the efficacy of Cymbalta and omits risk information. For the reasons discussed below, DDMAC should withdraw the letter.[1]

Unlawful Objections to Efficacy Claims Based on Data From Clinical Investigations

DDMAC's allegation that the mailer overstates the efficacy of Cymbalta highlights DDMAC's firmly established policy of allowing only those prescription drug promotional claims that are supported by "substantial evidence." According to DDMAC, the reference cited by Lilly to support the claim of less pain interference with overall functioning "does not constitute substantial evidence because it reports pooled efficacy data from multiple studies" and relies on

[1] In previous correspondence with you, and in a citizen petition filed on August 7, 2006 (Docket No. 2006P-0319), we listed all of the earlier letters in which we explained our objections to DDMAC's efforts to regulate the content of prescription drug communications. For the sake of brevity, we are discontinuing that practice. All of the concerns WLF is raising in this letter to you have been raised before.

"post-hoc analysis." In addition, DDMAC states that the pain interference subscale of the Brief Pain Inventory—Interference Portion (BPI), which was used to obtain pain interference ratings from study subjects, has not been validated.

DDMAC's position, that promotional claims may only rely for substantiation on sources that meet FDA's high standard—the same standard used to determine whether a drug is approvable—not only harms the public health by keeping new scientific developments from health care practitioners, but also raises significant questions under the First Amendment. As a legal matter, a prescription drug manufacturer is entitled to make statements in its promotional materials based on sources of information that do not meet the "substantial evidence" standard.

It is a bedrock of First Amendment law that the government may not ban speech based on its potential to mislead, if the speech is presented in a manner that is truthful and non-misleading. The most obvious way for DDMAC to comply with this principle would be to allow sponsors to make promotional claims based on clinical investigations and on other sources of data and information as long as those claims are presented with any necessary disclaimers. *Central Hudson Gas & Elec. Corp. v. Public Serv. Comm'n*, 447 U.S. 557, 565 (1980) ("The State cannot regulate speech that poses no danger to the asserted state interest, nor can it completely suppress information when narrower restrictions on expression would serve its interest as well."); *Bates v. State Bar*, 433 U.S. 350, 375 (1977) ("the preferred remedy is more disclosure, rather than less"). Consistent with these constitutional principles, DDMAC must allow manufacturers to convey information about their products to health care practitioners—even if that information is obtained from clinical studies that do not meet DDMAC's exacting standards.

In this instance, Lilly is entitled to make truthful and non-misleading statements in its promotional materials, regardless of whether DDMAC considers the data to be sufficiently "substantial." FDA is not a peer-review mechanism for the medical community. *Washington Legal Found. v. Friedman*, 13 F. Supp. 2d 51, 67 (D.D.C. 1998). Because scientific viewpoints may differ as to the usefulness of any particular study in clinical practice, the only course that respects First Amendment values is for DDMAC to allow truthful and non-misleading claims about all studies, whether or not they are deemed acceptable by DDMAC. *West Virginia State Bd. of Educ. v. Barnette*, 319 U.S. 624, 642 (1943). DDMAC's approach of precluding Lilly from making efficacy claims based on data that DDMAC does not find sufficiently "substantial" would deprive physicians of useful information about therapeutic products in violation of the First Amendment. *Virginia State Bd. v. Virginia Citizens Consumer Council*, 425 U.S. 748, 757 (1976) (The Court has not "recognized any . . . limitation on the independent right of the listener to receive the information sought to be communicated."); *Roe v. Ingraham*, 364 F. Supp. 536, 543 (S.D.N.Y. 1973) ("the First Amendment has been held to include a correlative right to receive information and ideas"). To the extent that any claims may be misleading, under the First Amendment, manufacturers are entitled to use, and DDMAC is required to accept, disclaimers sufficient to ensure that the statements are truthful and non-misleading. *See Pearson v. Shalala*, 164 F.3d 650 (D.C. Cir.), *reh'g denied*, 172 F.3d 72 (D.C. Cir. 1999).

DDMAC's position is not only constitutionally suspect but also problematic under the FDCA. As a matter of straightforward statutory interpretation, claims are not per se misleading merely because they are based on data or other information not satisfying the "substantial evidence" standard. If that were the case, then several provisions of the FDCA and FDA regulations that

expressly allow claims based on lower evidentiary standards would conflict with other statutory and regulatory prohibitions against false or misleading labeling and advertising. *See* 21 U.S.C. § 352(a) (allowing health care economic information in labeling based on "competent and reliable scientific evidence"); 21 C.F.R. § 202.1(e)(5)-(7) (allowing claims in advertising based on "substantial clinical experience"). Unless DDMAC intends to advocate a reading of the statute and regulations that renders these provisions incoherent, it must acknowledge that not all claims must meet the highest standard of substantiation to be truthful and non-misleading.

Moreover, the FDCA and FDA regulations recognize the principle that statements that might be misleading can nevertheless be accurate when put into their proper context. That is why, for example, prescription drug promotion must qualify claims by presenting material information about the consequences of use. 21 U.S.C. § 321(n); 21 C.F.R. § 1.21. These provisions reflect the importance of relying on the use of disclosures of more information rather than addressing the potential for a claim to mislead by reducing or eliminating the flow of information.

Indeed, DDMAC routinely accuses prescription drug manufacturers of making unsubstantiated and/or misleading claims of superiority, efficacy, and safety, alleging that references cited in support of claims do not constitute substantial evidence. Since the inception of DDMAC Watch, the Division has alleged that claims were unsubstantiated and/or misleading on the following bases:

- the reference cited contained data from nonclinical studies
- the study generated only *in vitro* data
- the reference cited discussed pharmacokinetic findings
- the reference cited contained data from animal studies
- the study assessed tissue data
- the study was open-label
- the study was a pilot trial
- the study was a retrospective pooled analysis
- the study had a single-arm design
- the study was a replacement trial
- the study lacked a concurrent control group
- the study was baseline controlled
- the study used an historical control
- the study lacked blinding
- the study lacked predefined endpoints
- the study was a meta-analysis
- the study was a titration-to-effect comparison
- the study did not compare drugs administered at their maximum approved dosages
- the study results conflicted with results from other trials
- the reference cited was not a "complete" study report
- the reference cited was a survey
- the data were based on a post-hoc subgroup analysis
- the study protocol required that patients stay on the same medication for 12 months

- the study did not take into account factors that affect patient adherence and did not reflect adherence rates for "real-world use"
- the study's experimental conditions did not "mimic the clinical usage" of the product
- the study did not specifically evaluate efficacy for a stand-alone symptom
- the data were not clinically significant
- the data were not statistically significant
- the study did not "specifically evaluate" the drug product
- the study was not "specifically designed" to evaluate the proposed claims
- the study was not designed to look for statistically significant differences between treatment groups prospectively
- the study was not sufficiently powered
- the study was not replicated
- the reference cited was a poster presentation and contained "inadequate" information
- the study's statistical analysis did not "adjust for multiple comparisons"
- the study used an "unacceptable" primary efficacy variable
- the study's active comparison was not "clearly planned"
- the study used a secondary endpoint to support a conclusion of superiority
- the study relied on a "questionable" definition of "response"
- the study relied on a definition of "clinical cure" different than that in the pivotal studies
- the data were based on patient self-reported information
- the data were not from a "head-to-head clinical comparison"
- the study relied on measurements that "have not been shown to correlate with clinical efficacy"

The frequency with which DDMAC objects to use of various sources, and the sheer breadth of the grounds on which DDMAC has objected, make clear that the existing regulations are not sufficient to notify regulated industry of DDMAC's expectations in this area. *See* 21 C.F.R. § 314.126. Although DDMAC has issued guidance on certain issues relating to the development of clinical study designs to support approval, no guidance is available as to the characteristics of studies that would be objectionable or desirable in the context of claims. At a minimum, DDMAC should, based on its firmly established policy and practice of citing manufacturers for relying on the "wrong" sources, provide clear guidance to industry on claims substantiation.

Problematic Policy of Requiring Double Disclosure of Risk Information

DDMAC also alleges that the mailer is misleading because it presents efficacy claims for Cymbalta but does not present certain risk information. DDMAC's objection ignores the fact that the mailer was disseminated with copies of the FDA-approved labeling—which contained the full risk information—and that the mailer directed recipients to the labeling. Health care practitioners thus had ready access to the very information that DDMAC alleges was omitted, and that information was presented in precisely the manner dictated by FDA. Moreover, DDMAC does not present any evidence that health care practitioners reading the mailer were misled by the manner in which the risk information was presented.

DDMAC's position that prescription drug manufacturers must present risk and other information not only in the FDA-approved labeling that accompanies the promotional communication, but also in the "creative" part of the labeling piece itself, is both legally vulnerable and inconsistent with broader FDA policies. FDA's drug advertising regulations, 21 C.F.R. § 202.1(e)(3), specifically address the use of a cross-reference instead of duplicative disclosure of qualifying information:

> If any part or theme of the advertisement would make the advertisement false or misleading by reason of the omission of appropriate qualification or pertinent information, that part or theme shall include the appropriate qualification or pertinent information, which *may be concise if it is supplemented by a prominent reference on each page to the presence and location elsewhere in the advertisement of a more complete discussion of such qualification or information*.

This regulation states that qualifying information may appear concisely in each part of an advertisement if accompanied by a reference to more complete qualifying information elsewhere in the piece. DDMAC has effectively read that important language out of the regulation. Nowhere does DDMAC's letter acknowledge that FDA's own regulations contemplate promotional materials that do not present risk information verbatim in two separate places.[2]

Moreover, DDMAC's position raises constitutional questions. The First Amendment requires the government to justify requiring manufacturers to present risk and other information deemed "material" by DDMAC in the main body of a piece. *See Pearson v. Shalala*, 164 F.3d at 659 ("[A]ll the government offers in support is the FDA's pronouncement that 'consumers would be considerably confused' . . . . [T]he government . . . must still meet its burden of justifying a restriction on speech—here the FDA's conclusory assertion falls far short.") (citations and footnote omitted). Given that comprehensive risk information and the complete labeled indication appear in the brief summary or full disclosure, it seems highly doubtful that such justification could be provided.

Even if DDMAC's position were tenable in substance, it would be invalid for procedural reasons. At one time, FDA's view was that promotional communications for prescription drugs had only to refer the reader to the location of complete risk information, which could appear on a separate page. *See* 50 Fed. Reg. 36,677 (1985) ("[T]he brief summary is intended to ensure a 'fair balance' between a drug's potential benefits and risks in all prescription drug advertisements."). As of 1996, the agency's position had changed. *See* 61 Fed. Reg. 48,708 (1996) (FDA "traditionally" has required risk information in the body of the advertisement). FDA's failure to use notice-and-comment rulemaking or to provide a reasoned analysis justifying this change of position renders its current stance invalid. *See Motor Vehicle Mfrs. Ass'n v. State Farm Mut. Auto. Ins. Co*., 463 U.S. 29, 42 (1983); *Alaska Prof. Hunters Ass'n, Inc. v. Federal Aviation Admin.*, 177 F.3d 1030, 1033-34 (D.C. Cir. 1999).

[2] As you know, DDMAC often relies on the Part 202 advertising regulations by analogy in regulating promotional labeling.

Finally, the "double-disclosure" policy presents important policy questions. FDA has recognized repeatedly that disclosing too much risk information in promotional material can cause "information overload," precluding comprehension and/or distracting attention from the most important facts. In finalizing new regulations intended to make package inserts easier for practitioners to use by, among other things, focusing the risk-information sections on scientifically substantiated risks, FDA stated that "labeling that includes theoretical hazards not well-grounded in scientific evidence can cause meaningful risk information to lose its significance . . . . Overwarning, just like underwarning, can . . . have a negative effect on patient safety and public health." *See* Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products, 71 Fed. Reg. 3,922, 3,935 (Jan. 24, 2006).

Consistent with this sensible position, FDA has also taken steps to evaluate effective risk communication in patient-directed materials. In 2004, in a draft guidance document intended to improve patient comprehension of risk information in print advertisements by reducing the volume and improving the format of that information, CBER and CDER stated: "In general, FDA believes that exhaustive lists of minor risks distract from and make it difficult to comprehend and retain information on the more important risks." *See* CBER & CDER, Guidance for Industry: Brief Summary: Disclosing Risk Information in Consumer-Directed Print Advertisements (DRAFT) (Jan. 2004). The double-disclosure theory is irreconcilable with FDA's "less is more" theory of risk communication and is therefore invalid. *Harco Holdings v. United States*, 977 F.2d 1027, 1035-36 (7th Cir. 1992) (agency position "is not only new and unsupported by agency practice or rulings, . . . [but also] internally inconsistent" and therefore "deserves no deference").

In addition, the over-disclosure of risk information may adversely affect the public health. Perhaps the most well-known recent example of overwarning involves depression drugs. Beginning in 2004, FDA began focusing on reports that adolescent patients taking drugs in the selective serotonin reuptake inhibitor (SSRI) class were having suicidal thoughts shortly after beginning drug therapy. After consulting with advisory committees regarding the appropriate risk management strategy in response to these reports, FDA decided to seek labeling revisions for all SSRIs. On March 22, 2004, FDA issued a Public Health Advisory recommending that labeling be modified to reflect potential suicide risks. FDA noted in the Advisory that it had "not concluded that [SSRI side effects] are a precursor to either worsening of depression or the emergence of suicidal impulses," but it still recommended the change to alleviate "concern." Public Health Advisory, FDA, Worsening Depression and Suicidality in Patients Being Treated With Antidepressant (Mar. 22, 2004), *available at* http://www.fda.gov/cder/drug/antidepressants/AntidepressanstPHA.htm.

Shortly after the labeling change, the psychiatric community, patients, and caregivers began expressing concern about undertreatment of depression and a sudden spike in suicidal behavior. Pediatric antidepressant prescriptions had fallen by about 50 percent between 2003 and 2005, according to a study published in June 2007 in *The American Journal of Psychiatry.* Anne M. Libby, Ph.D. et al., *Decline in Treatment of Pediatric Depression After FDA Advisory on Risk of Suicidality With SSRIs*, 164 Am. J. Psychiatry 884, 887 (2007). A September 2007 study in that journal reported that, as pediatric antidepressant prescriptions fell in 2003-2004, the adolescent

suicide rate rose by 14 percent.[3] The authors of the study reasoned that "the public health warnings may have left some of the most vulnerable youths untreated." Robert D. Gibbons, Ph.D. et al., *Early Evidence on the Effects of Regulators' Suicidality Warnings on SSRI Prescriptions and Suicide in Children and Adolescents*, 164 Am. J. Psychiatry 1356, 1358-1359 (2007).

As this recent experience demonstrates, the public health consequences of overwarning can be devastating. DDMAC should closely re-examine its double-disclosure policy accordingly.

Conclusion and Requested Action

We request that DDMAC immediately withdraw the untitled letter to Lilly concerning Cymbalta. We also urge DDMAC to cease the issuance of warning and untitled letters and advisory correspondence that contain allegations the same as or similar to those described above.

The deficiencies described in this letter do not necessarily constitute an exhaustive list. DDMAC must ensure that its actions with respect to prescription drug promotion, and to other forms of commercial speech, comply with the First Amendment, and do not exceed FDA's statutory authority under the Federal Food, Drug, and Cosmetic Act.

Sincerely,

Richard A. Samp
Chief Counsel

cc: Gerald F. Masoudi (GCF-1)

[3] Data available from the Centers for Disease Control and Prevention on U.S. suicide rates was only available at the time of the study through 2004.