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December 10, 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 # 22-059**
**TYKERB (lapatinib) Tablets**
**MACMIS # 15851**

Dear Mr. Abrams:

On November 21, 2007, the Division of Drug Marketing, Advertising, and Communications (DDMAC) sent a warning letter to GlaxoSmithKline (GSK) alleging that three Dear Healthcare Practitioner Letters for Tykerb were misleading in that they omitted and minimized risk information and selectively presented efficacy information. Therefore, DDMAC alleged, the letters misbranded the drug in violation of the Federal Food, Drug, and Cosmetic Act (FDCA), 21 U.S.C. §§ 352(a) and 321(n); *Cf.* 21 C.F.R. § 202.1(e)(5)(i), (iii), and (e)(6)(i). For the reasons discussed below, DDMAC should withdraw the letter.[1]

**Problematic Double Disclosure Policy**

DDMAC alleges in the warning letter that the Dear Healthcare Practitioner Letters omitted two kinds of important information: (1) information regarding the use of two different assessment methods in the clinical trial supporting approval of TYKERB; and (2) certain information regarding the risks associated with use of the product. DDMAC's allegations are unfounded.

[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.

First, the letters in fact contained and/or were accompanied by both assessment information and risk information. It is uncontested that the letters specifically disclosed that there were differences in the investigator-conducted and independent assessments. Indeed, this disclosure appears prominently in the body of the letter, in the same paragraph as the presentation of the clinical trial data demonstrating efficacy. In addition, as DDMAC acknowledges, GSK included information regarding the most common and least severe adverse effects. It also included information on one of the least common and most severe adverse effects—left ventricular ejection fraction (LVEF).

DDMAC's position, essentially, is that promotional materials must disclose material information twice—once in the main body, and again in the accompanying brief summary or prescribing information. For reasons outlined in greater detail in previous correspondence, DDMAC's position is without regulatory or legal support.

Second, DDMAC fails to mention that the letters refer the reader to the accompanying full prescribing information. The letters that were in e-mail format provided links to the full prescribing information, and the direct mail letters were accompanied by the full prescribing information. The audience for the letters therefore had immediate access to all of the information DDMAC alleges was omitted, and that information was presented in precisely the manner dictated by FDA.

Requiring duplicative disclosures of risk information is in tension with broader agency initiatives intended to improve comprehension of risk information by focusing on the most important risk information and eliminating indiscriminate lists of risks. *See* CBER & CDER, Guidance for Industry: Brief Summary: Disclosing Risk Information in Consumer-Directed Print Advertisements (DRAFT) (Jan. 2004), *available at* www.fda.gov/cder/ guidance/5669dft.doc ("In general, FDA believes that exhaustive lists of minor risks distract and make it difficult to comprehend and retain information on the more important risks"); CBER & CDER, Guidance for Industry: Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products—Content and Format (Jan. 2006), *available at* www.fda.gov/cder/guidance/5537fnl.htm ("In general, the ADVERSE REACTIONS section includes only information that would be useful to health care practitioners making treatment decisions and monitoring and advising patients. Exhaustive lists of every reported adverse event, including those that are infrequent and minor . . . should be avoided . . . . Such lists are not informative and tend to obscure the more clinically meaningful information"); Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products, 71 Fed. Reg. 3,922, 3,935 (Jan. 2006) ("FDA has previously found 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 similarly have a negative effect on patient safety and public health . . . Similarly, State-law attempts to impose additional warnings can lead to labeling that does not accurately portray a product's risks, thereby potentially discouraging safe and effective use of approved products or encouraging inappropriate use and undermining the objectives of the act.").

WLF encourages DDMAC to re-examine its policy of requiring double disclosure of risk and other important information according to these policy, regulatory, and legal principles.

**Unsubstantiated Allegations of Misleadingness**

According to DDMAC, the Dear Healthcare Practitioner Letters "suggest to healthcare professionals" that the drug "is safer and more effective than has been demonstrated." Yet DDMAC presents no data to substantiate its specific interpretations of the letters. Nor does DDMAC present data demonstrating that the letters were false or misleading. Given that the allegedly missing information actually appears both in and with the letters, as discussed above, it is hard to see how the agency could meet its burden in any enforcement action.

Before DDMAC may take action with respect to promotional materials alleged to be misleading, it must develop data demonstrating that the materials, in fact, are misleading. In the warning letter to GSK, DDMAC does not even allege that anyone was actually misled. Rather, DDMAC appears to be merely fearful that someone might be misled. This approach is incompatible with the First Amendment. *See Virginia State Bd. v. Virginia Citizens Consumer Council*, 425 U.S. 748, 769, 773 (1976).

The only apparent basis for DDMAC's allegations is the individual judgment of the DDMAC personnel involved in preparing and reviewing the warning letter. DDMAC's action is therefore an example of "we know it when we see it" regulation. This is inconsistent with the Administrative Procedure Act (APA), which provides for judicial invalidation of agency action that is "in excess of statutory jurisdiction," arbitrary, or capricious. 5 U.S.C. § 706; *see also Pearson v. Shalala*, 164 F.3d 650, 660 (D.C. Cir.), *reh'g denied*, 172 F.3d 72 (D.C. Cir. 1999) ("To refuse to define the criteria [FDA] . . . is applying is equivalent to simply saying no without explanation.").

The APA also provides for invalidation of agency action that is "contrary to constitutional right." 5 U.S.C. § 706. It is beyond dispute that professional promotional materials qualify as protected speech. *Washington Legal Found. v. Friedman*, 13 F. Supp. 2d 51, 62 (D.D.C. 1998) (citing *Keyishian v. Board of Regents*, 385 U.S. 589, 603 (1967), and *Board of Trustees of Leland Stanford Junior University v. Sullivan*, 773 F. Supp. 472, 474 (D.D.C. 1991)), *appeal dism'd*, 202 F.3d 331 (D.C. Cir. 2000). Accordingly, the government bears the burden of justifying any restrictions it seeks to impose on that speech. *Edenfield v. Fane*, 507 U.S. 761, 770-771 (1993) ("It is well established that the party seeking to uphold a restriction on commercial speech carries the burden of justifying it. This burden is not satisfied by mere speculation or conjecture; rather, a governmental body seeking to sustain a restriction on commercial speech must demonstrate that the harms it recites are real and that its restriction will in fact alleviate them to a material degree.") (citations and internal quotation marks omitted).

To fulfill its constitutional obligation, DDMAC must do more than simply declare that the letters are misleading. *See Pearson*, 164 F.3d at 659 (citations and footnote omitted). Because that is all that DDMAC has seen fit to do, the warning letter cannot be reconciled with the First Amendment.

**Lack of Clear Standards for Evaluating Promotional Material**

The FDCA and FDA regulations provides relatively little guidance to industry on many issues of major importance in the development of promotional materials for prescription drugs. Thus, drug manufacturers must rely on DDMAC to enunciate the standards by which it evaluates promotional materials.

DDMAC encourages sponsors to submit promotional materials prior to dissemination or publication, but then takes too long to provide comments. Congress recognized the unacceptable amount of time that DDMAC takes in reviewing direct-to-consumer (DTC) advertising, and included in the Food and Drug Administration Amendments Act of 2007 a new DTC user fee program beginning in fiscal year 2008. Pub. L. No. 110-85, § 104 (2007). However, no mechanism exists to expedite the review of other types of promotional materials. As a result, drug companies have two choices at launch: either wait an unacceptable period for DDMAC's comments on proposed launch materials, or launch without the benefit of DDMAC's recommendations at risk. For those electing the former option, DDMAC's delay in providing comments amounts to a *de facto* moratorium on launch campaigns.

Of particular concern to industry for some time has been the lack of guidance from DDMAC on the presentation of risk information in launch materials. Because DDMAC cannot act against promotional materials that follow recommendations provided by DDMAC in the past without first issuing a "change of opinion" letter, 21 C.F.R. § 202.1(j)(4), the comments provided by DDMAC on launch materials provide a template for companies to follow in developing future materials. In the absence of specific comments on a launch campaign, a company must rely on the general provisions in the FDCA and FDA regulations. These authorities do not contain specific provisions on the presentation of risk information in promotional materials. Although DDMAC has been promising guidance on this topic for some time, none has yet been provided.

It is inappropriate for DDMAC to take action against manufacturers on the ground that they have not achieved fair balance in their promotional materials in the absence of sufficient guidance on this issue. WLF encourages DDMAC to develop such guidance immediately.

**Conclusion and Requested Action**

We request that DDMAC immediately withdraw the warning letter to GSK concerning Tykerb. 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)