WASHINGTON LEGAL FOUNDATION
2009 MASSACHUSETTS AVENUE, NW
WASHINGTON, D.C. 20036
(202) 588-0302

July 6, 2006

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 # 21-716
Hydase™ (Hyaluronidase Injection, USP) 150 Units/mL
MACMIS # 14365

NDA # 18-604
Zovirax® (acyclovir) Ointment 5%
MACMIS # 14382

Dear Mr. Abrams:

On June 29, 2006, the Division of Drug Marketing, Advertising, and Communications (DDMAC) sent a warning letter to PrimaPharm, Inc. (PrimaPharm) alleging that two sales aids for Hydase™ (Hyaluronidase Injection, USP) 150 Units/mL misbranded the drug "in violation of" 21 U.S.C. §§ 352(a) and 321(n). DDMAC contended that the sales aids failed to "communicate any risks associated with . . . use" of the drug. The following day, DDMAC sent a warning letter to GlaxoSmithKline (GSK) alleging that the "Clinical Trials" and "What Can I Do To Treat It?" pages of a web site for Zovirax® (acyclovir) Ointment 5% (www.zoviraxoiontment4.com) and a consumer-directed STD Awareness Deck Card misbranded the drug "in violation of" 21 U.S.C. §§ 352(a) & (n) and 321(n). In DDMAC's view, the web pages and Deck Card "broaden[ed] the indication" of the drug, overstated its effectiveness, and omitted material facts including the indication and "important risk information."

The Washington Legal Foundation (WLF) launched a new program on June 21, 2005, called "DDMAC Watch." Under the program, WLF monitors the warning and untitled letters issued by DDMAC and by analogous personnel in the Center for Biologics Evaluation and Research. Where letters raise substantial legal or policy issues, WLF identifies those issues in correspondence back to the agency. Since launch, we have sent 21 letters to DDMAC and five letters to CBER setting forth our concerns. As the letters issued over the past year make clear, DDMAC has put into place many policies and procedures that, although not publicly articulated, obviously affect how you exercise day-to-day oversight in this area.

We have consistently requested that you undertake a systematic review of policies and procedures relating to the promotion of prescription drugs. As yet, we have received no response to this request. Nor have we detected any change in your approach to the regulation of prescription drug promotion. Indeed, the letters issued with respect to Hydase and Zovirax raise many of the concerns we have identified in our letters to you, and appear to be among the most egregious letters issued by DDMAC since the DDMAC Watch program began.

WLF requests, once again, that you undertake a systematic analysis of the policies and procedures DDMAC follows in regulating prescription drug promotional communications. DDMAC's practices directly affect the ability of pharmaceutical manufacturers and marketers—who represent a vital part of the nation's health care system—to provide accurate health information to health care practitioners and patients. Your advisory and enforcement actions therefore have a substantial impact on the public's health. For these reasons, and for the legal and policy reasons outlined below, we ask that you withdraw the warning letters and commence immediately the systematic analysis described above.

Unsubstantiated Allegations of Misleadingness

In the warning letters issued with respect to Hydase and Zovirax, DDMAC characterizes several statements as false or misleading in violation of federal law:

- DDMAC contends that the "What Can I Do To Treat It?" page of the Zovirax website is false or misleading. DDMAC asserts that references to viral shedding and disease transmission imply that Zovirax "may prevent transmission of genital herpes infections[.]" DDMAC objects, further, on the ground that the page claims a "soothing" effect at the application site. (According to DDMAC, disclaimers appearing on that page of the website are not sufficient to "correct the misleading suggestion" or "mitigate the misleading claim.")

- DDMAC also asserts that the "Clinical Trials" page of the Zovirax website is false or misleading. DDMAC states that a suggestion that physicians help patients remember the importance of early treatment implies that Zovirax is effective for the treatment of recurrences. DDMAC also states that a reference to time to complete healing in a clinical trial in initial primary genital herpes overstates the drug's efficacy.

An essential contention of each of these complaints is that a promotional communication is false or misleading based on DDMAC's own interpretation of selected statements on the web pages. DDMAC has provided no evidence that the intended audience—indeed, any individual—was actually misled, or that the cited disclaimers were insufficient to prevent any individual from becoming misled. (DDMAC takes a similar approach in asserting, without appropriate corroboration, that a "help-seeking" piece relating to genital herpes actually constitutes a full product claim piece because www.zoviraxointment4.com appears on the front and back. It is not at all clear that patients would interpret that web site address as a product reference. It is also particularly troubling that DDMAC has effectively begun enforcement action on this issue even though its guidance on disease awareness communications (issued in draft form well over two years ago) has not yet been finalized.

Before the government may take action with respect to a communication alleged to be misleading, the government must develop data demonstrating that the omission has, in fact, made the communication misleading. In these two warning letters, 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). It is also a bedrock principle of First Amendment jurisprudence that the use of disclosures to address any potential of commercial speech to be misleading to its intended audience is preferred to an outright ban. *See Pearson v. Shalala*, 164 F.3d 650 (D.C. Cir.), *reh'g denied*, 172 F.3d 72 (D.C. Cir. 1999).

We have previously commented on the importance of developing data substantiating interpretations of promotional pieces in letters dated June 21, 2005 (Strattera), June 30, 2005 (FluMist), September 27, 2005 (Travatan), January 20, 2006 (Cenestin), April 21, 2006 (Sotradecol), and June 2, 2006 (Spiriva Handihandler and generic bupropion). As we there observed, DDMAC has speech regulatory powers under the Federal Food, Drug, and Cosmetic Act that are extremely broad and that have a tremendous impact on the public health. DDMAC has a corresponding obligation to ensure that, in the exercise of its authority, it does not run afoul of the First Amendment, which affords substantial protection for commercial speech. Under these circumstances, we would hope and expect DDMAC to corroborate its own interpretations of promotional pieces—and its own bald assertions regarding the alleged insufficiency of disclaimers—with appropriate, valid data before alleging legal violations or initiating regulatory action.

Impermissible Ban on the Use of Clinical Studies in Promotion

DDMAC objects to GSK's claims that Zovirax is effective in reducing the transmission of the genital herpes virus on the ground that "FDA is unaware of substantial evidence or substantial clinical experience" to support the claims. DDMAC also contends that the "Clinical Trials" web page is false or misleading because it suggests that Zovirax is appropriate for the treatment of recurrent episodes of genital herpes, when such a claim has not "not been demonstrated by substantial evidence or substantial clinical experience." Finally, DDMAC asserts that the web page claims that Zovirax is more effective than has been "demonstrated by substantial evidence or substantial clinical experience."

GSK has a First Amendment right to disseminate information about clinical investigations, whether or not they meet FDA's definition of "substantial evidence or substantial clinical experience." It is a bedrock principle of First Amendment law that the government may not ban speech based on its potential to mislead, if the speech may be 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 if 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").

We have previously objected, in letters dated June 30, 2005 (Lidoderm), July 20, 2005 (Survanta), August 25, 2005 (Nipent), September 9, 2005 (Lumigan), September 27, 2005

(Travatan), January 17, 2006 (Loprox), and June 12, 2006 (ReFacto), to DDMAC and OCBQ's issuance of warning and untitled letters stating that companies may not use clinical investigations or other sources of information in promotional materials unless DDMAC or OCBQ has determined that these sources are satisfactory. DDMAC clearly has an established practice and policy of banning any statements, even if truthful and non-misleading, that are based on clinical investigations that DDMAC deems inadequate.

Problematic Policy of Requiring Double Disclosure of Risk Information

DDMAC objects to the Deck Card on the ground that, although it includes the full FDA-approved labeling, it does not present "the indication and risk information in conjunction with the representations on the promotional body of the piece." Similarly, DDMAC contends that the sales aids for Hydase are false or misleading because they present risk information in the accompanying full FDA-approved labeling, but do not provide such information in the "creative" part of each piece.

The Deck Card and sales aids, in fact, included all of the risk information that DDMAC alleges was missing. The full FDA-approved prescribing information was printed on the inside of the deck card and on the back of the sales aids. Thus, the audience for these pieces had immediate access to all of the information DDMAC alleges is omitted, and that information was presented in precisely the manner dictated by FDA. DDMAC's contention that this presentation of risk information is insufficient is without regulatory or legal support.

It is true that one of FDA's prescription drug advertising regulations, 21 C.F.R. § 202.1(e)(3), states that the statutory "true statement" requirement "applies to the entire advertisement," but as we have noted in previous correspondence, this regulation is not by itself sufficient to support DDMAC's allegation—particularly here, where the pieces at issue are not advertising within the meaning of the FDCA. As we have previously explained to you, DDMAC's interpretation of this regulation, under which every advertisement would have to include risk information in both the "creative" part and in the accompanying PI or brief summary, would lead to absurd results and would raise substantial First Amendment questions. DDMAC's imposition of its interpretation without first going through notice-and-comment rulemaking is also inconsistent with FDA's Good Guidance Practice requirements, and with the Administrative Procedure Act. *See* 21 U.S.C. § 371(h) (requiring public participation and the opportunity for public comment on guidance documents that set forth an initial interpretation of a statute or regulation, changes in interpretation or policy that are of more than a minor nature, complex scientific issues, or highly controversial issues); 21 C.F.R. § 10.115(e) (FDA "may not use documents or other means of communication that are excluded from the definition of a guidance document to informally communicate new or different regulatory expectations to a broad public audience for the first time."). Finally, requiring duplicative disclosures of risk information is, at least, 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* http://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*

http://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. 3922, 3935 (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 has raised this issue with you on eight prior occasions. By letters dated June 30, 2005 (Lidoderm), July 20, 2005 (Survanta), August 25, 2005 (Nipent), September 9, 2005 (Lumigan), November 8, 2005 (Vitrase) January 17, 2006 (Loprox), April 6, 2006 (Infergen), and April 21, 2006 (Sotradecol), WLF objected to DDMAC letters that alleged, without an adequate legal basis, that sponsors had failed to disclose risk information in promotional materials. It is apparent from the warning and untitled letters that DDMAC has issued that the Division has an established practice and policy of banning promotional materials that do not disclose risk information twice. We understand that DDMAC is working on a guidance document designed to provide recommendations to sponsors on how to achieve "fair balance" in prescription drug promotion. We hope that the guidance will address the questions raised above. In the meantime, DDMAC should not issue warning and untitled letters to manufacturers alleging that presenting risk information in a more concise fashion is unlawful.

Lack of Guidance Regarding Internet Promotions

Several of the claims regarding Zovirax to which DDMAC objects are, according to the warning letter, found at selected pages of two web sites. WLF has previously objected to DDMAC's failure to develop guidance on internet communications. In letters dated June 30, 2005 (VisionBlue), July 27, 2005 (Tracleer), and April 21, 2006 (Sotradecol), WLF objected to three warning letters in which DDMAC took issue with promotional pieces appearing on product web sites. In those letters, WLF explained that FDA's past promises to issue guidance on internet promotions had remained unfulfilled, and objected to the issuance of warning and untitled letters by DDMAC in the absence of such guidance.

WLF reiterates those objections here. It is simply inappropriate for DDMAC to take action against the internet communications of prescription drug manufacturers, such as GSK, without first providing guidance to those exercising their First Amendment rights about its expectations.

No Authority to Seek Corrective Advertising

DDMAC's request that PrimaPharm and GSK disseminate "corrective" promotional messages is unauthorized by statute, unconstitutional, and imprudent. As WLF previously advised you in at least eleven previous letters, DDMAC's authority to require corrective advertising is, at best, unclear. The specific listing of enforcement actions appearing in the Federal Food, Drug, and Cosmetic Act conspicuously omits any authority for DDMAC (or any other FDA component) to request or require that a firm disseminate "corrective" promotional messages to anyone. 21 U.S.C. § 331 *et seq.* Moreover, a requirement that a company disseminate information—with which it might disagree—about one of its own products on behalf of the government presents potentially grave First Amendment issues. *See, e.g., International Dairy Foods Ass'n v. Amestoy*, 92 F.3d 67 (2d Cir. 1996).

My testimony at DDMAC's Part 15 hearing on November 2, 2005, emphasized the urgent need for DDMAC to reconsider its apparent policy of always requesting corrective messaging in warning letters. Although WLF has repeatedly presented our views to DDMAC on the inappropriateness of invoking this extra-statutory remedy, we have received no response from you and have seen no lull in the issuance of warning letters invoking it. We again request that you address our concerns in writing and undertake a systematic review of your use of this remedy to ensure it does not exceed your authority and sufficiently respects the First Amendment rights of sponsors and their audiences.

Conclusion and Requested Action

For the reasons discussed above, we request that DDMAC immediately withdraw the warning letters to PrimaPharm and GSK and cease the issuance of warning and untitled letters and advisory correspondence that contains allegations the same as or similar to those described above. We request that you review, in a systematic fashion, all of your policies and procedures to ensure that they provide sufficient room for sponsors to disseminate, and health care practitioners and patients to receive, truthful and non-misleading information about prescription drugs. We request, further, that you respond to the numerous legal and policy issues we have raised in our correspondence with you since last year.

The deficiencies described in this letter do not necessarily constitute an exhaustive list. It is DDMAC's responsibility to ensure that its actions comply with the First Amendment, and do not exceed FDA's statutory authority.

Sincerely,

Richard A. Samp
Chief Counsel

cc: Sheldon Bradshaw (GCF-1)