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

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

Re: NDA # 13-174
Dyrenium® (triamterene) Capsules
MACMIS ID # 14823

Dear Mr. Abrams:

On December 19, 2006, the Division of Drug Marketing, Advertising, and Communications (DDMAC) sent an untitled letter to WellSpring Pharmaceutical Corporation alleging that a professional print advertisement (DYR PPO 0021) for Dyrenium® (triamterene) Capsules "misbrands" the drug "in violation of" sections 502(n) and 201(n) of the Federal Food, Drug, and Cosmetic Act (FDCA), 21 U.S.C. §§ 352(n) and 321(n). For the reasons discussed below, WLF requests that DDMAC withdraw the untitled letter. WLF requests, further, that DDMAC initiate a comprehensive review of its policies and procedures to assure that they comply with the First Amendment and do not exceed FDA's authority under the FDCA.[1]

Unsubstantiated Allegations of Misleadingness

According to DDMAC, the professional print advertisement for Dyrenium "suggests" that the drug "will prevent enhanced lipid peroxidation and accelerated growth response in vessel walls caused by magnesium deficiency." DDMAC provides no data to corroborate its interpretation. Nor does DDMAC present any data to support its accusation that the advertisement is "misleading."

[1] In previous correspondence with you, we have listed all of the previous 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.

The only apparent basis for DDMAC's allegations is the individual judgment of the DDMAC personnel involved in preparing and reviewing the untitled 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 the professional print advertisement qualifies 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 manner in which WellSpring has described Dyrenium is misleading. *See Pearson*, 164 F.3d at 659 (citations and footnote omitted). Because that is all that DDMAC has seen fit to do, the untitled letter cannot be reconciled with the First Amendment.

Before DDMAC may take action with respect to an advertisement alleged to be misleading, the government must develop data demonstrating that the advertisement, in fact, is misleading. In the untitled letter to WellSpring, 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).

Impermissible Approach to the Dissemination of Scientific Information

The untitled letter to WellSpring illustrates DDMAC's continued policy and practice of banning the dissemination of truthful, non-misleading, adequately substantiated scientific information. DDMAC states that lipid peroxidation and accelerated growth response in vessel walls caused by magnesium deficiency "have no relation to Dyrenium's indicated use for edema." DDMAC thus implies that the advertisement promotes the drug off-label in violation of the FDCA. Analytically, DDMAC treats the alleged off-label nature of the putative claim ("These latter suggested processes have no relation to Dyrenium's indicated use for edema.") as distinct from the alleged lack of substantiation for the claim ("Moreover, . . . FDA is unaware of evidence showing that . . . ."). The implication of this approach is that an off-label statement is unlawful even if fully substantiated, truthful, and non-misleading. DDMAC also objects to WellSpring's

reliance on published animal and human data to substantiated claims regarding the effectiveness of Dyrenium.

WellSpring has a First Amendment right to disseminate scientific information. 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 nonmisleading. The most obvious way for DDMAC to comply with this principle would be to allow sponsors to make promotional claims based on preclinical investigations and on other sources of data and information so 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 WellSpring to convey information about its products to health care practitioners—even if that information is (in DDMAC's view) off-label or obtained from animal studies or clinical studies that do not meet DDMAC's high standards.

In this instance, WellSpring is entitled to make truthful and non-misleading statements in its promotional materials, regardless of whether FDA is aware of the supporting data, or considers the data to be insufficiently "substantial." FDA is not a peer-review mechanism for the medical community. *Washington Legal Found. v. Friedman*, 13 F. Supp. 2d at 67. 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 FDA. *West Virginia State Bd. of Educ. v. Barnette*, 319 U.S. 624, 642 (1943). DDMAC's approach of precluding WellSpring from making promotional claims based on data of which FDA is not aware, or does not find sufficiently "substantial," would deprive physicians of useful information about therapeutic products in violation of the First Amendment. *Virginia State Bd.*, 425 U.S. at 757 (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 of WellSpring's claims may be misleading, under the First Amendment, WellSpring is 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 approach to animal data is objectionable for an additional reason. FDA has recognized that animal data can be clinically relevant. FDA requires manufacturers to include animal data in their premarket submissions, 21 C.F.R. § 314.50, and FDA regulations provide for the presentation of animal data in safety and efficacy-related sections of the package insert. 21 C.F.R. § 201.57(b)(1), (f)(5), (f)(6)(i)(a)-(e). DDMAC's attempt to preclude WellSpring from using animal data is inconsistent with these regulatory requirements.

Problematic Policy of Requiring Double Disclosure of Risk Information

In alleging that WellSpring omitted risk information, DDMAC fails to mention that the advertisement refers the reader to the accompanying brief summary of prescribing information. The audience for the sales aid 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. DDMAC's position, essentially, is that print advertisements must disclose risk information twice—once in the main body, and again in the brief summary.

This position does not accord with the relevant statutory and regulatory authorities. Section 502(n) of the FDCA, 21 U.S.C. § 352(n), provides, in relevant part:

> A drug shall be deemed to be misbranded . . . In the case of any prescription drug distributed or offered for sale in any State, unless the manufacturer, packer, or distributor thereof includes in all advertisements and other descriptive printed matter issued or caused to be issued by the manufacturer, packer, or distributor with respect to that drug a true statement of . . . information in brief summary relating to side effects, contraindications, and effectiveness as shall be required in regulations . . . .

Based on the language used and the citations appearing in the letter, it is apparent that DDMAC is relying on 21 C.F.R. § 202.1(e)(5)(i) or (iii), which is among the regulations FDA promulgated to implement Section 502(n):

> An advertisement does not satisfy [Section 502(n)] . . . if:
>
> (i) It is false or misleading with respect to side effects, contraindications, or effectiveness; 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 advertisement.

To prove a violation, therefore, DDMAC would have to establish that the print advertisement for Dyrenium "is false or misleading" in its presentation of risk information by virtue of its failure to reveal material facts. (This interpretation is bolstered by the fact that DDMAC cites 21 U.S.C. § 321(n) in the letter.) Yet DDMAC presents no data to substantiate its assertion that the advertisement is false or misleading in any way. Given that the risk information that DDMAC claims is omitted actually appears in the advertisement, it is hard to see how the agency could meet its burden in any enforcement action.

Moreover, although FDA's drug labeling and advertising regulations elucidate some of the circumstances in which advertising is or may be misleading in violation of Section 502(n), they do not explain sufficiently how a manufacturer should disclose risk information in such materials to satisfy the statutory standard. FDA has yet to provide manufacturers with guidance in this area, despite repeated promises to do so.

Before requiring manufacturers to present risk information twice in the same promotional piece, DDMAC must go through notice-and-comment rulemaking or, at minimum, issue a guidance document consistent with FDA's Good Guidance Practices. *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.").

Requiring duplicative disclosures of risk information is also 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. 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.").

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.

Conclusion and Requested Action

For the reasons discussed above, we request that DDMAC immediately withdraw the untitled letter to WellSpring 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 patents 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 2005.

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)