DDMAC Watch: THE YEAR IN REVIEW

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On June 21, 2005, the Washington Legal Foundation (WLF) announced a new program, known as DDMAC Watch, to monitor federal regulation of prescription drug advertising and other promotional communications by the Food and Drug Administration (FDA). This report documents the findings of WLF's program after its second year of operation.

WLF is a public interest law and policy center based in Washington, D.C., with supporters nationwide. Since its founding in 1977, WLF has engaged in litigation and advocacy to defend individual rights and to promote a limited and accountable government. WLF for many years has been actively involved in efforts to decrease federal government restrictions on the flow of truthful, non-misleading, scientifically substantiated information about FDA-approved drugs and medical devices, and to limit the circumstances under which the government may compel individuals and companies to speak against their will. For example, in 1998 WLF successfully challenged the constitutionality of FDA restrictions on the ability of health care practitioners and patients to receive truthful, non-misleading, scientifically substantiated information about off-label uses of FDA-approved medications. See Washington Legal Found. v. Friedman, 13 F. Supp. 2d 51 (D.D.C. 1998), appeal dism'd, 202 F.3d 331 (D.C. Cir. 2000).

The DDMAC Watch program is part of WLF's long-standing effort to ensure that federal regulators do not hinder the free flow of truthful, non-misleading, scientifically substantiated information to health care practitioners and patients and that they respect the First Amendment rights of health care practitioners and patients to receive, and prescription drug manufacturers to provide, such information. Under the

DDMAC Watch program, when FDA's Division of Drug Marketing, Advertising, and Communications (DDMAC) (or its counterpart in the Center for Biologics Evaluation and Research (CBER), the Office of Compliance and Biologics Quality (OCBQ)) sends a "warning" or "untitled" letter to a prescription drug manufacturer objecting to promotional communications based on legal theories that are deficient or ill-advised, WLF sends a letter back to DDMAC or OCBQ identifying the specific ways in which this is so.

Also under DDMAC Watch, WLF issues annual reports analyzing DDMAC and OCBQ warning and untitled letters sent during the previous year. The purpose of this analysis is to detect patterns in the federal government's regulation of prescription drug promotion that raise legal or other issues, and to bring to public attention any and all ill effects of this regulation. WLF issued the first annual report, describing the findings of the DDMAC Watch program after one year of analyzing DDMAC and OCBQ letters, approximately a year ago. WLF also formally submitted the report to FDA as a citizen petition requesting—as we did in every response letter submitted to the agency under the program's auspices—a systematic review of FDA policies and procedures relating to the promotion of prescription drugs. This review is sorely needed to align the agency's overly restrictive regulatory regime with the legitimate informational needs of health care practitioners and patients, with the limits established by Congress on the exercise of FDA's authority, and with the First Amendment. To date, WLF has received no response to our repeated requests.[1]

[1] The citizen petition was received by FDA on August 11, 2006, and assigned a docket number of 2006P-0319. WLF has not received any response to the citizen petition since a letter dated February 7, 2007, in which FDA stated that it had been "unable to reach a decision on your petition because it raises complex issues requiring extensive review and analysis" and promised to "respond to your petition as soon as we have reached a decision on your request."

What follows is the second annual report to be issued under the DDMAC Watch program.

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I. EXECUTIVE SUMMARY

WLF's review of warning and untitled letters issued by DDMAC[2] through the second year of the DDMAC Watch program (July 2006-June 2007) reveals many legal and policy issues raised by FDA's regulation of prescription drug promotion. In particular, these letters demonstrate that DDMAC has an established policy of allowing prescription drug manufacturers to make promotional claims only if those claims are supported by "substantial evidence." Such evidence is equivalent, in terms of type and quantity, to the evidence required for drug approval. Thus, DDMAC completely bans even statements that are truthful and non-misleading, if they are based on clinical investigations or other sources of information that officials deem not to satisfy the gold standard. This is despite the First Amendment requirement that the government refrain from imposing a blanket ban on speech that is at most potentially misleading when any such potential can be obviated through use of disclaimers. "[T]he collective effect of FDA's conduct has been to discourage manufacturers from disseminating information that they would otherwise have chosen to distribute. The result is that doctors . . . have been prevented from receiving information which they claim to have an interest in receiving." Washington Legal Found. v. Kessler, 880 F. Supp. 26, 35-36 (D.D.C. 1995).

Moreover, DDMAC does not determine that a promotional piece actually has misled any health care practitioners or patients before it decides that promotional materials are, in fact, misleading. DDMAC does not provide any data to support its interpretation of a promotional piece before it censors promotional claims because they

[2] OCBQ did not issue any warning or untitled letters between July 2006 and June 2007. However, the issues raised by WLF in this annual report with respect to DDMAC are also applicable to past warning and untitled letters issued by OCBQ.

are “misleading.” Rather, DDMAC takes a “we know it when we see it” approach to regulation—an approach that courts have definitively rejected.

In addition, DDMAC has now decisively established its policy of requesting corrective promotion in virtually every warning letter issued with respect to prescription drug promotion. Corrective promotion is a radical measure, because it effectively compels a private party to make statements to the public with which it might disagree. To our knowledge, FDA has never performed a systematic analysis of the effects of corrective promotion. There is reason to believe that use of this remedy in the drug promotion context actually adds to health care practitioner and patient confusion.

DDMAC also has established a consistent pattern of using warning and untitled letters to establish policy. This is problematic because federal law and FDA’s regulations generally require the agency to provide notice and an opportunity for interested parties to comment before the agency communicates new regulatory expectations for the first time. This does not happen in connection with warning or untitled letters.

In addition, DDMAC requires drug manufacturers to include duplicative risk information in printed promotional materials, such as scientific journal advertisements aimed at health care practitioners. Under this policy, manufacturers must communicate publicly about their products in ways that overemphasize the risks of drug use and underemphasize their benefits. This conflicts with recent FDA policy statements centering on the importance of tailoring risk information to health care practitioners and patients, to avoid “information overload” and to ensure that risks are discussed in the context of clinical benefits. There also are sound legal reasons to

question the validity of FDA's "double disclosure" policy for risk information and other types of qualifying information.

Although FDA characterizes warning and untitled letters as merely "advisory," these communications have real consequences. As we discuss in greater detail below, WLF has determined that DDMAC's current regulation of prescription drug promotion:

- Deprives patients and health care practitioners of truthful, non-misleading, scientifically substantiated information without adequate justification and in violation of the First Amendment;
- Irrationally determines that promotional claims are "misleading" without providing evidence that anyone, in fact, has been deceived or an explanation for DDMAC's interpretation of the promotional piece; and
- Exceeds the scope of its legal authority, both in the practices it seeks to regulate and in the remedies it orders.

Many of the concerns expressed above were also highlighted in our first annual DDMAC Watch report; the abusive practices described in that report have continued unabated. Moreover, we are also concerned by DDMAC's apparent determination to find new ways to exceed the scope of its legal authority. During the past year, DDMAC has sent two warning letters objecting to drug manufacturer communications intended to provide information to pharmacists and state pharmacy and therapeutics (P&T) committees. As discussed further below, DDMAC's recent emphasis on this new category of materials is alarming, because it signals a commitment to expanding the breadth of FDA's regulatory authority despite the continued lack of clear guidance in areas more traditionally thought to be subject to agency regulation.

I. BACKGROUND: FDA REGULATION OF PRESCRIPTION DRUG PROMOTION THROUGH WARNING AND UNTITLED LETTERS

FDA asserts authority to regulate almost all promotional communications made in the United States by or on behalf of prescription drug manufacturers for their products. The Federal Food, Drug, and Cosmetic Act (FDCA) and FDA implementing regulations establish ample requirements for the content of "labeling" and "advertising" for prescription drugs. 21 U.S.C. § 352(a) & (n); 21 C.F.R. parts 201 & 202.[3] Materials subject to FDA regulation include print and broadcast advertisements (both patient- and professional-directed) as well as visual aids used by drug manufacturer sales representatives in promotional discussions with health care professionals. 21 C.F.R. § 202.1(l).[4]

DDMAC and OCBQ are the FDA components with day-to-day responsibility for overseeing prescription drug promotion. DDMAC is in the Center for Drug Evaluation and Research (CDER), while OCBQ is part of the Center for Biologics Evaluation and Research (CBER). Together, DDMAC and OCBQ oversee all drug

[3] FDA also indirectly regulates the external communications of pharmaceutical companies by taking the position that these communications can create a new intended use for a drug, for which "adequate directions" are required under FDCA § 502(f)(1), 21 U.S.C. § 352(f)(1), and cause a drug to be a "new drug" for which approval of a new drug application (NDA) is required, 21 U.S.C. §§ 355(a) & 321(p). This policy and practice, which is not addressed here, raises substantial legal questions. See, e.g., Ass'n of Am. Physicians and Surgeons v. FDA, 226 F. Supp. 2d 204 (D.D.C. 2002).

[4] The FDCA defines "labeling" to include "written, printed, or graphic matter (1) upon any article or any of its containers or wrappers, or (2) accompanying such article." 21 U.S.C. § 321(m). There is no statutory definition of "advertisement." FDA has claimed authority to regulate the content of certain categories of communications, such as oral statements by sales representatives, that do not qualify as "labeling" or "advertising" under the Federal Food, Drug, and Cosmetic Act. See, e.g., Lars Noah, Death of a Salesman, 47 Food & Drug L. J. 309, 326 (1992) (FDA has no direct authority to control such statements); David A. Kessler & Wayne Pines, The Federal Regulation of Prescription Drug Advertising and Promotion, 264 J.A.M.A. 2409, 2411 (1990) (oral statements is one area in which FDA's authority is unclear). WLF submitted a citizen petition to FDA on April 17, 2001, requesting that FDA adopt a rule, policy, or guidance stating that information presented or available on an internet web site does not constitute "labeling" under the statute. FDA denied the petition by letter dated November 1, 2001. This is another legally doubtful FDA position.

promotion in the United States. Their principal vehicle for conveying regulatory expectations to industry is warning and untitled letters.

Under established FDA policy, use of warning letters is limited to those situations in which alleged violations are deemed to be of "regulatory significance." If a supposed violator does not promptly and adequately correct the alleged violation, then FDA may initiate enforcement action. See FDA, Regulatory Procedures Manual § 4-1-1 (Mar. 2004), available at http://www.fda.gov/ora/compliance_ref/rpm/pdf/ch4.pdf. FDA policy is to send a warning letter for allegedly unlawful prescription drug promotional activities if CDER or CBER would support further regulatory action. Id. § 4-1-5. Warning letters are addressed to the target company's CEO and, in addition to alleging specific legal violations, threaten formal enforcement action unless the company immediately stops the conduct to which the letter objects. Id. § 4-2-1. Enforcement action can include product seizure, an injunction, criminal fines, and imprisonment. 21 U.S.C. §§ 332-34.

Untitled letters allege specific FDCA violations that do not reach the level of "regulatory significance" and do not threaten enforcement action. They are addressed to a regulatory affairs person in the recipient company. Although less serious than a warning letter, an untitled letter can generate considerable press coverage, which can harm a company's reputation and suggest that a drug is unsafe or ineffective. FDA, Regulatory Procedures Manual, ch. 4, Exhibit 4-1, § 4, available at http://www.fda.gov/ora/compliance_ref/rpm/pdf/ch4.pdf. Both warning and untitled letters are frequently used against drug manufacturers in product liability cases.

DDMAC issues warning and untitled letters on its own initiative based on its analysis of materials submitted by manufacturers,[5] as well as in response to competitor complaints. Warning and untitled letters are posted on DDMAC's web page (http://www.fda.gov/cder/ddmac/index.htm) under the heading "Laws, Regulations, Guidances, and Enforcement Actions" and by OCBQ under the heading "Violative Advertising & Promotional Labeling Letters for Approved Biological Products."[6] Employees of both DDMAC and OCBQ routinely discuss warning and untitled letters at industry meetings to clarify their respective views on matters of policy and legal interpretation. See, e.g., The Pink Sheet, Sept. 29, 2006.

Because the applicable statutes and regulations are unclear, DDMAC and OCBQ sometimes use guidance documents to clarify their regulatory expectations to prescription drug manufacturers. This practice is consistent with, and necessitated by, legal provisions requiring FDA to establish policy through an appropriate procedure in which interested parties have a meaningful opportunity to participate. "Appropriate" procedures generally include publishing guidance documents first in draft form. It can finalize them only after providing time for public comment and reviewing and addressing those comments. Unfortunately, FDA has established a pattern of issuing draft guidance documents for comment but never finalizing them. This practice leaves industry without final recommendations on important subjects.

[5] Such submissions are required under FDA regulations. 21 C.F.R. § 314.81(b)(3)(i) (requiring submission of specimens of mailing pieces and any other labeling or advertising devised for promotion at the time of initial dissemination or publication).

[6] WLF does not oppose the practice of posting warning and untitled letters on FDA's web site. We do, however, advocate: (1) characterizing the letters not as "enforcement actions," but rather as "advisory actions," as provided by the Regulatory Procedures Manual; and (2) including in every letter a statement to the effect that the letter represents the best judgment of the sender but does not itself impose binding legal requirements, consistent with 21 C.F.R. § 10.85(k). As discussed below in Part III, FDA's use of warning and untitled letters in the area of prescription drug promotion to establish regulatory expectations raises serious legal issues.

Moreover, FDA has not yet provided guidance relating to prescription drug promotion in a number of areas in which there is an industry-wide need for guidance, despite repeated promises to do so. In 1997, for example, FDA published a list of all of the information statements the agency had made in previous years on promotion-related issues and a list of all of the guidance documents the agency intended to issue to provide up-to-date guidelines to prescription drug manufacturers. See FDA, Prescription Drug Advertising and Promotional Labeling; Development and Use of FDA Guidance Documents: Request for Comments, 62 Fed. Reg. 14,912 (Mar. 28, 1997). This plan has never been implemented, leaving manufacturers without guidance on such subjects as the scientific support necessary for comparative claims, limitations on and formats for advertising not-yet-approved drugs, and the extent to which manufacturers are entitled to participate in legitimate scientific exchange about unapproved products. Id. at 14,914.

It is against this backdrop—in which policy is made on an ad-hoc basis, letter by letter, instead of in a systematic manner with appropriate public participation—that WLF considers the warning and untitled letters issued by DDMAC and OCBQ.

II. DDMAC AND OCBQ WARNING AND UNTITLED LETTERS

A. ANALYSIS OF ALL LETTERS

Between July 2006 and June 2007, DDMAC issued 22 warning and untitled letters to prescription drug manufacturers objecting to their drug promotion. In response, WLF sent 19 letters to DDMAC, addressing the many ways in which these letters advance theories that raise serious legal and policy questions.

Table 1 lists the warning and untitled letters issued by DDMAC from July 1, 2006 through June 30, 2007. The warning and untitled letters are listed according to

the date of issuance, the name of the company to which the letter was addressed, and the drug(s) at issue. The tables also indicate whether the promotional materials targeted by DDMAC were aimed at health care practitioners or patients, and whether the correspondence was a warning letter or an untitled letter. The rest of the tables analyze the content of the letters, focusing on the following theories, which WLF has identified as especially problematic:

- **Improper Reliance on "Regulatory History."** DDMAC cites previous correspondence in a warning or untitled letter. WLF objects to this practice because it implies that the recipient company is a repeat offender when, in fact, the previous communications are frequently many years old and/or involve only tangentially related or entirely unrelated issues. Warning and untitled letters that improperly rely on out-dated or irrelevant "regulatory history" can be a boon to plaintiffs' lawyers, who use this "history" to argue that the recipient company is a bad actor.

- **"Substantial Evidence."** DDMAC purports to forbid companies from relying on sources of scientific information that, in the regulators' view, do not meet their overly narrow view of the "substantial evidence" standard. This practice harms the public health by denying credible and reliable scientific information to patients and health care practitioners. It also raises First Amendment concerns.

- **Double Disclosure of Risk Information.** DDMAC requires companies to include in their promotional communications the risk information from the FDA-approved package insert not once but twice, including in the main body or "creative" part of the piece. This policy is objectionable because it is not consistent with FDA's own regulations, is not justified by any genuine public health need (and thus conflicts with the First Amendment), and was not established through an appropriate administrative procedure.

- **Unsubstantiated Allegations of Misleadingness.** DDMAC alleges that promotional communications are false or misleading without providing any data or other evidence to support their contentions, other than the judgment of agency personnel. Empirical evidence is required by the First Amendment before the government is entitled to regulate the content of commercial speech.

- **Failure to Provide Guidance/Comply with GGPs.** DDMAC uses warning and untitled letters to establish and communicate policy. WLF objects to this practice based on basic principles of administrative law. FDA should use notice-and-comment procedures to communicate new regulatory expectations for the first time.

- **Corrective Promotion.** DDMAC has a continuing policy of requesting that pharmaceutical companies engage in "corrective" messaging. DDMAC lacks statutory authority to request "corrective" messaging; the FDCA does not include the authority to request "corrective" messages as one of the agency's enforcement tools. 21 U.S.C. § 331 et seq. In addition to being unauthorized, "corrective" messaging is violative of the First Amendment because it compels speech with which pharmaceutical manufacturers may disagree.

The tables below show which particular letters reflect these problematic theories. In the first annual report, WLF identified these same issues in earlier warning and untitled letters. WLF believes that DDMAC and OCBQ have engaged in a clear pattern of speech-restrictive behavior for several years. The practical effect of these letters is to interfere in the provision of truthful, non-misleading, scientifically substantiated information about prescription drugs to health care practitioners and patients. The de facto policies established through these letters is actionable, despite the fact that DDMAC has not formally embodied its objectionable positions in regulations or even guidance documents. See Washington Legal Found. v. Kessler, 880 F. Supp. 26, 35 (D.D.C. 1995) (mem. op.) ("Although the FDA characterizes the 'regulatory letters' . . . as merely 'advisory,' the court must not be blind to the practical effects of these letters . . . .").

As the tables note, WLF did not respond to every warning and untitled letter issued by DDMAC. Rather, WLF has responded to letters as it deemed warranted by deficiencies in the letters. Following the tables is a detailed analysis of several of the problematic theories that WLF has determined are the most troubling from a public health and legal perspective.

Table 1. Overview of July 2006-June 2007 DDMAC/OCBQ Warning/Untitled Letters

Date of Issuance	Recipient	Drug	Audience for Promotion		Warning or Untitled?		Improper Reliance on "Regulatory History"	"Substantial Evidence"	Double Disclosure of Risk Information	Unsubstantiated Allegations of Misleadingness	Failure to Provide Guidance/ Comply with GGPs	Corrective Messaging
			HCP	Pt	W	U						
7/27/06	Eli Lilly	Alimta (premetrexed for injection)		√		√			√	√		
8/31/06	Astellas Pharma US, Inc.	Prograf (tacrolimus capsules and injection)	√		√			√		√		√
9/14/2006	Reliant Pharmaceuticals, Inc.	Rythmol SR (propafenone HCl) extended release capsules	√		√			√	√			√
9/21/06	DAVA Pharmaceuticals, Inc.	VoSpire ER (albuterol sulfate) extended release tablets	√		√				√	√		√
10/11/06	BioMarin Pharmaceuticals, Inc.	Orapred (prednisolone sodium phosphate oral solution)	Web		√				√	√		√
10/13/06	Mallinckrodt, Inc.	MD-GASTROVIEW (Diatrizoate Meglumine and Diatrizoate Sodium Solution USP), OptiMARK (Gadoversetamide Injection)	√		√		√		√			√
10/19/06	3M Pharmaceuticals	Maxair Autohaler (pirbuterol acetate inhalation aerosol)	√		√			√	√	√		√
10/20/06	Alcon, Inc.	Nevanac (nepaenac ophthalmic suspension) 0.1%	√		√		√	√	√	√	√	√
10/23/06	Ligand Pharmaceuticals, Inc.	ONTAK (denileukin diftitox), Targretin (bexarotene) capsules	√		√				√	√		√
11/16/06	AstraZeneca Pharmaceuticals LP	Seroquel (quetiapine fumarate) tablets	√			√			√	√	√	

Date of Issuance	Recipient	Drug	Audience for Promotion		Warning or Untitled?		Improper Reliance on "Regulatory History"	"Substantial Evidence"	Double Disclosure of Risk Information	Unsubstantiated Allegations of Misleadingness	Failure to Provide Guidance/ Comply with GGPs	Corrective Messaging
			HCP	Pt	W	U						
12/19/06	WellSpring Pharmaceutical Corporation	Dyrenium (triamterene) capsules	√			√		√	√	√		
1/12/07	Daiichi Sankyo, Inc.	Evoxac capsules (cevimeline hydrochloride)	√		√				√			√
1/29/07	MGI PHARMA, Inc.	Gliadel Wafer (polifeprosan 20 with carmustine implant)	√			√		√	√	√		
2/27/07	Cephalon, Inc.	Provigil (modafinil) tablets [C-IV]	State Dept. of Health and Mental Hygiene		√					√		√
3/5/07	Takeda Pharmaceuticals North american, Inc.	Rozerem (ramelteon) tablets		√		√			√	√		
4/20/07	DUSA Pharmaceuticals, Inc.	Levulan Kerastick (aminolevulinic acid HCl) for topical solution, 20%	√		√				√	√	√	√
4/20/07	Alcon Laboratories, Inc.	Ciprodex (ciprofloxacin 0.3% and dexamethasone 0.1%) sterile otic suspension	√		√			√	√	√		√
5/7/07	Schering Corporation	Nasonex (mometasome furoate monohydrate) nasal spray, 50 mcg	√			√		√		√		
5/7/07	GlaxoSmithKline	Flonase (fluticasone propionate) nasal spray, 50 mcg	√			√		√	√	√		
5/17/07	KV Pharmaceutical Company	Clindesse (clindamycin phosphate) vaginal cream, 2%	√			√		√	√	√	√	

Date of Issuance	Recipient	Drug	Audience for Promotion		Warning or Untitled?		Improper Reliance on "Regulatory History"	"Substantial Evidence"	Double Disclosure of Risk Information	Unsubstantiated Allegations of Misleadingness	Failure to Provide Guidance/ Comply with GGPs	Corrective Messaging
			HCP	Pt	W	U						
5/21/07	Enzon Pharmaceuticals, Inc.	Abelcet (amphotericin B lipid complex injection)	√		√			√		√		√
5/25/07	Allergan, Inc.	ACULAR LS (ketorolac tromethamine ophthalmic solution) 0.4%	√		√			√	√	√		√

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B. ISSUES OF PARTICULAR CONCERN

Three issues of particular concern to WLF arose repeatedly in the letters we reviewed. First is the question whether DDMAC can, consistent with the First Amendment, forbid a manufacturer from providing truthful, non-misleading, scientifically substantiated information to the public about a legitimate clinical investigation merely because it has determined that the study does not satisfy it overly restrictive and incorrect interpretation of the "substantial evidence" standard. Second is the question whether DDMAC is permitted to allege that promotional materials are "misleading" without proffering any data or other information substantiating its interpretation of the materials. Third is the manner in which DDMAC routinely exceeds its legal authority, both in the practices it seeks to control and in the remedies it prescribes. Each of these issues is discussed below.

1. Substantial Evidence Standard

a. Facts

DDMAC continues to pursue a constitutionally suspect policy of prohibiting communication of truthful, non-misleading, scientifically substantiated information. This approach bars manufacturers from making promotional claims not supported by clinical investigations meeting DDMAC's overly restrictive interpretation of the "substantial evidence" standard. The FDCA defines "substantial evidence" to include "evidence consisting of adequate and well-controlled investigations . . . by experts qualified . . . to evaluate the effectiveness of the drug involved." 21 U.S.C. § 355(d). Although the statute articulates this standard as an evidentiary requirement for new drug approval,

FDA has expanded its scope to describe the evidence required to support promotional claims. See, e.g., 21 C.F.R. § 202.1(e)(4)(ii).

This expansive approach is amply illustrated by a letter to Astellas Pharma, in which DDMAC challenged superiority claims for Prograf® (tacrolimus capsules and injection) directed at health care practitioners. The claims were based on two multicenter clinical studies published in the journal Transplantation, the most-cited journal in the field of transplant medicine. Both studies were subject to rigorous peer review before publication, and FDA accepted one of the studies for inclusion in the approved product labeling for Prograf®. The study authors are nationally recognized kidney transplant experts. Despite these robust indicia of legitimacy, DDMAC argued that the study data did not satisfy the "substantial evidence" standard and could not be used in support of promotional claims.

In addition to challenging clinical data, DDMAC has attempted to suppress the promotional use of animal study results. In an advertisement for Nevanac™ (nepafenac ophthalmic suspension), Alcon relied upon animal data to support the product's efficacy in treating ocular conditions involving the posterior portion of the eye. This reliance on nonclinical data was fully disclosed in the promotional materials. Nonetheless, DDMAC issued a warning letter to Alcon, claiming that favorable nonclinical results do "not constitute substantial evidence or substantial clinical experience" and are consequently misleading. The warning letter acknowledged Alcon's qualification regarding the source of the data, but dismissed it as insufficient to cure the alleged potential for misleadingness.

Letters to other drug companies express variations on these themes. DDMAC objected to MGI Pharma's promotional use of in vitro and animal data taken from high quality, peer-reviewed research. DDMAC criticized 3M Pharmaceuticals for citing lung deposition data in promotional materials for the Maxair™ Autohaler™, despite an explicit disclaimer about the unknown clinical significance of the data. (Other cases in which DDMAC objected to the use of scientific information are listed in Table 1, above.)

In each of these instances, DDMAC sought to remedy what it deemed a potentially misleading claim through an outright prohibition on communication. DDMAC exhibited an unwillingness to accept truthful, non-misleading, scientifically substantiated statements with appropriate qualifications, preferring to eliminate information access altogether. This draconian approach ignores the myriad benefits that patients and health care practitioners derive from exposure to reputable scientific research, thereby posing serious risks to the public's health.

b. Analysis

In forbidding companies from relying on sources of scientific information that, in DDMAC's view, do not meet its overly narrow view of the "substantial evidence" standard, DDMAC not only harms the public health by denying credible and reliable scientific information to patients and health care practitioners, but also raises First Amendment concerns. Drug companies are entitled to provide information to health care practitioner and patients about their products. Washington Legal Found. v. Friedman, 13 F. Supp. 2d 51, 62 (D.D.C. 1998) (citing Keyishian v. Bd. of Regents, 385 U.S. 589, 603 (1967), and Bd. of Trs. of Leland Stanford Junior Univ. v. Sullivan, 773 F. Supp. 472, 474 (D.D.C. 1991)), appeal dism'd, 202 F.3d 331 (D.C. Cir. 2000); Cent.

Hudson Gas & Elec. Corp. v. Public Serv. Comm'n, 447 U.S. 557, 566 (1980). It is not DDMAC's role to "protect" health care practitioners or patients from the potential adverse impact of truthful information. Thompson v. W. States Med. Ctr., 535 U.S. 357, 374 (2002) ("We have previously rejected the notion that the Government has an interest in preventing the dissemination of truthful commercial information in order to prevent members of the public from making bad decisions with the information"); 44 Liquormart, Inc. v. Rhode Island, 517 U.S. 484, 497 (1996) ("[A] State's paternalistic assumption that the public will use truthful, non-misleading commercial information unwisely cannot justify a decision to suppress it.").

It is also clear from the case law that disclaimers are preferable to speech suppression. The government may not prohibit a promotional claim it believes to be misleading if the potential deception may be cured by including qualifying information. See Pearson v. Shalala, 164 F.3d 650, 657-58 (D.C. Cir. 1999), reh'g denied, 172 F.3d 72 (D.C. Cir. 1999). The First Amendment requires DDMAC to accept disclaimers sufficient to ensure that promotional materials are non-misleading. Bates v. State Bar, 433 U.S. 350, 375 (1977) ("the preferred remedy is more disclosure, rather than less").

The healthcare marketplace relies upon the free flow of scientific information to optimize treatment and improve patient outcomes. Edenfield v. Fane, 507 U.S. 761, 767 ("The commercial marketplace, like other spheres of our social and cultural life, provides a forum where ideas and information flourish"). Because scientific viewpoints frequently differ as to the usefulness of study results, the only course that respects First Amendment values is to allow truthful, non-misleading, scientifically substantiated claims about all studies, whether or not they are deemed acceptable by

the FDA. DDMAC's current approach, which deprives patients and health care practitioners in the health care process of accurate, clinically relevant information, threatens these goals. In so doing, it violates the First Amendment rights of listener and speaker alike. Id. at 767 ("The general rule is that the speaker and the audience, not the government, assess the value of the information presented.").

2. Unsubstantiated Allegations of Misleadingness

a. Facts

In its most frequently cited objection—appearing in 19 out of 22 letters—DDMAC alleged that manufacturers' promotional materials were "misleading." In none of these letters, however, did DDMAC proffer any data or other information substantiating its interpretation of the promotional piece in question. This practice, under which DDMAC serves as the sole and final arbiter of meaning, is incompatible with both the Administrative Procedure Act (APA) and the First Amendment. It also establishes an unreasonable double standard: manufacturers must marshal "substantial evidence" in support of their promotional claims, while DDMAC is free to censor those claims with minimal evidentiary support.

For example, in an untitled letter to MGI Pharma, DDMAC objected to a journal advertisement for the Gliadel® Wafer (polifeprosan 20 with carmustine implant) directed at health care practitioners. DDMAC argued that the advertisement misleadingly supported effectiveness claims with in vitro and animal study data. Additionally, the advertisement allegedly misled readers by juxtaposing factually true statements about treatment with Gliadel® Wafer versus standard radiation therapy. Without providing any support for its position, DDMAC concluded that the advertisement "presents unsubstantiated claims [and] therefore misbrands the drug."

DDMAC also criticized Takeda for a reminder advertisement for Rozerem™ (ramelteon) Tablets. In that piece, various school-related images were accompanied by the statements "Rozerem™ would like to remind you that it's back to school season" and "Ask your doctor today if Rozerem™ is right for you." DDMAC interpreted this promotional sequence to imply that Rozerem is indicated for and can be safely used in the pediatric population. Because Rozerem™ is not approved for pediatric use, such an interpretation of the advertisement would indeed suggest that the advertisement was misleading. As with the letter to MGI Pharma, however, DDMAC presented no evidence indicating that its interpretation was the most reasonable one, or that it was the interpretation adopted by any potential consensus.

Lastly, in a warning letter to 3M Pharmaceuticals, DDMAC objected to communications for the Maxair™ Autohaler™ directed at physicians. According to the regulators, the statement "Maxair™ Autohaler™ helps your patients breathe easier" necessarily implied a superiority claim relative to other drugs. DDMAC's objection—which again contained no supporting evidence—ignored the equally valid interpretation that an autohaler improves drug delivery for patients with poor inhaler technique, or that using an autohaler is superior to using no drugs whatsoever.

b. Analysis

Before DDMAC may take action with respect to an promotional piece alleged to be misleading, the government must develop data demonstrating that the promotional piece is, in fact, misleading. In each of the letters cited above, the only apparent basis for DDMAC's position was the judgment of DDMAC personnel involved in preparing and reviewing the untitled or warning letter. No objective criteria were

referenced to support the division's stance, nor did DDMAC allege that anyone was actually misled. This approach is a classic example of "we know it when we see it" regulation, an approach that courts have resoundingly rejected. See, e.g., Pearson, 164 F.3d at 660 ("It simply will not do for a government agency to declare—without explanation—that a proposed course of private action is not approved").

Furthermore, DDMAC's actions are inconsistent with the APA, which provides for judicial invalidation of agency action that is "in excess of statutory jurisdiction," arbitrary, or capricious. 5 U.S.C. § 706. In applying this provision, the Pearson court acknowledged that a federal agency may legitimately establish standards on a case-by-case basis. Pearson, 164 F.3d at 661. Nonetheless, "it must be possible for the regulated class to perceive the principles which are guiding agency action." Id. Because DDMAC cites no objective indicia of misleadingness in support of its admonitions, it is impossible for drug manufacturers to discern such guiding principles.

The APA also provides for invalidation of agency actions that are "contrary to constitutional right." 5 U.S.C. § 706. As noted in Part I, supra, it is beyond dispute that promotional pieces qualify as speech protected by the First Amendment. To fulfill its constitutional obligation, DDMAC must do more than simply declare that a manufacturer's statements about a product are misleading. Pearson, 164 F.3d at 659 ("If the protections afforded commercial speech are to retain their force, we cannot allow rote invocation of the words 'potentially misleading' to supplant the [government's] burden to demonstrate that the harms it recites are real and that its restriction will in fact alleviate them to a material degree.") (quoting Edenfield, 507 U.S. at 771).

It is worth noting that DDMAC's regulatory stance not only offends manufacturers' First Amendment rights, but also does so unfairly. In its letter objecting to promotional materials for the Gliadel® Wafer, DDMAC discounted claims based upon "rat and monkey studies—not human studies." And yet, FDA has recognized that animal data can often be clinically relevant. For example, FDA's prescription drug labeling regulations provide for the presentation of animal data in safety- and efficacy-related sections. 21 C.F.R. § 201.57(b)(1), (f)(5), (f)(6)(i)(a)-(e). Furthermore, applications for the approval of new drugs require the inclusion of data from any animal tests conducted by the manufacturer. See 21 C.F.R. § 314.50. Yet nowhere does DDMAC explain its conclusion that the animal data cited in the promotional piece for the Gliadel® Wafer cannot be used. Thus, in addition to the statutory and constitutional concerns raised above, DDMAC's attempt to preclude MGI from using animal data is inconsistent with FDA's own regulatory requirements.

3. Unwarranted Expansion of Regulated Categories of Promotional Materials and Use of Corrective Messaging

a. Facts

DDMAC routinely exceeds the scope of its legal authority, both in the practices it seeks to control and in the remedies it prescribes. In what appears to be a disturbing trend, warning and untitled letters have objected to communications directed at both pharmacists and state Pharmacy and Therapeutics (P&T) committees—audiences traditionally outside of DDMAC's regulatory orbit. The practice of requesting corrective messaging also continues unabated, appearing in all 14 of the warning letters issued between July 2006 and June 2007.

In a letter to Reliant Pharmaceuticals, DDMAC objected to promotional materials that allegedly omitted risk information and encouraged off-label use of Rythmol SR® (propafenone HCl) extended release capsules. The "promotional pieces" to which DDMAC objected in the warning letter were manifestly directed to pharmacists, advertising the availability of a new 60-count "unit-of-use" package for Rythmol SR®.

Similar allegations were leveled against Cephalon for its promotion of Provigil® (modafinil) tablets to the Maryland Department of Health and Mental Hygiene's P&T committee. The promotional material in question was distributed to the committee at a public meeting regarding the inclusion of Provigil® on the state's Preferred Drug List (PDL). It is routine practice for the committee to solicit drug industry input when compiling or updating the PDL. Committee members are licensed pharmacists and physicians with substantial experience evaluating the clinical efficacy and cost effectiveness of drugs. MD. CODE REGS. 10.09.03.12 (2007). Nonetheless, DDMAC issued a warning letter arguing that this audience might be misled by Cephalon's promotional materials.

In both of these letters—as well as in 12 other letters finding fault with communications directed at health care practitioners—DDMAC instructed the recipients "to disseminate truthful, non-misleading, and complete corrective messages . . . to the audience(s) that received the violative promotional materials." The letters do not indicate what form these messages should take, nor do they offer any empirical basis to support the efficacy of corrective messaging.

b. Analysis

Traditionally, DDMAC has implemented the promotional labeling and advertising provisions of the FDCA by focusing on detail aids, print advertisements, and other promotional materials aimed at health care practitioners acting as prescribers or (more recently) patients. These communications qualify as promotion because they recommend or suggest use of a product in a promotional context and propose that the prescriber order (or the patient request an order of) the drug. For DDMAC to turn its attention to materials aimed at completely different audiences constitutes a significant change in the categories of materials that DDMAC traditionally has regulated.

This expansionist trend, although recently intensified, is not entirely new. As early as 1994, DDMAC began interfering with the ability of drug manufacturers to provide information about their products to managed care organizations to assist in coverage determinations. Congress responded to this alarming trend by amending the FDCA to make clear that FDA could not take action against truthful, non-misleading prescription drug information provided to specific categories of entities involved in making coverage determinations, as long as the information met the "competent and reliable scientific evidence" standard that had been developed by the Federal Trade Commission. See 21 U.S.C. § 352(a). As Congress recognized, these entities are more than capable of evaluating complex drug information for the purpose of making formulary decisions. See S. Rep. No. 105-43, at 42-43 (1997); H.R. Rep. No. 105-310, at 65-67 (1997). DDMAC's latest intrusion into this area is, at the very least, in tension with that recognition.

The determination that communications directed at managed care organizations and similar non-prescriber health care practitioner audiences are subject to the same content regulation as conventional promotional labeling and advertising represents an inadvisable extension of DDMAC's authority. For DDMAC to apply the usual "rules"—themselves inadvisable even in the context of traditional promotional communications intended for physicians and patients—to this additional category of materials is to undermine Congress's intention to encourage the provision of drug information to facilitate coverage decisions. DDMAC's error is exacerbated by its failure to provide even rudimentary guidance on the meaning of the "competent and reliable scientific evidence" standard, or to complete the task it undertook years ago of developing comprehensive guidance on the promotion of prescription drugs to managed care organizations.

Finally, DDMAC's request that manufacturers disseminate "corrective" promotional messages is unauthorized by statute and unconstitutional, and represents bad policy. The statutory listing of FDCA enforcement authority conspicuously omits any authority for DDMAC (or any other FDA division) to request or require that a firm disseminate "corrective" messages. 21 U.S.C. et seq. Additionally, a requirement that a company disseminate information—with which it might disagree—about its own products on behalf of the government presents serious First Amendment issues. See, e.g., Zauderer v. Office of Disciplinary Counsel, 471 U.S. 626, 651 (1985) (acknowledging that "unjustified or unduly burdensome disclosure requirements might offend the First Amendment by chilling protected commercial speech").

In a series of cases addressing the constitutionality of federally mandated corrective messaging, courts have established that corrective messaging orders must be no more burdensome than necessary to serve the government's objective. See, e.g., Novartis Corp. v. FTC, 223 F.3d 783 (D.C. Cir. 2000); American Home Prods. Corp. v. FTC, 695 F.2d 681, 700-02 (3d Cir. 1982); National Comm'n on Egg Nutrition v. FTC, 570 F.2d 157 (7th Cir. 1977); Warner-Lambert Co. v. FTC, 572 F.2d 749 (D.C. Cir. 1977). For such compelled speech to pass First Amendment muster, the allegedly offending advertisement must (1) have played a substantial role in creating or reinforcing in the public's mind a false belief about the product and (2) caused the belief to linger after the false advertising ceased. Novartis, 223 F.3d at 787. There must also have been a lengthy history of deception before a court will uphold a corrective advertising order. See, e.g., Warner-Lambert, 562 F.2d at 756 (upholding corrective messaging where "a hundred years of false cold claims have built up a large reservoir of erroneous consumer belief").

Despite these requirements, DDMAC did not once provide evidence in its warning letters to support demands for corrective messaging, nor did it allege that any health care practitioners or patients were actually misled. To the contrary, its position appears to be based solely on a fear that manufacturers' promotional pieces might mislead health care practitioners or patients. This practice stands in sharp contrast to both Warner-Lambert and Novartis, in which the FTC utilized expert witnesses and marketing studies to demonstrate deeply-embedded erroneous consumer beliefs. PBM Prods., Inc. v. Mead Johnson & Co., 174 F. Supp. 2d 417, 422 (E.D. Va. 2001). Also,

the promotional pieces criticized by DDMAC ran only for a short period of time, unlike the eight-year and 100-year campaigns at issue in and Novartis and Warner-Lambert.

In addition to these general constitutional infirmities, DDMAC's attempt to target pharmacists and P&T committees with corrective messaging is even more problematic. Rehabilitative commercial speech may be compelled only when "there is clear and continuing injury . . . to the consuming public [caused by] consumers continu[ing] to make purchasing decisions based on the false belief." Novartis, 223 F.3d at 787 (quoting Warner-Lambert, 562 F.2d at 762). Both pharmacists and P & T Committee members are trained professionals whose knowledge and judgment about drug products far surpass that of the "consuming public." As such, they are less likely to develop "false belief" based upon promotional materials. Furthermore, neither group is positioned to impact health care practitioner or patient decisions. It is, therefore, particularly inappropriate for DDMAC to impose this corrective messaging burden upon manufacturers.

Constitutional considerations aside, it is also questionable whether corrective messaging achieves the desired impact. A recent Government Accountability Office investigation found that FDA-mandated corrective messages were disseminated, on average, a full thirteen months after the allegedly violative materials first appeared. Gov't Accountability Office, Pub. No. GAO-07-54, Prescription Drugs: Improvements Needed in FDA's Oversight of Direct-to-Consumer Advertising 27 (2006). In light of this delay, corrective promotion is almost always inappropriate as a public health matter. Distributing corrective communications more than a year after the fact is likely to be ineffective, at best, and highly confusing to health care providers and patients, at worst.

To our knowledge, FDA has never performed a systematic analysis of the effects of corrective advertising. There is good reason to believe that use of this tactic in the drug promotion context actually contributes to consumer confusion. Many studies have shown that the addition of corrective messages to an ad reduced the frequency of the original false belief, but increased the number of consumers holding other false beliefs.[7] In effect, the corrective message itself was deceptive to at least some people. FDA does not determine that an advertisement actually misled any consumers or health care practitioners before it requests corrective advertising. Consumers could therefore be misled by the very advertising that FDA intended to be corrective.

III. CONCLUSION

From our analysis of warning and untitled letters issued by DDMAC from July 2006 through June 2007, it appears that these regulators have made little effort to comply with the First Amendment in regulating promotional communications for prescription drugs.

Two recurring, broad themes emerge from our review. First, FDA regulation of prescription drug promotion has little or no grounding in science. In its warning and untitled letters, DDMAC does not present any evidence that anyone was actually misled by the censored materials. DDMAC does not even claim in these letters that anyone was actually misled. Rather, DDMAC appears to assume that someone might be misled. This non-evidence-based approach is incompatible with the First

[7] See, e.g., Kuehl & Dyer, Applications of the "Normative Belief Technique" for Measuring the Effectiveness of Deceptive and Corrective Advertisements, 4 ADVANCES IN CONSUMER RESEARCH 204, 209 (W. Perrault ed. 1977); Mazis & Atkinson, An Experimental Evaluation of a Proposed Corrective Advertising Remedy, 13 J. MARKETING RESEARCH 178, 181-82 (1976); see also Jacoby, Nelson & Hoyer, Corrective Advertising and Affirmative Disclosure Statements: The Potential for Confusing and Misleading the Consumer, 46 J. MARKETING 61, 70 (Winter 1982).

Amendment. See Virginia State Bd. v. Virginia Citizens Consumer Council, 425 U.S. 748, 769, 773 (1976).

Second, FDA is ignoring its constitutional duty to show that speech restrictions are carefully tailored to address a genuine problem. Edenfield v. Fane, 507 U.S. 761, 770-71 (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).

The effect of these policies is to undermine a primary purpose of the First Amendment: to prevent indiscriminate government interference with speech. Unfortunately, to date DDMAC officials have chosen not to respond to the deficiencies identified by WLF. In particular, they have failed to respond to the first annual report, which WLF submitted to FDA in August of last year. Citizen Petition of Washington Legal Foundation to FDA, Docket No. 2006P-0319 (Aug. 7, 2006). In the coming year, WLF intends to look for ways to persuade FDA to provide such a response.

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For further information, contact WLF Chief Counsel Richard Samp, 202-588-0302. Copies of the letters WLF has sent to DDMAC under the DDMAC Watch program are posted on the WLF web site, www.wlf.org.