EXHIBIT A

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 first year of operation.

WLF is a public interest law and policy center with supporters in all 50 states. WLF for many years has been actively involved in efforts to decrease federal government restrictions on the flow of truthful 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.

The DDMAC Watch program is part of WLF's long-standing effort to ensure that federal regulators do not interfere in 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 to receive, and prescription drug manufacturers to provide, such information. Under the program, when FDA's Division of Drug Marketing, Advertising, and Communications (DDMAC) (or its counterpart for biological drugs, the Office of Compliance and Biologics Quality, or 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 plans to issue annual reports analyzing DDMAC and OCBQ warning and untitled letters sent during the previous year. The

purpose of this analysis is to determine whether there are 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. What follows is the first 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 and OCBQ through the first year of the DDMAC Watch program (June 2005-June 2006) reveals many legal and policy issues raised by FDA's regulation of prescription drug promotion. Of greatest concern is a consistent FDA pattern of using such letters as a vehicle for establishing policy. This pattern is problematic from a legal perspective, 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. The substance of a number of these new FDA policies is also troubling, both as a legal matter and from a public health perspective.

In particular, FDA's letters reveal that the agency has a firmly established policy of allowing drug manufacturers to make promotional claims regarding FDA-approved products only if those claims are supported by FDA's overly narrow definition of "substantial evidence." FDA essentially requires companies, before they can make a claim, to amass evidence in support of the claim that is equivalent, in terms of type and quantity, to the evidence required for the drug to have been approved in the first instance. Thus, FDA completely bans even statements that are truthful and non-misleading, if they are based on clinical investigations or other sources of information that agency officials deem less than 100% certain, regardless how carefully the manufacturer qualifies its claims. It is also apparent that FDA has an established policy of not allowing companies to employ disclaimers to address any potential of a statement to mislead, despite the First Amendment requirement that the government refrain from imposing a blanket ban on potentially misleading speech 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).

FDA also has established a policy of requiring 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 are required to communicate publicly about their products in ways that overemphasize the risks of drug use and underemphasize their benefits. This is contrary to recent FDA policy statements focusing on the importance of tailoring risk information to health care practitioners and consumers, to avoid "information overload" and to ensure that risks are discussed in the context of clinical benefits. There are also sound legal reasons to question the validity of FDA's "double disclosure" policy for risk information.

WLF's review of warning and untitled letters also shows that FDA has now firmly established its policy of requesting corrective advertising in virtually every warning letter issued with respect to prescription drug promotion. Corrective advertising is a drastic 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 advertising. There is good reason to believe that use of this tactic in the drug promotion context actually contributes to consumer confusion. Moreover, FDA does not determine that an advertisement actually has 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.

Although FDA characterizes the "regulatory letters" and other statements of FDA officials as merely "advisory," these communications have real practical consequences. As we discuss in greater detail in our report, WLF has determined that FDA's current regulation of prescription drug promotion:

- Deprives patients and consumers of truthful, non-misleading scientific information without adequate justification and in violation of the First Amendment;
- Irrationally compels drug manufacturers to disclose drug risk information twice in the same advertisement, misleading consumers and health care practitioners into believing that products are riskier than they actually are; and
- Improperly relies on corrective advertising, which FDA has never determined to be effective in addressing misleading promotion and which is used routinely by FDA without any analysis of whether the allegedly deceptive manufacturer advertisement did, in fact, deceive anyone.

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

FDA asserts authority to regulate virtually 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 comprehensive 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.[1] 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 practitioners. 21 C.F.R. § 202.1(l).[2]

DDMAC and OCBQ are the FDA components with day-to-day responsibility for regulating 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, these groups oversee all of the advertising and promotional labeling issued in the United States with respect to

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[1] 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 are not addressed here, raise substantial legal questions. See, e.g., Ass'n of Am. Physicians and Surgeons v. FDA, 226 F. Supp. 2d 204 (D.D.C. 2002).

[2] 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.

prescription drugs (including biological drugs). Their principal vehicle for communicating regulatory expectations to industry is warning and untitled letters.

Under established FDA policy, warning letters are supposed to be used only to allege violations of "regulatory significance." This means that FDA may initiate enforcement action in the absence of prompt, adequate correction. 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.

By contrast to warning letters, 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 substantial 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,[3] as well as in response to competitor complaints. In 1976, the Deputy Assistant Commissioner for Public Affairs at FDA said about regulatory letters, "we do not ring a fire bell when one is dispatched. That, I believe, would be an unfair flexing of our public information muscle." Wayne L. Pines, Regulatory Letters, Publicity and Recalls, 31 Food Drug Cosm. L. J. 352, 353 (1976). It seems FDA no longer has this view. 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."[4] Employees of both DDMAC and OCBQ routinely discuss warning and untitled letters at industry gatherings to explain their respective views on matters of policy and legal interpretation. See, e.g., The Pink Sheet, Sept. 20, 2004, at 24.

DDMAC and OCBQ sometimes use guidance documents to communicate their regulatory expectations to prescription drug manufacturers. This 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. Providing such an opportunity means FDA generally must publish guidance documents first in draft form. It can finalize them only after providing time for public

[3] 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).

[4] 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 II.B.4, FDA's use of warning and untitled letters in the area of prescription drug promotion to establish regulatory expectations raises serious legal issues.

comment and reviewing and addressing those comments. Thus, for example, on February 10, 2004, FDA announced the availability of three draft guidances for industry to improve information provided to consumers and health care practitioners by medical product firms about medical products and health conditions. 69 Fed. Reg. 6,308. Two of the documents, entitled "Brief Summary: Disclosing Risk Information in Consumer-Directed Print Advertisements" and "Help-Seeking and Other Disease Awareness Communications by or on Behalf of Drug and Device Firms," concerned prescription drug promotion. Id.

Unfortunately, FDA has established a pattern of issuing draft guidance documents for comment but never finalizing them. Neither of the 2004 guidance documents cited above has been finalized, leaving manufacturers without final recommendations on these important subjects. Other guidance documents intended to address issues relating to prescription drug promotion have remained in draft form for many years, with no schedule for making them final. For example, a draft guidance document issued by FDA in 1999 and entitled "Product Name Placement, Size, and Prominence in Advertising and Promotional Labeling" and another issued in 1997 entitled "Promoting Medical Products in a Changing Healthcare Environment; I. Medical Product Promotion by Healthcare Organizations or Pharmacy Management Companies (PBMs)" have never been finalized.

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 develop to provide up-to-date recommendations 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.

III. DDMAC AND OCBQ WARNING AND UNTITLED LETTERS

A. ANALYSIS OF ALL LETTERS

Since WLF launched the DDMAC Watch program in June 2005, DDMAC and OCBQ have issued 33 warning and untitled letters to prescription drug manufacturers objecting to their advertising and promotional labeling. In response, WLF has sent 27 letters to DDMAC and OCBQ, addressing the many ways in which these letters advance theories that raise serious questions under the First Amendment and other legal principles.

Table 1 lists the warning and untitled letters issued by DDMAC and OCBQ, commencing from the date on which the DDMAC Watch program was launched through the end of the first year of the program, June 30, 2006. Table 2 covers the warning and untitled letters issued in 2005 before the launch of the DDMAC Watch

program. In each table, 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 FDA were aimed at health care practitioners (HCP) or patients (Pt), 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 and OCBQ cite 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 and OCBQ purport 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 and OCBQ require 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 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 and OCBQ allege 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 and OCBQ use 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.

The tables below show which particular letters contained these problematic theories. As the tables note, WLF did not respond to every warning and untitled letter issued by DDMAC or OCBQ. Rather, since June 2005, 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 June 2005-June 2006 DDMAC/OCBQ Warning/Untitled Letters; Letters Issued After Launch of DDMAC Watch

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						
6/14/2005	Eli Lilly	Strattera (atomoxetine HCl)		√		√				√		
6/21/2005	MedImmune Vaccines, Inc.	FluMist [Influenza Virus Vaccine Live, Intranasal]			√					√		√
6/28/2005	Endo Pharmaceuticals Inc.	Lidoderm (lidocaine patch 5%)	√		√		√	√	√			√
6/28/2005	Dutch Ophthalmic USA	VisionBlue (trypan blue ophthalmic solution)	√		√						√	√
7/15/2005	Hoffman-LaRoche, Inc.	Fuzeon (enfuvirtide) for Injection	√			√						
7/15/2005	Abbott Laboratories	Survanta (beractant) intratracheal suspension)	√			√		√			√	
7/18/2005	Cytogen Corporation*	Quadramet (samarium SM 153 lexidronam) Injection		√	√							√
7/20/2005	Actelion Pharmaceuticals US, Inc.	Tracleer (bosentan) Tablets	Web		√							√
7/20/2005	Pfizer, Inc.	Zyvox (linezolid) injection, tablets, and oral suspension	√		√			√				√

* WLF did not submit a response to this letter.

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						
8/18/2005	SuperGen, Inc.	Nipent (pentostatin) for Injection	√		√			√				√
8/31/2005	Octapharma USA, Inc.*	OCTAGAM 5% [Immune Globulin Intravenous (Human)]	√		√							√
9/6/2005	Allergan, Inc.	Lumigan (bimatoprost) ophthalmic solution	√		√		√	√	√			√
9/9/2005	Eli Lilly*	Cymbalta (duloxetine)	√			√						
9/22/2005	Alcon Research, Ltd.	Travatan (travoprost ophthalmic solution)	√			√		√		√		
9/29/2005	Nephrx	Calcitrol Injection 1 mcg/mL	√		√				√			√
11/1/2005	GenTrac, Inc	THROMBIN-JMI [Thrombin, Topical, U.S.P. (Bovine Origin)]	√		√						√	√
11/2/2005	ISTA Pharmaceuticals, Inc.	Vitrase (hyaluronidase injection)	√			√			√	√	√	
11/8/2005	Critical Therapeutics, Inc.*	Zyflo Filmtab (zileuton tablets)	√		√							√

* WLF did not submit a response to this letter.

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						
12/15/2005	Biogen Idec Inc.	Zevalin (ibritumomab tiuxetan)	√			√			√			
1/4/06	Medicis Pharmaceutical Corp.	Loprox Shampoo (ciclopirox) 1%	Web			√	√	√	√		√	
1/4/06	Duramed Pharmaceuticals, Inc.	Cenestin (synthetic conjugated estrogens, A) tablets	√		√				√	√		√
1/6/06	Sankyo Pharma Inc.	Benicar (olmesartan medoxomil) Tablets, Benicar HCT (olmesartan medoxomil/ hydrochlorothiazide) Tablets	√		√				√		√	√
2/1/06	ZLB Behring LLC	Rhophylac [Rh0(D) Immune Globulin Intravenous (Human) 1500 IU (300 μg)]	√			√		√			√	
2/1/06	Mayne Pharma (USA), Inc.	M.V.I.-12 (Multi-Vitamin Infusion without vitamin K)	√		√				√			√

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						
2/16/06	Palatin Technologies, Inc.	NeutroSpec [Kit for the Preparation of Technetium (99m Tc) fanolesomab]	√			√			√	√		
3/24/06	VaxGen, Inc.	*Bacillus anthracis* Recombinant Protective Antigen 102 (rPA102) (anthrax vaccine) with Alum	††		√					√		
3/28/06	InterMune, Inc.	INFERGEN (Interferon alfacon-1)	√			√		√	√	√		
4/4/06	Bioniche Pharma Group Limited	Sotradecol (sodium tetradecyl sulfate injection)	Web		√				√	√	√	√
4/13/06	Wyeth Pharmaceuticals, Inc.	ReFacto Antihemophilic Factor (Recombinant)		√		√		√		√		
5/25/06	Boehringer Ingelheim Pharmaceuticals, Inc.	Spiriva Handihaler (tiotropium bromide inhalation powder)	√			√				√		

†† The VaxGen warning letter was highly irregular because the target "audience" for the allegedly violative materials was neither health care practitioners nor patients. The materials were allegedly distributed at the 4th Annual Federal Biodefense Research FY 2006 meeting on October 17-19, 2005, in Washington, DC. This meeting was a gathering of the biodefense research community. The purpose of the event was to assemble leaders from government departments and agencies funding the nation's biodefense research to discuss research priorities, programs, and funding for FY 2006. This was the only warning letter in our review for which FDA did not request corrective messaging.

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						
5/26/06	Sandoz, Inc.	Bupropion hydrochloride extended-release tablets (SR)	√			√				√		
6/29/06	PrimaPharm, Inc.	Hydase (hyaluronidase Injection, USP) 150 Units/mL	√		√				√			√
6/30/06	GlaxoSmithKline	Zovirax (acyclovir) Ointment 5%	Web and Pt		√			√	√	√	√	√

Table 2. Overview of 2005 DDMAC/OCBQ Warning/Untitled Letters; Letters Issued Before Launch of DDMAC Watch

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						
1/6/2005	Nabi Biopharmaceuticals	Nabi-HB [Hepatitis B Immune Globulin (Human)]	Web			√				√		
1/10/2005	Pfizer Inc.	Celebrex (celecoxib) Tablets; Bextra (valdecoxib) Tablets	√	√		√						
1/13/2005	Cangene Corp	WinRho SDF [Rho(D) Immune Globulin Intravenous (Human)]	√			√		√				
1/31/2005	GlaxoSmithKline	Coreg (carvedilol) Tablets	√			√		√				
2/11/2005	Centocor	Remicade (infliximab)	√			√		√	√			
2/18/2005	Amgen	Enbrel (etanercept)		√	√							√
3/8/2005	AstraZeneca Pharmaceuticals LP	Crestor (rosuvastatin calcium)		√		√						
3/16/2005	F. Vericat Cadesas	Flebogamma 5% [Immune Globulin Intravenous (Human)]	√		√				√			√
3/22/2005	Boehringer Ingelheim Pharmaceuticals,	Aggrenox (aspirin/extended-release	√			√		√	√			

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						
	Inc.	dipyridamole) Capsules										
3/30/2005	Presutti Laboratories, Inc.	Tindamax (tinidazole tablets)	√		√							√
4/13/2005	Bayer Pharmaceuticals	Levitra (vardenafil HCl) Tablets		√		√						
4/13/2005	United Therapeutics Corp.	Remodulin (treprostinil sodium) Injection	√	√	√			√				√
4/13/2005	Pfizer, Inc.	Zyrtec (cetirizine HCl)	√		√							√
4/27/2005	Alcon Laboratories, Inc.	CIPRO HC Otic (ciprofloxacin hydrochloride and hydrocortisone otic suspension)	Web		√		√	√				√
6/2/2005	Ovation Pharmaceuticals, Inc.	Panhematin [Hemin for Injection]	√		√				√			√

B. ISSUES OF PARTICULAR CONCERN

Three issues of particular concern to WLF arose repeatedly in the letters we reviewed. First is the question whether FDA can, consistent with the First Amendment, forbid a manufacturer from providing truthful and non-misleading information to the public about a legitimate clinical investigation merely because the agency has determined that the study does not comply with the detailed requirements for the design of clinical investigations used to support new drug approval. Second is the question whether the regulations and the First Amendment permit FDA to require manufacturers to disclose risk information both in the body of a promotional piece and in the accompanying risk disclosure. Third is whether FDA has the authority to compel manufacturers to disseminate corrective messages and whether it can do so without running afoul of the First Amendment. Each of these issues is discussed below.

1. Ban on Most Clinical Studies

a. Facts

Among the most prevalent and troubling of these policies—reflected in 17 letters—is the repeated contention that a manufacturer may not make any promotional statement at all if its claim is based on a clinical investigation that regulators believe does not meet their overly narrow interpretation of the "substantial evidence" standard. Under the FDCA, FDA cannot approve a new drug if "there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling thereof." 21 U.S.C. § 355(d). The statute defines "substantial evidence" to mean "evidence consisting of adequate and well-controlled investigations, including clinical

investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved." Id.[6] FDA has imported this concept into the promotional context, taking the position that the same type and quantity of proof required for approval is necessary to support promotional claims, even for drugs that have already been approved. See, e.g., 21 C.F.R. § 202.1(e)(6)(i) (prohibiting ads that contain "a representation or suggestion, not approved or permitted for use in the labeling, that [the] drug is better, more effective, useful in a broader range of conditions or patients . . . [or] safer . . . than has been demonstrated by substantial evidence or substantial clinical experience . . .").

This restrictive policy harms the public health by denying credible and reliable scientific information to patients and health care practitioners. And it does so merely on the insubstantial ground that the information comes from clinical investigations that might not be deemed sufficient in the context of premarket review. It should be obvious that clinical investigations can provide information relevant to the use of a drug, even if the investigation is not designed as rigorously as trials intended to demonstrate that the drug is safe and effective and thus approvable. FDA's approach assumes that health care practitioners are incapable of understanding that information pertinent to clinical decisions can come from a variety of sources. It therefore interferes

[6] FDA by regulation has defined "adequate and well-controlled investigation" to mean a study having the following characteristics: (1) a protocol containing a clear statement of the study's objectives and methods of analysis; (2) a design that permits a valid comparison with a control; (3) a method of selecting subjects that assures they actually have the disease being studied; (4) a method of assigning subjects to treatment and control groups that minimizes bias and is intended to assure comparability of the groups with respect to pertinent variables, such as severity of disease, duration of disease, and use of other therapies; (5) adequate measures to minimize bias, such as blinding; (6) well-defined and reliable methods for assessing subject response; and (7) analysis of results that is adequate to assess the effects of the drug. 21 C.F.R. § 314.126

with the dissemination of truthful, non-misleading, scientifically substantiated scientific information to health care practitioners and patients.

To illustrate, in an untitled letter to Abbott Laboratories, DDMAC objected to effectiveness claims for Survanta® (beractant) intratracheal suspension that appeared in a direct mail piece directed to health care practitioners. The claims were based on a study report published in the journal Pediatrics. Pediatrics is the official peer-reviewed journal of the American Academy of Pediatrics, and is the most-cited journal in the field of pediatrics. The study reported the results of a prospective, randomized, double-blind, multicenter clinical investigation. These results were presented at the annual meeting of the Society for Pediatric Research in 1994 and at the American Academy of Pediatrics annual meeting in 1995. Despite this pedigree, DDMAC said that the study results did not constitute "substantial evidence" and, therefore, could not lawfully be relied upon by Abbott to substantiate its claims.[7]

Similarly, in a warning letter to Endo Pharmaceuticals, DDMAC objected to claims for Lidoderm® (lidocaine patch 5%), a topical anesthetic patch. The product is made of an adhesive material containing 5 percent lidocaine. It has been approved by FDA to be applied to intact skin to relieve pain associated with post-herpetic neuralgia—a type of nerve pain sometimes seen after shingles. The letter concerned statements about the effectiveness of Lidoderm appearing in two direct mailing pieces intended for health care practitioners. These statements were based on an open-label,

[7] DDMAC cited 21 U.S.C. § 352(a), which forbids labeling that is false or misleading "in any particular." DDMAC relies on the "labeling" provisions because it believes virtually all written, printed, or graphic materials disseminated by or on behalf of a drug manufacturer that are not paid, third-party placements (e.g., DTC television advertisements) constitute labeling. See 21 C.F.R. § 202.1(l)(2) ("labeling" includes "literature, and reprints and similar pieces of printed, audio, or visual matter descriptive of a drug . . . for use by medical practitioners . . . containing drug information supplied by the manufacturer . . . of the drug and which are disseminated by or on behalf of its manufacturer").

nonrandomized clinical investigation that included 332 subjects, the results of which were reported in Pain Medicine, the official scientific journal of the American Academy of Pain Medicine. The lead author of the report, a physician, was at the time of publication affiliated with Harvard Medical School. Additional authors came from Endo itself and from the University of Rochester School of Medicine and Dentistry. The details of the study design were prominently disclosed in the study report and in the abstract, readily available to any practitioner reviewing the article. Nevertheless, DDMAC objected to the mailing pieces on the ground that the study did not constitute "substantial evidence."

Other manufacturers received similar communications. DDMAC objected to Pfizer's citation of a retrospective analysis of data from two randomized, double-blind clinical investigations, even though the promotional piece at issue disclosed comprehensive information about the studies' design and included the p-values. DDMAC prohibited Allergan from relying on a study published in the American Journal of Ophthalmology because of certain aspects of the study's design. Other instances in which DDMAC and OCBQ objected to the use of scientific information are identified in Tables 1 and 2, above.

It is important to note that these warning and untitled letters did not merely raise questions about the design of the studies. Rather, they stated without qualification that data from these studies could not be used—at all—in manufacturer promotional communications about their products. It was irrelevant to regulators that these studies had been performed by reputable scientists and had been accepted for publication by

scientific journals. Nor did it matter that the information generated by these studies would be useful to health care practitioners and therefore of benefit to patients.

b. Analysis

DDMAC's position—that manufacturers may only cite clinical studies and other sources of information that meet FDA's standards for study design—not only harms the public health by keeping new scientific developments from health care practitioners, but also presents substantial questions under the First Amendment. In the case involving Pediatrics, for example, the clinical study results were subjected to multiple levels of scrutiny—the journal's peer-review process, and review at two professional meetings. The information in the study was clearly clinically relevant, as demonstrated by practitioner decisions to publish the results and present them at the meetings. Under these circumstances, it is hard to see how the decision to prohibit any use of the study at all makes sense from a public health perspective.

As a legal matter, a prescription drug manufacturer is entitled to make statements in its promotional materials based on sources of information that do not meet federal regulators' definition of an adequate and well-controlled clinical investigation. To the extent that any statement about data from a study is potentially misleading, the First Amendment entitles the manufacturer to use, and requires DDMAC and OCBQ to accept, disclaimers sufficient to ensure that the statement is truthful and non-misleading. 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) (FDA may not simply ban claims that are not supported by "significant scientific agreement," but must instead consider whether disclaimers will make the claims not misleading). Any potential of the claims to mislead, based on design issues for example, can be addressed through the use of appropriate

disclaimers. It may not be addressed by DDMAC through a total ban on speech. 44 Liquormart v. Rhode Island, 517 U.S. 484, 501 (1996) ("[C]omplete speech bans . . . are particularly dangerous because they all but foreclose alternative means of disseminating certain information.").

Put simply, FDA is not the ultimate arbiter of scientific truth for the medical community. Washington Legal Found. v. Friedman, 13 F. Supp. 2d 51, 67 (D.D.C. 1998) ("'[T]he FDA is not a peer review mechanism for the scientific community.'") (citing Lars Noah & Barbara A. Noah, Liberating Commercial Speech: Product Labeling Controls and the First Amendment, 47 Fla. L. Rev. 63, 96 (1995)), appeal dism'd, Washington Legal Found. v. Henney, 202 F.3d 331 (D.C. Cir. 2000). FDA's responsibility with respect to clinical studies is to determine whether they provide sufficient support for approval of new drugs, or new uses of existing drugs—but only if a manufacturer seeks to rely on them for such approval. Regulators do not have a roving mandate to ban all statements by prescription drug manufacturers based on data from clinical studies regarding FDA-approved drugs, based solely on their personal views about study design.

Because scientific viewpoints may differ as to the usefulness of any particular study in clinical practice, the only course that adequately respects First Amendment values would be for DDMAC to allow truthful and non-misleading claims about a clinical study, whether or not it is deemed an acceptable study by FDA. West Virginia State Bd. of Educ. v. Barnette, 319 U.S. 624, 642 (1943) ("If there is any fixed

star in our constitutional constellation, it is that no official, high or petty, can prescribe what shall be orthodox in . . . matters of opinion . . .").[8]

The current approach of banning promotional claims based on studies that FDA does not believe meet the "substantial evidence" standard deprives health care practitioners of useful information about therapeutic products. It thus violates the First Amendment rights of speakers and listeners alike. Virginia State Bd. v. Virginia Citizens Consumer Council, 425 U.S. 748, 757 (1976) (The Court has not "recognized any . . . limitation on the independent right of the listener to receive the information sought to be communicated."); Roe v. Ingraham, 364 F. Supp. 536, 543 (S.D.N.Y. 1973) ("[T]he First Amendment has been held to include a correlative right to receive information and ideas.").

2. Double Disclosure of Risk Information

a. Facts

Another established policy reflected in the letters we reviewed—18 of them—concerns the double disclosure of risk information in promotional communications about prescription drugs. The position of DDMAC and OCBQ is that prescription drug manufacturers must present risk information not only in the "brief summary" (or, for promotional labeling, the FDA-approved package insert) that accompanies the promotional communication, but also in the "creative" part of the advertisement or labeling piece itself.

[8] It may be that certain studies are so flawed that any discussion of them would be inherently misleading. But FDA would have to show that health care practitioners would be misled by anything that could or would be said about such studies. In any event, FDA has not limited its enforcement of this speech-restrictive policy to such a narrow class of studies.

For example, in an untitled letter to ISTA Pharmaceuticals, Inc., DDMAC objected to a journal advertisement for Vitrase® (hyaluronidase injection) directed at health care practitioners. DDMAC claimed that the advertisement omitted certain risk information appearing in the FDA-approved package insert. The print advertisement included the "brief summary" for Vitrase, which replicated the sections of the package insert that contain the risk information for the drug. The advertisement thus contained the very information that the untitled letter alleged had been omitted.

In the warning letter to Endo described above, DDMAC alleged that the two physician-directed promotional pieces were false or misleading because they did not disclose particular items of risk information and included other risk information in a discrete part. DDMAC alleged, further, that Endo's characterization of adverse event information in the pieces was unlawful because it was "insufficient to describe the myriad of [sic] application site reactions associated with Lidoderm use, as presented in the PI." DDMAC threatened enforcement action against Endo if it did not discontinue use of these materials, even though the two pieces about which it complained were disseminated with copies of the FDA-approved package insert. The package insert contained all of the information that FDA determined was necessary for safe and effective use of the drug, including risk information and information about the drug's indications. Recipients of the pieces thus had ready access to all of the information that DDMAC alleged was omitted or insufficiently presented, and that information was presented in precisely the manner dictated by FDA.

In a warning letter to SuperGen, DDMAC objected to communications for Nipent® (pentostatin) for Injection that were aimed at health care practitioners.

According to the regulators, the promotional materials omitted risk information that appeared in the FDA-approved package insert for the drug. DDMAC's objection ignored the fact that the materials were disseminated with copies of the package insert, and the front page of one piece directed recipients to that information. Health care practitioners thus had ready access to all of the information that DDMAC alleged was omitted or insufficiently presented, and that information was presented in precisely the manner dictated by FDA.

In none of these cases did DDMAC present evidence that health care practitioners reading the piece were misled by the manner in which the risk information was presented.

b. Analysis

FDA has relied on 21 C.F.R. § 202.1(e)(3) to support the theory that risk information must appear twice in prescription drug promotional materials. But this regulation states that qualifying information may appear concisely in each part of an advertisement if accompanied by a reference to more complete qualifying information elsewhere in the piece:

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

FDA has effectively read that important qualifier out of the regulation. In the ISTA untitled letter, for example, ISTA included in the creative part of the advertisement both adverse event information and a reference to the complete risk information for Vitrase

appearing in the brief summary. Nowhere does the letter acknowledge that FDA's own regulations contemplate advertisements that do not present risk information verbatim in two separate places.

If § 202.1(e)(3)(i) meant that all risk information must appear in the creative part of the advertisement, then every advertisement would presumably have to include all the risk information appearing in the package insert both in the creative part of the advertisement and in the brief summary part of the advertisement. This would be an absurd result, and is clearly not contemplated by the regulation.

Moreover, such a view would raise grave constitutional questions. The First Amendment requires the government to justify requiring manufacturers to disclose risk information in the creative part of an advertisement when this information already appears in the accompanying brief summary. See Pearson v. Shalala, 164 F.3d at 659 ("[A]ll the government offers in support is the FDA's pronouncement that 'consumers would be considerably confused' . . . . [T]he government . . . must still meet its burden of justifying a restriction on speech—here the FDA's conclusory assertion falls far short.") (citations and footnote omitted). Given that the complete risk information sections of the package insert appear in the brief summary, it seems highly doubtful that such justification could be provided.

Even if this position were tenable in substance, it would be invalid for procedural reasons. At one time, FDA's view was that promotional communications for prescription drugs had only to refer the reader to the location of complete risk information, which could appear on a separate page. See 50 Fed. Reg. 36,677 (1985) ("[T]he brief summary is intended to ensure a 'fair balance' between a drug's potential

benefits and risks in all prescription drug advertisements."). As of 1996, the agency's position had changed. See 61 Fed. Reg. 48,708 (1996) (FDA "traditionally" has required risk information in the body of the advertisement). FDA's failure to use notice-and-comment rulemaking or to provide a reasoned analysis justifying this change of position renders its current stance invalid. See Motor Vehicle Mfrs. Ass'n v. State Farm Mut. Auto. Ins. Co., 463 U.S. 29, 42 (1983); Alaska Prof. Hunters Ass'n, Inc. v. Federal Aviation Admin., 177 F.3d 1030, 1033-34 (D.C. Cir. 1999).

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

Consistent with this sensible position, FDA has also taken steps to evaluate effective risk communication in patient-directed materials. In 2004, in a draft guidance document intended to improve patient comprehension of risk information in print advertisements by reducing the volume and improving the format of that

information, CBER and CDER stated: "In general, FDA believes that exhaustive lists of minor risks distract from and make it difficult to comprehend and retain information on the more important risks." See CBER & CDER, Guidance for Industry: Brief Summary: Disclosing Risk Information in Consumer-Directed Print Advertisements (DRAFT) (Jan. 2004).

The double-disclosure theory is irreconcilable with FDA's "less is more" theory of risk communication and is therefore invalid. Harco Holdings v. United States, 977 F.2d 1027, 1035-36 (7th Cir. 1992) (agency position "is not only new and unsupported by agency practice or rulings, . . . [but also] internally inconsistent" and therefore "deserves no deference"). Moreover, for the reasons articulated by FDA in its January 2006 statement on labeling, double disclosure of risk information is poor public health policy.

3. Corrective Messaging

a. Facts

Finally, DDMAC and OCBQ requested corrective messaging in all but one of the 26 warning letters they have issued from January 2005 through June 2006, reflecting a firm policy that all violations of "regulatory significance" must be remedied using this method. Indeed, WLF understands that agency officials have turned the concept of "regulatory significance" on its head. Historic agency policy—which remains in effect today—contemplates that, if a violation reaches the level of "regulatory significance," then a warning letter is appropriate. See FDA, Regulatory Procedures Manual § 4-1-1 (Mar. 2004), available at http://www.fda.gov/ora/compliance_ref/rpm/pdf/ch4.pdf. Contrary to this policy, regulators no longer begin by examining the "regulatory significance" issue; rather, they

deem the "regulatory significance" standard to have been satisfied, and a warning letter warranted, if they believe that corrective messaging is warranted.

FDA specifically requested comment on this issue in a Federal Register notice announcing the public hearing FDA held on consumer-directed advertising in November 2005. See 70 Fed. Reg. 54,054, 54059 (Sept. 13, 2005) ("In some cases, for . . . consumer-directed pieces, FDA also asks sponsors to run corrective advertisements or issue corrective promotional materials to remedy misimpressions created by false or misleading materials. The agency is interested in hearing views on this type of enforcement approach for consumer-directed promotional materials as well as other enforcement approaches that might protect the public health."). WLF presented testimony at that meeting, questioning FDA's suggestion in the notice that warning and untitled letters merely "ask" sponsors to run corrective advertisements or issue corrective promotional materials. WLF also objected to DDMAC's failure to develop an empirical record supporting the need for corrective messaging. Finally, WLF pointed out that the practice of seeking corrective messaging is vulnerable under the First Amendment and exceeds FDA's authority under the FDCA.

b. Analysis

First, nothing in FDA's principal enabling statute gives DDMAC or OCBQ the authority to require (or even to "request," under penalty of its displeasure and potential retaliation) corrective advertising. The remedies available to FDA under the FDCA are injunction, criminal fines and imprisonment, and seizure. 21 U.S.C. §§ 332 (violations may be restrained), 333 (violations are subject to imprisonment for up to three years and fines of up to $10,000, or both), 334 (violative drugs may be "proceeded against . . . on libel of information and condemned in any district court . . . within the

jurisdiction of which the article is found").[9] This explicit grant of authority precludes FDA from creating supplementary remedies, like corrective messaging. See Ragsdale v. Wolverine World Wide, Inc., 535 U.S. 81 (2002); American Bus Ass'n v. Slater, 231 F.3d 1 (D.C. Cir. 2000); Pacific Legal Found. v. Goyan, 664 F.2d 1221 (4th Cir. 1981). Indeed, by "requesting" corrective messaging, DDMAC and OCBQ are essentially admitting that they lack the authority to impose it.[10]

The insistence on corrective messaging in DDMAC and OCBQ warning letters conflicts with FDA's admonition, discussed above, against overloading patients with information. Neither DDMAC nor OCBQ, to our knowledge, considers consumer comprehension in devising corrective messaging. Yet, by compelling manufacturers to disseminate information ostensibly to address misimpressions left by earlier promotion, regulators might very well be increasing consumer confusion. See, e.g., Jacob Jacoby et al., Corrective Advertising and Affirmative Disclosure Statements: Their Potential for Confusing and Misleading the Consumer, 46 J. Mktg. 61, 70 (1982). Because neither DDMAC nor OCBQ systematically examines whether the original, allegedly violative, promotion was false or misleading in fact, they could actually be engendering confusion where none existed before. This is plainly bad policy, and at odds with the First Amendment.

The case law addressing First Amendment limitations on the authority of federal agencies to order corrective advertising arises in the context of the Federal

[9] FDA also possesses statutory publicity authority, but it is carefully limited to two situations: imminent danger to health, or gross deception of consumers. 21 U.S.C. § 375. We are aware of no instance in which FDA has relied upon this provision to issue warning or untitled letters.

[10] Some courts have determined that FDA also may request that courts, in an exercise of their traditional equitable powers, order those who have violated the FDCA to disgorge profits wrongfully gained or to make restitution to victims of their wrongdoing. Regardless whether those decisions are a correct statement of the law, they are of no assistance to FDA here: it cannot seriously be contended that corrective advertising is within the traditional equitable powers of a court.

Trade Commission's enforcement of federal false advertising laws. 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 (3rd Cir. 1982); National Comm'n on Egg Nutrition v. FTC, 570 F.2d 157 (7th Cir. 1977); Warner-Lambert Co. v. FTC, 562 F.2d 749 (D.C. Cir. 1977).[11]

Under these cases, to pass muster under the First Amendment, a corrective advertising order must be no more restrictive than necessary to serve the government's objective. To fulfill this requirement: (1) the allegedly offending advertisement must have played a substantial role in creating or reinforcing in the public's mind a false belief about the product; and (2) this belief must have lingered after the advertising stopped. Both factors depend on empirical evidence (e.g., market survey data). The cases indicate that a long history of deception must be shown before a court will uphold a corrective advertising order.

Yet DDMAC has requested, in all but one of the warning letters we reviewed, that the manufacturer submit to DDMAC a "comprehensive plan of action to disseminate truthful, non-misleading, and complete corrective messages about the issues discussed in this letter to the audience(s) that received the violative promotional materials." DDMAC has not presented any evidence, in the form of expert testimony, market research, or otherwise, that anyone was actually misled. FDA does not even allege in the warning letters that anyone was actually misled. Rather, FDA appears to have acted based solely on a fear that these advertisements might mislead consumers. Such unsubstantiated fears are insufficient to justify infringing free speech rights. See

[11] In some cases involving the authority of a federal agency to require corrective advertising, the challenger did not raise First Amendment arguments. See, e.g., FTC v. Simeon Mgmt. Corp., 532 F.2d 708 (9th Cir. 1976); Ward Labs, Inc. v. FTC, 276 F.2d 952, 955-56 (2d Cir. 1960). These cases generally arose before the Supreme Court recognized that commercial speech is entitled to First Amendment protection. Virginia State Board of Pharmacy, 425 U.S. 748 (1976).

Virginia State Bd. of Pharmacy, 425 U.S. at 769, 773 (rejecting the Virginia Board of Pharmacy's attempt to suppress commercial speech about prescription drug prices based on a mere fear that the information could have a negative effect on pharmacists and consumers); PBM Products, Inc. v. Mead Johnson & Company, 174 F.Supp. 2d 417, 422 (E.D. Va. 2001) (citing Warner-Lambert and Novartis, and explaining, "[i]n both of these cases, the FTC presented extensive evidence showing a pervasive and deeply entrenched consumer belief in the accuracy of the defendant's statements."). In the absence of actual evidence that the advertisements at issue in the warning letters led readers to adopt false beliefs regarding the drugs' safety and/or effectiveness, and that such beliefs would linger absent corrective advertising, corrective advertising is constitutionally impermissible because it is a more extensive remedy than necessary to satisfy FDA's interest in avoiding misleading advertising.

Moreover, common sense suggests that FDA could not have provided sufficient evidence of actual deception even if it had attempted to do so, given that the advertisements at issue in the 25 warning letters ran only for a short period, in contrast to the 100-year advertising campaign in Warner-Lambert and the eight-year campaign in Novartis. Advertisements that run for only a short period of time are inherently less likely to impress a false belief about a product upon customers; and because they are not reinforced over a long period of time, any belief actually impressed is less likely to linger after the advertising is stopped.

Due to FDA's lack of evidence that any of the advertisements at issue in the 25 warning letters for which corrective messaging was requested played a substantial role in creating a false belief about a product that would linger even after

cessation of the advertising, any corrective advertisement is a more extensive remedy than necessary to serve FDA's interest in avoiding misleading advertising. It therefore contravenes the First Amendment.

Corrective messaging also raises First Amendment concerns under a separate theory: the government may not indiscriminately order private parties to make statements with which they disagree. See, e.g., Wooley v. Maynard, 430 U.S. 705, 716-17 (1977) (the state of New Hampshire's interests in easily identifying passenger vehicles and communicating state pride did not trump plaintiff's First Amendment right not to use a license plate bearing the state motto "Live Free or Die," which he found offensive on religious and political grounds); Int'l Dairy Foods Assoc. v. Amestoy, 92 F.3d 67, 73-74 (2d Cir. 1996) (consumer curiosity regarding whether milk contained a growth hormone not associated with any health risk was not a sufficiently substantial interest to justify compelling dairy manufacturers to disclose use of the hormone on product labeling).

4. Use of Letters To Communicate Policy

a. Facts

As noted above, in the area of prescription drug promotion, DDMAC and OCBQ consistently use warning and untitled letters to establish and communicate their regulatory expectations. For example, on June 30, 2005, WLF responded to a DDMAC warning letter that objected to a web site that, DDMAC asserted, misbranded an ophthalmic drug. WLF pointed out that DDMAC was using warning and untitled letters to announce policy on the regulatory treatment of web sites, despite repeated promises from FDA officials to issue formal guidance documents in this area. Indeed, FDA has been signaling its intention to issue such guidance since 1996; yet, instead of working

on a guidance document with appropriate public input, the agency has issued warning and untitled letters to various drug companies objecting to the content of their web sites.

FDA's use of warning and untitled letters as a substitute for guidance documents extends to other areas. FDA has taken the position that FDCA § 502(a), 21 U.S.C. § 352(a), which prohibits labeling that is false or misleading "in any particular," requires manufacturers to present risk information with a prominence and readability reasonably comparable to that used for effectiveness claims. This interpretation is not spelled out in any regulation or guidance document. DDMAC nevertheless sent an untitled letter to Abbott Laboratories on July 15, 2005, declaring promotional material "misbranded" because it did not fulfill DDMAC's expectation regarding the presentation of risk information.

Despite WLF's request, in its response to the Abbott Laboratories letter, that DDMAC stop articulating its interpretive theories without providing notice and an opportunity for public comment, the Division sent yet another untitled letter reflecting a novel regulatory interpretation. A November 2, 2005 DDMAC letter requested the discontinuance of a journal advertisement on the ground that it failed to reproduce certain risk information appearing in the "brief summary" portion in the creative part. As WLF explained in our response, and as we discuss above, FDA's position historically was that duplicative disclosure of risk information was not required; a manufacturer satisfied its "fair balance" obligation by presenting product risks in the "brief summary" alone. FDA's position changed, and by 1996 the agency was asserting that its double disclosure policy represented a view it had "traditionally" taken.

In each of these cases, DDMAC advanced interpretations of regulatory requirements for prescription drug promotion that it is not entitled to promulgate until after FDA has provided notice and an opportunity for comment. As discussed below, DDMAC's actions in this regard are legally problematic.

b. Analysis

The use of warning and untitled letters instead of guidance documents to convey policy decisions contravenes legal requirements that FDA follow Good Guidance Practices. 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.").

The FDCA authorizes FDA, instead of initiating formal enforcement action, to provide "suitable written notice or warning" with respect to minor violations. 21 U.S.C. § 336. Citing this authority, FDA in 1972 began using two types of letters: the Regulatory Letter and the Report of Inspectional Finding (also known as an Information Letter). The primary purpose of both letters was to solicit prompt correction by management. Neither letter was intended to commit the agency to initiating legal action if the target company failed to institute appropriate remedial measures.

In 1978, FDA proposed to replace Information Letters with Notices of Adverse Findings. 43 Fed. Reg. 27,498 (1978). In the same notice, FDA proposed regulations establishing criteria for issuing both types of correspondence. The

proposed rule was later withdrawn. 45 Fed. Reg. 60,449 (1980). In 1991, FDA announced that, under revisions made to the Regulatory Procedures Manual, Regulatory Letters and Notices of Adverse Findings would henceforth be known as Warning Letters. 56 Fed. Reg. 27,026 (1991). FDA then began using "notice of violation" letters, which were later redesignated "untitled" letters.

Warning and untitled letters are thus "quasi-statutory" remedies invented by FDA in the 1970s as a way of correcting violations without having to go to court. With no judicial safeguards to protect against abuses, FDA can and does use warning and untitled letters to establish policies that instead should be established only after providing notice and an opportunity for interested parties to comment. DDMAC is among the worst offenders, as outlined above.

One apparent reason for FDA's resort to warning and untitled letters instead of guidance documents is to evade legal challenges to its new policies. FDA takes the position that warning and untitled letters are not subject to judicial review. When FDA devised regulatory letters, they were intended to represent final statements of enforcement policy subject to court challenge. Peter B. Hutt & Richard A. Merrill, Food and Drug Law: Cases and Materials 1194 (2d ed. 1991); see also Eugene I. Lambert, Recalls, Regulatory Letters and Publicity—Quasi-Statutory Remedies, 31 Food Drug Cosm. L. J. 360, 363 (1976) ("[T]he issuance of a regulatory letter indicates a decision by the Agency that it has adequate legal grounds to initiate formal court proceedings" and "normally represents a firm decision."). FDA has since characterized regulatory letters as informal communications that do not constitute final agency action. In the past, some courts have agreed with this position. Hutt & Merrill, supra, at 1194

(citing Biotics Research Corp. v Heckler, 710 F.2d 1375 (9th Cir. 1983)). It is thus extremely difficult for a manufacturer receiving a warning or untitled letter to challenge that letter in court. This is so even though such letters can have dramatic reputational, product liability, and other consequences, and are often in furtherance of well-established agency policy.

There was at one time an arguably good reason for FDA and the courts to treat warning and untitled letters as informal: FDA's lawyers were not involved in the process of developing such letters and had no control over their content or issuance. Agency officials could plausibly argue that they should not be forced to defend such unreviewed documents in court when the documents did not necessarily represent FDA's official position. Hutt & Merrill, supra, at 1194. In November of 2001, however, the Deputy Secretary of the Department of Health and Human Services (of which FDA is a part) issued a memorandum requiring internal legal review of all FDA warning and untitled letters before issuance. See FDA, Regulatory Procedures Manual § 4-1 (Mar. 2004), available at http://www.fda.gov/ora/compliance_ref/rpm/pdf/ch4.pdf. It is therefore likely that warning and untitled letters will henceforth be deemed final agency action that may be challenged in court. Accordingly, resort to warning and untitled letters as an alternative to formal guidance not only is legally suspect but also is unlikely to continue to accomplish FDA's litigation avoidance purpose.

Treating warning and untitled letters as final agency action would be consistent with the rationale of Washington Legal Foundation v. Kessler, which involved a challenge to speech-restrictive FDA policies that had become evident through a pattern of agency behavior, including warning and untitled letters. FDA argued that

these letters did not amount to official agency policy. The court rejected this contention: "Whether FDA has officially adopted a final policy . . . is not determinative. . . . [I]t is the effect of the agency's conduct which is most important in determining whether an agency has adopted a final policy." 880 F. Supp. 26, 34 (D.D.C. 1995). Kessler establishes that FDA actions that, in the aggregate, communicate agency expectations with real-world consequences are subject to judicial scrutiny, regardless of the form those actions take. Thus, evidence that FDA is manipulating the regulatory process – that is, it uses warning and untitled letters to establish new policies precisely because it seeks to avoid judicial review – increases the likelihood that courts will deem such letters to constitute final agency action.

IV. CONCLUSION

From our analysis of warning and untitled letters issued by DDMAC and OCBQ from January 2005 through June 2006, it appears that these regulators have made little effort to comply with the First Amendment in regulating promotional communications for prescription drugs.

Two broad themes emerge from our review. First, FDA regulation of prescription drug promotion has little or no detectable scientific basis. In their warning and untitled letters, neither DDMAC nor OCBQ presents any evidence, in the form of expert testimony, market research, or otherwise, that anyone was actually misled by the materials deemed violative. FDA does not even allege in these letters that anyone was actually misled. Rather, FDA appears to be merely fearful that someone might be misled. This non-evidence-based approach is incompatible with the First Amendment. See Virginia State Bd. v. Virginia Citizens Consumer Council, 425 U.S. 748, 769, 773 (1976).

Second, FDA is systematically ignoring its constitutional obligation to demonstrate 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 net effect of these policies is to thwart a fundamental purpose of the First Amendment: to prevent indiscriminate government interference with speech. WLF intends to continue the DDMAC Watch program by monitoring warning and untitled letters issued by DDMAC and OCBQ through June 2007. In 2006, we have already responded to 14 such letters, and patterns observed in 2005 show every sign of continuing in 2006. For example, as recently as June 30, 2006, DDMAC issued a particularly egregious warning letter to GlaxoSmithKline concerning Zovirax® (acyclovir) Ointment 5%. This letter provides prime examples of four FDA policies that WLF has identified as especially troubling: a ban on publicizing most clinical studies; requiring double disclosure of risk information; calling on manufacturers to engage in corrective messaging; and using letters to establish new policy.

Unfortunately, to date DDMAC officials have chosen not to respond to the deficiencies identified by WLF. In the coming year, WLF intends to look for ways to induce 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.