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September 13, 2002

BY HAND DELIVERY

Dockets Management Branch (HFA-305)
Food and Drug Administration
Room 1061
5630 Fishers Lane
Rockville, Maryland 20852

Re: Request for Comments on First Amendment Issues
Docket No. 02N-0209

Dear Sir or Madam:

We appreciate the opportunity to submit comments in response to the Food and Drug Administration's ("FDA" or "agency") Request for Comments on First Amendment Issues published in the Federal Register on May 16, 2002.¹ Having submitted an amicus curiae brief in Thompson v. Western States Medical Center, we welcome FDA's solicitation of comments on these important constitutional and regulatory issues.

¹ 67 Fed. Reg. 34,942 (May 16, 2002).

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We wish to take this opportunity to comment on two specific regulatory provisions that, in light of recent court cases involving FDA, appear to violate protections of speech granted by the First Amendment to the U.S. Constitution. First, FDA should abandon the requirement that an applicant submitting a new drug application (“NDA”) subject to FDA’s accelerated approval regulations² must submit to the agency for review copies of all promotional materials associated with the drug before the materials are disseminated. This particular provision constitutes an unconstitutionally-imposed prior restraint on speech. Alternatively, it is an impermissible government restriction imposed on protected commercial speech.

Governmental restrictions on commercial speech are unconstitutional unless they pass a four-part test. FDA’s mandate of prior review of promotional materials fails the

² 21 C.F.R. Part 314, Subpart H (“Subpart H” or “accelerated approval regulations”). FDA promulgated companion regulations that provide for the accelerated approval of biological products for serious or life-threatening diseases. 21 C.F.R. Part 601, Subpart E. The biologics regulations parallel the accelerated approval regulations for new drugs, and therefore also require that all promotional materials be submitted to FDA for review before they are disseminated or published. 21 C.F.R. § 601.45. The agency also recently promulgated regulations regarding the quantum and quality of evidence needed to demonstrate effectiveness of new drugs and biologics when human efficacy studies are not ethical or feasible. See 67 Fed. Reg. 37,988 (May 31, 2002) (final rule) (codified at Part 314, Subpart I (21 C.F.R. §§ 314.600 – 314.650), and Part 601, Subpart H (21 C.F.R. §§ 501.90 – 601.95)). All promotional materials associated with drugs or biologics subject to these regulations must also be submitted to FDA for review before they are disseminated or published. See 21 C.F.R. §§ 314.640, 601.94. While the comments provided herein specifically address Subpart H of FDA’s NDA regulations, they apply with equal force to Subpart E of the agency’s biologics licensing regulations, and to the new Subparts I and H.

final part of that test – that the restrictions be “[no] more extensive than necessary to serve [the government’s] interest.”³ The agency can ensure the safe use of regulated products through a multitude of alternative measures already at its disposal that do not restrict speech. These alternatives include, but are not limited to, restricting distribution to specially trained physicians, requiring specific medical procedures be performed in conjunction with use of the product, requiring specific postmarketing studies and postmarketing safety reports, requiring special packaging (e.g., child-resistant containers), requiring a post-approval Risk Management Program, issuing Warning Letters, initiating expedited withdrawal of product approval, and taking various enforcement actions such as seizure, injunction, or prosecution. With so many other ways to achieve its objectives, FDA’s pre-approval of promotional materials can not pass constitutional muster. Indeed, when it recently struck down another FDA restriction on commercial speech, the Supreme Court clearly spelled out the need to pursue other options that do not restrict communication: “If the First Amendment means anything, it means that regulating speech must be a last – not a first – resort.”⁴

The second provision we address concerns distribution of scientifically valid off-label information. FDA should abandon any policy, formal or informal, that restricts the dissemination of truthful scientific information that may discuss off-label uses of approved products. Under Supreme Court commercial speech jurisprudence, such scientific

³ Central Hudson Gas & Elec. Co. v. Pub. Serv. Comm’n of N.Y., 447 U.S. 557, 566 (1980).

⁴ Thompson v. W. States Med. Ctr., 535 U.S. _____ (2002), 122 S. Ct. at 1497, 1507 (2002).

information, which may be presented in the form of scientific journal articles, abstracts, posters, etc., is constitutionally protected provided it is truthful and not misleading. Rather than respect this broad constitutional protection, FDA has historically placed various restrictions on the dissemination of off-label information. Notably, FDA has impermissibly accorded greater rights to peer-reviewed scientific materials that discuss off-label uses. However, sponsors enjoy a constitutionally-protected right to disseminate truthful, non-misleading scientific information about regulated products.

I. Submission of Promotional Materials Pursuant to FDA's Accelerated Approval Regulations.

Subpart H of FDA's NDA regulations establishes accelerated approval procedures for drugs that are intended to treat "serious or life threatening illnesses and that provide meaningful therapeutic benefit to patients over existing treatments."⁵ As a condition of accelerated approval, applicants must abide by restrictions that are not imposed on other

⁵ 21 C.F.R. § 314.500. The accelerated approval regulations provide that FDA can approve new drugs for serious or life threatening illnesses under two sets of circumstances. First, "FDA may grant marketing approval for a new drug product on the basis of adequate and well-controlled clinical trials establishing that the drug product has an effect on a surrogate endpoint that is reasonably likely . . . to predict clinical benefit or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity." 21 C.F.R. § 314.510 ("the surrogate endpoint provision"). Additionally, the agency may grant accelerated approval status to new drugs for serious or life threatening illnesses that can be shown to be effective but that "can be safely used only if distribution or use is restricted." 21 C.F.R. § 314.520 ("the restricted distribution and use provision"). The two categories are not mutually exclusive. Under Subpart H, a new drug whose accelerated approval is predicated on surrogate endpoints can also be subject to the regulation's distribution and use restrictions.

NDA applicants. One of these restrictions is the requirement that the applicant submit all “promotional materials”⁶ associated with the drug to FDA for review before the materials are disseminated. Specifically:

[U]nless otherwise informed by the agency, applicants must submit to the agency for consideration during the preapproval review period copies of all promotional materials, including promotional labeling as well as advertisements, intended for dissemination or publication within 120 days following marketing approval. After 120 days following marketing approval, unless otherwise informed by the agency, the applicant must submit promotional materials at least 30 days prior to the intended time of initial dissemination of the labeling or initial publication of the advertisement.⁷

Other applicants seeking approval of drug products, by contrast, must submit copies of promotional materials at the time the materials are first disseminated or published.⁸

Subpart H’s promotional materials prior submission requirement violates the First Amendment.

⁶ FDA has ascribed a broad interpretation to the term “promotional materials:” “[T]he term *promotional materials* includes promotional labeling and advertisements. Examples of labeling include, but are not limited to, brochures, booklets, detailing pieces, bulletins, calendars, motion pictures, and slides. (21 C.F.R. § 202.1(1)(2)). Advertisements include, but are not limited to, materials published in journals, magazines, other periodicals, and newspapers, and advertisements broadcast through media such as radio, television, and telephone communication systems (§ 201.1(1)(1)).” FDA Draft Guidance: Accelerated Approval Products – Submission of Promotional Materials (March 1999) at 1 (“Promotional Materials Guidance”).

⁷ 21 C.F.R. § 314.550.

⁸ 21 C.F.R. § 314.81(b)(3)(i).

A. Prior Restraint

Any governmental restriction that seeks to prevent speech from occurring, rather than punishing it after it has occurred, is a prior restraint. Although prior restraints are not unconstitutional *per se*,⁹ “[a]ny system of prior restraint . . . ‘comes to [the] [c]ourt bearing a heavy presumption against its constitutional validity.’”¹⁰ The presumption is born of “a theory deeply etched in our law: a free society prefers to punish the few who abuse rights of speech *after* they break the law than to throttle them and all others beforehand.”¹¹ The courts view prior restraints with an even higher degree of suspicion than other constraints on speech because they are more likely to chill the exercise of First Amendment rights for all those subject to the restraints than would subsequent punishment.¹²

The regulatory regime established by the agency’s Subpart H regulations is an unconstitutional prior restraint on speech. Applicants are required to submit all promotional materials to the agency before they are disseminated. In the case of promotional materials related to the drug product’s launch, i.e., those intended for dissemination within 120 days after the product’s approval, applicants must submit the materials even before FDA has decided whether to approve the product.

⁹ See Bantam Books, Inc. v. Sullivan, 372 U.S. 58, 70 n.10 (1963) (citing Times Film Corp. v. Chicago, 365 U.S. 43 (1961)).

¹⁰ Southeastern Promotions, Ltd. v. Conrad, 420 U.S. 546, 558 (quoting Bantam Books, 372 U.S. at 70) (citations omitted).

¹¹ Id. at 559.

¹² See id.

In an apparent attempt to forestall constitutional challenges, FDA has stated that it “does not intend specifically to approve promotional materials.”¹³ It is abundantly clear from the manner in which the agency has implemented the requirement, however, that pre-approval of promotional materials is contemplated. The agency, for example, states in its draft Promotional Materials Guidance of March 1999 that for promotional materials intended to be disseminated or published within 120 days after a product’s approval, “[t]he Agency expects that materials will *not* be disseminated or published until the Agency’s objections are resolved” (emphasis in the original).¹⁴ Similarly, for promotional materials intended for dissemination after the initial 120 days, FDA states that “[i]f the Agency notifies the sponsor of significant objections to the proposed materials, the Agency expects that these materials will not be disseminated or published until the Agency’s concerns have been resolved.”¹⁵

Calling this review of materials a “consideration” rather than “approval” does not obviate the constitutional infirmities. A company must submit materials to the government before they can be disseminated. The semantic label of “consideration” does not save this restriction from being unconstitutional.

An applicant with a pending NDA subject to FDA’s accelerated approval regulations has no choice but to revise its promotional materials to address FDA’s objections for fear that the agency might not otherwise approve its drug product. An applicant who has

¹³ 57 Fed. Reg. 13,234, 13,237 (April 15, 1992) (proposed rule); see also 57 Fed. Reg. 58,942, 58,949 (Dec. 11, 1992) (final rule).

¹⁴ Promotional Materials Guidance at 2.

¹⁵ Id. at 4.

secured an approval is similarly without options because failing to comply might lead FDA to withdraw the drug from the market on an expedited basis.¹⁶ Even if labeled a “consideration,” the requirement of prior submission and review imposes significant restraints on the ability of applicants to communicate freely. Moreover, needing to wait at least thirty days for FDA’s “consideration” is inconsistent with the First Amendment. The First Amendment does not permit the government to compel companies to wait thirty days to exercise their constitutional right to free speech. The inevitable chilling effect that FDA’s *de facto* promotional materials pre-approval regime has on applicants’ speech is precisely the danger that the courts have sought to eliminate with their prohibitions on prior restraint.

The agency cannot find refuge in the argument that the doctrine of prior restraint does not apply to commercial speech. In Nutritional Health Alliance v. Shalala, FDA argued before the Court of Appeals for the Second Circuit that a challenged provision of the Nutritional Labeling and Education Act that mandated prior agency approval of health claims appearing on dietary supplement labels was not an unconstitutional restriction on speech because the prior restraint doctrine does not apply to commercial speech.¹⁷ The court, however, rejected the agency’s argument, observing that the Second Circuit had already established that “the prior restraint doctrine does play a role in evaluating the

¹⁶ 21 C.F.R. § 314.530(a)(5).

¹⁷ Nutritional Health Alliance v. Shalala, 144 F.3d 220, 227 (2nd Cir. 1998), *cert. denied*, 525 U.S. 1040, (1998).

regulation of commercial speech.”¹⁸ In an earlier case, the Second Circuit had concluded that:

Although the Supreme Court has indicated that commercial speech may qualify as one of the exceptions to the ban on prior restraints, (*see Central Hudson*, 447 U.S. at 571 n.13,) we see no reason why the requirement of procedural safeguards [in prior restraint cases] should be relaxed whether speech is commercial or not. We consider prior restraints to be particularly abhorrent to the First Amendment in part because they vest in governmental agencies the power to determine important constitutional questions properly vested in the judiciary.¹⁹

For these reasons, FDA must revise its Subpart H regulations so that applicants submitting NDAs for accelerated approval need not submit promotional materials prior to dissemination or publication. The revised regulations should direct applicants seeking accelerated approval to submit the materials at the time they are either first disseminated or published, as is the case with drugs approved pursuant to the agency’s conventional approval procedures.²⁰

¹⁸ Id.

¹⁹ New York Magazine v. The Metro. Transp. Auth., 136 F.3d 123, 131 (2nd Cir. 1998), *cert. denied*, 525 U.S. 824, (1998). The court also observed that “[s]ome circuits have explicitly indicated that the requirement of procedural safeguards in the context of a prior restraint indeed applies to commercial speech.” Id. at 132 (citing Desert Outdoor Adver. v. City of Moreno Valley, 103 F.3d 814, 819 (9th Cir. 1996); In re Search of Kitty’s East, 905 F.2d 1367, 1371-72 n.4 (10th Cir. 1990)). For its part, the Supreme Court has only alluded to the possibility that prior restraint might not apply to commercial speech, but has never addressed the issue directly. See Virginia State Bd. of Pharmacy v. Virginia Citizens Consumer Council, 425 U.S. 748, 772 (1976), Central Hudson, 447 U.S. at 571 n.13 (1980).

²⁰ 21 C.F.R. § 314.530(a)(5).

B. Commercial Speech

Even assuming FDA's accelerated drug approval regulations are not an unconstitutional prior restraint on speech, the provision mandating prior review of promotional materials must give way because it is a constitutionally-impermissible regulation of protected commercial speech, and because FDA has at its disposal many other means to meet safety objectives without restricting speech. The promotional materials that FDA seeks to regulate under Subpart H – labeling and advertising – fall within the ambit of commercial speech.²¹ The Supreme Court's commercial speech jurisprudence establishes that the government may not regulate commercial speech unless the restrictive provisions meet a four-part test set forth in Central Hudson Gas & Electric Co. v. Public Service Commission.²² Under the Central Hudson test, commercial speech may be prohibited or restricted if it is inherently false or misleading, or if it espouses an unlawful activity. The government may prohibit or restrict commercial speech that is neither false or misleading nor concerned with unlawful activity only if "the asserted governmental interest is substantial," the regulation in question "directly advances the governmental interest asserted," and is "[no] more extensive than is necessary to serve that interest."²³

The Supreme Court applied and reaffirmed its Central Hudson analysis in a recent case involving an FDA restriction on commercial speech. In Thompson v. Western States Medical Center, the court held that a provision in Section 503A of the Federal Food, Drug, and Cosmetic Act ("FDCA") prohibiting a compounding pharmacy, pharmacist, or

²¹ See Bolger v. Youngs Drug Prod. Corp., 463 U.S. 60 (1983).

²² Central Hudson, 447 U.S. 557.

²³ Id. at 566.

physician from advertising that it could compound a particular drug or category of drugs is a constitutionally-impermissible restriction of protected commercial speech.²⁴ The court found that the government's restriction failed the fourth prong of the Central Hudson test, i.e., the "Government . . . failed to demonstrate that the speech restrictions are 'not more extensive than is necessary to serve [its] interests'" in regulating the speech in the first instance.²⁵ The court went on to say that FDA had at its disposal several "non-speech-related means" to achieve its goal.²⁶ Likewise, FDA's mandate for pre-approval of promotional materials for Subpart H drugs fails the fourth prong because the agency has its choice of "non-speech-related means" to ensure safe use of the product.²⁷

As with the restriction challenged in Western States, the agency's regulation of commercial speech through its accelerated drug approval process is unconstitutional because it is more extensive than necessary to serve the government's interests. In addition, FDA's mandated prior review of promotional materials fails the third part of the Central Hudson test, i.e., it does not directly advance the interests that the agency has asserted.

²⁴ Western States, 122 S. Ct. at 1509.

²⁵ Id. at 1506 (quoting Central Hudson, 447 U.S. at 566).

²⁶ Id.

²⁷ These alternatives include, but are not limited to, restricting distribution to specially trained physicians, requiring specific medical procedures be performed in conjunction with use of the product, requiring specific postmarketing studies and postmarketing safety reports, requiring special packaging (e.g., child-resistant containers), requiring a post-approval Risk Management Program, issuing Warning Letters, initializing expedited withdrawal of product approval, and taking various

1. Direct Advancement of Governmental Interests

The government may not satisfy the third prong of the Central Hudson test with mere speculation. Instead it must offer evidence that its asserted harms are real and that its restrictions on speech will materially ameliorate the asserted harms.²⁸ Additionally, the government's regulatory scheme will fail the third prong of the Central Hudson test if it is irrational.²⁹ FDA's restrictions on speech as set forth in Subpart H of its NDA regulations fail to directly advance the government's asserted interests on both counts.

The interests that the agency has asserted in mandating prior review of promotional materials for drugs subject to accelerated approval are nebulous at best, and the agency's assertion that restricting speech will protect the public is based on mere speculation. The agency appears indirectly to assert the safety, health, and welfare of patients who might use drugs approved under Subpart H as its substantial interest. The harm that it seeks to guard against, however, is entirely unsubstantiated. FDA has justified the restriction on the grounds that:

Because drugs approved under the restricted use provision may be highly toxic or otherwise potentially harmful, [it] is concerned that certain promotional claims could cause inappropriate and, therefore, unsafe use.

enforcement actions such as seizure, injunction, or prosecution.

²⁸ Edenfield v. Fane, 507 U.S. 761, 770-771 (1993) ("It is well established that 'the party seeking to uphold a restriction on commercial speech carries the burden of justifying it.' This burden is not satisfied by mere speculation or conjecture; rather, a governmental body seeking to sustain a restriction on commercial speech must demonstrate that the harms it recites are real and that its restriction will in fact alleviate them to a material degree.") (citations omitted).

²⁹ See Rubin v. Coors Brewing Co., 514 U.S. 476, 488 (1995).

Similarly, the risk/benefit balance for drugs approved based on evidence of the drug's effect on a surrogate endpoint could readily be adversely affected by promotion that does not appropriately reflect the proper use of the product.³⁰

These justifications may be sufficient for purposes of establishing a regulatory rationale for the types of drugs eligible for accelerated approval and conditions of approval that do not limit speech. They fail to support the agency's restrictions on speech, however, as is required by the third prong of the Central Hudson test. The agency has not proffered any evidence, for example, demonstrating that drugs approved under the restricted distribution and use provision of its accelerated approval regime are, in fact, more highly toxic or more potentially harmful than products approved through its conventional approval procedures. Similarly, FDA has not proffered evidence demonstrating that, nor explained how or why, promotional materials issued by drug manufacturers without prior review by the agency will adversely affect the "risk/benefit" balance of drugs subject to the accelerated approval program. The agency has failed to meet its evidentiary burden of showing that its asserted harms are real, and that its promotional materials pre-approval requirement will alleviate its asserted harms. Accordingly, Subpart H's prior approval requirement fails the Central Hudson test because it does not directly advance the government's interests.

Subpart H's restriction on commercial speech also fails the third prong of the Hudson Central test because it is irrational when compared to FDA's regulation of promotional materials for drugs that are approved via other mechanisms that the agency has created to expedite the approval process. In addition to Subpart H, the agency has created

³⁰ 57 Fed. Reg. at 13,237; see also 57 Fed. Reg. at 58,945.

alternative regulatory avenues to hasten market approval for certain drug products, such as Subpart E of FDA's Investigational New Drug regulations³¹ and mechanisms to designate certain NDAs and biological license applications for priority review.³² Neither of these provisions, however, mandate that applicants must submit promotional materials for review before the materials are disseminated or published. The restrictions on speech contained in Subpart H cannot "directly advance[] the governmental interest asserted" in the face of discordant provisions because the agency's singling out of Subpart H drugs is irrational.³³

2. No More Extensive Than Necessary

Even assuming that the restrictions on speech in Subpart H do directly advance the asserted governmental interests, the provision still fails constitutional scrutiny because it cannot meet the final requirement of the Central Hudson test, i.e., it is more extensive than necessary to serve the agency's interests.

As the Supreme Court recently reiterated in Western States, "if the Government could achieve its interests in a manner that does not restrict speech, or that restricts less

³¹ 21 C.F.R. Part 321, Subpart E (Drugs Intended to Treat Life-Threatening and Severely-Debilitating Illnesses).

³² See FDA, Center for Drug Evaluation and Research, MAP 6020.3, Priority Review Policy (April 22, 1996); FDA, Center for Biologics Evaluation and Research, SOPP 8405, Complete Review and Issuance of Action Letters (May 1, 1998).

³³ Coors Brewing Co., 514 U.S. at 486, 488-89 (quoting Central Hudson, 477 U.S. at 566) (holding that federal regulations prohibiting the disclosure of alcohol content on beer labels fail to directly advance the government's interests because the government's regulatory regime was irrational in that it also allowed for alcohol content disclosure in beer advertising in some states, and allowed for, and in some cases required, the disclosure of alcohol content on labels of wines and spirits).

speech, [it] must do so.”³⁴ A number of other provisions contained in FDA’s Subpart H regulations, and elsewhere in the FDCA and its implementing regulations, allow the agency to directly achieve its stated interests in ways that do not impermissibly impinge upon protected speech. For example, applicants whose drugs are subject to Subpart H typically must, as a condition of approval, agree to conduct post-marketing studies to verify the drugs’ clinical benefit and safety.³⁵ FDA also reserves the right to approve drugs under Subpart H on the condition that their distribution be restricted to “facilities or physicians with special training or experience” or their use be “conditioned on the performance of specified medical procedures.”³⁶ In addition, the agency reserves the right to withdraw drugs subject to Subpart H from the market on an expedited basis.³⁷ And, FDA can also bring to bear its other enforcement sanctions, such as seizures, injunctions, and prosecutions in case of violative promotional practices. In short, Subpart H’s promotional materials pre-approval requirement is more restrictive than needed to address the purported risks and therefore is an unconstitutionally-impermissible restriction on commercial speech.

For these reasons, FDA should revise its accelerated drug approval regulations to abolish the promotional materials pre-approval requirement. The agency can avoid running afoul of First Amendment issues by treating promotional materials for drugs subject to Subpart H the same way that it treats other drugs, i.e., requiring that Subpart H applicants

³⁴ Western States, 122 S. Ct. at 1506 (citing Coors Brewing Co., 514 U.S. at 490-91).

³⁵ 21 C.F.R. § 314.510.

³⁶ 21 C.F.R. § 314.520.

³⁷ 21 C.F.R. § 314.530.

submit all promotional materials at the time they are first disseminated or published.³⁸ The agency could require that these submissions be identified as Subpart H promotional materials, then subject the submissions to priority reviews, and communicate any concerns that it might have, or requests for corrective actions, to applicants on an expedited basis.³⁹ Accelerated review post-dissemination is constitutionally permissible; prior submission is not.

II. FDA Should Clarify its Policy on the Dissemination of Constitutionally-Protected Scientific Information Discussing Off-label Uses.

Current FDA policy on the dissemination of scientific materials that discuss off-label uses of approved products is not clear, but the law is: The First Amendment protects truthful, non-misleading speech from “unwarranted governmental regulation.”⁴⁰ Accordingly, FDA should revise its policy so that it does not infringe on the constitutional right to disseminate truthful, non-misleading scientific information about regulated products, including information on off-label uses. FDA should also recognize that this constitutional protection is not limited to scientific materials that have undergone “peer review.”

³⁸ 21 C.F.R. § 314.81(b)(3)(i).

³⁹ FDA states in its draft Promotional Materials Guidance that when reviewing promotional materials submitted for review pursuant to Subpart H, “[its] goal is to provide comments in a timely manner, usually within 15 working days of the day the materials are received.” Promotional Materials Guidance at 2. Thus, the agency has asserted that it is capable of reviewing Subpart H promotional materials very expeditiously.

⁴⁰ Central Hudson, 447 U.S. at 561 (1980) (citations omitted).

A. Background: Constitutional Protection of Commercial Speech and Washington Legal Foundation Litigation

When disseminated by a manufacturer, scientific information, such as journal articles, abstracts, posters, etc., that discuss off-label uses of its products at a minimum fits the category of constitutionally-protected commercial speech.⁴¹ As noted above, courts will strike down laws that restrict truthful, non-misleading commercial speech unless the government can show that the restriction on speech meets the requirements of the Central Hudson test.

FDA does not regulate the off-label use of approved products, but it prohibits manufacturers from promoting such uses. Historically, that prohibition included a policy that essentially banned manufacturers' unsolicited distribution of peer-reviewed scientific journal articles that discuss off-label uses.⁴² Several years ago, the Washington Legal Foundation ("WLF") sued FDA and successfully argued that that policy was unconstitutional. The court found that while FDA was able to demonstrate a substantial interest in regulating the speech (i.e., protecting public health), it failed the Central Hudson test because the restriction burdened more speech than necessary. The court issued an injunction that barred FDA from restricting the distribution of off-label, peer-reviewed reprints that discussed approved products and were not false or misleading.⁴³

⁴¹ It can be argued that these materials are not, in fact, commercial speech and are therefore entitled to a higher level of protection.

⁴² FDA, Guidance to Industry on Dissemination of Reprints of Certain Published, Original Data, 61 Fed. Reg. 52,800, 52,801 (Oct. 8, 1996).

⁴³ Washington Legal Found. v. Friedman, 13 F. Supp. 2d 51 (D.D.C. 1998).

Shortly thereafter, the Food and Drug Administration Modernization Act of 1997 (“FDAMA”) went into effect. FDAMA allowed manufacturers to distribute off-label reprints, subject to numerous conditions. FDA asked the court to clarify how the injunction applied to FDAMA. The court held that the FDAMA provisions were likewise unconstitutional.⁴⁴

FDA appealed that decision. During oral argument, FDA clarified its position by stating that if a manufacturer violated the FDCA by illegally promoting a product, the agency would use distribution of off-label reprints as evidence, but that the distribution of off-label reprints could not be the sole basis for the violation.⁴⁵ The court said that in response to FDA’s concession, WLF no longer objected on constitutional grounds. Because of this apparent agreement between the parties, the court vacated the injunction. Nonetheless, the underlying constitutional protections survive this outcome.

After the injunction was vacated, FDA issued a Federal Register Notice stating its policy on the distribution of off-label information. FDA said it may proceed with enforcement – on a case-by-case basis – of off-label promotion based at least in part on written materials disseminated by manufacturers. The Notice states that in any such enforcement action, a manufacturer could raise a First Amendment defense.⁴⁶

⁴⁴ Washington Legal Found. v. Henney, 56 F. Supp. 2d 81 (D.D.C. 1999).

⁴⁵ Washington Legal Found. v. Henney, 202 F.3d 331 (D.C. Cir. 2000).

⁴⁶ 65 Fed. Reg. 14,286 (Mar. 16, 2000). Subsequently, the WLF filed a motion to confirm and enforce the earlier injunction. The court denied that motion, noting that the injunction had been wholly vacated. See Washington Legal Found. v. Henney, 128 F. Supp. 2d 11 (D.D.C. 2000).

Thus, eight years of litigation have culminated in an FDA policy pronouncement so unsound that it invites a constitutional challenge upon the agency's first attempt at enforcement. As Judge Lamberth noted in the most recent WLF opinion:

After six years' worth of briefs, motions, opinions, Congressional acts, and more opinions, the issue remains 100% unresolved, and the country's drug manufacturers are still without clear guidance as to their permissible conduct. To say that FDA's March 16, 2000 Notice finally clarifies the situation is a farce; the Notice specifically invites a constitutional challenge to each and every one of its enforcement actions.⁴⁷

FDA's policy should be revised and should not attempt to restrict the dissemination of truthful, non-misleading scientific information, including materials that discuss off-label uses of regulated products. The failure to do so, as Judge Lamberth noted, invites a constitutional challenge.

B. Dissemination of Non-Peer-Reviewed Scientific Information

FDA should expressly provide for the dissemination of truthful, non-misleading scientific information that has not been previously peer-reviewed or otherwise published. Historically, the agency has distinguished between scientific information that is peer-reviewed and that which is not. The policy statement and FDAMA sections which were struck down in the WLF litigation, for example, provided only for the dissemination of unabridged reprints or copies of peer-reviewed articles, or of reference publications generally available in bookstores or other venues where medical textbooks are sold.⁴⁸

⁴⁷ See Washington Legal Found. v. Henney, 128 F. Supp. 2d at 15.

⁴⁸ See former FDCA § 552, 21 U.S.C. § 360aaa.

This distinction, however, is without merit. In drawing the distinction, FDA appears to implicitly suggest that the imprimatur of peer review automatically imbues scientific information with an inherent or elevated level of truthfulness or validity, and that materials that are not peer-reviewed are presumptively more likely to be false or misleading. However, when FDA argued in one of the WLF cases that it is the agency's job to be the arbiter of truth, the court resoundingly rejected the assertion, stating that the agency "exaggerates its overall place in the universe."⁴⁹

Peer review is not a constitutional talisman. The distinction between peer-reviewed and non-peer-reviewed scientific information falls in the face of constitutional scrutiny on First Amendment grounds. In the first instance, any blanket prohibition on the dissemination of non-peer-reviewed materials would violate the doctrine of prior restraints. Even if, for the sake of argument, the doctrine of prior restraints did not apply, FDA would only be able to restrict the dissemination of non-peer-reviewed information if it met the requirements of the Central Hudson test, i.e., if it could show either that the specific materials were false or misleading, or that it had a substantial interest in regulating the dissemination, that its restrictions directly advanced that interest, and that the restrictions

⁴⁹ Washington Legal Found. v. Friedman, 13 F. Supp. 2d at 67. The WLF litigation challenged a policy which addressed peer-reviewed articles. Since the court was not asked to address other materials, FDA cannot argue that restrictions on other scientific articles are valid. Although the constitutionality of prohibiting off-label abstracts and other scientific materials was not directly presented to the court, its finding that constitutional protections are afforded to peer-reviewed journal articles extends equally to other scientific documents.

were no more extensive than necessary.⁵⁰ FDA would be hard pressed to devise a regulatory regime restricting the dissemination of non-peer-reviewed scientific information that would satisfy the fourth prong of the Central Hudson test. The agency can take other, less draconian measures. As the Supreme Court said in Western States, “[i]f the First Amendment means anything, it means that regulating speech must be a last – not first – resort.”⁵¹ Accordingly, FDA should revise its policies to expressly provide for the dissemination by manufacturers of all truthful and non-misleading scientific information, including that which is not-peer-reviewed.

To the extent that FDA’s policy is based, at least in part, on the impermissible notion that the material disseminated will lead recipients to make poor choices, it fails constitutional muster. Manufacturers of regulated products often have the best access to the latest scientific information related to their products. Such scientific information may discuss new uses and may be presented in a wide variety of formats, including but not limited to scientific journal articles, abstracts, and posters, some of which may be peer-reviewed, but some of which may not. Dissemination of such scientific information by manufacturers should be unfettered. Provided that the scientific information is truthful and not misleading, barring its dissemination on the notion that recipients of the speech may make bad decisions is impermissible.

⁵⁰ Central Hudson, 447 U.S. at 566. Thus, under the approach we advocate, FDA can take enforcement action against a company that does distribute false or misleading materials.

⁵¹ Western States, 122 S. Ct. at 1507.

Supreme Court jurisprudence is replete with examples of such paternalistic restrictions on speech being rejected. In Western States, for example, the court disagreed with the government's argument that FDA restrictions on the advertising of compounded drugs were justified because consumers may convince their doctor to prescribe unneeded drugs.⁵² The court posited an alternative: "That alternative is to assume that this information is not in itself harmful, that people will perceive their own best interests if only they are well enough informed, and that the best means to that end is to open the channels of communication rather than to close them."⁵³ Indeed, the Court has recognized that government restrictions of truthful, non-misleading commercial speech "usually rest solely on the offensive assumption that the public will respond 'irrationally' to the truth."⁵⁴

In WLF, Judge Lamberth used a similar analysis:

To endeavor to support a restriction upon speech by alleging that the recipient needs to be shielded from that speech for his or her own protection, which is the gravamen of FDA's claim [with regard to dissemination of off-label use

⁵² Id.

⁵³ Id. at 1508 (quoting Virginia Board of Pharmacy, 425 U.S. at 770) (emphasis added).

⁵⁴ 44 Liquormart v. R.I., 517 U.S. 484, 503 (1996) (citing Linmark Associates, Inc. v. Willingboro, 431 U.S. 85, 96 (1977); see also Pearson v. Shalala, 164 F.3d 650, 655 (D.C. Cir. 1999) ("[The government's] . . . argument runs along the following lines: that health claims lacking 'significant scientific agreement' are inherently misleading because they have such an awesome impact on consumers as to make it virtually impossible for them to exercise any judgment *at the point of sale*. It would be as if the consumers were asked to buy something while hypnotized, and therefore they are bound to be misled. We think this contention is almost frivolous.").

information], is practically an engraved invitation to have the restriction struck.⁵⁵

FDA's restrictions on the dissemination of non-peer-reviewed information by manufacturers to the medical community is particularly suspect. That is, the manufacturers' intended audience – physicians and others in the scientific and medical community – are highly educated, learned intermediaries whose education, training, and experience leaves them well-suited to judge for themselves the value and validity of the disseminated scientific materials.⁵⁶

⁵⁵ Washington Legal Found. v. Friedman, 13 F. Supp. 2d at 70.

⁵⁶ See id. (“In this instance, the government’s notion that the scientific research product which the manufacturers seek to distribute needs to be withheld for the ‘good of the recipient’ is even more unsupportable than usual. First, it must be noted that the manufacturers are not seeking to distribute this information to the general consumer public, who likely lack the knowledge or sophistication necessary to make informed choices on the efficacy of prescription drugs. (citations omitted) Rather, they seek to disseminate this information exclusively to physicians. A physician’s livelihood depends upon the ability to make accurate, life-and-death decisions based upon the scientific evidence before them. They are certainly capable of critically evaluating journal articles or textbook reprints that are mailed to them, or the findings presented at [continuing medical education] seminars. (footnote omitted) Furthermore, the FDA does not question a physician’s evaluative skills when an article about an off-label use appears among a group of articles in the *New England Journal of Medicine*, or when one physician refers a peer physician to a published article he recently perused, or even when a physician requests a reprint from a manufacturer. Why the ability of a doctor to critically evaluate scientific findings depends upon how the article got into the physician’s hands . . . is unclear to this court.”).

Accordingly, FDA should now clearly state that the dissemination of all truthful, non-misleading scientific materials discussing off-label uses, including those that have not been peer-reviewed, is permissible.

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Thank you, once again, for the opportunity to submit these comments. We look forward to engaging the agency in a dialogue regarding these very important issues.

Dated: September 13, 2002

Sincerely,

Paul J. Lenari FOR

Jeffrey N. Gibbs