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April 21, 2008

Via Email and U.S. Mail
Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

Re: Draft Guidance for Industry on Good Reprint Practices for the Distribution of Medical Journal Articles and Medical or Scientific Reference Publications on Unapproved New Uses of Approved Drugs and Approved or Cleared Medical Devices; 73 Fed. Reg. 9342 (Feb. 20, 2008)

Dear Sir/Madam:

The Washington Legal Foundation (WLF) submits these comments in response to the Food and Drug Administration's draft Guidance for Industry on reprint practices regarding articles/medical text that contain off-label information regarding approved drugs and medical devices (the "Draft Guidance"). WLF has grave concerns regarding a number of the provisions of the Draft Guidance. The document appears to violate the terms of a permanent injunction issued against FDA in 1999. Quite apart from the issue of that injunction, the Draft Guidance raises serious First Amendment concerns regarding the rights of manufacturers to speak truthfully regarding important health care issues. In characterizing this Draft Guidance as an appropriate follow-on to a now-expired provision of the Food and Drug Modernization Act, FDA appears to misunderstand the nature of that "safe harbor" provision.

If FDA intends to go forward with these new restrictions on manufacturer speech, it should substantially revise them to ensure that they violate neither the terms of the court injunction nor the First Amendment. In particular, FDA should: (1) eliminate any reference to "adequate and well-controlled clinical investigation," a reference that might well be interpreted as imposing severe limitations on the types of articles that may be disseminated; (2) scale back on the requirements that the article be accompanied by a comprehensive bibliography and articles/texts expressing contrary or different conclusions; and (3) scale back on the "disclaimer" requirements, particularly the requirement regarding "significant risks or safety concerns" of the off-label use.

I. *Interests of WLF*

The Washington Legal Foundation is a public interest law and policy center with members and supporters in all 50 States. WLF regularly appears before federal and State courts and administrative agencies to promote economic liberty, free enterprise, and a limited and accountable government. In particular, WLF has devoted substantial resources over the years to promoting the free speech rights of the business community, appearing before numerous federal courts in cases raising First Amendment issues. *See, e.g., Nike v. Kasky*, 539 U.S. 654 (2003). WLF has successfully challenged the constitutionality of FDA restrictions on speech by pharmaceutical manufacturers. *Washington Legal Found. v. Friedman,* 13 F. Supp. 2d 51 (D.D.C. 1998), *appeal dism'd,* 202 F.3d 331 (D.C. Cir. 2000). As a result of that litigation, FDA is subject to a permanent injunction limiting FDA authority to suppress manufacturer dissemination of certain journal articles/medical texts discussing off-label uses of their FDA-approved products. A lawsuit filed by WLF against the federal Centers for Medicare and Medicaid Services, raising a First Amendment challenge to CMS restrictions on truthful speech by health care providers, is pending in federal court in the District of Columbia. *Washington Legal Found. v. Leavitt*, No. 06-1490 (D.D.C. No. 06-1490).

WLF also regularly participates in FDA administrative proceedings in support of expanded First Amendment rights. *See, e.g.,* FDA Citizen Petition No. 2006P-0319/CPI (August 11, 2006) (documenting repeated First Amendment violations by FDA's Division of Drug Marketing, Advertising, and Communications (DDMAC) and calling on DDMAC to conform to constitutional constraints on its activities); FDA Docket No. 02N-0209 (October 28, 2002) (response to FDA's request for public comments on First Amendment issues).

II. *FDA's Statutory Authority*

Congress adopted the Federal Food, Drug, and Cosmetic Act (the "FDCA"), 21 U.S.C. §§ 301 *et seq.*, in 1938 to regulate the sale of drugs and medical devices to the public. In 1976, Congress adopted the Medical Device Amendments of 1976 (the "MDA"), 21 U.S.C. § 360c *et seq.*, to give it greater regulatory authority over medical devices.

Section 505(a) of the FDCA, 21 U.S.C. § 355(a), provides that no "new drugs" may be introduced into interstate commerce unless they are approved by FDA. The MDA imposes similar restrictions on new medical devices. Once FDA has approved a drug or device for introduction into interstate commerce, it has only limited statutory authority to control dissemination of information regarding the product. For example, FDA is authorized by statute to restrict what manufacturers have to say about their drugs and medical devices to the extent that such materials constitute "labeling" of those products within the meaning of § 201(m) of the FDCA, 21 U.S.C. § 321(m). FDA's statutory authority also extends to "adver-

tisements" of prescription drugs (21 U.S.C. § 352(n)) and a small subset of medical devices referred to as "restricted" devices, *i.e.*, hearing aids (21 U.S.C. § 352(q)). The FDCA grants FDA no authority to control what those other than manufacturers and distributors say about the proper uses of FDA-approved drugs and medical devices.

III. *The Importance of Off-Label Use*

When it approves a drug or medical device for introduction into interstate commerce, FDA reviews the product labeling. The labeling sets forth the indications approved by FDA. FDA requires all such drugs or devices to bear labeling which list their approved uses, and prohibits such labeling from listing any use that has not been approved by FDA.

The medical community's knowledge regarding the safety and efficacy of FDA-approved drugs and devices inevitably outpaces FDA-approved labeling. Physicians who regularly work with such drugs and devices learn of safe and efficacious uses for the drugs/devices that are not included within the labeling (generally referred to as "off-label" uses). In some fields such as oncology, the great majority of medically-accepted treatments involves off-label uses of FDA-approved drugs and medical devices. Accordingly, were doctors limited to using therapeutic products only as labeled, doctors would be providing sub-optimal care to their patients. In many cases, doctors simply could not treat their patients properly without resort to off-label uses. Indeed, the U.S. Supreme Court has officially recognized off-label treatments as an important part of medical care in this country. *See Buckman Co. v. Plaintiffs' Legal Committee*, 531 U.S. 341, 350, 351 n.5 (2001) ("'[O]ff-label' usage of medical devices (use of a device for some other purpose than that for which it has been approved by the FDA) is an accepted and necessary corollary of the FDA's mission to regulate in this area without directly interfering with the practice of medicine. . . . Off-label use is widespread in the medical community and often is essential to giving patients optimal medical care, both of which medical ethics, FDA, and most courts recognize."). The Draft Guidance purports to recognize the import role in health care played both by off-label uses and by dissemination of truthful information about such uses:

> These off-label uses or treatment regimens may be important and may even constitute a medically recognized standard of care. Accordingly, the public health may be advanced by healthcare professionals' receipt of medical journal articles and medical or scientific reference publications on unapproved or new uses of approved or cleared medical products that are truthful and not misleading.

Draft Guidance at 4. Congress similar recognizes the importance of off-label uses; for example, it imposed a outright prohibition on previous FDA efforts to limit the authority of

physicians to put FDA-approved products to off-label uses. *See* 21 U.S.C. § 396 (providing that "nothing in [the FDCA] shall be construed to limit or interfere with the authority of a health care practitioner to prescribe or administer any legally marketed device to a patient for any condition or disease within a legitimate health care practitioner-patient relationship.").

A corollary to the need for doctors to employ off-label uses of therapeutic products is that they must be able to learn which such uses are medically recognized. The need for knowledge does not stop with graduation from medical school; new drugs and devices are constantly entering the market, and new uses for these products are constantly being discovered. The discovery that an approved product is beneficial in treating an off-label condition is of no help to a patient unless his/her physician knows about that use. Accordingly, it is highly important (both to the nation and (presumably) to FDA) that information about new uses be widely disseminated within the medical community. Disseminating this information takes both effort and resources. Manufacturers – who have both the necessary resources and the incentive to exert the necessary effort – have traditionally played a large and beneficial role in supporting the dissemination of information about new uses of marketed products. For example, they have arranged for the distribution of textbooks and reprints from medical journals. They have helped support continuing medical education (CME) programs. They have helped sponsor scientific seminars and symposia at which peers discuss their cutting-edge research.

IV. *FDA's Rationale for Issuing the Draft Guidance*

As a result of the permanent injunction issued against FDA in *Washington Legal Found. v. Friedman*, medical product manufacturers have had considerable freedom throughout the past decade to disseminate journal articles and medical texts that contain truthful information about off-label uses of their products. WLF nonetheless recognizes that FDA has a strong interest in ensuring that such dissemination does not cause confusion among doctors and patients. Accordingly, it applauds FDA efforts to provide guidance regarding its views on the limits of manufacturers' constitutional rights to engage in such dissemination. By establishing a clear line marking FDA's views regarding the limits of the First Amendment rights at issue, FDA provides a real service to manufacturers. They obviously have a strong interest in knowing what steps they can take without incurring FDA's regulatory wrath.

WLF was nonetheless dismayed by FDA's stated rationale for issuing the Draft Guidance. FDA stated that it was acting to fill a void supposedly left by the September 2006 expiration of § 401 of the Food and Drug Modernization Act (FDAMA), 21 U.S.C. § 331(z) and § 360aaa, *et seq.* (2006). Section 401 was a "safe harbor" provision that described certain types of dissemination of journal articles and medical text in which manufacturers could engage without having to worry that its actions could be deemed a violation of the FDCA. But

the § 401 "safe harbor" was so restricted in its application that few manufacturers ever bothered to come within its terms. Instead, those manufacturers wishing to engage in dissemination of journal articles and medical texts have been doing so pursuant to the First Amendment rights recognized in the *WLF* litigation. It is inexplicable for FDA to be issuing a Draft Guidance in this area without any explanation regarding what it views as the extent of manufacturers' First Amendment rights.

V. *History of the WLF Litigation*

In order to explain why the Draft Guidance's reference to § 401 makes absolutely no sense, it is necessary to provide an extended history of WLF's litigation against FDA in this area. The absence of any reference to that history in the Draft Guidance suggests that current FDA officials may be unaware of that history.

Despite its endorsement of off-label use as an important part of medical care, FDA in the early 1990s became increasingly hostile to manufacturer dissemination of off-label information in the form of journal articles and medical text (hereinafter referred to collectively as "enduring materials."). Beginning no later than 1992, FDA adopted a policy designed to restrict manufacturer distribution of enduring materials. The policy declared that any such unsolicited distribution constituted unauthorized "labeling" of the products discussed and rendered the manufacturer's entire stock of the drug or device "misbranded" and therefore subject to seizure. FDA took that position regardless of the independence of the publisher of the enduring materials, regardless whether the materials were accompanied by a sales solicitation, and regardless whether the manufacturer made any effort to highlight discussion of its products within the materials distributed.

Initially, the FDA policy was not set forth in any formal fashion. Rather, FDA set forth its policy through a series of letters and telephone calls to drug manufacturers in which FDA warned the manufacturers against distributing enduring materials in which off-label uses of their products were discussed.[1] Later, the FDA policy was formalized through issuance of two guidance documents. *See* "Guidance to Industry on Dissemination of Reprints of Certain Published, Original Data," 61 Fed. Reg. 52800 (Oct. 8, 1996) (the "Reprint Guidance"); "Guidance for Industry Funded Dissemination of Reference Texts," 61 Fed. Reg. 52800 (Oct. 8, 1996) (the "Textbook Guidance"). A copy of those guidance documents is attached hereto.

WLF filed a Citizen Petition with FDA in October 1993 (Docket No. 92N-0434/CP1), objecting to FDA's crackdown as a violation of the First Amendment rights of doctors and

[1] Examples of such FDA actions were discussed at length in the *WLF* litigation.

patients to receive truthful information about off-label uses. Following denial of its Citizen Petition, WLF filed suit in 1994 against FDA in U.S. District Court for the District of Columbia, seeking an injunction against further violations of First Amendment rights. *Washington Legal Found. v. Kessler*, No. 1:94CV01306 (RCL). In 1998, the district court granted WLF's motion for summary judgment and denied FDA's cross-motion for summary judgment. *Washington Legal Found. v. Friedman*, 13 F. Supp. 51 (D.D.C. 1998) ("*WLF I*"). The court rejected FDA's initial argument that the challenged policies regulated conduct instead of speech and thus were not subject to First Amendment review. The court explained, "[T]he activities at issue in this case are only 'conduct' to the extent that moving one's lips is 'conduct,' or to the extent that affixing a stamp and distributing information through the mails is 'conduct.' . . . This court is hard-pressed to believe that the agency is seriously contending that 'promotion' of an activity is conduct and not speech, or that 'promotion' is entitled to no First Amendment protection." *Id.* at 59. The court then determined that the speech at issue should be deemed "commercial speech" and thus that its regulation should be subject to review under the standards set forth in *Central Hudson Gas & Elec. Corp. v. Public Serv. Comm'n*, 447 U.S. 557 (1980).[2] *Id.* at 62-66. The court rejected FDA's contention that the speech for which WLF sought dissemination (peer-reviewed enduring materials) could be deemed inherently misleading (and thus not subject to commercial speech protection) simply because FDA had not approved it. The court explained:

> [I]n asserting that any and all scientific claims about the safety, effectiveness, contraindications, side effects, and the like regarding prescription drugs are presumptively untruthful or misleading until FDA has had the opportunity to evaluate them, FDA exaggerates its overall place in the universe.

Id. at 67. The Court explained that, notwithstanding the absence of FDA evaluation, there are sound reasons for believing that peer-reviewed journal articles and medical texts contain accurate information.

Applying *Central Hudson*, the court determined that although FDA had a substantial interest in encouraging manufacturers to bring new uses for a product "on label," and although the FDA speech restrictions directly advanced that interest (by providing manufacturers with strong incentives to apply for new labeling authority in order to increase what they could say

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[2] Under *Central Hudson*, the government may regulate commercial speech that is neither inherently misleading nor related to an unlawful activity only upon a showing that: (1) the government has a substantial interest that it seeks to achieve; (2) the regulation directly advances the asserted interest; and (3) the regulation serves that interest in a narrowly tailored manner. *Id.* at 566.

about the new uses), *id.* at 70-72, the FDA speech restrictions violated the First Amendment because they were more extensive than necessary to achieve the agency's permissible goals. *Id.* at 72-74. The court determined that FDA's goals could be fully achieved were it to require "full, complete, and unambiguous disclosure by the manufacturer" that the enduring materials being disseminated (or the CME activities being financed) contained discussion of off-label product uses not approved by FDA. *Id.* at 73. The court entered an injunction that provided in pertinent part:

> Defendants SHALL NOT in any way prohibit, restrict, sanction or otherwise seek to limit any pharmaceutical or medical device manufacturer or any other person:
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> a) from disseminating or distributing to physicians or other medical professionals any article concerning prescription drugs or medical devices previously published in a bona fide peer-reviewed professional journal, regardless of whether such article includes a significant or exclusive focus on uses of drugs or medical devices other than those approved by FDA and regardless of whether such article reports the original study on which FDA approval of the drug or device in question was based;
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> b) from disseminating or redistributing to physicians or other medical professionals any reference textbook (including any medical textbook or compendium) or any portion thereof published by a bona fide independent publisher and otherwise generally available for sale in bookstores or other distribution channels where similar books are normally available, regardless of whether such reference textbook or portion thereof includes a significant or exclusive focus on uses of drugs or medical devices other than those approved by FDA.

Id. at 73-74.[3]

FDA thereafter filed a motion to alter or amend the judgment. FDA's motion noted that between the time that WLF had filed its motion for summary judgment (in November 1997) and the time that the court granted that motion, Congress had passed FDAMA and FDA had issued regulations implementing § 401 of FDAMA (relating to manufacturer dissemination of enduring materials that discuss off-label uses). Noting that § 401 of FDAMA

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[3] The injunction also applied to the "CME Guidance," an FDA effort to restrict manufacturers from suggesting content or speakers for continuing medical education (CME) programs. That injunction was later dissolved as moot after FDA told the courts that it never adopted any policy that limited manufacturers in making such suggestions.

came within the literal terms of the court's injunction, FDA asked the court to modify its injunction so as to: (1) limit its scope to the Reprint Guidance, the Textbook Guidance, and the CME Guidance; and (2) state explicitly that the injunction was inapplicable to § 401.[4]

In February 1999, the court denied FDA's motion. *Washington Legal Found. v. Friedman*, 36 F. Supp. 2d 16 (D.D.C. 1999) ("*WLF II*"). The court stated that FDA was "mistaken about the intended scope of the Court's opinion and injunction." *Id.* at 18. The court explained that it had not intended merely to address the validity of the two guidance documents – which, after all, had not even existed at the time that WLF filed suit in 1994 – but rather to address the validity of "the policies underlying the Guidance Documents," policies which had pre-existed the issuance of those documents. *Id.* Thus, it concluded, "The Court's decision and injunction must be read to apply to the underlying policies of the FDA, and not merely to the express provisions of the Guidance Documents." *Id.* The court concluded, nonetheless, that an additional round of briefing was warranted before it determined whether § 401 of FDAMA fell within the terms of the existing injunction, because the parties' previous briefs – filed before FDAMA took effect – had not addressed that issue. *Id.* at 20.

Following additional briefing, the court in July 1999 once again denied FDA's motion to amend the judgment and issued a "final amended order granting summary judgment and permanent injunction." *Washington Legal Found. v. Henney,* 56 F. Supp. 81 (D.D.C. 1999) ("*WLF III*").[5] The court made clear that § 401 of FDAMA and its implementing regulations fell within the terms of the prior injunction, and thus it enjoined enforcement of those provisions. *Id.* at 88. The court repeated its *Central Hudson* analysis from *WLF I* and concluded that FDAMA was not sufficiently narrowly tailored to survive scrutiny under that analysis. *Id.* at 87. The court concluded that § 401 of FDAMA amounted to an unconstitutional condition because it required manufacturers unwilling to subject themselves to an onerous supplemental application process to waive their First Amendment rights to speak

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[4] Following FDA's adoption of the Reprint Guidance and the Textbook Guidance, Congress in 1997 adopted FDAMA – including § 401, which addressed the same subject matter as the two guidances. Section 401 of FDAMA took effect in 1998, after FDA adopted implementing regulations. 21 C.F.R. Part 99. Despite issuing those regulations, FDA took no action to withdraw the Reprint Guidance and the Textbook Guidance until after the district court issued its 1998 injunction.

[5] The wording of the final injunction was altered slightly, with WLF's consent, from the July 1998 wording, in order to allay FDA's concern that the injunction might be read as permitting manufacturer dissemination of information about products that had never been approved by FDA for *any* use.

truthfully regarding their products: "The supplemental application requirement of [FDAMA] amounts to a kind of constitutional blackmail – comply with the statute or sacrifice your First Amendment rights. It should go without saying that this tactic cannot survive judicial scrutiny." *Id.*[6] The court doubted the sincerity of FDA's claims that unsolicited manufacturer dissemination of enduring materials relating to off-label use raised serious health concerns, stating:

> [FDA's] true perception of the speech at issue here is revealed by their attitude toward the same speech disseminated under other circumstances. For example, [FDA has] no concern over the exchange of article reprints and reference texts among physicians; more telling, defendants do not even object to a manufacturer providing such information to a health care provider upon such person's request. Only when the manufacturer initiates the exchange does the FDA choose to label the speech false or inherently misleading. The Supreme Court has recently addressed this situation with the following observation: "Even under the degree of scrutiny that we have applied in commercial speech cases, decisions that select among speakers conveying virtually identical messages are in serious tension with the principles undergirding the First Amendment." *Greater New Orleans Broad. Assoc. v. United States*, 527 U.S. 173 (1999).

Id. at 86-87.

FDA appealed from that decision. In its appellate briefs, FDA challenged the merits of the district court's decision, arguing that it had every right to restrict manufacturers' activities in the manner that WLF alleged. At oral argument before the appeals court, however, FDA radically shifted its position. FDA attorneys argued: (1) the Reprint Guidance and the Textbook Guidance had been "superseded" by FDAMA and therefore the validity of those documents was no longer at issue; (2) § 401 of FDAMA was a mere "safe harbor" provision that imposed no new obligations on manufacturers but rather merely provided them with a blueprint for avoiding sanctions that might otherwise be imposed on them based on other provisions of the FDCA; and (3) the CME Guidance was similarly a mere "safe harbor"

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[6] At no time in connection with its motion to amend did FDA suggest to the district court that FDAMA § 401 was a mere "safe harbor" provision that did not prohibit any speech. Rather, the thrust of FDA's entire argument was that § 401 imposed restrictions that were fully justified when analyzed under First Amendment case law. It was only later, during oral argument in the court of appeals, that FDA adopted a fanciful "safe harbor" interpretation of §401.

document that imposed no obligations on manufacturers.

The appeals court responded with a decision that dismissed FDA's appeal without reaching the merits of the First Amendment issues raised by the case. *Washington Legal Foundation v. Henney*, 202 F.3d 331 (D.C. Cir. 2000) ("*WLF IV*"). The court said that it would accept FDA's limiting construction of § 401, even though (as the court noted) the result of that "safe harbor" construction was to deprive § 401 of all teeth.[7] *Id.* at 335 ("Were a pharmaceutical company to send out reprints of an article devoted to its drug's off-label uses to thousands of physicians tomorrow, the government agreed – indeed stipulated – that the agency would draw no independent prosecutorial authority from FDAMA to buttress any enforcement proceeding.") The appeals court also accepted FDA's contention that the CME Guidance was nothing more than a "safe harbor" document. Thus, the appeals court determined, there was no longer a live controversy between the parties regarding "whether the statute and [CME] guidance document facially violate the First Amendment." *Id.* at 336. In light of that mootness determination, the appeals court "vacate[d] the district court's decisions and injunctions insofar as they declare the FDAMA and the CME Guidance unconstitutional." *Id.* at 337.

All that remained for decision was the district court's July 1998 determination (in *WLF I*) that the Reprint Guidance and the Textbook Guidance violated the First Amendment and its February 1999 determination that the injunction against FDA extended not just to those two documents but to "the policies underlying the Guidance Documents," which policies had pre-existed the issuance of those documents. *WLF II*, 36 F. Supp. 2d at 18. In light of FDA's extraordinary about-face at oral argument and its position that the validity of the Reprint

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[7] That construction appears to be at odds with the plain language of one portion of § 401 (codified at 21 U.S.C. § 331(z)), which specifically prohibited manufacturer "dissemination of information in violation of" § 401. The appeals court was nonetheless willing to defer to FDA's interpretation of its own statute, given that the result was to reduce FDA's enforcement powers. But the court explicitly warned that FDA would be bound by that limiting construction in the future, regardless whether FDA still perceived a tactical litigation advantage in sticking with that construction:

> The government has announced here nothing less than an official interpretation of the FDAMA which the agency may not change unless it provides a reasoned explanation for doing so. . . . It goes without saying that an attempt to evade judicial review in this case would hardly be a legitimate basis.

Id. at 336-37 (citations omitted).

Guidance and the Textbook Guidance was no longer at issue, the appeals court determined that FDA had abandoned its appeal on those issues; in other words, the appeals court determined that the district court's ruling on those issues remained intact. The court held that it was irrelevant that FDA was contending that FDAMA § 401 had "superseded" the Reprint Guidance and the Textbook Guidance because:

> [E]ven if they were not superseded, they would be unenforceable, since the FDA does not challenge on appeal the district court's decision and injunction insofar as they pertain to the Enduring Materials Guidances. *See WLF I*, 13 F. Supp. at 74.

WLF IV, 202 F.3d at 334 n.4. To drive home its conclusion that, by dismissing the appeal and vacating portions of the district court's decisions and injunction, it was not disturbing those portions of the district court opinion from which FDA had abandoned its appeal, the court of appeals concluded its decision by stating:

> [W]e certainly do not criticize the reasoning or conclusions of the district court. As we have made clear, we do not reach the merits of the district court's First Amendment holdings and *part of its injunction still stands*.

Id. at 337 n.7 (emphasis added). The appeals court thus could not have been clearer that while a portion of the district court's decisions had been vacated, left intact was that portion of the decisions that had struck down the Reprint Guidance and the Textbook Guidance and had held that the FDA policies underlying those guidance documents were unconstitutional because they violated WLF's First Amendment rights. FDA did not seek review of the appeals court's decision.

VI. *Relevance of WLF Litigation and § 401 to the Proposed Guidance*

The preceding discussion makes two points abundantly clear: (1) the expiration of § 401 has no relevance regarding whether FDA should be issuing a guidance document in this area and, if so, what form that guidance should take; and (2) given the history of litigation in this area, FDA guidance can only be meaningful if crafted with First Amendment constraints in mind.

With respect to § 401, its recent expiration was a complete non-event. FDA was prohibited by a federal court injunction from enforcing the statute during the first two years of its existence (1998-2000). That injunction was lifted as moot in 2000 only after FDA (on appeal) re-interpreted the statute into meaninglessness by contending that § 401 merely created a "safe harbor" and that manufacturers were free to ignore the statute without negative

consequences. In the ensuing years, manufacturers did just that: because of § 401's onerous terms, virtually no manufacturers sought to avail themselves of its "safe harbor" protection. Those manufacturers who have disseminated enduring materials that discuss off-label uses of their products have done so by-and-large without bothering to comply with § 401. Accordingly, FDA is wrong to suggest that that statute's expiration provides justification for FDA to "provid[e] its current views" on the subject.[8] The Draft Guidance would be an appropriate follow-on to § 401 only if the Draft Guidance were similarly intended as nothing more than a "safe harbor" that manufacturers were free to ignore. But the Draft Guidance clearly is not intended to be so limited: FDA states that the guidance is one that manufacturers "should" follow. Draft Guidance at 2. In light of the Draft Guidance's substantive content, it can only be viewed as an FDA effort to establish a policy that manufacturers ignore at their peril – notwithstanding FDA's statement that compliance is not necessarily "required."

Because FDA appears intent on beginning development of a substantive policy in this area, it is inexplicable that it has done so without reference to existing First Amendment case law. In particular, it is incumbent on FDA to explain how it intends to regulate manufacturer conduct in this area without running afoul of the federal district court injunction.

VII. The Draft Guidance Violates the *WLF* Injunction

The terms of the federal district court injunction against FDA are set forth above. WLF intends to ensure compliance with its injunction and will seek contempt of court citations against FDA officials who violate its terms. Accordingly, before FDA issues its Draft Guidance in final form, it should think long and hard about issuing any policy document that conflicts with the terms of the injunction.

Specifically, the injunction provides that FDA "shall not in any way prohibit, restrict, sanction or otherwise seek to limit" manufacturers from disseminating articles that have been published in "a bona fide peer-reviewed professional journal" (or from disseminating a medical textbook) based solely on the fact that the article contains accurate information about off-label uses of one of the manufacturer's products. *WLF I* at 73-74. The injunction applies even if the journal article reports on a study "other than the original study on which FDA

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[8] The Draft Guidance states (at 3):

> In light of [§ 401's] sunset, FDA is providing its current views on the dissemination of medical journal articles and medical or scientific reference publications on unapproved uses of approved drugs and approved or cleared medical devices to healthcare professionals and healthcare entities.

approval of the drug or device in question was based." *Id.* Several provisions of the Draft Guidance appear to run afoul of the injunction.

In pointing out the conflicts between the Draft Guidance and the injunction, WLF does not mean to suggest that FDA is powerless to regulate in this field. To the contrary, the injunction grants FDA considerable room within which to operate. For example, FDA is entitled to make reasonable determinations regarding what does and does not constitute a "bona fide peer-reviewed professional journal." Clearly, the New England Journal of Medicine qualifies. A special publication funded solely by the manufacturer whose product is the subject of the article probably does not, even if the publication claims to subject all articles to peer review. Thus, WLF does not see any conflict between the injunction and the first portion of § IV.A of the Draft Guidance (defining the types of "scientific or medical journal articles" that may be disseminated). Similarly, the injunction does not purport to prevent FDA from regulating dissemination of studies that it has examined and determined to be inaccurate or misleading in some material respect; rather, the injunction prevents FDA from seeking to prevent dissemination when its objection to the study is that FDA has not reviewed and approved the off-label claims included in the article. Moreover, the district court made clear that FDA is free to impose reasonable disclaimer requirements designed to ensure that the disseminated study is not even potentially misleading.

Perhaps the most glaring inconsistency between the Draft Guidance and the injunction is the former's provision that limits disseminatable journal articles to those that "address adequate and well-controlled clinical investigations." The term "adequate and well-controlled" study is often used by FDA as a term of art to refer to studies that are sufficient to support a new drug application to FDA. If that is FDA's intent in this instance, the Draft Guidance violates the injunction, which specifically bars FDA from restricting dissemination of studies that do not meet those exacting standards. If FDA has in mind permitting dissemination of studies that do not meet those exacting standards, it ought to amend the Draft Guidance to make clear precisely what standards it expects the underlying studies to meet. Obviously, FDA ought to be permitted to impose some reasonable standards; few would argue, for example, that a "study" consisting of the anecdotal observations by a doctor of four of her patients could convey anything of scientific value. On the other hand, many valuable studies have passed through the peer-review process and been accepted for publication by reputable journals without meeting FDA's usual definition of an adequate and well-controlled study. For example, while an open study is generally not deemed as authoritative as a double-blind study, it is well accepted that open studies can impart valuable information. As the injunction makes clear, FDA may not prohibit dissemination of peer-reviewed journal articles unless it has very good reason to believe that the study being reported is of absolutely no scientific value.

The Draft Guidance is also problematic in terms of the quantity of disclaimers it requires to be attached to the disseminated journal articles. At some point, disclaimers become so burdensome that they become *de facto* prohibitions against dissemination. Such excessively burdensome disclaimer requirements are wholly inconsistent with the injunction. Thus, for example, WLF deems it reasonable that the Draft Guidance requires that disseminated article "be accompanied by the approved labeling for the drug or medical device." But the approved labeling will by definition already include all "significant risks or safety concerns known to the manufacturer" concerning the approved uses of the product; thus, there can be no justification for requiring that those concerns be listed a second time (in connection with the final item in Sec. IV.B of the Draft Guidance) unless the manufacturer is aware of significant risks and safety concerns associated with off-label use that are not also associated with approved uses. Similarly, there can be no justification for requiring the manufacturer to prepare a "comprehensive bibliography" and to attach all articles reaching "different conclusions." Not only would such a requirement be extremely burdensome to the point of chilling truthful speech, but it compels manufacturers to utter speech with which they may very well disagree. Moreover, FDA is imposing a double standard: while imposing minimum quality standards on the study that the manufacturer wishes to disseminate, it would require the manufacturer to attach all studies reaching "different conclusions" without regard to the quality of those other studies. Finally, the provision leaves manufacturers without any meaningful yardstick for measuring whether the conclusion in another study is "different"; for example, would conclusions be "different" simply because two reports disclosed slightly different effectiveness rates for a drug?

Nor is FDA free to argue that the injunction issued in *WLF I* applies only to the Reprint Guidance and the Textbook Guidance, and thus is moot because FDA is no longer seeking to enforce those documents. FDA raised that precise argument in its motion to alter or amend the initial injunction, arguing that the injunction should not apply to FDAMA § 401 because that statute was not referenced by name in the injunction. The district court squarely rejected that argument in *WLF II*. It held that the injunction covered not only the two challenged guidance documents but also "the policies underlying the Guidance Documents." *WLF II* 36 F. Supp. 2d at 18. Thus, because the Draft Guidance is based on the same FDA policy that underlay the Reprint Guidance and the Textbook Guidance, it continues to be governed by the existing injunction.

VIII. The Draft Guidance Violates the First Amendment

WLF is well aware that FDA in the past has taken the position that the injunction issued by the district court in *WLF I* and *WLF III* is no longer in place. Given the clear language to the contrary in the D.C. Circuit's *WLF IV* decision (quoted above), WLF has never understood how FDA can make that argument in good faith.

But even if FDA were somehow correct that the injunction is no longer in effect, that would still leave FDA with a major First Amendment problem. Before FDA adopts a guidance document that imposes new restrictions on manufacturer speech, it is incumbent on the agency to square those restrictions with First Amendment constraints. The leading cases on FDA authority to restrict a manufacturer's dissemination of peer-reviewed medical journal articles containing off-label information are *WLF I* and *WLF III*. In dismissing FDA's appeal from the district court's injunction (and in partially vacating the injunction as moot), the D.C. Circuit went out of its way to emphasize that it "certainly [was] not criticiz[ing] the reasoning or conclusions of the district court." *WLF IV*, 202 F.3d at 337 n.7. Yet, FDA has made no effort to explain why the district court's reasoning does not apply here to render the Draft Guidance patently unconstitutional.

The district court cogently explained why FDA's efforts to suppress manufacturers' dissemination of enduring materials that discuss off-label uses of FDA-approved products run afoul of the First Amendment. *See WLF I, WLF II,* and *WLF III*. WLF will not repeat all those arguments here.

Suffice to say that FDA has been on an extended losing streak in the courts in its efforts to resist First Amendment limitations on its enforcement activities. For example, the U.S. Court of Appeals for the District of Columbia Circuit held recently that the First Amendment imposes strict limitations on FDA's power to restrict health claims made by manufacturers of dietary supplements, even when the claims are made on the product label. *Pearson v. Shalala,* 164 F.3d 650 (D.C. Cir. 1999) ("*Pearson I*"). In overturning a district court decision that had upheld FDA's outright ban on such claims when use of disclaimers might have responded fully to FDA's concerns, the appeals court stated:

> The government insists that it is never obliged to utilize the disclaimer approach, because the commercial speech doctrine does not embody a preference for disclosure over outright suppression. Our understanding of the doctrine is different. . . . In more recent cases, the [Supreme] Court has . . . repeatedly point[ed] to disclaimers as constitutionally preferable to outright suppression.

Id. at 657. The court added, "[W]hen government chooses a policy of suppression over disclosure – at least where there is no showing that disclosure would not suffice to cure misleadingness – government disregards a 'far less restrictive' means" of achieving its policy interests. *Id.* at 658 (quoting *Bd. of Trustees of State Univ. of New York v. Fox,* 492 U.S. 469, 479 (1989)).

On remand, FDA's First Amendment arguments were again rejected. The district court granted a preliminary injunction against FDA's continued violation of First Amendment rights;

the court required FDA to approve a health claim (for inclusion on product labeling for folic acid) regarding the positive relationship between consumption of folic acid and prevention of birth defects. *Pearson v. Shalala*, 130 F. Supp. 2d 105 (D.D.C. 2001) ("*Pearson II*"). The district court was harshly critical of FDA's continued resistance to court orders that it comply with the First Amendment; the court said:

> [I]t is clear that the FDA simply failed to comply with the constitutional guidelines outlined in *Pearson* [*I*]. Indeed, the agency appears to have at best, misunderstood, and at worst, deliberately ignored, highly relevant portions of the Court of Appeals Opinion.

Pearson II, 130 F. Supp. 2d at 112. The court held that under the First Amendment, FDA "must shoulder a very heavy burden if it seeks to totally ban a particular health claim." *Id.* at 118. The court held that FDA had failed to meet that burden; it held that "[t]he mere absence of significant affirmative evidence in support of a particular [health] claim . . . does not translate into negative evidence 'against' it." *Id.* at 115. In other words, the court held, any FDA efforts to regulate manufacturer dissemination of unapproved health claims must take the form of disclaimer requirements rather than outright bans on the claims, unless FDA can demonstrate that the claims are "against" the great weight of the scientific literature.[9] The district court later denied FDA's motion for reconsideration of the preliminary injunction order. Noting that FDA's "arguments contained in the motion for reconsideration further demonstrate Defendants' reluctance to fully comply with *Pearson I*," the court reiterated its conclusion:

> [T]he philosophy underlying *Pearson I* is perfectly clear: that the First Amendment analysis in *Central Hudson* . . . applies in this case, and that if a health claim is not inherently misleading, the balance tilts in favor of disclaimers rather than suppression. In its motion for reconsideration, the FDA has again refused to accept the reality and finality of that conclusion by the Court of Appeals.

Pearson v. Thompson, 141 F. Supp. 2d 105, 112 (D.D.C. 2001).

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[9] Significantly, the district court simply ignored FDA's argument that its efforts to ban the folic acid health claims were not subject to First Amendment review because FDA was not banning speech *directly* but rather was simply using the speech as evidence that the manufacturer intended to market its product as a drug. (And, of course, FDA was asserting that dissemination of the health claims would render the folic acid subject to seizure as an unapproved new drug, because FDA has never approved the marketing of folic acid as a drug.)

The U.S. Supreme Court has been equally dismissive of FDA's defenses to First Amendment claims. That court held that a FDAMA provision that restricted pharmacists from advertising the availability of compounded drugs could not survive the final two prongs of the *Central Hudson* test and thus violated the First Amendment. *Thompson v. Western States Medical Center*, 535 U.S. 357 (2002). Noting that the FDAMA provision at issue allowed pharmacists to initiate discussions about a compounded drug once a patient presented a prescription for another drug, the district court in that same case found it "difficult to see how the communication of the same information can both serve and undermine the public health, depending on which party initiates the contact or the method used to communicate it." *Western States Medical Center v. Shalala*, 69 F. Supp. 2d 1288, 1299 (D. Nev. 1999).

A strong argument can be made that manufacturer dissemination of enduring materials should not be deemed commercial speech at all but rather is noncommercial speech entitled to the highest level of First Amendment protection. *See, e.g.*, Glenn C. Smith, "Avoiding Awkward Alchemy -- In the Off-Label Drug Context and Beyond: Fully Protected Independent Research Should Not Transmogrify Into Mere Commercial Speech Just Because Product Manufacturers Distribute It," 34 WAKE FOREST L.REV. 963 (1999). But even if analyzed under a commercial speech standard, FDA's enduring material's policy cannot withstand First Amendment scrutiny. The evidence is overwhelming that FDA's policy objectives could be achieved in a much more narrowly tailored manner. As the district court found in *WLF I*, *WLF II*, and *WLF III*, a regime based on disclaimers and a continued ban on *labeling* for uses not approved by FDA would ensure that: (1) doctors would not be misled into believing that off-label uses described in a journal reprint had been approved by FDA; and (2) manufacturers would continue to have an incentive to seek supplemental labeling authority for the most popular off-label uses.

In sum, the Draft Guidance is constitutionally acceptable to the extent that it imposes reasonable disclaimer requirements on manufacturer seeking to disseminate peer-reviewed journal articles that discuss off-label uses of the manufacturer's product. But the First Amendment does not tolerate the Draft Guidance's efforts to prevent such dissemination altogether, except when the article is so deficient that it could not possible meet minimal scientific standards – in which event it would not be appearing in a peer-reviewed journal in the first place.

IX. *Conclusion*

WLF respectfully submits that the Draft Guidance violates the terms of the injunction issued against FDA in *WLF I* and *WLF III* and, in any event, violates First Amendment norms. If FDA intends to go forward with these new restrictions on manufacturer speech, it should substantially revise them to ensure that they violate neither the terms of the court injunction

nor the First Amendment. In particular, FDA should: (1) eliminate any reference to "adequate and well-controlled clinical investigation," a reference that might well be interpreted as imposing severe limitations on the types of articles that may be disseminated; (2) scale back on the requirements that the article be accompanied by a comprehensive bibliography and articles/texts expressing contrary or different conclusions; and (3) scale back on the "disclaimer" requirements, particularly the requirement regarding "significant risks or safety concerns" of the off-label use.

Sincerely,

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Chairman and General Counsel

/s/ Richard A. Samp
Richard A. Samp
Chief Counsel