Docket No. FDA-2008-D-0053

COMMENTS

of

THE WASHINGTON LEGAL FOUNDATION

to the

FOOD AND DRUG ADMINISTRATION
DEPARTMENT OF HEALTH & HUMAN SERVICES

Concerning

REVISED DRAFT GUIDANCE FOR INDUSTRY ON DISTRIBUTING SCIENTIFIC AND MEDICAL PUBLICATIONS ON UNAPPROVED NEW USES – RECOMMENDED PRACTICES

IN RESPONSE TO THE PUBLIC NOTICE PUBLISHED
AT 79 *FED. REG.* 11793 (MARCH 3, 2014)

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May 15, 2014

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Division of Dockets Management (HFA-305)
Food and Drug Administration
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Re: Revised Draft Guidance for Industry on Distributing Scientific and Medical Publications on Unapproved New Uses—Recommended Practices
79 Fed. Reg. 11793 (March 3, 2014)

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The Washington Legal Foundation (WLF) submits these comments in response to the Food and Drug Administration's draft guidance for industry on reprint distribution practices regarding articles/medical texts that contain off-label information regarding approved drugs and medical devices (the "Draft Guidance"). WLF has grave concerns regarding several provisions of the Draft Guidance. The document appears to violate the terms of a permanent injunction WLF obtained against FDA in 1999. Quite apart from the specific issue of that injunction, the Draft Guidance raises serious First Amendment concerns regarding the rights of manufacturers to speak truthfully on important health care issues.

The Draft Guidance proposes revisions to a January 2009 final guidance entitled, "Good Reprint Practices for the Distribution of Medical Journal Articles and Medical or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" (the "2009 Guidance"). WLF has previously pointed out the numerous constitutional infirmities of the 2009 Guidance. WLF is dismayed that the Draft Guidance makes no effort to correct any of those infirmities; indeed, the Draft Guidance omits any reference to the First Amendment. That omission is particularly glaring when one considers that, in the five years since release of the 2009 Guidance, both the U.S. Supreme Court and the U.S. Court of Appeals for the Second Circuit have issued important decisions that strengthened the First Amendment rights of drug and device manufacturers to speak truthfully about off-label uses of their products. Moreover, while the Draft Guidance incorporates many of the features of the 2009 Guidance, most of its proposed revisions consist of imposing additional restrictions on manufacturers who wish to provide truthful information about medically accepted off-label uses of their products.

As FDA is no doubt aware, most manufacturers who disseminate reprints of journal articles and medical texts do not do so within the confines of the "safe harbor" established by § 401 of the Food and Drug Administration Modernization Act (FDAMA); that safe harbor

(which expired in 2006) was so narrow that reprint dissemination would end if manufacturers felt bound to comply with its strict terms. Rather, most manufacturers have disseminated reprints based on their understanding that the First Amendment provides far broader dissemination rights than those delineated in § 401. But by doing so, those manufacturers have assumed the risk that FDA may decide to test First Amendment limits by bringing enforcement actions against manufacturers operating outside the safe harbor. Other manufacturers, of course, are more risk averse and have been unwilling to assume that risk; the result is that significant amounts of truthful, constitutionally protected speech are being chilled as a result of the flawed 2009 Guidance, which sought to transform what had been a safe harbor into established FDA policy. The Draft Guidance, by ignoring the First Amendment altogether and restricting the reprint safe harbor still further, would compound the problem. WLF respectfully suggests that FDA is doing a major disservice to the cause of improved health care by its continued refusal to explain its understanding of First Amendment constraints and the extent to which the Constitution permits it to restrict truthful manufacturer speech.

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 permanent injunction nor the First Amendment. In particular, FDA should: (1) eliminate any reference to "adequate and well-controlled clinical investigation," a reference that likely will be interpreted as imposing severe limitations on the types of journal articles that may be disseminated; (2) narrow the overly burdensome "disclaimer" requirements, such as that the article be accompanied by a comprehensive bibliography and articles/texts expressing contrary or different conclusions; and (3) scale back on the limitations imposed on disseminating medical texts, particularly the distribution of individual chapters from a medical text. In the absence of such revisions, it will be virtually impossible for manufacturers to distribute reprints in a manner that complies with the Draft Guidance.

I. *Interests of WLF*

The Washington Legal Foundation is a public interest law and policy center with supporters nationwide. WLF regularly appears before federal and state courts and administrative agencies to promote economic liberty, free enterprise, the rule of law, 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.*, *Sorrell v. IMS Health Inc.*, 131 S. Ct. 2653 (2011); *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. More recently, WLF lawyers played a key role in overturning—on First Amendment grounds—the criminal conviction of a

pharmaceutical representative for conspiring to violate the FDCA; the representative's "crime" consisted of speaking truthfully about off-label uses of a drug manufactured by his company. *United States v. Caronia*, 703 F.3d 149 (2012).

WLF also regularly participates in FDA administrative proceedings in support of expanded First Amendment rights. *See, e.g.*,FDA Docket No. 2008-D-0053 (April 21, 2008) (response to FDA Draft Guidance on good reprint practices); 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. 2011-D-0868 (March 29, 2012) (response to FDA Draft Guidance on unsolicited requests for off-label information); 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 FDA 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 "advertisements" 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 people 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, and. FDA requires that it list 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.").

Congress similarly recognizes the importance of off-label uses; for example, it imposed an 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 disseminating 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.

The 2009 Guidance purports to recognize the important 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.

2009 Guidance at 3; *see also* Draft Guidance at 6 ("this draft guidance, like the 2009 guidance, recognizes the value to health care professionals of truthful and non-misleading scientific or medical publications on unapproved new uses.").

IV. *FDA's Rationale for Issuing the 2009 Guidance and 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 15 years 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. It thus would applaud any FDA effort to provide meaningful 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 would provide a real service to manufacturers. They obviously have a strong interest in knowing what steps they can take without incurring FDA's regulatory wrath.

Accordingly, WLF was astonished by FDA's stated rationales for issuing the 2009 Guidance and the Draft Guidance. FDA stated that it was acting to fill a void supposedly left by the September 2006 expiration of § 401 of 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 texts in which a manufacturer could engage without having to worry that its actions could be deemed a violation of the FDCA; it was *not* an effort to distinguish constitutionally protected speech from speech that FDA could and would suppress. Moreover, the § 401 safe harbor was so restricted in its application that few manufacturers ever bothered to come within its terms.[1] 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.

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[1] FDA errs in asserting that Congress, by adopting § 401, indicated its "expectation" that a manufacturer "would seek FDA approval" for any off-label uses discussed in literature it disseminated, and that this expectation was evidence that Congress "recognized the important public health value of FDA premarket review and approval" of all potential uses of an FDA-approved product. Draft Guidance at 5. To the contrary, § 401 was a safe harbor provision. As such, it provided safety for manufacturers who chose to comply with its terms, but they were free to ignore its provisions without negative consequences.

In sharp contrast to § 401, the 2009 Guidance and the Draft Guidance are not intended to establish safe harbors; *i.e.*, they provide no assurance that failure to abide by the guidances will not be held against a manufacturer. Rather, they set forth FDA's "recommended practices" for manufacturers when distributing journal reprints and medical texts to health care professionals. Draft Guidance at 1. While guidance documents represent no more than FDA's "current thinking on recommended practices" and are formally binding on neither manufacturers nor the agency, the 2009 Guidance and the Draft Guidance make clear that they expect manufacturers to abide by those documents in the normal course of events.

But if the Draft Guidance is to be a serious effort to distinguish constitutionally protected speech from unprotected speech—as opposed to a safe harbor standard of the sort exemplified by § 401—then it is incumbent on FDA to address First Amendment issues head-on. In the absence of any mention of the First Amendment in either the 2009 Guidance or the Draft Guidance, one can only conclude that the agency's "current thinking" includes no thoughts about the First Amendment. WLF urges FDA to withdraw the Draft Guidance and to undertake a serious effort to harmonize its speech restrictions with First Amendment limitations. As numerous court decisions make clear, FDA can no longer get by with its "the First Amendment does not apply to us" approach.

V. *History of the WLF Litigation*

In order to explain why it makes no sense for FDA to view the 2009 Guidance and the Draft Guidance as nothing more than a continuation of policies established under § 401, 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 texts (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 established 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.[2] 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").

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 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).[3] *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.

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

[3] 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.

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 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:
>
> 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;
>
> 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.[4]

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[4] 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

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 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.[5]

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*").[6] 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

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adopted any policy that limited manufacturers in making such suggestions.

[5] 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. *See* 21 C.F.R. Part 99 (1998). 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.

[6] 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.

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 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.*[7]

The court also 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 the *WLF III* 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

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[7] 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 for the first time interpreted §401 as a safe harbor.

FDCA; and (3) the CME Guidance was similarly a mere "safe harbor" 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.[8] *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 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

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[8] That construction was in considerable tension with the language of one portion of § 401 (codified at 21 U.S.C. § 331(z) (1999)), 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).

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. 2d 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 2009 Guidance and the Proposed Guidance*

The preceding discussion makes two points abundantly clear: (1) the expiration of § 401 has no relevance regarding whether FDA needed to issue a guidance document in this area and, if so, what form that guidance should take, because FDA is not purporting to issue safe harbor guidance documents; and (2) given the litigation history, FDA guidance can only be meaningful if crafted with First Amendment constraints in mind. Any guidance that does not mention the First Amendment will, by definition, fail to explain how FDA intends to harmonize its policy on dissemination of enduring materials with the existing district court injunction and the court's unchallenged First Amendment findings.

The expiration of § 401 several years ago 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 disseminated enduring materials that discussed off-label uses of their products did so by-and-large without bothering to comply with § 401. Accordingly, FDA was wrong to suggest that the statute's expiration created a justification for FDA to "provid[e] its current views" on the subject.[9] The 2009 Guidance and Draft Guidance would be appropriate follow-ons to § 401 only if they were similarly intended as nothing more than safe harbors that manufacturers would be free to ignore. But the 2009 Guidance and Draft Guidance are not intended to be so limited: FDA states that the guidances are ones that manufacturers "should" follow. 2009 Guidance at 1; Draft Guidance at 2. In light of the substantive content of the two guidance documents, they 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 enforce its injunction and will seek contempt of court citations against FDA officials who violate its terms. FDA to date has avoided judicial confrontations by declining to bring enforcement actions against manufacturers who do not comply with the 2009 Guidance. While a non-enforcement strategy may keep FDA out of court, WLF submits that it makes little sense for FDA to adopt the Draft Guidance in final form if it does not intend to ever enforce the document.

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

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[9] The 2009 Guidance states (at 2):

> 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.

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." But FDA cannot plausibly argue that prestigious journals such as the New England Journal of Medicine do not qualify.

WLF does not see any conflict at this time between the injunction and the portions of § III.A of the Draft Guidance that define the types of "peer-reviewed" publications that manufacturers may disseminate. 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 distributable journal articles to those that "address adequate and well-controlled clinical investigations." *See* § II.A.3. The term "adequate and well-controlled study' is often used by FDA as a term of art to refer to double-blind placebo studies, *i.e.*, 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.

FDA may impose some reasonable standards. But 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. 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.

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 a journal article "be disseminated with the approved labeling" for the manufacturer's product that is discussed in the article. § II.A.4. But 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 proposed 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 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 it 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 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, saying:

> [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.[10] 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).

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).

Similarly, the Supreme Court affirmed in *Sorrell* that "[s]peech in aid of pharmaceutical marketing . . . is a form of expression protected by the Free Speech Clause of the First Amendment." *Sorrell*, 131 S. Ct. at 2659. It observed that the First Amendment serves a particularly important function "in the fields of medicine and public health, where information can save lives." *Id.* at 2664. *Sorrell* struck down a Vermont law that sought to restrict truthful speech by drug companies that, Vermont feared, would cause doctors to write inappropriate and costly prescriptions. The Court held that regulation of truthful commercial speech can never be justified based on concern over how others might react to the speech. It repeated its prior admonition that "the 'fear that people would make bad decisions if given truthful information' cannot justify content-based burdens on speech." *Id.* at 2670-71 (quoting *Western States*, 535

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[10] 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.)

U.S. at 374). Such justifications for burdening speech were particularly inappropriate given that the targets of the speech (prescribing physicians) were "sophisticated and experienced consumers." *Id.* at 2671. Yet, the Draft Guidance makes no effort to explain how its efforts to burden speech directed at that same "sophisticated and experienced" group can be squared with the First Amendment.

Nor does the Draft Guidance address the Second Circuit's recent decision in *United States v. Caronia*, 703 F.3d 149 (2d Cir. 2012), which held that the First Amendment barred prosecution of a pharmaceutical salesman for speaking truthfully to a doctor about off-label uses of his employer's drug. The court explicitly rejected the federal government's claim that the prosecution did not implicate the First Amendment because it sought to regulate commercial conduct, not speech. 703 F.3d at 160-63. Indeed, the court flatly rejected FDA's broad reading of the FDCA's misbranding provisions, the provisions on which FDA principally relies to justify its restrictions on off-label promotion by manufacturers:

> [W]e decline to adopt the government's construction of the FDCA's misbranding provisions to prohibit manufacturer promotion alone as it would unconstitutionally restrict free speech. We construe the misbranding provisions of the FDCA as not prohibiting and criminalizing the truthful off-label promotion of FDA-approved prescription drugs. . . . [T]he government cannot prosecute pharmaceutical manufacturers and their representatives under the FDCA for speech promoting the lawful, off-label use of an FDA-approved drug.

Id. at 168-69.

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). Moreover, *Sorrell* held that restrictions on truthful commercial speech are subject to "heightened scrutiny"—above and beyond the intermediate level of scrutiny normally applied to commercial speech restrictions under *Central Hudson*—whenever (as here) the restrictions are imposed based on the identity of the speaker or the content of the speech. *Sorrell*, 131 S. Ct. at 2664. But even if analyzed under a commercial speech standard, FDA's enduring materials 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.

The Draft Guidance's restrictions on dissemination of medical texts are particularly objectionable under the First Amendment, because they could very well cause all such dissemination to cease. In particular, the Draft Guidance would bar distribution of individual chapters of a medical text if they are: (1) "published specifically at the request of a drug or device manufacturer"; or (2) "primarily distributed by a drug or device manufacturer; rather [the chapter from the medical text] should be generally available in bookstores or other independent distribution channels (e.g., subscription, Internet) where textbooks are sold." Draft Guidance at 13. FDA provides no explanation for these restrictions.

Why the restrictions are so onerous requires a brief explanation of how distribution of medical texts normally occurs. First, no one seriously disputes the objectivity and independence of the publishers who produce medical textbooks in this country. The textbooks routinely discuss medically-accepted off-label uses of FDA-approved products, but there is no evidence that such discussions are influenced by the manufacturers whose products are at issue. The textbooks routinely cover a broad spectrum of medical issues and generally retail for hundreds (and sometimes thousands) of dollars. Because of their cost and volume, entire medical textbooks have rarely been distributed by manufacturers to physicians. For one thing, the typical doctor will generally be interested in receiving only the chapter that relates to his/her specialty; for example, an oncologist would be interested in the chapter on oncology but far less interested in the chapter on heart disease. To meet that demand, small publishing companies have focused on republishing individual chapters from larger medical textbooks and marketing them to manufacturers, who then provide them for free to doctors in the appropriate specialty. The companies will arrange to obtain publishing rights for an individual chapter from the textbook publisher only if they have received an indication from a manufacturer that it is interested in distributing the chapter.

The textbook publishers generally do not otherwise make the individual chapters available for purchase by the general public. Doing so would make little business sense because it would tend to undercut sales of the complete textbook. Thus, the two FDA restrictions cited above would end virtually all manufacturer distribution of medical texts, because individual chapters (the only form in which medical texts can be practicably distributed): (1) are almost always published at the request of manufacturers who intend to distribute them to doctors and (2) are virtually never available for sale through bookstores or "other independent distribution channels." Yet, the Draft Guidance fails to provide any rationale for what is effectively (and what FDA likely intends to be) a ban on manufacturer dissemination of medical texts. If FDA is interested in ensuring that the content of medical texts is not inappropriately influenced by manufacturers, there are numerous more narrowly tailored means of accomplishing that purpose. In any event, no evidence exists that manufacturers have ever exercised inappropriate influence on the content of medical texts; for one thing, when individual chapters are separately published, their content remains unchanged.

The Draft Guidance also imposes highly onerous disclaimer requirements on

manufacturer dissemination of medical texts, including a requirement that the approved labeling be included "for each of the manufacturer's products that is included in the distributed chapter(s)." *Ibid*. But even a single chapter in a medical textbook generally discusses dozens of products. Even if FDA could plausibly demonstrate that a manufacturer could realistically keep track of all the product references and attach the requisite hundreds of pages of product labeling to each medical text distributed to a doctor (a highly doubtful proposition), FDA could not begin to demonstrate that the requirement would directly advance any substantial FDA interest, such as preventing doctors from being misled. Instead, FDA appears to have included such onerous disclaimer requirements for the purpose of discouraging manufacturer speech altogether, a purpose that cannot pass muster under the *Central Hudson* test.

In sum, the Draft Guidance is constitutionally acceptable to the extent that it imposes *reasonable* disclaimer requirements on manufacturers seeking to disseminate enduring materials that discuss off-label uses of their products. But the First Amendment does not tolerate the Draft Guidance's efforts to prevent such dissemination altogether, except when the materials are so deficient that they could not possibly meet minimal scientific standards—in which event they would not be appearing in a medical textbook or 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 strictures. If FDA intends to go forward with these new restrictions on manufacturer speech, it must substantially revise them to ensure that they violate neither the terms of the court injunction nor the First Amendment. In particular, FDA must: (1) eliminate any reference to "adequate and well-controlled clinical investigation," a reference that likely will be interpreted as imposing severe limitations on the types of journal 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) limit "disclaimer" requirements to those that FDA can demonstrate are likely to directly advance its interests in lessening the possibility that physicians will be misled by the material being disseminated.

Sincerely,

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/s/ Cory L. Andrews
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