Docket No. FDA-2016-N-1149

COMMENTS

of

WASHINGTON LEGAL FOUNDATION

to the

FOOD AND DRUG ADMINISTRATION
DEPARTMENT OF HEALTH & HUMAN SERVICES

Concerning

MANUFACTURER COMMUNICATIONS REGARDING UNAPPROVED USES OF APPROVED OR CLEARED MEDICAL PRODUCTS

IN RESPONSE TO THE PUBLIC NOTICE PUBLISHED
AT 81 FED. REG. 60299 (SEPTEMBER 1, 2016)

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Re: Manufacturer Communications Regarding Unapproved Uses of Approved or Cleared Medical Products
81 Fed. Reg. 60299 (September 1, 2016)

Dear Sir/Madam:

Washington Legal Foundation (WLF) is pleased to submit these comments in response to the Food and Drug Administration's (FDA) request for input on issues related to communications by manufacturers regarding FDA-regulated drugs and medical devices (the "Request for Comments"). WLF applauds FDA for its decision to "engage in a comprehensive review of its regulations and policies governing firms' communications about unapproved uses of approved/cleared medical products," a review that is long overdue. WLF provided its initial input in oral testimony given at FDA's November 9-10 hearing; these written comments expand on that testimony.

Although WLF is encouraged by this commitment to review FDA's off-label communications policy, we are disappointed that the Request for Comments makes no reference to the First Amendment. The First Amendment imposes significant constraints on FDA's authority to censor truthful manufacturer speech. Any consideration of FDA policy regarding off-label communications must be informed to a very large extent by those strictures. It must also take into account the limits imposed by Congress on FDA's authority to regulate speech. FDA's past failures to develop policy with reference to those constitutional and statutory constraints has led to a series of embarrassing courtroom defeats for the agency.

Accordingly, WLF focuses the majority of these comments on explaining why much of FDA's current off-label communications policy cannot pass constitutional muster. We then address a number of the specific questions posed by the Request for Comments and explain how First Amendment constraints dictate the manner in which FDA should address the issues raised by those questions.

In particular, because the First Amendment severely restricts FDA's power to censor manufacturers' dissemination of *truthful and non-misleading* information about off-label uses of FDA-approved drugs and medical devices, properly defining when speech should be deemed

"truthful and non-misleading" for First Amendment purposes is critical to determining the scope of FDA's authority. And while FDA in the past has asserted that information should be deemed truthful only after the agency has reviewed the information and given its blessing, the courts have uniformly rejected that position.

As we explain more fully below, FDA should be mindful that any speech's ability to mislead depends significantly on the audience. Listeners whose educational backgrounds enable them to more fully grasp the nuances of speech are less likely than ones lacking that background to be misled by truthful speech, even when the speech does not explicitly state all of the speaker's underlying assumptions. For example, doctors and other qualified health professionals are far less likely to be misled by off-label communications than are consumers who lack similar training. Accordingly, off-label communications directed at health professionals (including drug wholesalers and those responsible for compiling formularies) are entitled to significantly greater First Amendment protection than the very same communications directed at consumers. Differentiating FDA off-label communications policy based on the intended audience is not simply a good policy choice, it is mandated by constitutional law.

Nor is FDA permitted, when defining "truthful and non-misleading" speech, to apply idiosyncratic meanings to those terms. FDA quite rightly applies strict scientific standards when determining whether a medical product is sufficiently safe and effective to permit its sale and distribution in the United States. But off-label information about potential uses of an FDA-approved medical product can still qualify as truthful and non-misleading, as those terms are commonly understood, even if the information would be insufficient by itself to warrant FDA supplemental marketing approval. Off-label information about a medical product is "truthful" if an individual qualified in the relevant field would conclude that the information is of at least *some* scientific significance. If the information meets that commonsense understanding of "truthful," the First Amendment permits FDA to regulate the speech for the purpose of ensuring that the intended audience is not misled. But it may not ban the speech altogether so long as the possibility that listeners might be misled can be largely eliminated by requiring the speaker to include specified disclaimers with his speech.

I. *Interests of WLF*

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, a limited and accountable government, individual and business civil liberties, and the rule of law. 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.*, 564 U.S. 552 (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 played a key role in overturning—on First Amendment grounds—the criminal conviction of a pharmaceutical representative for conspiring to violate the Food, Drug, and Cosmetic Act (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. FDA-2015-N-2002 (November 24, 2015) (response to FDA Proposed Regulation defining "intended use"); FDA Docket No. FDA-2008-D-0053 (May 15, 2014) (response to revised FDA Draft Guidance on distributing scientific and medical publications on off-label uses); FDA Docket No. FDA-2013-N-1430 (April 14, 2014) (response to FDA Draft Guidance on postmarket submissions to FDA of interactive promotional media); FDA Docket No. FDA-2011-D-0868 (March 29, 2012) (response to FDA Draft Guidance on unsolicited requests for off-label information); 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. 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*

FDA's statutory authority over manufacturer "labeling" and "advertisements" of some medical products plays an important role in ensuring the health and safety of all Americans. FDA oversight provides assurance that consumers will not be misled by false medical-product information into taking actions injurious to their health. But off-label information is not synonymous with false information. Indeed, as FDA acknowledges, off-label information is often extremely valuable, and the manufacturer of a medical product will often be the best source of truthful off-label information about its product. FDA sets back public health if it unduly restricts dissemination of such information.

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 the listing of any use for which FDA has not approved the product's sale and distribution. FDA approval is generally regarded as the gold standard precisely because the public trusts that FDA will approve products and labeling only on the basis of high-quality data:

> When using a medical product for its FDA approved/cleared intended use, health care professionals and patients and their caregivers can be assured that the decision to use the product is supported by robust premarket review of scientific data and other appropriate scientific evidence by an independent scientific agency and that the benefits and risks of the use are described in the product's FDA-approved or required labeling.

Requests for Comments, 81 Fed. at 60300.

Nonetheless, 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).[1] In

[1] WLF urges FDA to cease referring to off-label uses as "unapproved" uses, a pejorative and inaccurate term. FDA lacks authority to approve or disapprove particular uses of a medical product. Its authority is limited to regulating the sale and distribution of medical products in interstate commerce. Once FDA has approved the sale and distribution of a product, doctors are

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.

FDA's January 2009 final guidance on Good Reprint Practices (the "2009 Guidance")

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free to prescribe the use of that product in any manner they deem medically appropriate.

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* March 2014 draft guidance on Distributing Scientific and Medical Publications (the "2014 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. *The First Amendment Imposes Significant Restrictions on FDA's Authority to Regulate Manufacturer Speech*

The federal courts have long recognized that the First Amendment, subject only to narrow and well-understood exceptions, does not countenance governmental control over the content of messages conveyed by private individuals. *See, e.g.*, *Texas v. Johnson*, 491 U.S. 397, 414 (1989). "As a general matter, 'state action to punish the publication of truthful information can seldom satisfy constitutional standards.'" *Barnicki v. Vopper*, 532 U.S. 514, 527 (2001) (quoting *Smith v. Daily Mail Publishing Co.*, 443 U.S. 97, 102 (1979)). The heavy burden of justifying content-based restrictions on speech rests on the government. *R.A.V. v. St. Paul*, 505 U.S. 377, 382 (1992) ("Content-based regulations are presumptively invalid," and the government bears the burden to rebut that presumption.).

"Speech in the aid of pharmaceutical marketing ... is a form of expression protected by the ... First Amendment ... ." *Sorrell*, 564 U.S. at 557. And when regulating purely commercial speech, the government must still "justify its content-based law as consistent with the First Amendment." *See id.* at 563-66, 571 (Regulation of speech in pharmaceutical marketing was "presumptively invalid" and the "outcome [was] the same whether a special commercial speech inquiry or a stricter form of judicial scrutiny applied."). "The government cannot 'completely suppress information when narrower restrictions on expression would serve its interests as well.'" *Caronia*, 703 F.3d at 164 (quoting *Central Hudson Gas & Elec. Corp. v. Pub. Serv. Comm'n of New York*, 447 U.S. 557, 565 (1980)). This is because "bans against truthful, nonmisleading commercial speech . . . usually rest solely on the offensive assumption that the public will respond 'irrationally' to the truth . . . ." *Liquormart, Inc. v. Rhode Island*, 517 U.S. 484, 503 (1996).

"The First Amendment directs us to be especially skeptical of regulations that seek to

keep people in the dark for what the government perceives to be their own good." *Ibid.* So when regulating non-misleading speech that concerns lawful activity, the government must prove that its regulation is "narrowly drawn" and advances a substantial government interest "to a material degree." *Id.* at 505; *Central Hudson*, 447 U.S. at 565-66.

Over the past several decades, federal courts have repeatedly held that FDA's restrictions on manufacturer speech are subject to significant First Amendment constraints and on numerous occasions have struck down FDA speech restrictions as constitutionally impermissible. *See, e.g.*, *United States v. Caronia*, 703 F.3d 149 (2d Cir. 2012); *Thompson v. Western States Med. Ctr.*, 535 U.S. 357 (2002); *Pearson v. Shalala*, 164 F.3d 650 (D.C. Cir. 1999); *Amarin Pharma, Inc. v. FDA*, 119 F. Supp. 3d 196 (S.D.N.Y. 2015); *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).

Given this history, it is essential that FDA's "comprehensive review" of off-label communications policy be informed by the considerable First Amendment constraints on its regulatory authority. To assist in that review, WLF focuses on several of FDA's current draft and final guidance documents and explains why they are constitutionally objectionable.

V. *The 2009 Guidance and 2014 Draft Guidance on Distributing Scientific and Medical Publications Violate Constitutional Constraints*

On March 3, 2014, FDA issued its "Revised Draft Guidance for Industry on Distributing Scientific and Medical Publications on Unapproved New Uses." 79 Fed. Reg. 11793. This Draft Guidance proposed revisions to a January 2009 Final Guidance on the same subject. As WLF previously explained in lengthy comments filed in response to each document, the Final Guidance and Draft Guidance—which impose severe limits on manufacturer distribution of truthful information about off-label uses of FDA-approved products—violate constraints imposed by the First Amendment. Indeed, they also violate the terms of the permanent injunction issued by a federal court against FDA in *Washington Legal Found. v. Friedman*.

WLF is well aware that FDA in the past has taken the position that the injunction issued by the district court in *Friedman* is no longer in place. 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 case on FDA authority to restrict a manufacturer's dissemination of peer-reviewed medical journal articles containing off-label information is *Friedman*. 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." *Washington Legal Found. v.*

Henney, 202 F.3d 331, 337 n.7. Yet, FDA has never attempted to explain why the district court's reasoning does not render the 2009 Final Guidance and the 2014 Draft Guidance patently unconstitutional.

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.[2] 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 federal statute 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 statute 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*, 564 U.S. at 557. 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 566. *Sorrell* struck down a Vermont law that sought to restrict truthful

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[2] 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.)

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 577 (quoting *Western States*, 535 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." *Ibid*. Yet, the 2009 Final Guidance and 2014 Draft Guidance make no effort to explain how FDA's efforts to burden speech directed at that same "sophisticated and experienced" group can be squared with the First Amendment.

Nor does the 2014 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.

The 2014 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 2014 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 2014 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)." Draft Guidance at 13. 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 2009 Final Guidance and the 2014 Draft Guidance are constitutionally acceptable to the extent that they impose *reasonable* disclaimer requirements on manufacturers seeking to disseminate journals and medical texts 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.

VI. *FDA's 2015 Proposed Regulations Redefining "Intended Uses" Also Unduly Restrict Truthful Speech*

A product's intended use is central in determining whether it is a drug or device subject to FDA regulation. The FDCA, 21 U.S.C. § 301 *et seq.*, defines a "drug" as an article *intended* either: (1) for use in the diagnosis, cure, mitigation, treatment, or prevention of disease; or (2) to affect the structure of the body. FDCA § 201(g)(1), 21 U.S.C. § 321(g)(1). The FDCA's definition of a "device" is very similar. FDCA § 201(h), 21 U.S.C. § 321(h). The principal feature that distinguishes these two categories is the presence or absence of a "chemical action"; a product is a device and not a drug if it "does not achieve its primary intended purposes through chemical action within or on the body of man or other animals." FDCA § 201(h)(3), 21 U.S.C. § 321(h)(3).

The FDCA bars the distribution and sale in interstate commerce of any drug or device without FDA approval or clearance. That approval requirement applies to each intended use of a drug or device; a drug may not be sold for a second intended use simply because FDA has approved it for one intended use. FDA's regulatory definition of "intended uses" is thus critically important to all manufacturers, because a manufacturer could face severe civil or criminal sanctions if FDA determines that the manufacturer intended that one of its products be used for an unapproved medical purpose. For the reasons set forth below, WLF submits that FDA proposed definitions of "intended uses"—set forth in proposed regulations issued in September 2015, 80 Fed. Reg. 57756 (the "Proposed 'Intended Use' Regulations")— are in significant tension with the First Amendment and should be revised.

FDA prohibits the "misbranding of any ... drug [or] device ... in interstate commerce," with a drug or device considered misbranded if its labeling does not bear "adequate directions for use." 21 U.S.C. §§ 331, 352. FDA has interpreted this governing statute to permit its regulation of all manufacturer speech concerning off-label uses. *See* 21 C.F.R. §§ 201.5 and 801.4. "The consequences for misbranding are criminal." *Caronia*, 703 F.3d at 154 (citing 21 U.S.C. § 333(a)(2)).

While FDA generally does not regulate a physician's off-label prescribing of an approved drug, and has recognized the propriety and potential value of such uses, *see Buckman Co. v. Plaintiffs' Legal Comm.*, 531 U.S. 341, 350 (2001), the government has prosecuted manufacturers for misbranding based on their representatives' promotion of a drug or device's off-label uses. *See Caronia*, 703 F.3d at 154 (collecting cases). The Proposed "Intended Use" Regulations go even further, threatening to base "intended use" findings on mere knowledge that *others* are using the drug or device off-label. 21 C.F.R. §§ 201.128 and 801.4. In other words, FDA's proposed regulations permit manufacturer liability for misbranding based on little more than its mere knowledge that a product is being prescribed for an off-label use.[3]

The U.S. Court of Appeals for the Second Circuit recently cast doubt on the permissibility of FDA's attempts "to prove intended use by reference to promotional statements made by drug manufacturers or their representatives." *Caronia*, 703 F.3d at 162 n.9 ("[I]t still remains unclear how the government would identify criminal misbranding from communications between drug manufacturers and physicians authorized to prescribe drugs for off-label use."). The court explained that this interpretation would lead to nonsensical results, such as allowing for the successful prosecution of a manufacturer shipping its product to a physician who placed an order with the stated intent of prescribing the drug for an off-label use, but not for the same shipment if the doctor never revealed the intended eventual off-label use. *See ibid.* This illustration demonstrates how untenable it is for FDA to equate knowledge with intent.

Moreover, isolated statements by a manufacturer's representative to a physician should never, alone, establish evidence of a drug or device's intended use. *See Caronia*, 703 F.3d at 168. Instead, FDA should determine intent based principally on a manufacturer's volitional speech such as the language contained either on the product label or immediately accompanying material—and to a lesser extent on language contained in widely circulated advertising material. FDA should revise its Proposed Regulations by removing entirely the following sentence: "It may be shown, for example, by circumstances in which the article is, with the knowledge of such persons or their representatives, offered and used for a purpose for which it is neither labeled nor advertised." 21 C.F.R. §§ 201.128 and 801.4. FDA should further revise its Proposed

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[3] In an apparent effort to soften the proposed regulations' "mere knowledge" language, FDA stated in its "Background" material, "As FDA has previously stated, however, the Agency would not regard a firm as intending an unapproved new use for an approved or cleared medical product based *solely* on the firm's knowledge that such product was being prescribed or used by doctors for such use." 80 Fed. Reg. at 57757 (emphasis added). But that assurance is cold comfort to manufacturers, particularly given FDA's inclusion of the word "solely." The FDCA requires "intent," not mere knowledge. 21 U.S.C. § 321(g)(1). Accordingly, the regulation should make clear that manufacturer knowledge of off-label use by others will *never* be used as evidence of a manufacturer's intent.

Regulations by adding the following statements: (1) FDA recognizes manufacturers' First Amendment right to speak truthfully about their products in appropriate settings without fear that such statements will be used to create new "intended uses" for the products; (2) in determining intent, FDA will focus principally on language contained either on the product label or on immediately accompanying material—and to a lesser extent on language contained in widely circulated advertising material; (3) isolated truthful statements by manufacturers or their representatives will not by themselves be sufficient to create an intended use; and (4) in determining intended uses, FDA will abide by restrictions on FDA authority imposed by federal courts in *United States v. Caronia*, 703 F.3d 149 (2d Cir. 2012), and similar First Amendment decisions.

VII. *Because Medical Professionals Are Unlikely to Be Misled by Truthful Off-Label Communications, the First Amendment Sharply Limits FDA's Power to Regulate Such Communications*

The Request for Comments asks for input on "factors that the Agency should consider in evaluating whether firms' communications about unapproved uses of approved/cleared medical products are truthful and nonmisleading." 81 Fed. Reg. 60302. As the preceding discussion demonstrates, the First Amendment bars FDA from censoring off-label speech unless it meets its burden of demonstrating that listeners could reasonably be misled by the speech. WLF is aware of *no* evidence suggesting that doctors are misled by truthful off-label communications, so long as the speaker makes clear that the uses being discussed are, in fact, off-label. Unless FDA, in the course of this review of current policy, develops a body of evidence suggesting that doctors and other medical professionals *are* regularly misled under such circumstances, it should abide by the First Amendment and end its current policy of severely limiting truthful speech.

WLF is aware of no doctors who are unaware of the distinction between on-label and off-label uses of FDA-approved drugs and devices. Once informed that information about an FDA-approved product is off-label, medical professionals are trained to apply a significant degree of skepticism to the information. In the absence of evidence that doctors in those circumstances are likely to be misled by off-label information that FDA has not determined to be untruthful, the First Amendment prevents FDA from entirely suppressing manufacturer dissemination of the information.

As FDA recognizes, "information about medical products, including information about unapproved uses of approved/cleared medical products, is now broadly available from a wide variety of sources." *Id.* at 60302. In light of the widespread availability of such information, FDA cannot seriously contend that—by preventing manufacturers from disseminating this information—it is protecting medical professionals from exposure to the information. To the contrary, a product's manufacturer is likely to be the entity best positioned to distinguish scientifically validated off-label information from off-label information that lacks solid scientific

support. Thus, by preventing manufacturers from being part of the conversation, FDA is likely causing medical professionals to make worse decisions regarding whether to make off-label use of FDA-approved products when treating their patients.

Manufacturers will, of course, have a natural tendency to portray their products to doctors in the most favorable light. Accordingly, FDA policy should establish disclosure standards to ensure that manufacturers' truthful off-label information includes disclaimers, where appropriate, about conflicting scientific information. But so long as the off-label information qualifies as "truthful" (as defined by the D.C. Circuit in *Pearson I*), the First Amendment prevents FDA from barring all manufacturer dissemination.

VIII. *Information About Off-Label Uses Qualifies as "Truthful" if an Individual Qualified in the Relevant Field Would Conclude that the Information Is of at Least Some Scientific Significance*

The permanent injunction issued against FDA in *Washington Legal Found. v. Friedman* invokes the First Amendment to prohibit FDA from, among other things, restricting medical-product manufacturers from disseminating any article published in "a bona fide peer-reviewed professional journal" or any "reference textbook" to "physicians or other medical professionals." 13 F. Supp. 2d at 73-74. FDA has never accepted the judicial determination that such information qualifies as "truthful." Instead, it has adhered to its view that scientific information does not qualify as "truthful" unless it is the product of a "well-controlled" medical study—*e.g.*, a placebo-controlled, double-blind study.

As the cases discussed above demonstrates, federal case law does not permit FDA to invoke that overly restrictive definition of "truthful" speech when seeking to justify its speech restrictions. In one recent case, a federal district court explicitly rejected FDA's challenge to the truthfulness of scientific information that, FDA claimed, did not meet its exacting requirements. *Amarin Pharma, Inc. v. FDA*, 119 F. Supp. 3d 196 (S.D.N.Y. 2015). Experience demonstrates that doctors and other medical professionals regularly make medical decisions on the basis of information lacking the pedigree demanded by FDA. If that were not so, off-label use would not be so prevalent within the medical profession. Thus, when the *New England Journal of Medicine* reports the results of an "open" study (*i.e.*, one in which doctors and patients are aware of the medication being administered) and those results suggest that off-label use of an FDA-approved medical product is effective in treating a condition for which the product is not FDA-approved, medical professionals will often rely on that information in treating their patients. They are particularly likely to rely on the information by prescribing off-label use of the product if there are no products that FDA has approved for treating the condition.

Of course, it is possible that the medical professional in question will see the off-label material in question even if it is not called to his attention by the product manufacturer. But if

the information is truthful, public-health considerations demand that FDA not rely on that happenstance. There are hundreds of medical journals published each year, and no medical professional reads all of them, or even all the ones most pertinent to his/her specialty. To ensure that doctors are making their treatment decisions based on the latest and best medical evidence, manufacturers—who have both access to the best information and an incentive to provide it—should not be discouraged from providing that information. Given the absence of evidence that medical professionals are being misled by the provision of truthful off-label information, the First Amendment bars FDA from seeking to suppress the dissemination of such information.

IX. *Conclusion*

WLF appreciates this opportunity to submit these comments related to communications by manufacturers regarding FDA-regulated drugs and medical devices. WLF believes that FDA has an important role to play in ensuring that such communications are truthful and non-misleading. However, for the reasons set forth above, WLF urges FDA to abandon its current, overly restrictive view of what constitutes truthful speech and to limit its speech-suppression efforts to speech that is truly false or misleading.

Sincerely,

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