

# HIDDEN TRUTH: THE PERILS AND PROTECTION OF OFF-LABEL DRUG AND MEDICAL DEVICE PROMOTION

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## INTRODUCTION

What can you do if you learn you have a life-threatening illness but there is no Food and Drug Administration-approved medicine to treat it? Sometimes, there is nothing to do but hope. Very often, though, your doctor will be able to prescribe a drug or medical device that has been approved by the Food and Drug Administration (FDA) for a different condition. This practice, called “off-label” prescribing, is perfectly legal, commonly practiced within the medical community, viewed as an essential component of good medical care, and offers greater choice in treatment options for millions of American patients. It is not without controversy, however.

Because the safety and efficacy of off-label uses have not been certified by FDA, some in government and the public health community have long criticized the practice.<sup>1</sup> And FDA has long forbidden drug and device makers from disseminating most information about off-label uses, often making it difficult for doctors and their patients to learn about important therapeutic options.<sup>2</sup>

No federal statute explicitly forbids manufacturers from promoting or otherwise disseminating information about off-label uses of their drugs and devices. FDA has, however, extended its authority over product labeling to encompass manufacturers’ speech in other contexts—including print and broadcast advertisements, brochures

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<sup>1</sup> See, e.g., Stephen Barlas, *New FDA Guidance on Off-Label Promotion Falls Short for Everyone: Obama Administration Is Likely to Revisit It*, 34 PHARMACY & THERAPEUTICS 122, 122 (2009); Henry A. Waxman, *A History of Adverse Drug Experiences: Congress Had Ample Evidence to Support Restrictions on the Promotion of Prescription Drugs*, 58 FOOD & DRUG L. J. 299, 300 (2003).

<sup>2</sup> See Sam Kazman, *A National Survey of Orthopedic Surgeons Regarding the Food and Drug Administration and the Availability of New Drugs*, COMPETITIVE ENTER. INST. (Jan. 30, 2007), <http://cei.org/studies-issue-analysis/national-survey-orthopedic-surgeons-regarding-food-and-drug-administration-an>.

and pamphlets, websites, conferences and seminars, and face-to-face communication.<sup>3</sup> The agency bars nearly all speech promoting an off-label use regardless of its veracity, and vigorously enforces this restriction even when the information is not being broadcast to lay audiences but is provided directly to physicians with sophisticated medical training.

Manufacturers may speak freely about off-label uses when physicians seek that information on their own accord.<sup>4</sup> And, in certain circumstances, the agency even permits drug and device makers to distribute unsolicited, peer-reviewed medical journal articles and textbook reprints describing off-label uses to physicians.<sup>5</sup> This is viewed not as “promotion,” but as “education.” If the distribution of such materials falls outside FDA’s narrow limits, however, the agency is likely to view that speech as unlawful promotion, regardless of whether the information provided is false or misleading.

Ironically, physicians and laymen not paid by a drug or device’s manufacturer are free to tout the benefits of off-label uses in any way and to any listener. Doctors are free, and indeed are often encouraged by the federal government, to prescribe drugs and devices for off-label uses.<sup>6</sup> But as legal scholars have noted, if two physicians were to provide identical truthful and non-misleading information about off-label uses to an identical audience, one of them can be hailed as a medical pioneer and the other convicted of a federal crime solely on the basis of the second doctor’s financial ties to a drug or medical device company.<sup>7</sup> Naturally, this inconsistency has raised questions about the constitutionality of FDA’s treatment of off-label promotion.

Commercial speech is afforded less constitutional protection than pure political or scientific speech. However, the First Amendment forbids the government from regulating truthful and non-misleading commercial speech about lawful conduct in a manner that is more

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<sup>3</sup> See *infra* Section III and accompanying notes.

<sup>4</sup> 21 C.F.R. § 99.1 (2010).

<sup>5</sup> U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY, 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 (2009) [hereinafter GOOD REPRINT GUIDANCE], available at <http://www.fda.gov/OHRMS/DOCKETS/98fr/FDA-2008-D-0053-gdl.pdf>.

<sup>6</sup> See John E. Calfee, *Public Policy Issues in Direct-to-Consumer Advertising of Prescription Drugs*, 21 J. PUB. POL’Y & MARKETING 174, 183 (2002) (noting that practice guidelines disseminated by agencies within the U.S. Department of Health and Human Services recommend off-label uses for certain indications).

<sup>7</sup> Ralph F. Hall & Elizabeth S. Sobotka, *Inconsistent Government Policies: Why FDA Off-Label Regulation Cannot Survive First Amendment Review Under Greater New Orleans*, 62 FOOD & DRUG L.J. 1, 1, 9-10 (2007).

restrictive than necessary to achieve a substantial governmental interest.<sup>8</sup> FDA insists that its bar on off-label promotion is necessary to achieve three interrelated governmental interests: protecting public health through its certification of drug and medical device safety, preserving the integrity of the drug and device approval process, and ensuring that physicians and patients do not receive inaccurate or biased information that may influence prescribing decisions.<sup>9</sup>

If manufacturers may promote medical products for off-label uses, the argument goes, there is no incentive for them to seek approval for these uses. Thus, the agency has no occasion to evaluate the scientific support for such claims, and physicians and their patients may be persuaded to use products that are unsafe or ineffective. FDA and other supporters of the ban recount sordid stories of snake oil salesmen peddling approved products for off-label uses with unproven, exaggerated, or fraudulent health claims, and they argue that eliminating the ban would open the floodgates for such objectionable conduct.<sup>10</sup>

The First Amendment does not protect false, fraudulent, or even unintentionally misleading speech, and federal courts have recognized FDA's substantial interest in policing off-label speech in order to protect the public from unsafe or ineffective uses of drugs and devices.<sup>11</sup> However, there are many less-burdensome alternatives that could promote the government's interests equally well, if not better. The near-total ban on off-label promotion is therefore overly-broad and far more restrictive than necessary to achieve the government's interests. Therefore, it fails the test for proscriptions of commercial speech established by the Supreme Court in *Central Hudson Gas & Electric Corp. v. Public Service Commission*.<sup>12</sup>

Section I of this Article examines the convention of off-label prescribing, its role in the practice of medicine, and its broad support within the medical community. It also sets out some of the pros and cons of the practice. Section II discusses the evolution of the Food,

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<sup>8</sup> *Cent. Hudson Gas & Elec. Corp. v. Pub. Serv. Comm'n*, 447 U.S. 557, 564 (1980); *see also* *Va. State Bd. of Pharmacy v. Va. Citizens Consumer Council, Inc.*, 425 U.S. 748, 761 (1976) (“[S]peech does not lose its First Amendment protection because money is spent to project it, as a paid advertisement . . .”).

<sup>9</sup> *Wash. Legal Found. v. Henney*, 202 F.3d 331, 337 (D.C. Cir. 2000); *Wash. Legal Found. v. Friedman (WLF I)*, 13 F. Supp. 2d 51, 69 (D.D.C. 1998).

<sup>10</sup> *See, e.g.*, *Mem. of Public Citizen as Amicus Curiae in Support of Def's Mot. for Summ. J. and in Opp'n to Pl.'s Mot. for a Prelim. Inj., Allergan, Inc. v. United States*, No. 09-1879 (D.D.C. dismissed 2010) [hereinafter *Public Citizen Br.*]; *Waxman*, *supra* note 1, at 300-01.

<sup>11</sup> *See, e.g.*, *United States v. Caputo*, 288 F. Supp. 2d 912, 921 (N.D. Ill. 2003); *WLF I*, 13 F. Supp. 2d at 69.

<sup>12</sup> *Cent. Hudson Gas & Elec. Corp.*, 447 U.S. at 566.

Drug and Cosmetics Act and FDA's role in the drug and device approval process.

Section III turns specifically to the regulation of medical product labeling and advertising, and discusses FDA's regulation of off-label speech. In particular, that section examines Congress's and the agency's effort to carve out limited exemptions for certain types of off-label speech, and it introduces a discussion of the treatment by federal courts of off-label speech restrictions. Section IV examines three recent court challenges to the off-label promotion ban, one of which was still on-going at the time of publication.

Section V discusses the scope of permissible commercial speech regulation and analyzes the constitutionality of off-label speech restrictions in light of applicable case law. It finds that FDA's current ban on off-label promotion is unconstitutional, but suggests less burdensome alternative restrictions that likely would pass constitutional muster while still advancing the government's asserted interests.

## I. WHAT IS OFF-LABEL PRESCRIBING?

All new drugs and biological products<sup>13</sup> and most new medical devices must be certified by FDA as both safe and effective for a specified use before they can be sold in the United States.<sup>14</sup> As part of the FDA-administered approval process, manufacturers must submit a proposed label that includes, among other things, the medical condition the drug or device is intended to treat, the appropriate dose and route of administration, relevant patient characteristics (such as age, health status, race, etc.), and any warnings or precautions regarding identified risks associated with the products, along with laboratory test data and clinical trial results demonstrating the products to be safe and effective when used as indicated.<sup>15</sup>

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<sup>13</sup> Biological products, or "biologics," are medical products derived from living organisms, including such things as vaccines, serums, antitoxins, whole blood and blood derivatives, etc., regulated under section 351 of the Public Health Services Act (PHSA) (42 U.S.C. § 262 (2006)) as well as under the drug provisions of the Food, Drug and Cosmetics Act (21 U.S.C. §§ 355-60 (2006)). The PHSA establishes a special approval scheme for biologics, but in all ways relevant to this article, the regulation of drugs and biologics is identical. *See* 21 U.S.C. § 352 (2006); GEOFFREY M. LEVITT, *THE DRUGS/BIOLOGICS APPROVAL PROCESS* 113, 155 (Kenneth R. Pina & Wayne L. Pines eds., 3d ed. 2008).

<sup>14</sup> *See* 21 U.S.C. § 355 for drugs; 42 U.S.C. § 262 for biologics; and 21 U.S.C. § 360e for devices.

<sup>15</sup> For drugs, *see* 21 U.S.C. § 355(b)(1) and 21 C.F.R. § 314.50(c)(2) (2010); for biologics, *see* 42 U.S.C. § 262 and 21 C.F.R. § 601.2(a); for devices, *see* 21 U.S.C. § 360e(c)(1)(F) and 21 C.F.R. § 801.1, 801.4, 801.5.

FDA evaluates applications and determines whether the products are safe and effective for their intended uses under the conditions set forth in the proposed labeling, and the agency makes an approval decision with respect to the indicated uses only.<sup>16</sup> Thus, when it approves a drug or device, FDA approves both the product itself and its accompanying label, and the label generally may not be changed without a subsequent agency approval.<sup>17</sup> This approved use is known as the product's "label indication" or "on-label" use.

FDA's regulatory authority does not extend to the practice of medicine, however. So, once a drug or device is placed on the market, physicians may legally prescribe it for any safe and effective off-label use, governed only by professional medical standards and the licensing authority in each state.<sup>18</sup> The U.S. Supreme Court<sup>19</sup> and FDA<sup>20</sup> have expressly recognized that health care professionals may legally prescribe approved drugs for off-label uses. Such uses may include prescribing the product for the approved medical condition but in a different dose, with a different frequency, to a patient outside the approved population, or via a different route of administration (i.e., via subcutaneous injection rather than in oral form).

Off-label uses may also include prescribing the product for a medical condition that is different from the approved, on-label use. For example, the oncology drug Platinol (cisplatin) has been approved for the treatment of bladder, testicular, and ovarian cancer, and it works by "halt[ing] the uncontrolled growth of cancer cells by interrupting the copying of DNA in growing cells."<sup>21</sup> But, because this mechanism of action makes it useful in combating many different kinds of cancerous tumors, Platinol is also frequently prescribed off-label to treat thyroid and lung cancers.<sup>22</sup>

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<sup>16</sup> 21 U.S.C. §§ 352, 355(b), 355(d); 21 C.F.R. §§ 201.5, 314.

<sup>17</sup> 21 U.S.C. § 355(d). *But see* 21 C.F.R. § 314.70(c) ("changes being effected" regulation permitting manufacturers to strengthen safety language without prior FDA approval).

<sup>18</sup> *See* David A. Kessler, *The Regulation of Investigational Drugs*, 320 *NEW ENG. J. MED.* 281, 285 (1989).

<sup>19</sup> *Buckman Co. v. Plaintiffs' Legal Comm.*, 531 U.S. 341, 350 (2001).

<sup>20</sup> Citizen Petition Regarding the Food and Drug Administration's Policy on Promotion of Unapproved Uses of Approved Drugs and Devices, 59 *Fed. Reg.* 59,820, 59,821 (Nov. 18, 1994).

<sup>21</sup> *Understanding the Approval Process for New Cancer Treatments; Q&A: Off-Label Drugs*, NAT'L CANCER INST., [www.cancer.gov/clinicaltrials/learning/approval-process-for-cancer-drugs/page5](http://www.cancer.gov/clinicaltrials/learning/approval-process-for-cancer-drugs/page5) (last visited Feb. 13, 2011).

<sup>22</sup> *Id.*

Similarly, the drug Rituxan (rituximab) was approved in 1997 to treat certain types of non-Hodgkins lymphoma.<sup>23</sup> It proved to be so beneficial, the drug was soon being used off-label to treat various other cancers and several conditions affecting the immune system, including lupus, multiple sclerosis, and arthritis.<sup>24</sup> These off-label uses, developed by practicing physicians, led the manufacturer to conduct clinical trials, eventually resulting in additional approvals for chronic lymphocytic leukemia and rheumatoid arthritis.<sup>25</sup>

The practice of off-label prescribing is widespread, and is common in every field of medicine. A survey of physicians conducted in 2001 indicated that 21% of 160 commonly prescribed drugs were used for off-label uses,<sup>26</sup> though others estimate that as many as 60% of all prescriptions are written for off-label uses.<sup>27</sup>

Off-label uses are frequently considered to be state of the art treatment “[b]ecause the pace of medical discovery runs ahead of the FDA’s regulatory machinery.”<sup>28</sup> Consequently, most private health insurance plans with prescription drug benefits cover various off-label uses, as do Medicare and Medicaid.<sup>29</sup> And practice guidelines disseminated by various agencies within the U.S. Department of Health and Human Services (FDA’s parent body), such as the National Cancer Institute and the National Cholesterol Education Program, specifically recommend certain off-label uses.<sup>30</sup> The American Medical Association (AMA) has noted that “clinically appropriate medical practice at times requires the use of pharmaceuticals for ‘off-label’ indications.”<sup>31</sup> Consequently, physicians may even be subject to malpractice liability if they do not use drugs and devices for off-label

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<sup>23</sup> Candice J. Bruce, *Rituxan® Anniversary: 10 Years of Progress*, ONCOLOGY BUS. REV., Nov. 2007, at 18, available at [http://www.oncbiz.com/documents/OBR\\_1107\\_RA.pdf](http://www.oncbiz.com/documents/OBR_1107_RA.pdf).

<sup>24</sup> *Id.* at 19.

<sup>25</sup> *Id.*

<sup>26</sup> David C. Radley et al., *Off-label Prescribing Among Office-Based Physicians*, 166 ARCHIVES INTERNAL MED. 1021, 1021 (2006).

<sup>27</sup> James M. Beck & Elizabeth D. Azari, *FDA, Off-Label Use, and Informed Consent: Debunking Myths and Misconceptions*, 53 FOOD & DRUG L.J. 71, 80 (1998).

<sup>28</sup> Richardson v. Miller, 44 S.W.3d 1, 13 n.11 (Tenn. Ct. App. 2000).

<sup>29</sup> See Joshua Cohen et al., *Off-Label Use Reimbursement*, 64 FOOD & DRUG L.J. 391 (2009).

<sup>30</sup> Calfee, *supra* note 6, at 183.

<sup>31</sup> American Medical Association, MEMORANDUM OF THE AMA HOUSE OF DELEGATES, *Resolution 820: Off-Label Use of Pharmaceuticals*, <http://tinyurl.com/yfpmwyo> (last visited Sep. 21, 2005).

indications when doing so constitutes the medically recognized standard of care.<sup>32</sup>

The AMA has repeatedly studied the practice and has voiced its “strong support for the autonomous clinical decision-making authority of a physician,” and agrees that “a physician may lawfully use an FDA approved drug product or medical device for an unlabeled indication.”<sup>33</sup> That is not surprising given the overwhelming amount of support among practicing physicians for maintaining the legality of off-label prescriptions. In a 2008 survey conducted by economists at George Mason University, 94% of the physician respondents said they would oppose any change in the law that would prevent doctors from prescribing drugs for off-label indications.<sup>34</sup> Just 2% said they would favor such a change, and 4% said they were not sure.<sup>35</sup>

Although it is used in every field of medicine, off-label prescribing is particularly prevalent in psychiatry, oncology, and pediatrics.<sup>36</sup> A 1991 study by the U.S. General Accounting Office (GAO, now known as the Government Accountability Office) found that one-third of the drugs prescribed for the treatment of cancer were off-label, and that more than half of all cancer patients received at least one drug for an off-label indication.<sup>37</sup> According to a 2007 study, off-label uses also account for nearly 50% of cardiac medications and anticonvulsant drug prescriptions.<sup>38</sup>

Similarly, patients with rare, or so-called “orphan” diseases, are especially dependent on off-label uses for their treatment because the number of patients with each orphan disease is often too low to justify the tremendous expense of seeking FDA’s approval for those indications.<sup>39</sup> An estimated 21% of all drugs prescribed to treat orphan dis-

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<sup>32</sup> Steven R. Salbu, *Off-Label Use, Prescription, and Marketing of FDA-Approved Drugs: An Assessment of Legislative and Regulatory Policy*, 51 FLA. L. REV. 181, 190-91 (1999).

<sup>33</sup> AM. MED. ASS’N, HEALTH AND ETHICS POLICIES OF THE AMA HOUSE OF DELEGATES 103-05 (Policy H-120.988), <http://www.ama-assn.org/ad-com/polfind/Hlth-Ethics.pdf> [hereinafter HEALTH AND ETHICS POLICIES].

<sup>34</sup> Daniel B. Klein & Alexander Tabarrok, *Do Off-Label Drug Practices Argue Against FDA Efficacy Requirements? A Critical Analysis of Physicians’ Argumentation for Initial Efficacy Requirements*, 67 AM. J. ECON. & SOC. 743, 750 (2008).

<sup>35</sup> *Id.*

<sup>36</sup> Muriel R. Gillick, *Controlling Off-Label Medication Use*, 150 ANN. INTERNAL MED. 344, 344 (2009).

<sup>37</sup> U.S. GOV’T GENERAL ACCOUNTING OFFICE, GAO/PEMD-91-14, OFF-LABEL DRUGS: REIMBURSEMENT POLICIES CONSTRAIN PHYSICIANS IN THEIR CHOICE OF CANCER THERAPIES 3 (1991).

<sup>38</sup> Radley et al., *supra* note 26.

<sup>39</sup> Bryan A. Liang & Tim Mackey, *Reforming Off-Label Promotion to Enhance Orphan Disease Treatment*, 327 SCI. 273, 273 (2010).

eases, and up to 83% for certain diseases, are off-label.<sup>40</sup> With clinical testing and the supplemental application process taking five to ten years and costing hundreds of millions of dollars,<sup>41</sup> getting on-label approval for an orphan disease could put the price of many treatment options out of reach for these vulnerable patients.

Unfortunately, not all off-label uses prove to be effective or safe. Occasionally, off-label uses that anecdotally appear to have substantial efficacy later are shown to be ineffective. Others may be used for years without physicians fully understanding their attendant risks. Throughout the 1980s and 1990s, for example, American doctors prescribed an unapproved combination of estrogen and progestin to millions of post-menopausal women in the expectation that this hormone replacement therapy would help prevent bone loss and relieve menopause symptoms.<sup>42</sup> A comprehensive study published in 2002, however, revealed that the off-label combination could increase the risk of breast cancer, heart attacks, strokes, and blood clots.<sup>43</sup> Similarly, an estimated six million patients were prescribed the unapproved combination of weight loss drugs fenfluramine and phentermine during the 1980s and 1990s “on the basis of a single study involving just 121 patients.”<sup>44</sup> But a study published in 1997 indicated that this “fen-phen” combination might cause heart valve defects in as many as one-third of patients.<sup>45</sup>

Still, for many conditions, off-label uses are considered to be essential for the practice of medicine, and their safety and efficacy have been demonstrated through substantial clinical testing. “In fact, a drug given off-label may have been proven to be safer and more beneficial than any drug labeled for that disease.”<sup>46</sup> According to the GAO’s Director of Health Services Quality and Public Health Issues, “this occurred with some frequency in the cancer area where drugs that had been approved for one form of cancer were subsequently shown to

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<sup>40</sup> *Id.*

<sup>41</sup> See, e.g., Joseph A. DiMasi et al., *The Price of Innovation: New Estimates of Drug Development Costs*, 22 J. HEALTH ECON. 151 (2003).

<sup>42</sup> See Gina Kolata & Melody Petersen, *Hormone Replacement Study a Shock to the Medical System*, N.Y. TIMES, July 10, 2002, at A1.

<sup>43</sup> *Id.*

<sup>44</sup> Gina Kolata, *How Fen-Phen, A Diet ‘Miracle,’ Rose and Fell*, N.Y. TIMES, Sept. 23, 1997, at F1.

<sup>45</sup> *Id.*

<sup>46</sup> *Off-Label Drug Use and FDA Review of Supplemental Drug Applications: Hearing Before the H. Subcomm. On Human Resources and Intergovernmental Relations of the H. Comm. on Government Reform and Oversight*, 104th Cong. 12 (1996) (statement of Sarah F. Jaggard).



have efficacy against other cancers, yet the label remained unchanged.”<sup>47</sup>

Once developed, physicians learn about beneficial off-label uses of drugs and devices through medical and science journals, medical specialty association newsletters, conferences, seminars, Internet sources, and from their colleagues.<sup>48</sup> Naturally, medical products companies are another important source for this information. Physicians try to keep abreast of new research findings, but they cannot read every issue of the hundreds of medical journals published in this country every year.<sup>49</sup> Manufacturers, on the other hand, tend to have accumulated the most information about the risks, benefits, and various on- and off-label uses of their own products.<sup>50</sup> Furthermore, drug and device makers have ample ability and incentive to distribute up-to-date information about off-label uses of their products.

As discussed below, however, many of these activities are heavily restricted by FDA because the agency wishes to preserve its ability to review the safety and efficacy claims that manufacturers make about their products. Supporters of the off-label promotion ban argue further that, in the absence of FDA oversight, manufacturers also have an incentive to skew promotional claims in a way that is false or misleading.<sup>51</sup> However, FDA off-label promotion policy bans all speech, not just that which is false or misleading.

## II. FDA AND THE APPROVAL PROCESS

Despite the widespread and essential use of drugs and devices for off-label treatment, FDA and medical products industry critics insist that curtailing manufacturer speech about off-label uses is an important consumer protection measure. According to one of the industry’s biggest critics, U.S. Rep. Henry A. Waxman (D-Cal.), the history of

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<sup>47</sup> *Id.*

<sup>48</sup> AM. MED. ASS’N, ANNUAL MEETING OF THE AMERICAN MEDICAL ASSOCIATION: REPORTS OF THE COUNCIL ON SCIENTIFIC AFFAIRS (1997), available at <http://www.ama-assn.org/ama1/pub/upload/mm/443/csaa-97.pdf>.

<sup>49</sup> *See id.*

<sup>50</sup> *See* *Wyeth v. Levine*, 129 S. Ct. 1187, 1202 (2009) (noting that manufacturers “have superior access to information about their drugs, especially in the post-marketing phase as new risks emerge”); Citizen Petition Regarding the Food and Drug Administration’s Policy on Promotion of Unapproved Uses of Approved Drugs and Devices, 59 Fed. Reg. 59,820, 59,821 (Nov. 18, 1994) (“Scientific departments within regulated companies generally maintain a large body of information on their products.”).

<sup>51</sup> *See, e.g.,* Public Citizen Br., *supra* note 10, at 8 (comparing manufacturers’ off-label promotion to “snake-oil salesmen touting products based on fraudulent or unproved claims”).

U.S. medical products regulation “demonstrates beyond question that without premarket safety *and* effectiveness requirements, deceptive, unsubstantiated claims about health-related products proliferate, at a tremendous cost in human lives.”<sup>52</sup>

The Food, Drug and Cosmetics Act of 1938 required drug manufacturers to submit evidence of safety, but not efficacy, for FDA’s review before placing a new drug on the market in the United States.<sup>53</sup> Prior to that time, and for the next two-and-a-half decades, manufacturers frequently promoted marketed drugs for various uses with little or no scientific support for efficacy claims.<sup>54</sup> FDA had the authority to police the marketplace and bring civil actions against manufacturers that promoted drugs with false or misleading claims, but post-marketing enforcement of deceptive claims proved difficult, time consuming, and therefore often ineffective.<sup>55</sup> An FDA analysis completed in 1984 concluded that there was insufficient scientific evidence supporting the effectiveness for any use of nearly one-third of the 3,443 prescription drugs on the market in 1962, when Congress enacted new legislation enhancing FDA’s regulatory authority.<sup>56</sup>

Some products on the market in 1962 were found to be not just ineffective, but unsafe for several of the indications for which manufacturers actively promoted them.<sup>57</sup> Few drugs are perfectly safe in the sense that they have no negative side effects. Consequently, the “safety” of any medical product may only be evaluated with reference to that product’s efficacy—that is, whether its benefits outweigh its risks. A drug that is highly effective at treating a life-threatening disease may be considered safe enough for use, even if it has serious negative side effects. On the other hand, FDA and many patients may consider that same drug to be unsafe when used to treat a minor condition like muscle aches or acne, or to treat a more serious condition with limited or no efficacy. Nevertheless, because reliable and objective evidence regarding safety and efficacy was difficult to find in the pre-1962 era, many physicians relied heavily on promotional claims disseminated by manufacturers.<sup>58</sup>

It was this long record of unsubstantiated and, at times, actively deceptive safety and efficacy claims that led Congress to pass the

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<sup>52</sup> Waxman, *supra* note 1, at 299.

<sup>53</sup> *Id.* at 300.

<sup>54</sup> *Id.* at 300-04.

<sup>55</sup> *Id.* at 301-03.

<sup>56</sup> *Id.* at 304.

<sup>57</sup> *Id.* at 304-06.

<sup>58</sup> *Id.* at 306.

Drug Act Amendments of 1962.<sup>59</sup> This statute required manufacturers to produce, using “adequate and well-controlled clinical studies,” evidence of safety *and* efficacy before FDA could approve new drugs for marketing.<sup>60</sup> The Medical Device Act of 1976 established a similar FDA approval process for evaluating the safety and efficacy of Class III, or “high risk” devices.<sup>61</sup>

In light of this history, FDA insists that barring manufacturers from promoting off-label uses is necessary to protect public health and safety.<sup>62</sup> According to the agency, its off-label promotion policy “rests on the premise—amply supported by the legislative history of the 1962 legislation—that drug manufacturers, when left to their own desires, frequently make *untruthful* claims about new uses,” and it “protects the public from promotional claims that are unsubstantiated at best, and false at worst.”<sup>63</sup> In addition, that policy provides manufacturers with “ample incentive to get previously unapproved uses on label,” thereby giving the agency an opportunity to review the adequacy of scientific evidence supporting those uses.<sup>64</sup> It also ensures that physicians “receive accurate and unbiased information so that they may make informed prescription choices.”<sup>65</sup> Nevertheless, the current off-label promotion restrictions curtail even accurate and unbiased information in at least three important ways.

First, the medical community,<sup>66</sup> federal courts,<sup>67</sup> and even FDA acknowledge that patients benefit when their physicians have access to “objective, balanced, and accurate information on important unapproved uses of approved products.”<sup>68</sup> All three agree that manufacturers are often in the best position to provide that information because they tend to have accumulated the most data about the risks, benefits, and various on- and off-label uses of their products.<sup>69</sup> Manufacturers

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<sup>59</sup> *Id.* at 301-06.

<sup>60</sup> 21 U.S.C. § 355(b)(1) (2006).

<sup>61</sup> *Id.* §§ 360c(a)(1)(C), 360e.

<sup>62</sup> Defendant’s Memorandum of Points and Authorities in Support of Motion to Dismiss or for Summary Judgment, *Allergan, Inc. v. United States*, No. 09-1879 (D.D.C. dismissed 2010).

<sup>63</sup> *Id.* at 27 (emphasis in original).

<sup>64</sup> *WLF I*, 13 F. Supp. 2d 51, 69 (D.D.C. 1998).

<sup>65</sup> *Id.*

<sup>66</sup> *See, e.g.*, HEALTH AND ETHICS POLICIES, *supra* note 33.

<sup>67</sup> *See, e.g.*, *WLF I*, 13 F. Supp. 2d at 69.

<sup>68</sup> Dissemination of Information on Unapproved/New Uses for Marketed Drugs, Biologics and Devices, 63 Fed. Reg. 64,556, 64,579 (Nov. 20, 1998).

<sup>69</sup> *See Wyeth v. Levine*, 129 S. Ct. 1187, 1202 (2009) (noting that manufacturers “have superior access to information about their drugs, especially in the post-marketing phase as new risks emerge”); Citizen Petition Regarding the Food and Drug Administration’s Policy on Promotion of Unapproved Uses of Approved Drugs

also have the ability and incentive to communicate this information to prescribers.<sup>70</sup> FDA's off-label promotion ban, however, often prevents these most well-informed speakers from communicating, which many physicians believe impedes their ability to learn about new uses for drugs and devices.<sup>71</sup>

Second, even when manufacturers intend to seek FDA approval for a new indication, it is undisputed that the agency's review mechanism often lags behind scientific validation.<sup>72</sup> One study examining off-label drug uses that were eventually approved by FDA concluded that these uses appeared in official treatment compendia an average of two and a half years before FDA approval.<sup>73</sup> But even once the necessary clinical trials are conducted and the supplemental application is filed with FDA, manufacturers are still forbidden to promote the off-label use. Thus, even after manufacturers take this substantial step toward satisfying FDA's interest in reviewing the scientific evidence supporting supplemental approvals for off-label uses, the policy continues to bar truthful speech.

Third, it is not always feasible to conduct the clinical trials necessary to support a supplemental application seeking approval for an off-label use. Particularly in such situations where the off-label use represents the medically accepted standard of care, "it may be unethical to conduct the necessary study" because doing so requires some patients to be randomized into the control arm of the trial, in which subjects are given a placebo or are treated with a product known or believed to be less effective.<sup>74</sup> Indeed, among physicians and medical ethicists, "[t]here is general agreement that placebo or untreated controls are not appropriate in trials of therapy for life-threatening condi-

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and Devices, 59 Fed. Reg. 59,820, 59,823 (Nov. 18, 1994) ("Scientific departments within regulated companies generally maintain a large body of information on their products"); HEALTH AND ETHICS POLICIES, *supra* note 33.

<sup>70</sup> See *Wyeth*, 129 S. Ct. at 1202; Citizen Petition Regarding the Food and Drug Administration's Policy on Promotion of Unapproved Uses of Approved Drugs and Devices, 59 Fed. Reg. 59,820, 59,821 (Nov. 18, 1994); HEALTH AND ETHICS POLICIES, *supra* note 33.

<sup>71</sup> See Kazman, *supra* note 2.

<sup>72</sup> See *Richardson v. Miller*, 44 S.W.3d 1, 13 (Tenn. Ct. App. 2000).

<sup>73</sup> J. Howard Beales, *New Uses for Old Drugs*, in COMPETITIVE STRATEGIES IN THE PHARMACEUTICAL INDUSTRY 281, 303 (Robert B. Helms ed., 1996).

<sup>74</sup> Brief of the National Spasmodic Torticollis Association, the National Spasmodic Dysphonia Association, Allied Educational Foundation, and Washington Legal Foundation as Amici Curiae in Support of Plaintiff's Motion for Preliminary Injunction at 15, *Allergan, Inc. v. United States*, No. 09-1879 (D.D.C. dismissed 2010) [hereinafter Patient Assn. Br.].

tions if a treatment that prolongs or preserves life is available.”<sup>75</sup> Consequently, “many doctors understandably will not encourage their patients to enter into a study where they might end up with a placebo rather than standard-of-care therapy.”<sup>76</sup> Forbidding off-label promotion even in cases where conducting the necessary clinical trials would be unethical can in no reasonable way help FDA promote the supplemental approval process.

### III. THE REGULATION OF OFF-LABEL SPEECH

The statutory provisions governing medical product advertising are contained in two brief paragraphs within the lengthy sections of the Food, Drug and Cosmetics Act describing the misbranding of drugs and devices.<sup>77</sup> These provisions establish that a drug shall be considered misbranded if any advertisement does not contain the “established” (i.e., non-proprietary) name of the product, its formula showing all ingredients, and a “brief summary relating to side effects, contraindications, and effectiveness as shall be required in regulations which shall be issued by the Secretary [of Health and Human Services] . . . .”<sup>78</sup> Devices are to be considered misbranded if the advertisement does not contain the product’s “established” name, a “brief statement of the intended uses of the device and relevant warnings, precautions, side effects, and contraindications,” and in some circumstances, a list of the device’s components and ingredients.<sup>79</sup> Neither section explicitly distinguishes between approved and unapproved uses.

Despite the seemingly modest restrictions on drug and device advertising enumerated within the Act, “[p]romotional materials issued by medical products companies or their agents are among the most regulated of all forms of communication in the United States.”<sup>80</sup> To erect such an edifice, FDA has had to piggy-back its regulations for medical product “advertising” on its statutory authority over drug and device “labeling,” by treating advertisements and other promotional material as part of the products’ labels.

Manufacturers are prohibited from marketing drugs whose *labels* “prescribe[], recommend[], or suggest[]” that they be used for an indi-

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<sup>75</sup> Richard Simon, *Are Placebo-Controlled Clinical Trials Ethical or Needed When Alternative Treatment Exists?*, 133 ANN. INTERNAL MED. 474, 474 (2000).

<sup>76</sup> Patient Assn. Br., *supra* note 74, at 15.

<sup>77</sup> 21 U.S.C. § 352(n), (r) (2006).

<sup>78</sup> *Id.* § 352(n).

<sup>79</sup> *Id.* § 352(r).

<sup>80</sup> WAYNE L. PINES, REGULATION OF PROMOTION AND DISTRIBUTION 320 (Kenneth R. Pina & Wayne L. Pines eds., 3d ed. 2008).

cation that FDA has not approved,<sup>81</sup> or whose *labels* contain any information that is “false or misleading in any particular.”<sup>82</sup> The Act defines a product’s “label” as any “written, printed, or graphic matter” on the product itself “or any of its containers or wrappers, or [other items] accompanying” the product.<sup>83</sup> The Supreme Court has construed the term “accompanying” to include matter that “supplements or explains” the attached label, even if it does not physically accompany the product, any time the two share a “common origin and a common destination” as part of an “integrated” transaction.<sup>84</sup>

FDA has taken this already broad view of the term “labeling” to re-define, by regulation, a drug’s label to include any:

[b]rochures, booklets, mailing pieces, detailing pieces, file cards, bulletins, calendars, price lists, catalogs, house organs, letters, motion picture films, film strips, lantern slides, sound recordings, exhibits, literature, and reprints and similar pieces of printed, audio, or visual matter descriptive of a drug and references published (for example, the “Physicians Desk Reference”) for use by medical practitioners, pharmacists, or nurses, containing drug information supplied by the manufacturer, packer, or distributor of the drug and which are disseminated by or on behalf of its manufacturer, packer, or distributor . . .<sup>85</sup>

Under this expansive definition, a manufacturer may not promote a drug by supplying doctors with a brochure describing scientific research on off-label uses because FDA will treat the brochure as a part of the drug’s label, which in turn causes the drug to be misbranded. Indeed, the agency has determined that nearly any kind of promotional communication by a manufacturer about one of its medical products is part of that product’s label, regardless of whether the information actually accompanies the product or is sent to the same destination as the product as part of an integrated transaction as required by the Supreme Court’s interpretation of the statute.<sup>86</sup>

Similarly, the Act deems a drug to be misbranded if its *label* does not contain “adequate directions for use.”<sup>87</sup> FDA regulations define a product’s “intended use” to include any use “objective[ly] inten[ded]

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<sup>81</sup> 21 U.S.C. § 355(a), (d) (2006).

<sup>82</sup> *Id.* § 352(a).

<sup>83</sup> *Id.* § 321(k), (m).

<sup>84</sup> *Kordel v. United States*, 335 U.S. 345, 348-50 (1948).

<sup>85</sup> 21 C.F.R. § 202.1(l)(2) (2011).

<sup>86</sup> *See, e.g., Hall & Sabotka, supra* note 7, at 8-10.

<sup>87</sup> 21 U.S.C. § 352(f)(1).

by] the persons legally responsible” for the product’s labeling.<sup>88</sup> And such intent “may be shown by the circumstances surrounding the distribution of the [product],” including information contained in “labeling claims, advertising matter, or oral or written statements by such persons or their representatives.”<sup>89</sup> Intent may also be shown any time at which, “with the knowledge of such persons or their representatives, [the product is] offered and used for a purpose for which it is neither labeled nor advertised.”<sup>90</sup> Thus, any communication that suggests or recommends an off-label use may be viewed as evidence of the manufacturer’s “intended uses” for the product.<sup>91</sup>

If promotional material suggests a use for which the product’s actual label—meaning information on or physically accompanying the drug—does not include “adequate directions” for use, FDA will consider such promotional material as a misbranding of the product.<sup>92</sup> Of course, unapproved uses, by definition, cannot be mentioned in the label.<sup>93</sup> Consequently, the presentation by a company scientist at a medical seminar of data from clinical research on off-label uses can be considered evidence of the manufacturer’s intended use, causing the product to be misbranded. So can a conversation between two physicians about off-label uses if one of them happens to have worked as a consultant for the manufacturer.

The federal government has aggressively prosecuted many drug and device manufacturers for providing unapproved information about off-label uses. From 2003 to 2007, FDA issued forty-two notices of violation demanding that drug companies cease disseminating information describing off-label uses.<sup>94</sup> And, during that period, the Department of Justice settled at least eleven civil and criminal cases involving off-label promotion.<sup>95</sup> In 2009, the drug manufacturer Pfizer pled guilty to criminal charges and paid a record \$2.3 billion to settle allegations that it promoted fourteen of its products for off-label uses.<sup>96</sup> Eli Lilly was forced to pay \$1.4 billion for promoting its schizophrenia drug Zyprexa for off-label uses.<sup>97</sup>

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<sup>88</sup> 21 C.F.R. § 201.128 (2010).

<sup>89</sup> *Id.*

<sup>90</sup> *Id.*

<sup>91</sup> *Id.*

<sup>92</sup> 21 C.F.R. § 201.100(c)(1).

<sup>93</sup> 21 U.S.C. § 355(a), (d) (2006).

<sup>94</sup> U.S. GOV’T ACCOUNTABILITY OFFICE, GAO-08-835, PRESCRIPTION DRUGS: FDA’S OVERSIGHT OF THE PROMOTION OF DRUGS FOR OFF-LABEL USES 6 (2008).

<sup>95</sup> *Id.*

<sup>96</sup> Peter Benesh, *Pharma Seeks Cure For Off-Label Woes*, INVESTOR’S BUS. DAILY, Oct. 26, 2009, at A14.

<sup>97</sup> *Id.*

The ban on off-label promotion applies not just to the pharmaceutical and medical device companies, but also to financially-interested third parties, such as physicians who participate in clinical trials or who are paid to promote the products on behalf of the manufacturer.<sup>98</sup> For example, in January 2010, FDA sent a warning letter to a Florida dermatologist and medical researcher for illegally mentioning in interviews with *Elle* and *Allure* magazines and NBC's Today show that an anti-wrinkle drug on which she was conducting clinical trials had shown positive results and was better than a competitor's product.<sup>99</sup>

In the words of one observer, "the same speech, delivered to the same audience by doctors with the same qualifications, [is] treated differently if one of those speakers has been funded by a pharmaceutical company."<sup>100</sup> Ironically, FDA permits financially *disinterested* physicians to promote off-label indications by "tell[ing] unsophisticated patients that they should use" them, but forbids other physicians from "mak[ing] the same suggestion to the sophisticated medical professionals doing the prescribing."<sup>101</sup> As one federal judge has reasoned,

the FDA does not question a physician's evaluative skills when an article about an off-label use appears among a group of articles in the *New England Journal of Medicine*, or when one physician refers a peer physician to a published article he recently perused, or even when a physician requests a reprint from a manufacturer. Why the ability of a doctor to critically

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<sup>98</sup> See Final Guidance on Industry-Supported Scientific and Educational Activities, 62 Fed. Reg. 64,074, 64,097 (Dec. 3, 1997).

<sup>99</sup> Natasha Singer, *F.D.A. Aims at Doctors' Drug Pitches*, N.Y. TIMES, Feb. 1, 2010, at B1; Letter from Shefali Doshi, Regulatory Review Officer, Food and Drug Admin., to Leslie Baumann, Baumann Cosmetic and Research Institute (Jan. 11, 2010), [available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/EnforcementActivitiesbyFDA/WarningLettersandNoticeofViolationLetterstoPharmaceuticalCompanies/UCM198400.pdf](http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/EnforcementActivitiesbyFDA/WarningLettersandNoticeofViolationLetterstoPharmaceuticalCompanies/UCM198400.pdf).

<sup>100</sup> Jacob Rogers, *Freedom of Speech and the FDA's Regulation of Off-Label Drug Uses*, 76 GEO. WASH. L. REV. 1429, 1432 (2008) (paraphrasing Ralph F. Hall & Elizabeth S. Sobotka, *Inconsistent Government Policies: Why FDA Off-Label Regulation Cannot Survive First Amendment Review under Greater New Orleans*, 62 FOOD & DRUG L.J. 1, 9-10 (2007)).

<sup>101</sup> Amicus Curiae Br. of Washington Legal Foundation in Support of Appellant Alfred Caronia and Reversal at 7, *United States v. Caronia*, No. 09-5006-CR (2d Cir. 2010).



evaluate scientific findings depends upon how the article got into the physician's hands . . . is unclear to this court.<sup>102</sup>

Although the agency may suspect that disinterested actors are less likely to disseminate biased, inaccurate, or misleading information, physicians are learned intermediaries with expert training whom patients and the government trust to “make accurate, life-and-death decisions based upon the scientific evidence before them.”<sup>103</sup> Surely they can be trusted to treat information disseminated by manufacturers with a requisite level of skepticism.

The agency's aggressive prosecution has come at a cost. A series of national surveys has shown that a large majority of physicians—including oncologists, cardiologists, emergency room physicians, orthopedic surgeons, neurologists and neurosurgeons—believe FDA has made it more difficult for them to learn about new uses for drugs and devices, and that the agency should not restrict information about off-label use.<sup>104</sup> The American Medical Association confirms that there is an “important need for physicians to have access to accurate and unbiased information about unlabeled uses of drugs and devices.”<sup>105</sup> Accordingly, that organization “supports the dissemination of independently derived scientific information about unlabeled uses by manufacturers to physicians, if the independent information is provided in its entirety, is not edited or altered by the manufacturer, and is clearly distinguished from manufacturer-sponsored materials.”<sup>106</sup>

#### A. Promotion Versus Education

By the late 1980s, many drug and device manufacturers began to subtly promote their approved products by distributing peer-reviewed medical journal articles and textbook reprints to physicians describing off-label uses. Some of these firms also began to sponsor or financially support medical symposia, continuing medical education programs, and other scientific or medical conferences at which off-label uses were discussed or demonstrated.<sup>107</sup> FDA recognized that off-label prescribing was an important component of medical practice, and that physicians and their patients benefit from having access to truthful and non-misleading scientific information describing off-label treatments. Nevertheless, the agency wished to prevent such activities

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<sup>102</sup> *WLF I*, 13 F. Supp. 2d 51, 70 (D.D.C. 1998).

<sup>103</sup> *Id.*

<sup>104</sup> See Kazman, *supra* note 2.

<sup>105</sup> HEALTH AND ETHICS POLICIES, *supra* note 33.

<sup>106</sup> *Id.*

<sup>107</sup> *WLF I*, 13 F. Supp. 2d at 57-58.

from being used for the purpose of *promoting* unapproved uses, rather than simply sharing scientific information. FDA explained that simple information sharing and “education” was permissible, but that “promotion” of off-label uses was not.<sup>108</sup> Nowhere, however, had the agency offered guidance in determining what distinguished lawful from unlawful conduct, so any information dissemination *could* “constitute[] improper labeling and/or promotion” when the off-label use of a manufacturer’s products was discussed.<sup>109</sup>

In 1995, the non-profit Washington Legal Foundation (WLF) mounted a court challenge to this then-informal policy restricting off-label promotion.<sup>110</sup> The organization argued that the restrictions on truthful and non-misleading communication violated the First Amendment right of physicians to receive information about off-label uses from manufacturers.<sup>111</sup>

While the case was pending, FDA formalized these policies by publishing guidance documents describing the conditions under which manufacturers could lawfully distribute journal article and textbook reprints to physicians<sup>112</sup> and support continuing medical education programs<sup>113</sup> without running afoul of the agency’s ban on off-label promotion. In 1997, the U.S. Congress enacted the Food and Drug Administration Modernization Act (FDAMA), one provision of which expressly permitted limited dissemination of medical journal articles and textbook reprints describing unapproved uses.<sup>114</sup>

FDAMA specifically permitted drug and device manufacturers to “disseminate to a health care practitioner, [insurance firm or related business, or government agency] . . . written information concerning the safety, effectiveness, or benefit of a use not described in the approved labeling,” if the manufacturer complied with certain conditions.<sup>115</sup> Among these were requirements that the manufacturer first submit an application requesting that FDA approve the use in ques-

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<sup>108</sup> See, e.g., Decision in *Washington Legal Foundation v. Henney*, 65 Fed. Reg. 14,286 (Mar. 16, 2000); Final Guidance on Industry-Supported Scientific and Educational Activities, 62 Fed. Reg. 64,074, 64,075-77 (Dec. 3, 1997).

<sup>109</sup> *Wash. Legal Found. v. Kessler*, 880 F.Supp. 26, 28 (D.D.C. 1995).

<sup>110</sup> *Id.*; *WLF I*, 13 F. Supp. 2d at 62-65.

<sup>111</sup> *Kessler*, 880 F.Supp. at 27-28.

<sup>112</sup> Guidance to Industry on Dissemination of Reprints of Certain Published, Original Data and Guidance for Industry Funded Dissemination of Reference Texts, 61 Fed. Reg. 52,800 (Oct. 8, 1996).

<sup>113</sup> See Final Guidance on Industry-Supported Scientific and Educational Activities, 62 Fed. Reg. at 64,096-99.

<sup>114</sup> Food and Drug Administration Modernization Act of 1997, Pub. L. No. 105-115, sec. 401, § 552 (1997).

<sup>115</sup> 21 U.S.C. § 360aaa(a) (Supp. 1998).

tion<sup>116</sup> and that the disseminated material bear a “prominently displayed statement” disclosing that the use had not been approved by FDA.<sup>117</sup>

The Act seemingly prohibited dissemination of any information regarding off-label uses that did not comply with the regulations.<sup>118</sup> But, if the statutory conditions *were* met, FDA could not use the distribution of approved information as evidence of “labeling, adulteration, or misbranding of the drug or device” or of the manufacturer’s intent that its product be prescribed for the unapproved use.<sup>119</sup> As discussed above, if not for this provision, the agency *could* use the dissemination of such information as evidence of illegal distribution and misbranding.

### B. The Off-Label Ban Goes to Court

With a set of formal policies now in place, the WLF expanded its challenge and alleged that FDA guidance documents and FDAMA off-label provisions specifically, as well as the agency’s underlying policies more generally, were unconstitutional speech restrictions. District Court Judge Royce C. Lamberth applied the four-part test for evaluating commercial speech restrictions announced by the Supreme Court in *Central Hudson Gas & Electric Corp. v. Public Service Commission*.<sup>120</sup> That decision directs the court to first inquire whether (1) a challenged rule restricts speech that is not misleading and concerns a lawful activity.<sup>121</sup> If this threshold requirement is satisfied, the court is then instructed to consider whether: (2) the government has asserted a substantial interest in regulating that speech, (3) the regulation directly advances that governmental interest, and (4) the restrictions are no more extensive than necessary to advance that interest.<sup>122</sup> Upon completing his analysis, Judge Lamberth agreed that the policies violated the First Amendment.<sup>123</sup>

The threshold condition of the *Central Hudson* test was satisfied because the activity promoted by the speech in question—the prescribing by physicians of drugs or devices for off-label uses—is law-

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<sup>116</sup> *Id.* § 360aaa(b)(1)(A), (b)(1)(B).

<sup>117</sup> *Id.* § 360aaa(b)(6).

<sup>118</sup> *Id.* § 331(z).

<sup>119</sup> *Id.* § 360aaa-6(b).

<sup>120</sup> *WLF I*, 13 F. Supp. 2d 51, 65-74 (D.D.C. 1998).

<sup>121</sup> *Cent. Hudson Gas & Elec. Corp. v. Pub. Serv. Comm’n*, 447 U.S. 557, 566 (1980).

<sup>122</sup> *Id.*

<sup>123</sup> *Wash. Legal Found. v. Henney (WLF III)*, 56 F.Supp.2d 81 (D.D.C. 1999); *WLF I*, 13 F. Supp. 2d at 72-73.

ful and the distribution of journal and text book reprints was not inherently misleading.<sup>124</sup> In parts two and three, Judge Lamberth rejected FDA's argument that it had a substantial interest in preventing manufacturers from distributing information on off-label uses because doing so prevents physicians from being misled.<sup>125</sup> He did, though, acknowledge that FDA had a substantial interest in "provid[ing] an incentive for manufacturers to go through the strict . . . preclinical and clinical trial process to get off-label uses on-label,"<sup>126</sup> and that the off-label promotion restrictions directly advanced that interest.<sup>127</sup> However, FDA's policies failed the fourth prong of the *Central Hudson* test.

Under the final part of the *Central Hudson* test, the government must make an effort to "reasonably fit its means to its ends sought."<sup>128</sup> FDA's policy "need not be the 'single best disposition, but one whose scope is in proportion to the interest served.'"<sup>129</sup> Furthermore, "if the governmental interest could be served as well by a more limited restriction on commercial speech, the excessive restrictions cannot survive."<sup>130</sup> Thus, a "commercial speech restriction will fail if it burdens 'substantially more speech than necessary.'"<sup>131</sup> FDA's policy failed First Amendment scrutiny because "there exist[ed] less-burdensome alternatives to this restriction on commercial speech," such as requiring "full, complete, and unambiguous disclosure by the manufacturer" that FDA had not approved the promoted use.<sup>132</sup>

Permitting the distribution of journal and textbook reprints with such a disclaimer would, according to Judge Lamberth, adequately promote FDA's and Congress's interests by alerting physicians that the product had not been demonstrated to be safe and effective to FDA's satisfaction.<sup>133</sup> It therefore "leaves more than adequate incentives" for manufacturers to seek approval for off-label indications.<sup>134</sup> Most importantly, "this alternative comports with the Supreme Court's preference for combating potentially problematic speech with

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<sup>124</sup> *WLF I*, 13 F. Supp. 2d at 65-68.

<sup>125</sup> *Id.* at 69 ("To the extent that the FDA is endeavoring to keep information from physicians out of concern that they will misuse the information, the regulation is wholly and completely unsupportable.").

<sup>126</sup> *Id.* at 70.

<sup>127</sup> *Id.* at 72.

<sup>128</sup> *Id.*

<sup>129</sup> *Id.* (quoting *In re R.M.J.*, 455 U.S. 191, 203 (1982)).

<sup>130</sup> *Cent. Hudson Gas & Elec. Corp. v. Pub. Serv. Comm'n*, 447 U.S. 557, 564 (1980).

<sup>131</sup> *WLF I*, 13 F. Supp. 2d at 73 (quoting *U.S. v. Edge Broad. Co.*, 509 U.S. 418, 430 (1993)).

<sup>132</sup> *Id.*

<sup>133</sup> *Id.*

<sup>134</sup> *Id.*

more speech.”<sup>135</sup> Judge Lamberth made clear that his opinion addressed only FDA’s restrictions on reprint distribution and sponsorship of scientific or medical seminars, however, suggesting that some restrictions on manufacturers’ off-label speech might pass constitutional muster. “Were manufacturers permitted to engage in *all* forms of marketing of off-label treatments, a different result might be compelled.”<sup>136</sup>

The court’s injunction covered not just FDAMA’s off-label provisions, but the guidance documents and FDA’s underlying policies as well, any time they prohibited manufacturers’ dissemination of journal and textbook reprints or sponsorship of medical seminars.<sup>137</sup> Nevertheless, the D.C. Circuit vacated the injunction upon concluding that a new argument made by FDA in light of circumstances surrounding FDAMA’s enactment rendered the constitutional question moot.<sup>138</sup>

As the D.C. Circuit’s opinion explains, FDA had, at times, argued that the Act and agency policies wholly barred off-label promotion outside the narrow exemption provided by the FDAMA.<sup>139</sup> At other times, including at oral argument before the D.C. Circuit, FDA insisted that its rules did not independently ban off-label promotion, but merely established a “safe harbor” under which drug and device manufacturers would be automatically deemed in compliance with the Act.<sup>140</sup>

Even though FDAMA appears to have expressly prohibited dissemination of any information regarding off-label uses that did not comply with the regulations,<sup>141</sup> FDA attorneys insisted that the agency would only use violations of the off-label rules as “*evidence* in a misbranding or ‘intended use’ enforcement action . . . [but] that nothing in either of the provisions challenged in [the WLF] case provides the FDA with independent authority to regulate manufacturer speech.”<sup>142</sup> The Washington Legal Foundation acknowledged that, in light of FDA’s new position, its constitutional claims were rendered moot, and the D.C. Circuit remanded with instructions that the district court lift its injunction.<sup>143</sup>

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<sup>135</sup> *Id.*

<sup>136</sup> *Id.*

<sup>137</sup> Wash. Legal Found. v. Friedman (*WLF II*), 36 F. Supp. 2d 16, 19 (D.D.C. 1999).

<sup>138</sup> Wash. Legal Found. v. Henney, 202 F. 3d 331, 335-36 (D.C. Cir. 2000).

<sup>139</sup> *Id.*

<sup>140</sup> *Id.*

<sup>141</sup> 21 U.S.C. § 331(z) (Supp. 1998).

<sup>142</sup> *Henney*, 202 F. 3d at 336 (citation omitted).

<sup>143</sup> *Id.*

### C. The FDA Offers Guidance

The collapse of the WLF litigation left the legality of disseminating off-label use information by manufacturers about as clear as mud. Some activity outside the FDAMA safe harbor was permissible, but there was still no guidance to help manufacturers distinguish educational activities from promotion. Adding still further to the confusion, the FDAMA safe harbor expired in 2006,<sup>144</sup> leaving no options that were unambiguously lawful. To help clear up some of the confusion and clarify some of the rights of drug and device firms, the agency published a guidance document in January 2009 describing how manufacturers could distribute information to physicians and other health care professionals without running afoul of the law.<sup>145</sup>

Like the FDAMA safe harbor, the *Good Reprint Practices for the Distribution of Medical Journal Articles and Medical or Scientific Reference Publications* (Good Reprint Practices) guidance explains that drug and device manufacturers are permitted to distribute peer-reviewed journal articles and reference documents containing studies of off-label uses as educational materials, but it carefully circumscribes the kinds of literature that may be distributed, to whom, and in what form.<sup>146</sup> Among other things, the material distributed should be: unabridged and neither highlighted nor summarized by the manufacturer; accompanied by the product's FDA-approved labeling; accompanied by a "comprehensive bibliography of publications discussing adequate and well-controlled clinical studies"; disseminated with a "representative publication, when such information exists, that reaches contrary or different conclusions regarding the unapproved use"; and "distributed separately from information that is promotional in nature."<sup>147</sup>

Because it is a guidance and not a regulation subject to notice and comment rulemaking, however, the document does "not establish legally enforceable rights" for manufacturers, nor does it "operate to bind the FDA."<sup>148</sup> Even if it were legally enforceable, though, the Good Reprint Practices guidance would still only return manufacturers to the position they were in under FDAMA, where the full breadth of their rights was manifestly unclear. Distributing *some* types of information describing off-label uses is lawful, even in *some* situations where the material does not comply with the criteria set forth in the

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<sup>144</sup> GOOD REPRINT GUIDANCE, *supra* note 5.

<sup>145</sup> *Id.*

<sup>146</sup> *Id.*

<sup>147</sup> *Id.*

<sup>148</sup> *Id.*

guidance document. But how do manufacturers determine what is and what is not unlawful “promotion”?

Trying to distinguish what falls into the former and what falls into the latter category may be a fool’s errand, however, since a lack of promotion would help manufactures skirt only the “intended use” rules. But those rules provide just one theory supporting the ban on off-label promotion. FDA’s advertising regulations explicitly define “literature, and *reprints*,”<sup>149</sup> disseminated by drug and device manufacturers as part of their products’ labeling, which in turn means that those items are categorically forbidden from mentioning off-label uses.<sup>150</sup> Thus, there is no surefire way for a manufacturer to protect itself from charges of product misbranding whenever off-label uses are discussed.

#### IV. NEW CHALLENGES TO THE OFF-LABEL PROMOTION BAN

Because the guidance’s availability leaves considerable uncertainty regarding manufacturers’ ability to disseminate information about off-label uses, and because the agency still aggressively prosecutes violations, we have not seen the last of First Amendment challenges. Still, despite several recent cases, FDA has so far escaped a clear ruling on the constitutionality of its policies. One on-going case<sup>151</sup> will soon be taken up by the U.S. Court of Appeals for the Second Circuit, however, and others are likely to follow. Manufacturers may well expect one of these cases to produce a conclusive holding that at least some off-label promotion is protected by the First Amendment.

##### *A. Allergan, Inc. v. United States*

In October 2009, drug manufacturer Allergan, Inc. filed a declaratory relief action in the U.S. District Court for the District of Columbia challenging FDA’s off-label rules to be both unconstitutional and inconsistent with the Food, Drug and Cosmetics Act.<sup>152</sup> Allergan is the manufacturer of the drug Botox (onabotulinumtoxin A), which has been approved by FDA for treating various muscle dysfunctions involving the head, neck, and eyes, and for adult upper-limb spasticity,

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<sup>149</sup> 21 C.F.R. § 202.1(l)(2) (2011) (emphasis added).

<sup>150</sup> 21 U.S.C. § 355(a), (d) (2006).

<sup>151</sup> *United States v. Caronia*, No. 09-5006 (2d Cir. 2010); *United States v. Caronia*, 576 F. Supp. 2d 385, 389-90 (E.D.N.Y. 2008).

<sup>152</sup> Complaint at 38-40, *Allergan, Inc. v. United States*, No. 09-1879 (D.D.C. dismissed 2010) [hereinafter *Allergan Complaint*].

as well as some of the product's more well known cosmetic uses.<sup>153</sup> Botox is also frequently used off-label by physicians to treat other unapproved muscle conditions including lower-limb spasticity in juveniles with cerebral palsy.<sup>154</sup>

Although Botox can be used safely and effectively for both its on-label and some off-label indications, the manufacturer and FDA have identified potentially serious risks associated with the drug when the botulinum toxin migrates beyond the immediate injection site, possibly due to overdosing.<sup>155</sup> Consequently, in 2008 and 2009, the agency took a series of actions intended to warn physicians about these risks. These included a change in the product's approved labeling that warned that these risks are "probably greatest in children treated for spasticity,"<sup>156</sup> even though the product had not been approved for such a use.

FDA also instructed Allergan to prepare a Medication Guide for patients and a "Dear Health Care Provider" letter informing users and prescribers of Botox's risks.<sup>157</sup> However, the agency explicitly rejected Allergan's proposal to warn physicians that, "[i]n clinical trials for pediatric cerebral palsy, doses greater than [eight units per kilogram of the patient's body weight] have not been adequately studied."<sup>158</sup> FDA suggested that, "as written, this implies that [lower doses] *have* been adequately studied" and approved by the agency.<sup>159</sup> The firm alleged, however, that this suggested dose is "comparatively lower" than the dose recommended by some treatment guidelines prepared by physician organizations and the dose actually used in many juvenile patients.<sup>160</sup> It was therefore necessary, according to Allergan, to warn physicians that a common clinical practice could pose serious risks to their pediatric patients.

Allergan proposed to go beyond the generalized warnings approved by FDA and to provide health care providers with more specific information regarding dosing, selection and number of injection sites and injection technique, frequency of administration, patient selection, etc., in an effort to provide improved guidance for physicians who choose to use Botox.<sup>161</sup> The circumstances seemed to fit squarely within FDA's category of permissible "educational" speech, not off-

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<sup>153</sup> *Id.* at 14-15.

<sup>154</sup> *Id.* at 15.

<sup>155</sup> *Id.* at 17-18.

<sup>156</sup> *Id.* at 18-20.

<sup>157</sup> *Id.*

<sup>158</sup> *Id.* at 18-19.

<sup>159</sup> *Id.* at 19 (emphasis added).

<sup>160</sup> *Id.* at 19.

<sup>161</sup> *Id.* at 21.



label promotion, but the company alleged that FDA's aggressive enforcement of off-label promotion chilled its ability to speak because it feared that doing so could "lead to criminal prosecution and severe civil penalties."<sup>162</sup> It therefore sought a court ruling that various FDA regulations prohibiting off-label promotion are facially unconstitutional, unconstitutional as applied to Allergan's proposed speech, or inconsistent with the Food, Drug and Cosmetics Act.<sup>163</sup>

In response, FDA asked the court to dismiss the complaint for lack of ripeness because Allergan had not yet been prevented from or punished for speaking.<sup>164</sup> Ironically, just a few months later, in September 2010, FDA and the U.S. Department of Justice negotiated a settlement agreement in which Allergan pled guilty to criminal misbranding charges related to the firm's promotion of Botox for off-label uses.<sup>165</sup> As a condition of the settlement, however, Allergan was required to withdraw its First Amendment lawsuit,<sup>166</sup> leaving yet another challenge unresolved.

#### B. *United States v. Caronia*

In 2008, Alfred Caronia, a pharmaceutical sales representative for Orphan Medical, was convicted of conspiring to introduce a misbranded drug into interstate commerce.<sup>167</sup> Caronia arranged a meeting between a Dr. Peter Gleason, a paid consultant for Orphan Medical, and another physician who was a confidential government informant.<sup>168</sup> At that meeting, the informant engaged Dr. Gleason in a conversation about off-label uses of the Orphan Medical drug Xyrem (gamma-hydroxybutyrate), in Caronia's presence, though neither party alleges that Caronia participated in the discussion.<sup>169</sup> Orphan Medical and several individual employees and consultants were at the

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<sup>162</sup> *Id.* at 24.

<sup>163</sup> *Id.* at 38-40.

<sup>164</sup> Def.'s Mem. of Points and Authorities in Support of Mot. to Dismiss or for Summ. J. at 13-15, *Allergan, Inc. v. United States*, No. 09-1879 (D.D.C. dismissed 2010) [hereinafter FDA Br.].

<sup>165</sup> Press Release, U.S. Dept. of Justice, Allergan Agrees to Plead Guilty and Pay \$600 Million to Resolve Allegations of Off-Label Promotion of Botox® (September 1, 2010), available at <http://www.justice.gov/opa/pr/2010/September/10-civ-988.html>.

<sup>166</sup> Press Release, Allergan Resolves United States Government Investigation of Past Sales and Marketing Practices Relating to Certain Therapeutic Uses of Botox® (Sept. 1, 2010), available at <http://agn.client.shareholder.com/releasedetail.cfm?ReleaseID=503974>.

<sup>167</sup> Br. and App. for Def.-Appellant Alfred Caronia at 5, *United States v. Caronia*, No. 09-5006 (2d Cir. 2010) [hereinafter Caronia Br.].

<sup>168</sup> *Id.* at 4.

<sup>169</sup> *Id.* at 4, 9.

time already under investigation for unlawful off-label promotion.<sup>170</sup> And, subsequent to that meeting, Gleason and Orphan Medical each pled guilty to counts of drug misbranding stemming from those activities.<sup>171</sup>

Prior to trial, Caronia moved to dismiss the charges on various grounds, including that FDA's restrictions on off-label promotion unconstitutionally restricted his freedom of speech.<sup>172</sup> District Judge Eric N. Vitaliano applied the four-part *Central Hudson* test and concluded that FDA's policy did not impermissibly restrict commercial speech.<sup>173</sup> Distinguishing the narrower holding in *Friedman*, which solely addressed the distribution of journal and textbook reprints and the sponsorship of medical seminars, the *Caronia* court held that preserving "some control over the off-label promotion of manufacturers does appear essential to maintaining the integrity of the FDA's new drug approval process."<sup>174</sup> Judge Vitaliano further concluded that he was "unable to identify non-speech restrictions that would likely constrain in any effective way manufacturers from circumventing that process."<sup>175</sup> Consequently, the off-label speech restrictions were held to be not more extensive than necessary to advance the government's interest, and the *Central Hudson* test was satisfied.<sup>176</sup>

Following his trial, Caronia appealed his conviction to the U.S. Court of Appeals for the Second Circuit, arguing among other things that FDA's off-label promotion policies are unconstitutional. That case is currently pending.<sup>177</sup>

### C. *United States v. Caputo*

*Caronia* is not the only recent district court decision upholding the constitutionality of FDA's off-label speech restrictions. In *United States v. Caputo*,<sup>178</sup> defendants were convicted of conspiracy, fraud, and the introduction of an altered or misbranded medical device into interstate commerce. Ross Caputo and other officers of the device manufacturer AbTox, Inc., fraudulently secured FDA approval for a small sterilization machine that the agency approved for use only on

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<sup>170</sup> See *United States v. Caronia*, 576 F. Supp. 2d 385, 388 n.1 (E.D.N.Y. 2008); *Doctor Indicted for Off-Label Drug Promotion*, 14 FDA ADVERTISING & PROMOTION MANUAL NEWSL. 9 (2006).

<sup>171</sup> *United States v. Caronia*, 576 F. Supp. 2d 385, 389-90 (E.D.N.Y. 2008).

<sup>172</sup> *Id.* at 390.

<sup>173</sup> *Id.* at 399-402.

<sup>174</sup> *Id.* at 401.

<sup>175</sup> *Id.*

<sup>176</sup> *Id.* at 401-02.

<sup>177</sup> *Caronia Br.*, *supra* note 167.

<sup>178</sup> 288 F. Supp. 2d 912 (N.D. Ill. 2003).

certain types of surgical instruments.<sup>179</sup> The defendants later produced a larger, modified device without securing the appropriate FDA clearance and promoted it as an all-purpose sterilizer despite the agency's refusal to approve even the smaller device for this broader use.<sup>180</sup>

The government filed an eighteen-count indictment, including several counts of introducing an adulterated or misbranded device into commerce and conspiracy to prevent FDA from ensuring that the device was accurately labeled.<sup>181</sup> Defendants sought to dismiss the indictment on various grounds, including that FDA regulations prohibiting off-label promotion violated the First Amendment. Like the court in *Caronia*, District Judge Ruben Castillo applied the four-part *Central Hudson* test and concluded that FDA's policy did not impermissibly restrict commercial speech.<sup>182</sup>

Judge Castillo held that, "unlike *Washington Legal Foundation*, Defendants' First Amendment challenge strikes at the very heart of FDA's ability to proscribe manufacturer promotion of off-label uses."<sup>183</sup> Having agreed with the *Washington Legal Foundation* decision that preserving manufacturer incentives to seek FDA approval for off-label uses is a substantial government interest, the court went on to conclude that "permitting Defendants to engage in *all* forms of truthful, non-misleading promotion of off-label use would severely frustrate the FDA's ability" to advance that interest.<sup>184</sup>

On appeal, the Seventh Circuit upheld the defendants' conviction, but did so without having to reach the constitutional issues.<sup>185</sup> The court reasoned that the constitutionality of FDA's off-label promotion policies was irrelevant because the defendants' device had not been approved for *any* on-label indications.<sup>186</sup> The decision did, however, revive the First Amendment debate by suggesting in dicta that commercial speech case law—particularly several recent Supreme Court decisions involving medical products advertising—established that FDA's off-label speech restrictions may be "unconstitutional in at least some applications."<sup>187</sup>

This non-binding language from the Seventh Circuit offers the strongest defense of constitutional protections for off-label promotion since Judge Lamberth's decisions in *Washington Legal Foundation*.

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<sup>179</sup> *Id.* at 915.

<sup>180</sup> *Id.*

<sup>181</sup> *Id.* at 916, 919.

<sup>182</sup> *Id.* at 922.

<sup>183</sup> *Id.*

<sup>184</sup> *Id.*

<sup>185</sup> *United States v. Caputo*, 517 F.3d 935 (7th Cir. 2008).

<sup>186</sup> *Id.* at 940 ("there were no lawful off-label uses to promote").

<sup>187</sup> *Id.* at 939.

The court suggested that, “if a given use is lawful, and thus can be written about freely in newspapers or blogs, and discussed among hospitals that already have purchased [the defendants’ device], doesn’t it make a good deal of sense to allow speech by the device’s manufacturer, which after all will have the best information? Why privilege speech by the uninformed?”<sup>188</sup> Further, discussing a string of Supreme Court decisions addressing commercial speech, the court insisted that “government cannot regulate by ensuring ignorance among consumers”<sup>189</sup> and “the Constitution forecloses an enforced ignorance based on a paternalistic view that informed consumers will make mistakes.”<sup>190</sup>

## V. THE SCOPE OF PERMISSIBLE OFF-LABEL SPEECH

The First Amendment does not protect false, fraudulent, or even unintentionally misleading speech, but it does not permit government to categorically bar truthful and non-misleading speech simply because its purpose is to promote a commercial transaction.<sup>191</sup> Nor may the government forbid truthful and non-misleading speech on the grounds that listeners cannot be trusted to use the information responsibly upon hearing it.<sup>192</sup> More specifically, the Supreme Court made clear in *Thompson v. Western States Medical Center* that communication promoting medical products, even those unapproved by FDA, retains some constitutional protection, and any restrictions must be analyzed under *Central Hudson*.<sup>193</sup> So, what restrictions on off-label promotion could be justified under the First Amendment and the *Central Hudson* test?

Although Judge Lamberth’s opinion in *Washington Legal Foundation v. Friedman* is not controlling law, the rationale he set forth is nevertheless instructive. Judge Castillo cited the case heavily in *Caputo*. And Judge Vitaliano followed the rationale very closely in *Caronia*, suggesting that “*Friedman* is the well-spring; analysis starts there.”<sup>194</sup> But, while *Friedman* revolved solely around the distribution of journal article reprints and support for continuing medical education programs, a more probing analysis suggests that the constitutional

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<sup>188</sup> *Id.*

<sup>189</sup> *Id.* at 938 (citing *Va. State Bd. of Pharmacy v. Va. Citizens Consumer Council, Inc.*, 425 U.S. 748, 761 (1976)).

<sup>190</sup> *Id.* at 938-39.

<sup>191</sup> *Va. State Bd. of Pharmacy*, 425 U.S. at 761.

<sup>192</sup> *Id.* at 765.

<sup>193</sup> 535 U.S. 357, 367 (2002).

<sup>194</sup> *United States v. Caronia*, 576 F. Supp. 2d 385, 399 (E.D.N.Y. 2008).

protection for off-label speech likely reaches a much broader range of promotional activity.

Federal courts that have addressed the matter agree that FDA has substantial interests in “[p]reserving the effectiveness and integrity of the [Act’s] new drug approval process”<sup>195</sup> and “provid[ing] an incentive for manufacturers to go through the strict FDA preclinical and clinical trial process to get off-label uses on-label.”<sup>196</sup> The agency also has a substantial interest in policing manufacturer speech in order to protect the public from unsafe or ineffective drugs and devices.<sup>197</sup>

It seems apparent, however, that the federal government not only has an interest in promoting FDA’s approval process, but also in ensuring that doctors and their patients receive truthful and non-misleading information about all available treatment options. “The Supreme Court has consistently held that the government has a substantial interest in protecting the health and safety of its citizens,” and this interest seems no more acute than when it involves the regulation of medical products.<sup>198</sup> Although courts have recognized that the FDA approval process for drugs and devices advances this interest, the agency itself has acknowledged that the public benefits from the “dissemination of objective, balanced, and accurate information on important unapproved uses of approved products.”<sup>199</sup> Yet even though non-financially motivated actors are free to communicate information regarding off-label uses, they do not always have sufficient incentive to do so, or to do so in the most effective way. Consequently, “off-label marketing may enable the greatest number of potential beneficiaries to receive the treatments best suited to their needs.”<sup>200</sup>

Also relevant to our analysis is the fact that physicians already commonly prescribe drugs and devices for off-label uses. The off-label promotion ban does not prevent doctors from prescribing or patients from taking drugs for indications FDA has not approved. It merely prevents some speakers from sharing information that could influence those decisions. The agency insists that formal approval of medical products and their label claims is needed to prevent manufacturers from disseminating false or misleading information about off-label uses. But at least one court has rejected the argument that the agency has a substantial interest in limiting manufacturer speech in

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<sup>195</sup> *Thompson v. W. States Med. Ctr.*, 535 U.S. 357, 369 (2002).

<sup>196</sup> *WLF I*, 13 F. Supp. 2d 51, 70 (D.D.C. 1998).

<sup>197</sup> *United States v. Lane Labs-USA Inc.*, 427 F.3d 219, 227 (3d Cir. 2005).

<sup>198</sup> *WLF I*, 13 F. Supp. 2d at 69.

<sup>199</sup> *Dissemination of Information on Unapproved/New Uses for Marketed Drugs, Biologics and Devices*, 63 Fed. Reg. 64,556, 64,579 (Nov. 20, 1998).

<sup>200</sup> Salbu, *supra* note 32, at 194.

order to ensure that physicians receive only FDA-approved information.<sup>201</sup> Furthermore, “[t]he 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.”<sup>202</sup> Government should therefore balance the benefits of better information regarding off-label use against its interest in promoting the approval process.

#### A. *Central Hudson* Part IV and the Reasonable Fit Requirement

“Under the *Central Hudson* test, commercial speech restrictions must advance the government’s interest in ‘a direct and material way,’”<sup>203</sup> but that alone is not sufficient. FDA’s policy need not be the “single best disposition,” but the First Amendment requires that it be “one whose scope is in proportion to the interest served,”<sup>204</sup> and a “commercial speech restriction will fail if it burdens ‘substantially more speech than necessary.’”<sup>205</sup>

In *Western States*, for example, the Supreme Court held that a statutory ban forbidding pharmacies from advertising unapproved compounded drugs<sup>206</sup> was unconstitutional because the restriction prohibited speech more broadly than necessary to further the governmental interest.<sup>207</sup> Congress enacted the advertising restriction in question to serve as a proxy for distinguishing between the small-scale compounding that it wanted to permit and the large-scale manufacturing that should remain subject to FDA’s approval process.<sup>208</sup> According to the Court, however, other, non-speech-related restrictions would more directly advance the government’s goals.<sup>209</sup>

When it comes to off-label promotion, however, several courts have suggested that *some* speech restrictions may indeed be necessary to provide sufficient incentives for manufacturers to seek FDA review of off-label claims. The district court in *WLF v. Friedman* held, for example, that “one of the few mechanisms available to FDA to com-

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<sup>201</sup> *WLF I*, 13 F. Supp. 2d at 69.

<sup>202</sup> 44 *Liquormart, Inc. v. Rhode Island*, 517 U.S. 484, 503 (1996).

<sup>203</sup> *WLF I*, 13 F. Supp. 2d at 71 (alteration in original) (citation omitted).

<sup>204</sup> *Id.* at 73 (quoting *In re R.M.J.*, 455 U.S. 191, 203 (1982)).

<sup>205</sup> *Id.* (quoting *U.S. v. Edge Broad. Co.*, 509 U.S. 418, 430 (1993)).

<sup>206</sup> “Drug compounding is a process by which a pharmacist or doctor combines, mixes, or alters ingredients,” in a way not approved by the FDA, “to create a medication tailored to the needs of an individual patient.” *Thompson v. W. States Med. Ctr.*, 535 U.S. 357, 360-61 (2002). The Food, Drug and Cosmetics Act exempts compounded drugs from the normal FDA approval process under certain conditions. 21 U.S.C. § 353a (2006).

<sup>207</sup> *W. States*, 535 U.S. at 371-72.

<sup>208</sup> *Id.* at 370-71.

<sup>209</sup> *Id.* at 374.

pel manufacturer behavior is to constrain their marketing options.”<sup>210</sup> Similarly, in *Caputo*, the district court held that permitting manufacturers “to engage in *all* forms of truthful, non-misleading promotion of off-label use would severely frustrate the FDA’s ability to evaluate the effectiveness of off-label uses.”<sup>211</sup>

According to FDA, the statutory and regulatory “scheme is designed to discourage manufacturers from seeking approval for one use (perhaps a quite narrow one), then promoting the drug for other uses for which it may be neither effective nor safe.”<sup>212</sup> The requirement that every intended use be evaluated independently “rests on the premise—amply supported by the legislative history of the 1962 legislation—that drug manufacturers, when left to their own desires, frequently make *untruthful* claims about new uses, and that encouraging manufacturers to evaluate and demonstrate the safety and effectiveness of their drugs before marketing them for new uses protects the public from promotional claims that are unsubstantiated at best, and false at worst.”<sup>213</sup> In *USV Pharmaceutical Corp. v. Weinberger*, the Supreme Court agreed that the pre-1962 statutory scheme that authorized FDA to police the marketplace but did not require premarket approval for new drugs or new uses, was a “slow, cumbersome method,” and that it seemed “utterly unsuited to the need.”<sup>214</sup>

Still, the question courts must ask is whether there are alternatives to the total ban on off-label promotion that would also advance the government’s interests in getting off-label uses on the label and providing doctors with more accurate and complete information. If there are, adopting one or more of these intermediate measures would provide a more proportional fit between the agency’s interests and its regulations. As Justice Powell wrote in his opinion for the Court in *Central Hudson*, “if the governmental interest could be served as well by a more limited restriction on commercial speech, the excessive restrictions cannot survive.”<sup>215</sup> Consequently, if alternative approaches to the regulation of off-label speech were likely to better relieve the tension between the government’s interests and the First Amendment’s free speech protections, and cease burdening “substantially

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<sup>210</sup> *WLF I*, 13 F. Supp. 2d at 72.

<sup>211</sup> *United States v. Caputo*, 288 F. Supp. 2d 912, 922 (N.D. Ill. 2003).

<sup>212</sup> FDA Br., *supra* note 164, at 27.

<sup>213</sup> *Id.*

<sup>214</sup> 412 U.S. 655, 665 (1973).

<sup>215</sup> *Cent. Hudson Gas & Elec. Corp. v. Pub. Serv. Comm’n*, 447 U.S. 557, 564 (1980).

more speech than necessary,”<sup>216</sup> then surely the courts would have to find the current policies unconstitutionally over-broad.

Our challenge under *Central Hudson*, therefore, is to determine whether the government could narrow the speech restrictions in a way that permits the communication of useful information while still providing sufficient incentive for manufacturers to seek FDA approval for off-label indications. If there are substantially less burdensome alternatives to an outright restriction on all forms of off-label promotion that could help FDA achieve its legitimate interests, the agency would be bound by the Constitution to consider them. In our search, we may be guided by the Supreme Court’s contention that the antidote to speech of which the government disapproves is “more speech, not enforced silence.”<sup>217</sup>

### B. Less-Burdensome Alternatives

Given that non-financially interested parties may disseminate information about off-label uses at will, that physicians are permitted and often encouraged to prescribe medical products for off-label uses, and that physicians are a sophisticated audience with the training requisite to understand FDA approval process<sup>218</sup> and treat manufacturer speech with requisite skepticism,<sup>219</sup> free speech advocates may be tempted to argue that the government can achieve its goal by requiring a simple disclaimer that FDA has not found the drug or device to be safe and effective for the proffered off-label use. However, courts have been skeptical of that view where broad-scale promotion is at issue because simple disclaimers alone may not be sufficient to incentivize manufacturers to navigate the supplemental approval process.

In *WLF v. Friedman*, for example, Judge Lamberth argued that a “full, complete, and unambiguous disclosure” would be sufficient where manufacturers intended to distribute journal and textbook reprints.<sup>220</sup> But he nevertheless suggested that additional restrictions on other off-label speech might be necessary “[w]ere manufacturers permitted to engage in *all* forms of marketing of off-label treatments.”<sup>221</sup> In *Caronia*, Judge Vitaliano was more insistent, concluding that he was “unable to identify non-speech restrictions that would likely con-

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<sup>216</sup> *Id.* (quoting *United States v. Edge Broad. Co.*, 509 U.S. 418, 430 (1993)).

<sup>217</sup> *Lorillard Tobacco Co. v. Reilly*, 533 U.S. 525, 586 (2001) (Thomas, J., concurring) (quoting *Whitney v. California*, 274 U.S. 357, 377 (1927)).

<sup>218</sup> *United States v. Caronia*, 576 F. Supp. 2d 385, 397 (E.D.N.Y. 2008).

<sup>219</sup> *United States v. Caputo*, 517 F.3d 935, 939 (7th Cir. 2008).

<sup>220</sup> *WLF I*, 13 F. Supp. 2d 51, 73 (D.D.C. 1998).

<sup>221</sup> *Id.*



strain in any effective way manufacturers from circumventing [the supplemental approval] process.”<sup>222</sup>

FDA and its supporters assert that a mere disclaimer would too easily permit manufacturers to skirt the approval process and mislead physicians and patients about the safety and efficacy of their products. As Rep. Waxman argues, a disclaimer that FDA had not reviewed the off-label use “would provide precisely the information known to every physician before 1962. . . . [A]s everyone knew, the government did not review the effectiveness of drugs” prior to that year.<sup>223</sup> Nevertheless, that knowledge “did not in any way assist physicians in determining which products would help their patients and which would not.”<sup>224</sup>

Still, even if we stipulate that complete freedom “to engage in *all* forms of truthful, non-misleading promotion of off-label use would severely frustrate the FDA’s ability to evaluate the effectiveness of off-label uses,”<sup>225</sup> we need not accept the theory that nothing short of a ban on off-label promotion would adequately protect the government’s interests in incentivizing manufacturers to submit off-label indications to FDA approval process and providing physicians and patients with comprehensive information. More complete and robust disclosure requirements may well be sufficient to advance those goals. One good place to look for ideas about how to structure such a disclosure requirement is FDA’s own Good Reprint Practices guidance document.<sup>226</sup>

That guidance establishes the requirements for distributing journal and textbook reprints, the foundational requirement of which is that the information be truthful and not misleading.<sup>227</sup> Other provisions require permissible materials to be distributed with: (1) the product’s FDA-approved labeling; (2) a “comprehensive bibliography of publications discussing adequate and well-controlled clinical studies”; and (3) a “representative publication, when such information exists, that reaches contrary or different conclusions regarding the unapproved use.”<sup>228</sup> Including such information helps place the veracity of claims in the distributed reprint in the appropriate scientific context, and a similar type of robust and comprehensive disclosure could just as easily be required for broader forms of off-label speech.

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<sup>222</sup> 576 F. Supp. 2d at 401.

<sup>223</sup> Waxman, *supra* note 1, at 311.

<sup>224</sup> *Id.*

<sup>225</sup> United States v. Caputo, 288 F. Supp. 2d 912, 921 (N.D. Ill. 2003).

<sup>226</sup> GOOD REPRINT GUIDANCE, *supra* note 5.

<sup>227</sup> *Id.*

<sup>228</sup> *Id.*

Manufacturers could, for example, be permitted to promote their products for off-label uses to physicians and other health care providers (as well as hospital and health facility administrators, pharmacies, government agencies, and insurers) by disseminating pamphlets, booklets, letters, and audio/video materials, or on websites and other new media applications, provided they meet the complete disclosure requirements listed above, clearly identify the use as one that has not been approved by FDA, and include scientific information demonstrating evidence of safety and efficacy, such as a summary of clinical trial results or a journal or textbook reprint. In addition, when engaging in off-label promotion, drug and device firms might also be required to disclose which of the included publications, materials, or bibliographic entries were prepared or funded by the manufacturer or a competing firm.

While this regime would free up the range of promotional activities in which manufacturers may engage, it would nevertheless retain substantial limitations on promotional activities, preserving a real incentive to seek FDA approval for the off-label indications at issue. Specifically, it is intended to require a substantive information disclosure that would provide more complete, accurate, and balanced information to health care providers, while making it impossible or impractical to engage in advertising and other promotional activities intended to reach patients directly. Only by securing supplemental approval would manufacturers be permitted to engage in the full range of unencumbered advertising. This burdened but not banned off-label speech would, however, provide a more reasonable and proportional fit between the government's interests and the regulations used to advance them.

For example, this type of comprehensive disclosure would add a non-trivial cost and labor burden to the process of off-label promotion. Perhaps most importantly, the burden of providing evidence of safety and efficacy would itself require the manufacturer or another entity to conduct at least one controlled clinical trial similar to those necessary to support a supplemental approval application, adding further to the cost of off-label promotion. Particularly burdensome would be the requirement to include a representative publication that reaches contrary conclusions regarding the unapproved use. The combination of all three would leave a potent incentive for manufacturers to secure supplemental approval for the off-label uses. Advertising for fully-approved indications need meet no such burdens, even though the medical literature is full of studies contradicting the safety or efficacy of many such uses.

Manufacturers could distribute these items to health care providers either in person or through the mail, but promotional activities that

are intended or likely to target lay consumers could remain forbidden. Similarly, sales representatives who conduct face-to-face meetings with doctors, or physician-consultants who give presentations at scientific conferences, could discuss off-label uses, but only within the considerable restraints of the complete disclosure requirement. Print materials satisfying the disclosure rule would have to be distributed to every participant in a conversation about off-label uses at the time of the conversation. And, where the required bibliography of clinical trials is small or dominated by manufacturer-funded studies, promotion that includes such disclosure could act as much to stigmatize as to encourage the off-label uses. Of course, even with a broadened scope of permitted off-label promotion, manufacturers would still be criminally and civilly liable for misrepresenting the safety or efficacy of their products for various off-label indications.

Importantly, the comprehensive disclosure requirement would have the benefit of improving physician understanding regarding the relative risks and benefits of the manufacturers' products. After all, many physicians are already prescribing drugs and devices for off-label uses without having such comprehensive information available. Off-label promotion combined with more complete disclosure could therefore be expected to improve physician knowledge and overall public health. Thus, it would actually help to promote one of FDA's stated goals even better than the off-label promotion ban does: ensuring that physicians and their patients receive complete and unbiased information.

Naturally, these are not the only alternatives. Scholars and at least one drug manufacturer have also suggested other restrictions on manufacturer *conduct*, rather than speech, which would more directly incentivize firms to seek supplemental approvals for off-label uses.<sup>229</sup> Some of these proffered solutions pose unique problems of their own that may make them impractical or ineffective, but others are likely to be useful for the government in meeting its First Amendment obligations.

For example, Ralph Hall and Elizabeth Sabotka suggest that Congress could affirmatively require manufacturers to submit supplemental approval "applications for products the manufacturer knows are being used in any *significant* off-label manner."<sup>230</sup> Drug maker Allergan offered a similar proposal in its First Amendment litigation, suggesting that a supplemental application could be required any time

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<sup>229</sup> See, e.g., Mem. of Law in Support of Mot. for Preliminary Inj. at 27-28, Allergan, Inc. v. United States, No. 09-1879 (D.D.C. dismissed 2010) [hereinafter Allergan Br.]; Hall & Sabotka, *supra* note 7, at 44-46.

<sup>230</sup> Hall & Sabotka, *supra* note 7, at 46 (emphasis added).

off-label use of a product passes some threshold of sales.<sup>231</sup> Allergan further suggested that manufacturers could be taxed more heavily on sales for off-label uses than for on-label ones.<sup>232</sup> FDA noted, however, that proposals such as these would be difficult, if not impossible, to administer.<sup>233</sup> Even if an appropriate threshold of use or sales could be defined, no entity other than individual physicians and patients record the specific use to which the products are actually put. Such information, “at best, would have to be aggregated from countless individual patients and/or physicians and is often unobtainable,”<sup>234</sup> making such proposals wholly impractical.

Alternatively, firms that do submit supplemental applications could be afforded greater freedom to promote the indications addressed in the applications.<sup>235</sup> But submitting an application for a supplemental indication is not the same as having that use approved. If applying for supplemental approval is the only requirement, there may be insufficient incentive to make the application strong enough to actually secure approval.<sup>236</sup> Manufacturers might be tempted to submit “sham” applications with the knowledge that doing so permits them to promote off-label uses freely. One backstop remedy for these concerns might, however, include a ban on all off-label promotion (even that currently permitted under the terms of the Good Reprint Practices guidance) for indications that FDA affirmatively rejects. That would, to some degree, discourage firms from submitting supplemental applications that they suspect would not pass FDA muster.

In an extreme alternative proposal, Congress could merely forbid doctors from using drugs and devices for off-label indications, or it could use the power of its purse and prevent Medicare and Medicaid from paying for off-label uses.<sup>237</sup> Doing so would necessarily “inject[] Congress and the federal government directly into the practice of medicine,” an area historically outside the reach of FDA’s authority.<sup>238</sup> But it would nevertheless be within the generally accepted scope of the federal government’s power to regulate commerce.<sup>239</sup> It would also, quite unfortunately, prevent hundreds of millions of patients from having access to important treatment options, a scenario that even FDA’s most ardent defenders are likely to oppose.

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<sup>231</sup> Allergan Br., *supra* note 229, at 27.

<sup>232</sup> *Id.*

<sup>233</sup> FDA Br., *supra* note 164, at 28-29.

<sup>234</sup> *Id.*

<sup>235</sup> Allergan Br., *supra* note 229, at 27.

<sup>236</sup> FDA Br., *supra* note 164, at 39-41.

<sup>237</sup> See Hall & Sabotka, *supra* note 7, at 44-46.

<sup>238</sup> *Id.* at 45.

<sup>239</sup> *Id.*

A more practical recommendation is for Congress to provide direct economic incentives for seeking supplemental approvals, such as tax rebates or credits to off-set the cost of preparing and submitting applications seeking approval for off-label indications.<sup>240</sup> And Congress or FDA could restructure the approval process for additional indications in a way that makes it less costly.<sup>241</sup> For example, the American Medical Association has proposed that Congress or FDA “streamlin[e] as much as possible” the supplemental application process by, among other things, “basing review decisions on already published literature” rather than requiring entirely new clinical trials.<sup>242</sup>

Although these economic measures would not selectively disadvantage off-label uses more than current policies do, and thereby provide incentive to seek supplemental approvals, other mechanisms could do just that. One proposal that would directly incentivize manufacturers to pursue supplemental approval is for Congress to provide extended patent protection or other market exclusivity protections for the addition of new indications to the label.<sup>243</sup> Congress could also statutorily preempt product liability lawsuits based on design defect or negligent failure to warn in cases involving on-label uses, while preserving liability for uses that have not been FDA approved.<sup>244</sup> Such a move would not be unprecedented, as manufacturers of Class III medical devices already enjoy such preemption for approved uses.<sup>245</sup> Alternatively, Congress could limit tort awards to compensatory damages, while barring punitive damages for approved uses. With tort liability not infrequently reaching tens or hundreds of millions of dollars per drug,<sup>246</sup> one might imagine that preemption of this type would provide a very potent incentive for seeking supplemental approvals.

Each of these options would advance the government’s interests in a manner that is less intrusive to manufacturers’ constitutional rights than FDA’s current policies. And the availability of so many

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<sup>240</sup> *Id.* at 46.

<sup>241</sup> *Id.*

<sup>242</sup> HEALTH AND ETHICS POLICIES, *supra* note 33.

<sup>243</sup> *Id.*

<sup>244</sup> Hall & Sabotka, *supra* note 7, at 46.

<sup>245</sup> 21 U.S.C. § 360k (2006) (No state may establish a requirement for medical devices “different from, or in addition to” any federal requirement that “relates to the safety or effectiveness of the device.”); *see also* Riegel v. Medtronic, Inc., 552 U.S. 312, 330 (2008) (holding that § 360k preempts state liability for common law tort claims).

<sup>246</sup> Near the extreme upper end, for example, drug manufacturer Merck established a \$4.85 billion fund in November 2007 to settle most of the claims arising from sales of its product Vioxx. Alex Berenson, *Merck Is Said to Agree to Pay \$4.85 Billion for Vioxx Claims*, N.Y. TIMES, Nov. 9, 2007, at A1.

possible alternatives demonstrates that the existing bar on truthful and non-misleading promotion of off-label uses is more extensive than necessary. With the few exceptions noted above, however, the government has not been asked by a court to explain why these proposals, alone or in combination, would be insufficient to achieve its legitimate interests. As legal challenges to the off-label promotion ban continue, however, that day may well come soon. If and when it does, “[i]t is well established that ‘the party seeking to uphold a restriction on commercial speech carries the burden of justifying it.’”<sup>247</sup> Consequently, FDA will not be able to meet its burden merely by claiming that these proposals would not work. If it expects to convince a court that these measures would leave an insufficient incentive for manufacturers to seek supplemental approval for off-label indications, it is the agency’s obligation to explain why.

### CONCLUSION

Every day, many thousands of treatment choices are made by physicians who must take into account individual patient characteristics and preferences, drug interactions, and biological variations that affect the safety and efficacy of therapeutic options. Within that world, off-label prescribing is not just useful, but essential to the proper provision of necessary medical care. Consequently, doctors and their patients both reap tremendous benefit from the distribution of truthful and non-misleading information about the effective off-label uses of drugs.

FDA’s ban on manufacturer promotion of off-label uses compromises the ability of doctors to learn about important treatment options that can help their patients. Although courts recognize that the government has an interest in protecting public health by ensuring that safety and efficacy claims are valid, the ban on off-label promotion silences the very speakers who have accumulated the most information about the risks, benefits, and various on- and off-label uses of their products, as well as those with the greatest incentive to share it.

There are many less burdensome alternatives that would promote the government’s interest in incentivizing manufacturers to seek supplemental approval for off-label indications while simultaneously providing physicians and patients with more complete information about off-label uses. The near total ban on off-label promotion is therefore overly-broad and far more restrictive than necessary to achieve the government’s interests. Indeed, courts may accept that the government has an interest in preserving FDA’s approval process.

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<sup>247</sup> *Edenfield v. Fane*, 507 U.S. 761, 770 (1993).

But, given the recognized value of open discourse on scientific and health matters, as well as the importance of off-label prescribing in patient care, it is far from clear that the blanket restrictions on off-label promotion actually advance the government's broader interest in promoting public health.