

# DON'T FIX WHAT AIN'T BROKEN—OFF-LABEL MARKETING, THE FDA'S REGULATORY REGIME, AND THE FIRST AMENDMENT

*Loren Jacobson\**

## INTRODUCTION

In 1962, Congress passed the Kefauver-Harris Amendments to the Federal Food, Drug, and Cosmetic Act (FDCA), requiring that drugs and devices be approved for safety and effectiveness for a particular use before companies could market them for that use. Prior to the amendments, once a manufacturer had a product approved for safety, it could market the product for any use whatsoever, regardless of effectiveness. The Congressional hearings leading up to the amendments demonstrated a pattern and practice of false and misleading promotion of drugs by the pharmaceutical industry.<sup>1</sup> These promotional practices encouraged physicians to prescribe drugs with very serious side effects for uses that were not proven to be effective. For example, Mellaril, which was reserved as a drug of last resort for schizophrenia because of its severe side effects and was pulled off the market in 2005 due to concerns that it increased the risk of cardiac arrhythmias and could cause sudden death,<sup>2</sup> was widely promoted for pregnant women with emotional symptoms in connection with childbirth, for chronic fatigue, insomnia, anxiety, apprehension, and vague digestive disorders.<sup>3</sup> Diethylstilbestrol (DES) was marketed widely to prevent miscarriage, even in normal pregnancies. But DES caused a high rate of reproductive abnormalities in the children of women given DES, including a rare form of vaginal cancer in girls, and a later study of the drug showed it to be completely ineffective in preventing miscarriages.<sup>4</sup> Without regulations requiring that drug companies prove their products to be safe and effective for a particular use before marketing them for that use, thousands of Americans suffered adverse consequences from drugs that were not even effective for the uses for which they were being promoted, often on the basis of anecdotal or other unreliable evidence.

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\* Assistant Professor of Law, UNT-Dallas College of Law.

<sup>1</sup> 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 (2003).

<sup>2</sup> *Antipsychotic Mellaril Removed from the Market*, <http://www.schizophrenia.com/sznews/archives/001377.html> (last visited July 5, 2017).

<sup>3</sup> Waxman, *supra* n.1, at 304.

<sup>4</sup> *Id.* at 306.

Yet ever since the Kefauver-Harris Amendments were put into place, pharmaceutical and device companies, whose ostensible purpose is to “work[] together for patients” and to “work together for a healthier world,”<sup>5</sup> have sought to undermine the prohibition on marketing until safety and effectiveness have been established. The companies and their defenders claim that the system is broken because marketing restrictions prevent patients with few other alternatives from getting life-saving drugs and devices and that the clinical trials required to “satisfy the FDA’s demanding standards” are expensive.<sup>6</sup>

The companies and their lobbyists have made some legislative in-roads. Last year, the state of Arizona passed a bill specifically allowing “a pharmaceutical manufacturer or its representative” to “engage in truthful promotion of an off-label use of a drug, biological product or device,” and prohibiting state officials from prosecuting a pharmaceutical manufacturer or cooperating with federal officials in a prosecution or other action for off-label promotion.<sup>7</sup> It remains to be seen what, if any, effect the bill will have, since Arizona likely already cooperates very little in prosecutions for off-label marketing since the state does not have a False Claims Act that would allow the state to recoup Medicaid payments made for prohibited off-label promotion, and in any case, the law is likely preempted by federal law.<sup>8</sup> In March 2017, U.S. Congressman Morgan Griffith introduced the “Medical Product Communications Act of 2017,” which seeks to amend the FDCA by allowing companies to make any communication about a product so long as it is “supported by scientifically appropriate and statistically sound data, studies, or analyses,” which according to the bill, includes dissemination of scientific findings in “lay media” and “letters to the editor in defense of public

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<sup>5</sup> “Working Together for Patients” is a slogan of Bristol-Myers Squibb, *see* <https://www.bms.com/about-us.html> (last visited July 5, 2017). “Working Together for a Healthier World” was a slogan trademarked by Pfizer, *see* Pharma Marketing Blog, Pfizer Inc: Working Together for a Healthier Investor,<sup>TM</sup> Feb. 3, 2011, <http://pharmamktng.blogspot.com/2011/02/pfizer-inc-working-together-for.html> (last visited July 5, 2007).

<sup>6</sup> Stephanie M. Greene & Lars Noah, *Off-Label Drug Promotion and the First Amendment*, 162 U. PA. L. REV. ONLINE 239, 250 (2014).

<sup>7</sup> Arizona H.B. 2382. The sponsor of the bill, Arizona House Representative Phil Lovas, joined the Small Business Association in April 2017. Mary Jo Pitzl, Arizona Rep. Phil Lovas Leaves Legislature for Trump Administration, *The Republic*, <http://www.azcentral.com/story/news/politics/politicalinsider/2017/04/15/arizona-rep-phil-lovas-leaves-legislature-trump-administration/100471958/> (last visited July 5, 2017).

<sup>8</sup> On preemption, *see PLIVA, Inc. v. Mensing*, 564 U.S. 604 (2011); on Arizona’s lack of a False Claims Act, *see* <http://taf.org/states-false-claims-acts> (last visited July 5, 2017).

challenges.”<sup>9</sup> The bill was referred to the Committee on Energy and Commerce, which held a hearing on it last July, but it has not made any further progress.<sup>10</sup>

But the pharmaceutical companies’ main weapon has been the First Amendment, and the weapon landed a massive blow when the United States Circuit Court for the Second Circuit ruled, in *United States v. Caronia*,<sup>11</sup> that the prosecution of a pharmaceutical sales representative for misbranding—promoting a drug for unapproved uses—violated the First Amendment. The court held that, while the First Amendment did not protect false or misleading speech, “the government cannot prosecute the pharmaceutical manufacturers and their representatives under the FDCA for speech promoting the lawful, off-label use of an FDA-approved drug.”<sup>12</sup> The opinion is striking because before it, courts had generally considered misbranding prosecutions not to even implicate the First Amendment.<sup>13</sup>

The decision, although from only one circuit court, seems to have chilled the ability or willingness of the federal Food & Drug Administration (FDA) to ensure that drug and device companies only promote their products for uses that have proven to be safe and effective. Since the decision, the Department of Justice has announced only three False Claims Act settlements involving unlawful drug promotion—one against Shire Pharmaceuticals that mainly settled claims relating to “false and misleading” promotion,<sup>14</sup> another against Genentech Inc. and OSI Pharmaceuticals LLC related to “misleading statements

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<sup>9</sup> H.R. 1703—Medical Product Communications Act of 2017, 115th Congress (2017–2018), available at <https://www.congress.gov/bill/115th-congress/house-bill/1703/text>.

<sup>10</sup> Energy & Commerce Committee, Sub-Committee on Health, Hearing on Examining Medical Product Manufacturer Communications, July 12, 2017, available at <https://energycommerce.house.gov/hearings/examining-medical-product-manufacturer-communications/> (last visited Feb. 18, 2018).

<sup>11</sup> 703 F.3d 149 (2d Cir. 2012).

<sup>12</sup> 703 F.3d at 169.

<sup>13</sup> See, e.g., *Whitaker v. Thompson*, 353 F.3d 947 (D.C. Cir. 2004).

<sup>14</sup> Department of Justice, Office of Public Affairs, *Shire Pharmaceuticals LLC to Pay \$56.5 Million to Resolve False Claims Act Allegations Relating to Drug Marketing and Promotion Practices*, Sept. 24, 2014, available at <https://www.justice.gov/opa/pr/shire-pharmaceuticals-llc-pay-565-million-resolve-false-claims-act-allegations-relating-drug> (last visited June 21, 2017). The FDA and the DOJ do appear to continue to be willing to go after *device* companies and their sales representatives for off-label promotion, even where that promotion is not patently false or misleading, likely because of the extra safety concerns involved with devices that are implanted in patients. See Department of Justice, Office of Public Affairs, *Former Acclarent, Inc. Executives Convicted of Crimes Related to the Sale of Medical Devices*, July 20, 2016, available at <https://www.justice.gov/usao-ma/pr/former-acclarent-inc-executives-convicted-crimes-related-sale-medical-devices> (last visited June 22, 2017); Department of Justice, Office of Public Affairs, *Johnson & Johnson Subsidiary Acclarent Inc. Pays Government \$18 Million to Settle False Claims Act Allegations*, July 22, 2016, available at <https://www.justice.gov/opa/pr/johnson-johnson-subsubsidiary-acclarent-inc-pays-government-18-million-settle-false-claims-act> (last visited June 22, 2017).

about the effectiveness of the drug Tarceva,”<sup>15</sup> and a third against Celgene for marketing two cancer drugs for unapproved uses.<sup>16</sup> Moreover, most recent criminal prosecutions of pharmaceutical companies appear to be related to promotion of drugs that have not been approved at all.<sup>17</sup> While it may be that pharmaceutical companies are engaging in less off-label promotion, the more plausible explanation for the paucity in the past five years of FCA settlements and prosecutions involving the off-label marketing of pharmaceuticals is the *Caronia* decision.<sup>18</sup>

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<sup>15</sup> Department of Justice, Office of Public Affairs, *Pharmaceutical Companies to Pay \$67 Million to Resolve False Claims Act Allegations Relating to Tarceva*, June 6, 2016, available at <https://www.justice.gov/opa/pr/pharmaceutical-companies-pay-67-million-resolve-false-claims-act-allegations-relating-tarceva> (last visited June 21, 2017).

<sup>16</sup> Department of Justice, U.S. Attorney’s Office, Central District of California, *Celgene Agrees to Pay \$280 Million to Resolve Fraud Allegations Related to Promotion of Cancer Drugs For Uses Not Approved by FDA*, July 24, 2017, available at <https://www.justice.gov/usao-cdca/pr/celgene-agrees-pay-280-million-resolve-fraud-allegations-related-promotion-cancer-drugs> (last visited, Feb. 18, 2018). Notably, the Department of Justice declined to intervene in this case, which was subsequently litigated by the relator who brought the case and her counsel.

<sup>17</sup> See, e.g., Department of Justice, Office of Public Affairs, *District Court Enters Permanent Injunction Against New Jersey Drug Manufacturer and Its President to Stop Distribution of Unapproved and Misbranded Drugs*, July 1, 2015, available at <https://www.justice.gov/opa/pr/district-court-enters-permanent-injunction-against-new-jersey-drug-manufacturer-and-its> (last visited June 22, 2017) (discussing consent decree in case regarding marketing of a prescription drug that had not received FDA approval for any use); Department of Justice, Office of Public Affairs, *United States Files Consent Decree of Permanent Injunction Against a Louisiana Drug and Dietary Supplement Manufacturer to Stop Distribution of Misbranded and Unapproved New Drugs and Misbranded and Adulterated Dietary Supplements*, Feb. 16, 2017, available at <https://www.justice.gov/opa/pr/united-states-files-consent-decree-permanent-injunction-against-louisiana-drug-and-dietary> (last visited June 22, 2017) (consent decree in case in which dietary supplements were marketed as drugs without FDA approval); Department of Justice, Office of Public Affairs, *District Court Enters Permanent Injunction Against Colorado Companies to Stop Distribution of Adulterated And Misbranded Dietary Supplements and Unapproved and Misbranded Drugs*, Mar. 15, 2017, available at <https://www.justice.gov/opa/pr/district-court-enters-permanent-injunction-against-colorado-companies-stop-distribution> (last visited June 22, 2017) (same).

As to device companies, in April 2015, the DOJ filed charges against William Facticeau and Patrick Fabian, the CEO and Vice President of Sales, respectively, of Acclarent device company, for among other things, misbranding, arising out of the promotion of a device approved as a sinus spacer for unapproved use as a delivery device for steroids. See *United States v. Facticeau*, 1:15-cr-10076-ADB, 2016 WL 4445741 (D. Mass. Aug. 22, 2016). On July 20, 2016, a jury convicted the men of 10 misdemeanor counts of introducing adulterated and misbranded medical devices into interstate commerce. Department of Justice, Office of Public Affairs, *Former Acclarent, Inc. Executives Convicted of Crimes Related to the Sale of Medical Devices*, July 20, 2016, available at <https://www.justice.gov/usao-ma/pr/former-acclarent-inc-executives-convicted-crimes-related-sale-medical-devices> (last visited July 15, 2017). On July 22, 2016, the Department of Justice announced an \$18 million False Claims Act settlement with Johnson & Johnson, Acclarent’s parent, arising out of the same allegations. Department of Justice, Office of Public Affairs, *Johnson & Johnson Subsidiary Acclarent Inc. Pays Government \$18 Million to Settle False Claims Act Allegations*, July 22, 2016, available at <https://www.justice.gov/opa/pr/johnson-johnson-subsidiary-acclarent-inc-pays-government-18-million-settle-false-claims-act> (last visited July 15, 2017).

<sup>18</sup> Skadden, *FDA Publications Double Down on Agency’s ability to Prohibit Off-Label Communications, but Narrow Scope of Debate*, Feb. 1, 2017, available at <https://www.skadden.com/insights/>

Nevertheless, on the eve of the change in administrations, the FDA released a Memorandum and two draft guidances on drug and device manufacturer communications and opened a public comment period for the draft guidances.<sup>19</sup> The Memorandum provides a robust defense of the FDCA and a strong rebuttal to *Caronia*. While it is unclear what the current administration's position will be,<sup>20</sup> this essay posits that the current laws, regulations, and rules that control the marketing of drugs and devices for off-label use properly balance providing physicians reliable information so that they soundly exercise their discretion to assist their patients with protecting those patients from ineffective and dangerous products. Moreover, the regulatory system currently in place does not violate drug and device companies' First Amendment rights. The FDA has robust arguments for why *Caronia* was wrongly decided and the current system strikes the right balance under the First Amendment. Further, the fact that the FDA provides safe harbors to drug and device companies to provide information about off-label uses of their products and the recent amendments made to the FDCA by the 21<sup>st</sup> Century Cures Act, which broaden these safe harbors, show that to the extent the FDCA constrains off-label marketing, such constraints are narrowly tailored to effectuate the compelling need to protect the public from harmful and ineffective drugs.

Thus, this essay posits that the FDA should protect the current regime put in place by the Kefauver-Harris Amendments and continue to prosecute drug and device companies and their employees for putting patient lives in danger by marketing their products for off-label use. The essay focuses on the pharmaceutical companies, but device companies are subject to the same regulations. In fact, in 2015, the Department of Justice filed charges, including

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publications/2017/02/fda-publications-double-down-on-agencys-ability-to (last checked June 22, 2017) (noting the "perceived decrease in off-label enforcement actions" in the wake of *Caronia*).

<sup>19</sup> See FDA, Memorandum, Public Health Interests and First Amendment Considerations Related to Manufacturer Communications Regarding Unapproved Uses of Approved or Cleared Medical Products 3 (Jan. 2017), 82 F.R. 6367, 6367–68, available at <https://www.regulations.gov/document?D=FDA-2016-N-1149-0040> (last checked June 21, 2017) (hereinafter "FDA Memorandum"); FDA, Medical Product Communications That Are Consistent with the FDA-Required Labeling—Questions and Answers, Guidance for Industry (Jan. 2017), 82 FR 6575, 6575–78 available at <https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm537130.pdf> (last visited July 5, 2017); FDA, Drug and Device Manufacturer Communications With Payors, Formulary Committees, and Similar Entities—Questions and Answers; Draft Guidance for Industry and Review Staff; Availability (Jan. 2017), 82 F.R. 6568, 6568–71.

<sup>20</sup> Dr. Scott Gottlieb, the current head of the FDA, has "been an advocate for autonomy in the practice of medicine and the use of medical products for off-label uses. He has opined that doctors are appropriately trained to make medical decisions based on the best interest of their patients." Anne K. Walsh, *FDA, Under New Leadership, Seeks More Comments on Rules Affecting Off-Label* Communications, FDA Blog, May 18, 2017, available at [http://www.fdalawblog.net/fda\\_law\\_blog\\_hyman\\_phelps/2017/05/fda-under-new-leadership-seeks-more-comments-on-rules-affecting-off-label-communications-.html](http://www.fdalawblog.net/fda_law_blog_hyman_phelps/2017/05/fda-under-new-leadership-seeks-more-comments-on-rules-affecting-off-label-communications-.html) (last visited July 5, 2017).

claims for putting misbranded and adulterated products in interstate commerce, against two Acclarent executives, William Facteau and Patrick Fabian, for the promotion of a device approved as a sinus spacer for unapproved use as a steroid delivery system.<sup>21</sup> Facteau and Fabian were convicted of misdemeanor misbranding and adulteration charges, and the case is still working its way through the judicial system.<sup>22</sup>

In the meantime, as this essay makes clear, legislative efforts to allow broader off-label marketing are short-sighted, ignoring both the terrible consequences visited on patients prior to the Kefauver-Harris Amendments. The current regime rightly allows the pharmaceutical and device companies to provide reliable, accurate, and truthful information to physicians so that they can make the best decisions possible for their patients, while ensuring that drugs and devices are only marketed for uses for which they are scientifically proven to be safe and effective.

## I. THE REGULATORY AND LEGAL BACKGROUND

### A. *The FDCA and Limits on Off-Label Marketing*

The FDCA prohibits the “introduction or delivery for introduction into interstate commerce any . . . drug [or] device . . . that is adulterated or misbranded” and also prohibits “the adulteration or misbranding of any . . . drug [or] device . . . in interstate commerce.”<sup>23</sup> A drug or device is misbranded if, among other things, its labeling does not bear “adequate directions for use,”<sup>24</sup> which include directions that allow a layperson to use the drug safely “and for the purposes for which it is intended.”<sup>25</sup> The FDA considers the promotion of a drug or device for a use other than one that has been approved by the FDA—what is known as “off-label” promotion—to violate the misbranding proscriptions because when a drug or device is promoted for an unapproved use, the label contains no instructions about how to safely use the drug for the unapproved use.

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<sup>21</sup> *United States v. Facteau*, 1:15-cr-10076-ADB, 2016 WL 4445741 (D. Mass. Aug. 22, 2016).

<sup>22</sup> Department of Justice, Office of Public Affairs, *Former Acclarent, Inc. Executives Convicted of Crimes Related to the Sale of Medical Devices*, July 20, 2016, available at <https://www.justice.gov/usao-ma/pr/former-acclarent-inc-executives-convicted-crimes-related-sale-medical-devices> (last visited July 15, 2017).

<sup>23</sup> 21 U.S.C. § 331(a) & (b) (Dec. 13, 2016).

<sup>24</sup> 21 U.S.C. § 352(f).

<sup>25</sup> 21 C.F.R. § 201.5. Any person who violates these provisions is subject to imprisonment for not more than one year, a \$1,000 fine or both. 21 U.S.C. § 333(a)(1).

In order to market a drug for a specific use, a company must receive FDA approval for the product for that use through the new drug application (NDA) or supplemental new drug application (SNDA) process. Under this process, a pharmaceutical company can only secure approval for a new use of a drug by submitting an NDA or SNDA, which comprises a compilation of materials that must include “full reports of [all clinical] investigations,”<sup>26</sup> relevant nonclinical studies, and “any other data or information relevant to an evaluation of the safety and effectiveness of the drug product obtained or otherwise received by the applicant from any source.”<sup>27</sup> The NDA or SNDA must also include “the labeling proposed to be used for such drug,”<sup>28</sup> and “a discussion of why the [drug’s] benefits exceed the risks [for the specified use] under the conditions stated in the labeling.”<sup>29</sup>

The FDA may approve an NDA or SDNA only if it determines that the drug in question is “safe for use” under “the conditions of use prescribed, recommended, or suggested in the proposed labeling thereof.”<sup>30</sup> In order for the FDA to consider a drug safe, the drug’s “probable therapeutic benefits must outweigh its risk of harm”<sup>31</sup> for its intended use. The NDA and SNDA process ensures that drugs are marketed only for uses that have met the FDA’s requirements of safety and effectiveness.<sup>32</sup>

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<sup>26</sup> 21 U.S.C. § 355(b)(1)(A).

<sup>27</sup> 21 C.F.R. §§ 314.50(d)(2) and (5)(iv); see *Mutual Pharm. Co., Inc. v. Bartlett*, 133 S. Ct. 2466, 2470–71 (2011) (explaining the FDA approval process).

<sup>28</sup> 21 U.S.C. § 355(b)(1)(F); 21 C.F.R. § 314.50(c)(2)(i).

<sup>29</sup> 21 C.F.R. § 314.50(d)(5)(viii); § 314.50(c)(2)(ix).

<sup>30</sup> 21 U.S.C. § 355(d); *Bartlett*, 133 S. Ct. at 2470.

<sup>31</sup> *FDA v. Brown & Williamson Tobacco Corp.*, 529 U.S. 120, 140 (2000).

<sup>32</sup> See FDA Memorandum, *supra* note 19, at 3 (“Despite the distinctions in the legal frameworks and associated differences in premarket review pathways and processes, underlying them all are goals of spurring innovation based on reliable scientific evidence of effectiveness and of ensuring the safety and effectiveness of medical products for each intended use.”).

Devices are approved in a different manner, but also must meet the requirements of safety and effectiveness to be marketed. The FDCA classifies medical devices in three categories: Classes I, II, and III. 21 U.S.C. § 360c(a). Class III devices include those that present a potential unreasonable risk of illness or injury. *Id.* § 360c(a)(1)(C). Because of the risk associated with such devices, manufacturers of such devices must submit premarket approval (“PMA”) applications to the FDA and obtain premarketing clearance before offering the devices for sale 42 C.F.R. § 405.201(b). Class III devices that do not have PMA approval cannot be marketed and are considered “adulterated.” 21 U.S.C. § 351(f)(1)(B); 42 C.F.R. § 405.201(b). In order to receive approval through the PMA process, the drug company must provide sufficient valid scientific evidence to allow the FDA to conclude that the device is safe and effective for its intended use. 21 C.F.R. § 814.2(a). “It is ‘a ‘rigorous’ process in which the manufacturer submits to the FDA extensive study reports, design specifications and descriptions, samples of the device, and proposed labeling, and the FDA conducts a comprehensive review an evaluation of all the submitted documents and materials [.]’” *U.S. ex rel. Modglin v. DJO Glob. Inc.*, 48 F. Supp. 3d 1362, 1369 (C.D. Cal. 2014), *aff’d sub nom. United States v. DJO Glob., Inc.*, 678 F. App’x 594 (9th Cir.

In order to determine whether a drug is being marketed for a use for which the drug (or a device) has not received an approved label, the FDA must rely upon the marketing materials—the label, written disseminated materials, drug representatives’ statements—to determine whether the “intended use” for which the drug is being promoted is the use for which the company received approval from the FDA or whether the drug is “misbranded.”

While the restrictions on “misbranding” prohibit pharmaceutical companies from marketing a drug for which the FDA has not approved a label, they do not prohibit physicians from prescribing a drug for a use not approved by the FDA. The FDA has said:

Once a drug has been approved for marketing, a physician may prescribe it for uses or in treatment regimens or patient populations that are not included in approved labeling. Such “unapproved” or, more precisely, “unlabeled” uses may be appropriate and rational in certain circumstances, and may, in fact, reflect approaches to drug therapy that have been extensively reported in medical literature.<sup>33</sup>

But the FDA has expressed concern that “the public health is not well served” when physicians’ judgments about what drugs to prescribe their patients “rest on anecdotal experience or even preliminary scientific study,” since “too often, the promise of safety and effectiveness made by such sources has not been demonstrated when adequate and well-controlled clinical studies are completed.”<sup>34</sup>

Thus, the FDA has sought to ensure that drug companies provide physicians with scientifically accurate information about unapproved uses of their drugs. In doing so, following the Food and Drug Administration Modernization Act of 1997, the FDA has issued a series of guidances that provide drug and device companies with “safe harbors”—allowing them to disseminate scientifically accurate information about unapproved uses of their products without fear of prosecution.<sup>35</sup> These safe harbors are quite broad and provide the companies

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2017) (citing *Kashani–Matts v. Medtronic, Inc.*, No. SACV 13-01161-CJC (RNBx), 2013 WL 6147032, \*1 (C.D.Cal. Nov. 22, 2013)).

<sup>33</sup> U.S. Food and Drug Admin., *FDA Drug Bulletin*, 12 FDA Drug Bull. 1, 5 (1982).

<sup>34</sup> FDA, *Guidance for Industry Distributing Scientific and Medical Publications on Unapproved Uses—Recommended Practices 2* (Feb. 2014), available at <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM387652.pdf> (last visited July 5, 2017) (hereinafter “2014 Reprint Guidance”).

<sup>35</sup> The Food and Drug Administration Modernization Act of 1997, Pub. L. No. 105-115, 111 Stat. 2296 (FDAMA) specifically authorizes manufacturers to disseminate “written information concerning the safety, effectiveness, or benefit of a use not described in the approved labeling of a drug or device,” 21 U.S.C. § 360aaa *et seq.*, if it complied with certain requirements, including submitting an NDA for the drug. The current



with a great deal of latitude to promote their products for uses that have not yet met the FDA's standards of safety and effectiveness. The two most important guidances with respect to the safe harbors were published in 2009—before the *Caronia* decision—and in 2014.<sup>36</sup> The latter broadens even further the ways in which pharmaceutical companies can market unapproved uses of their drugs.

The 2009 safe harbors guidance allows drug and device companies to distribute scientific or medical journal articles about off-label uses that are published by an organization “with an editorial board that uses experts who have demonstrated expertise in the subject of the article under review by the organization and who are independent of the organization”; are peer-reviewed and published in accordance with the peer-review procedures of the organization; and do not appear in the form of a special supplement or publication that has been funded in whole or in part by one or more of the manufacturers of the product that is the subject of the article.<sup>37</sup> The 2009 Guidance makes clear that articles that are published by, or show undue influence of, pharmaceutical or device companies—for example, they are written or edited by a company or anyone who has received significant payments from the company—do not fall within the safe harbor. The 2009 Guidance also states that scientific and medical journal article reprints be provided in an unabridged form; “contain information that describes and addresses adequate and well-controlled clinical investigations that are considered scientifically sound by experts with scientific training and experience to evaluate the safety or effectiveness of the drug or device”; be disseminated with their approved labeling and a comprehensive bibliography, when such information exists, of other publications related to the off-label use of the drug, as well as a representative publication, when such information exists, that reaches contrary or different conclusions regarding the unapproved use.<sup>38</sup> The 2014 Guidance, which supersedes the 2009 Guidance, retains these same safe harbors and requirements.

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guidelines are even broader than this, because they allow dissemination of materials even for uses for which no NDA has been submitted. FDA, *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* (Jan. 2009), available at <https://www.fda.gov/regulatoryinformation/guidances/ucm125126.htm> (last visited July 5, 2017) (hereinafter “2009 Reprint Guidance”); 2014 Reprint Guidance, *supra* note 34. According to these guidances, “if manufacturers distribute scientific or medical publications as recommended in this guidance, FDA does not intend to use such distribution as evidence of the manufacturer’s intent that the produce be used for an unproved new use.” *Id.* at 6.

<sup>36</sup> 2009 Reprint Guidance, *supra* note 35; 2014 Reprint Guidance, *supra* note 34.

<sup>37</sup> 2009 Reprint Guidance, *supra* note 35.

<sup>38</sup> 2009 Reprint Guidance, *supra* note 35; 2014 Reprint Guidance, *supra* note 34, at 7–8.

Notably, the pharmaceutical industry does not seem to believe that these requirements are inappropriate. In a document entitled “Principles on Responsible Sharing of Truthful and Non-Misleading Information About Medicines with Health Care Professionals and Payers,” BIO, the biotechnology trade association, and PhRMA, the pharmaceutical industry group, noted that in distributing a reprint involving the off-label use of a drug, in order to “communicate information about the content of the reprint . . . in a truthful and non-misleading manner” the company should disclose, among other things:

(a) accurate and balanced information about the approved product labeling (including the indication, limitations of use, efficacy and safety data described therein); (b) the type of research that is the subject of the reprint (including the study design, method of analysis, and appropriate, context-specific disclosures regarding the limitations with retrospective meta-analysis); (c) the results reported in the reprint, including the statistical significance and confidence intervals of each result; and (d) other relevant evidence that is necessary to an informed medical judgment, including peer-reviewed contrary evidence.<sup>39</sup>

The FDA’s 2014 Guidance also further broadens the information about off-label uses that pharmaceutical companies can provide to physicians. It allows pharmaceutical companies to distribute scientific and medical reference texts and clinical practice guidelines without fear of prosecution. Like the 2009 Guidance, the 2014 Guidance places some reasonable limits on the distribution of this information to ensure that it is scientifically reliable, accurate, and is not misleading.<sup>40</sup> Thus, although the FDA generally considers off-label use of a drug “misbranding,” the safe harbors give the pharmaceutical and device companies significant leeway to provide unbiased, evidence-based, medically and scientifically accurate information to physicians about unapproved uses of their products.

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<sup>39</sup> BIO & PhRMA, *Principles on Responsible Sharing of Truthful and Non-Misleading Information About Medicines with Health Care Professionals and Payers* 10 (July 27, 2016), available at [https://www.bio.org/sites/default/files/PrinciplesReport\\_FINAL.pdf](https://www.bio.org/sites/default/files/PrinciplesReport_FINAL.pdf) (last visited July 5, 2017). BIO and PhRMA’s only apparent quibble with the reprint guidelines is the prohibition on the distribution of studies funded by the pharmaceutical industry.

<sup>40</sup> For example, dissemination of reference texts is limited to texts that are, among other things, based on a systematic review of the existing evidence, are published by an independent publisher, represent the most current version of the text, and are peer-reviewed by experts. 2014 Reprint Guidance, *supra* note 34, at 11. Dissemination of Clinical Practice Guidelines is limited to a CPG that is, among other things, based on a systematic review of the existing evidence, is developed by a knowledgeable, multidisciplinary panel of experts and representatives from key affected groups, and be based on “an explicit and transparent process by which the CPG is developed and funded that minimizes distortions, biases, and conflicts of interest.” *Id.* at 14–15.

The 21st Century Cures Act, passed and signed into legislation in December 2016, further broadens the scope of manufacturers' ability to promote off-label uses of their products. Specifically, Section 3037 of the Act amends the FDCA to allow pharmaceutical manufacturers to provide health care economic data to certain entities related to an unapproved use of a drug. The Act also requires the FDA to conduct public meetings and issue guidance within 18 months (by mid-2019) addressing changes to clinical trial designs and the use of real world evidence to help support approval of new indications for an approved drug. In other words, the 21st Century Cures Act allows drug manufacturers to provide a specific category of off-label information to certain entities and encourages the FDA to make the approval of new uses of already approved drugs easier and cheaper. The safe harbors and the promise of an easier path to approvals for new uses shows that any restrictions on speech that may be the by-product of misbranding prosecutions are "limited and targeted" and reasonably fit the FDA's substantial interest in ensuring the unfortunate consequences wrought by the unlimited marketing of drugs in the 1950s and 1960s do not recur.<sup>41</sup>

### *B. Pharmaceutical Marketing and the First Amendment*

Since the 1970s, the Supreme Court has had occasion to consider whether limits on pharmaceutical marketing violate the First Amendment, although it has never directly considered whether prosecutions for misbranding implicate or violate the First Amendment. The opinions with respect to other forms of pharmaceutical marketing acknowledge that some commercial information is protected by the First Amendment, but the protection is not categorical. Instead, the Court generally balances the government's substantial interest in restricting speech with the public interest in the free flow of information. The Court in these cases has tended to acknowledge the government's "substantial interests," but has also often characterized them as "paternalistic." The Court has also tended to ignore whether the information that is being provided really gives the intended audience the complete information it needs to engage in rational decision-making; instead the assumption is usually that more information, of whatever quality, helps inform the economic decisionmaker. In other words, more information equals more truth. The dissents in these cases—two authored by Justice Breyer—take issue with the Court substituting its own judgment for that of more expert and democratic legislatures and agencies.

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<sup>41</sup> See *United States v. Caronia*, 703 F.3d 149, 168 (2d Cir. 2012) (finding that the government has not established a "'reasonable fit' among its interests in drug safety and public health, the lawfulness of off-label use, and its construction of the FDCA to prohibit off-label promotion" and suggesting "the government's interests could be served equally well by more limited and targeted restrictions on speech.")

In *Virginia State Board of Pharmacy v. Virginia Citizens Consumer Council, Inc.*,<sup>42</sup> the first of these cases, the Court ruled that a state law prohibiting pharmacists from posting drug prices violated the First Amendment. The Court found, for the first time, that commercial speech was protected by the First Amendment.<sup>43</sup> It then ruled that the ban on posting drug prices was unconstitutional because it prohibited the free flow of information to consumers. The Court held: “So long as we preserve a predominantly free enterprise economy, the allocation of our resources in large measure will be made through numerous private economic decisions. It is a matter of public interest that those decisions, in the aggregate, be intelligent and well informed. To this end, the free flow of commercial information is indispensable.”<sup>44</sup> The Court considered the benefits of the ban, but rejected those as being “highly paternalistic.”<sup>45</sup> The Court was particularly concerned that the “State’s protectiveness of its citizens rests in large measure on the advantages of their being kept in ignorance.”<sup>46</sup> It emphasized the importance of the free flow of information and having a “marketplace of ideas” that allows individual citizens to make proper decisions—whether political or economic—lies at the heart of the First Amendment’s protections.

In a dissent, Justice Rehnquist acknowledged that the free flow of information is important, but noted that when it comes to commercial information, that concern should be for the legislature, which can more properly balance the need for the free flow of information against other concerns.<sup>47</sup> More specifically, Justice Rehnquist did not believe it appropriate for the Court to impose an “open door policy” towards commercial advertising related to pharmaceuticals because on the one hand, he felt that an individual’s interest in commercial information is relatively low because it affects economic decisions, not political or social ones, while on the other hand, “the societal interest against the promotion of drug use for every ill, real or imaginary, seems . . . extremely strong.”<sup>48</sup> He argued, therefore, that balancing these concerns was better left to the legislature than to the court.

In *Thompson v. Western States*, a group of compounding pharmacists challenged a provision of the Food and Drug Administration Modernization Act

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<sup>42</sup> 425 U.S. 748 (1976).

<sup>43</sup> *Id.* at 770.

<sup>44</sup> *Id.* at 765.

<sup>45</sup> *Id.* at 770.

<sup>46</sup> *Id.* at 769.

<sup>47</sup> *Id.* at 784 (Rehnquist, J., dissenting).

<sup>48</sup> *Id.* at 790.

of 1997 that exempted providers of compound drugs from the FDA's drug approval requirements so long as they abided by several restrictions, including, for the purposes of the lawsuit, a prohibition on advertising or promoting the compounding of any particular drug, class of drug, or type of drug.<sup>49</sup> The parties agreed that the prohibition involved commercial speech. Thus, in deciding whether the advertising prohibition violated the First Amendment, the Court applied the commercial speech test set out in *Central Hudson Gas & Elec. Corp. v. Public Serv. Comm'n of N.Y.*<sup>50</sup> Under the *Central Hudson* test, the Court first determines whether the commercial speech that is banned concerns unlawful activity or is false or misleading.<sup>51</sup> If so, it can be prohibited. If not, the Court applies a three-part test. First, it asks whether the asserted governmental interest that prohibits or curtails the commercial speech is "substantial."<sup>52</sup> If it is, the Court then asks whether "the regulation directly advances the governmental interest asserted."<sup>53</sup> The Court then analyzes whether there is a reasonable fit between the governmental interest and the curtailment of speech, looking at whether the regulation "is not more extensive than is necessary to serve the interest."<sup>54</sup>

In analyzing whether the advertising prohibition violated the First Amendment, the Court gave credit to the government's stated substantial interests. Specifically, the Court held that "[p]reserving the effectiveness and integrity of the FDCA's new drug approval process is clearly an important governmental interest, and the Government has every reason to want as many drugs as possible to be subject to that approval process."<sup>55</sup> The Court also recognized that the government has to be able to draw the line between small-scale compounding and large-scale drug manufacturing.<sup>56</sup> But the Court found problematic the use of advertising as a proxy for whether a compounding pharmacy was engaged in large-scale advertising. The Court noted that there were several other non-speech-related means of drawing a line between compounding and large-scale manufacturing, including prohibiting pharmacists from compounding drugs without a prescription, from selling products at wholesale to commercial entities, or limiting the number of prescriptions a compounding pharmacy could fill. Thus, the Court held that the speech

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<sup>49</sup> 535 U.S. 357, 364–65 (2002).

<sup>50</sup> 447 U.S. 557 (1980).

<sup>51</sup> 535 U.S. at 367 (citing *Central Hudson*, 447 U.S. at 566).

<sup>52</sup> *Id.*

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

<sup>54</sup> *Id.*

<sup>55</sup> *Id.* at 369.

<sup>56</sup> *Id.* at 370.

restrictions were more extensive than necessary to serve the government's interest in distinguishing between small- and large-scale drug manufacturers.<sup>57</sup>

The Court rejected the notion that one of the important government interests served by the prohibition was protecting the health and safety of the public by ensuring compounding drugs were not sold to patients who do not clearly need them because while the dissent suggested this interest, the Government itself did not.<sup>58</sup> The Court noted that the *Central Hudson* test is not a rational basis test—which allows the Court to uphold the regulation if any rational basis for the regulation can be articulated—but rather applies a heightened level of scrutiny requiring the government to articulate an important interest advanced by the regulation.<sup>59</sup> The Court also stated that even if it were to assume that protecting consumers was an interest advanced by the advertising prohibition, it could not accept it as important, since the concern “amounts to a fear that people would make bad decisions if given truthful information about compounded drugs,” which is “paternalistic” and therefore inappropriate.<sup>60</sup>

Following Rehnquist's dissent in *Virginia State Board of Pharmacy*, Justice Breyer, in a dissent in *Western States*, admonished the majority for substituting its own judgment for that of the legislature. Justice Breyer opined that the statutory history showed that one of the important interests served by the advertising prohibition was to protect the public health and safety by ensuring that patients get the individualized therapy they actually need. The restrictions, he noted, “diminish the likelihood that those who do not genuinely need untested compound drugs will not receive them.”<sup>61</sup> Justice Breyer criticized the majority's unwillingness to seriously credit these interests and its willingness, instead, to “too readily assume[] the existence of practical alternatives.”<sup>62</sup> He stated his concern that the test imposed by the Court was too strict and transformed “what ought to be a legislative or regulatory decision about the best way to protect the health and safety of the American public into a constitutional decision prohibiting the legislature from enacting necessary protections.”<sup>63</sup>

The most recent of the Court's decisions involving pharmaceutical marketing and the First Amendment is *Sorrell v. IMS Health Inc.*,<sup>64</sup> which held

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<sup>57</sup> *Id.* at 371–72.

<sup>58</sup> *Id.* at 373.

<sup>59</sup> *Id.* at 374.

<sup>60</sup> *Id.* at 374–75 (citing *Virginia Bd. of Pharmacy*, 425 U.S. at 770).

<sup>61</sup> *Id.* at 382 (Breyer, J., dissenting).

<sup>62</sup> *Id.* at 388.

<sup>63</sup> *Id.* 389.

<sup>64</sup> 564 U.S. 552 (2011).

that a Vermont law that prohibited pharmacy records that show the prescribing habits of doctors to be sold to pharmaceutical companies or used for marketing violated the First Amendment. While the law did not restrict speech, the majority opinion characterized it as enacting “content- and speaker-based restrictions on the sale, disclosure, and use of prescriber-identifying information.”<sup>65</sup> Because it disfavored marketing—a form of speech—the majority stated it was appropriate to apply “heightened judicial scrutiny” to the law.<sup>66</sup> The Court then applied the *Central Hudson* standard to the law, first considering the state’s interest in the law.

Vermont contended that the law was necessary to “protect medical privacy, including physician confidentiality, avoidance of harassment, and the integrity of the doctor-patient relationship” and that it also led to “improved public health and reduced healthcare costs.”<sup>67</sup> The majority indicated that such purposes were “proper,” but ultimately concluded that they did not provide sufficient justification for the law.<sup>68</sup> Since the majority essentially found that the State’s interests were not substantial or permissibly furthered by the law, the Court did not reach any of the other *Central Hudson* factors.

As to Vermont’s justifications for the law, the Court held that with respect to protecting physicians from harassment, pharmaceutical marketing constituted “benign and, many would say, beneficial speech” and “fear that speech might persuade provides no lawful basis for quieting it.”<sup>69</sup> The Court noted that detailing by pharmaceutical sales reps could be “instructive” and selectively pointed to the record, which showed “some Vermont doctors view targeted detailing based on prescriber-identifying information as ‘very helpful’ because it allows detailers to shape their messages to each doctor’s practice.”<sup>70</sup> The Court also credited the testimony of a Vermont physician who said “information is power. And the more you know, or anyone knows, the better decisions can be made.”<sup>71</sup> Indeed, the Court noted that the law’s concern over the adverse effects of pharmaceutical marketing to doctors could be characterized as a fear that the Court routinely has held not to be a permissible basis to infringe upon the First Amendment: the “fear that people would make bad decisions if given truthful

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<sup>65</sup> *Id.* at 563–64.

<sup>66</sup> *Id.* at 565.

<sup>67</sup> *Id.* at 572.

<sup>68</sup> *Id.* at 577.

<sup>69</sup> *Id.* at 576.

<sup>70</sup> *Id.* at 578.

<sup>71</sup> *Id.*

information.”<sup>72</sup> On this point, the Court stated that it should be particularly skeptical of regulations “that seek to keep people in the dark for what the government perceives to be their own good” and that such “precepts apply with full force when the audience, in this case prescribing physicians, consists of ‘sophisticated and experienced’ consumers.”<sup>73</sup> In other words, the Court would not let “paternalism” get in the way of allowing pharmaceutical marketers to target and harass physicians based on their prescribing habits. Instead, in line with its conviction that more information is always better, the Court noted that the way for the State to combat its concerns would be to express its view “that detailers who use prescriber-identifying information are effective in promoting brand-name drugs” through “its own speech.”<sup>74</sup>

In a dissent, Justice Breyer decried the majority’s use of heightened scrutiny in the case, characterizing the law not as a content- and speaker-based proscription on information—the law “neither forbids nor requires anyone to say anything”<sup>75</sup>—but rather as prohibiting certain entities from accessing information collected pursuant to a State regulatory scheme. Justice Breyer also found that the law met the *Central Hudson* factors. First, he held that the protection of public health is a substantial interest that falls within the traditional scope of the State’s police powers and that the law advanced these interests. Justice Breyer cited to the “substantial legislative record” that showed data mining allowed drug companies to manipulate their messages to physicians, so that physicians would not necessarily get “fair and balanced” information.<sup>76</sup> Thus, Justice Breyer credited the parts of the record that showed that “more information” does not necessarily equal “more truth.” Justice Breyer also found that the law was narrowly tailored to meet its objectives. He criticized the majority for not being able to point to “any adequately supported, similarly effective ‘more limited restriction,’”<sup>77</sup> and discredited the respondents’ suggestion that pharmaceutical company manipulation could be combatted with more speech from the State (letting doctors know their prescribing information is being used, “educating” doctors about generics). Justice Breyer noted that such informative programs have “been in effect for some time in Vermont or other States, without indication that they have prevented the imbalanced sales

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<sup>72</sup> *Id.* at 577.

<sup>73</sup> *Id.* (citing *44 Liquormart, Inc. v. Rhode Island*, 517 U.S. 484, 503 (1996) and *Edenfield v. Fane*, 507 U.S. 761, 775 (1993)).

<sup>74</sup> *Id.* at 578.

<sup>75</sup> *Id.* at 585.

<sup>76</sup> *Id.* at 597–98.

<sup>77</sup> *Id.* at 599.



tactics at which Vermont's statute takes aim.”<sup>78</sup> Ultimately, Justice Breyer opined, as he did in *Western States*, that courts ought to defer “significantly to legislative judgment” when reviewing regulatory legislation that indirectly affects speech.<sup>79</sup>

C. *United States v. Caronia*<sup>80</sup>

Although pharmacists and pharmaceutical companies had been victorious in using the First Amendment as a shield against regulation in the Supreme Court, until 2012, no one had suggested that the FDCA's entire regulatory scheme—requiring approval for a drug use before a company can promote it—was unconstitutional. Indeed, in his dissent in *IMS Health*, Justice Breyer stated (perhaps presciently), that “[n]o one has yet suggested that substantial portions of federal drug regulation are unconstitutional.”<sup>81</sup> But in *Caronia*, the Second Circuit, relying mainly on *IMS Health*, held that misbranding prosecutions violate the First Amendment, striking a blow to the FDA's entire drug (and device) approval process.

In the case, the United States had prosecuted Alfred Caronia, a pharmaceutical sales representative, for violating the FDCA's misbranding provisions by promoting Xyrem, which the FDA approved to treat narcolepsy in patients with cataplexy and patients with excessive daytime sleepiness, by promoting the drug for insomnia, fibromyalgia, periodic leg movement, restless leg syndrome, and Parkinson's disease, among other things. Caronia also promoted Xyrem for patients under the age of 16, a population for which it had not received FDA approval. Notably, because of its very serious adverse side effects, the FDA required Xyrem's manufacturer, Orphan Medical (now Jazz Pharmaceutical), to place a black box warning on the label. At trial, the government relied on Caronia's statements to the physicians to show that he “misbranded” the drugs, meaning that he allowed Xyrem to be used without labeling bearing “adequate directions for use,”<sup>82</sup> because he intended that it be used for purposes other than those contained in the FDA-approved label. Caronia was convicted of misbranding, and he challenged his conviction as violating the First Amendment.

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<sup>78</sup> *Id.* at 600–01.

<sup>79</sup> *Id.* at 584.

<sup>80</sup> 703 F.3d 149 (2d Cir. 2012).

<sup>81</sup> 564 U.S. at 598.

<sup>82</sup> 21 U.S.C. § 352(f).

The government argued that its prosecution of Caronia had no First Amendment implications because it was not prosecuting Caronia for his speech; instead, it used his speech as evidence of the “intended use” of Xyrem. The Second Circuit summarily dismissed this argument, contending that “the government’s theory of prosecution identified Caronia’s speech alone as the proscribed conduct.”<sup>83</sup> Concluding, then, that the prosecution of Caronia for misbranding implicated the First Amendment, the Second Circuit turned to the *Central Hudson* analysis.

Under the first prong of *Central Hudson*, the court determined whether the effect of the misbranding prosecution—disallowing off-label speech—concerned unlawful activity or false or misleading statements. Again, without any analysis, the court noted that “the promotion of off-label drug use is not in and of itself false or misleading.”<sup>84</sup> The court then went on to consider whether the government had a substantial interest that was directly advanced by the prosecution. The government asserted that its interest was “preserving the effectiveness and integrity of the FDCA’s drug approval process, and an interest in reducing patient exposure to unsafe and ineffective drugs.”<sup>85</sup> In considering whether this interest was substantial and advanced by the regulation, the court did not consider the legislative history of the Kefauver-Harris amendments at all. Instead, it concluded that because physicians were allowed to prescribe drugs off-label, “prohibiting the truthful promotion of off-label drug usage by a particular class of speakers would [not] directly further the government’s goals of preserving the efficacy and integrity of the FDA’s drug approval process and reducing patient exposure to unsafe and ineffective drugs.”<sup>86</sup> Following *Sorrell*, the court also essentially accepted that more information equals more truth, opining that prohibiting off-label promotion “‘paternalistically’ interferes with the ability of physicians and patients to receive potentially relevant treatment information.”<sup>87</sup>

The *Caronia* court also concluded that the government’s construction of the misbranding regulation to prohibit off-label promotion was not narrowly drawn to achieve its purpose. Ignoring the safe harbors, which even in 2011 gave substantial leeway to drug companies to provide reprints and other reliable information about off-label uses to physicians, the court instead offered up its own apparently more narrowly drawn regulatory suggestions as solutions to the

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<sup>83</sup> 703 F.3d at 162.

<sup>84</sup> *Id.* at 165.

<sup>85</sup> *Id.* at 166.

<sup>86</sup> *Id.*

<sup>87</sup> *Id.*

problem of off-label promotion. The court suggested that “the government could [put] ceilings or caps on off-label prescriptions”; could “remind physicians and manufacturers of, and even perhaps further regulate, the legal ability surrounding off-label promotion and treatment decisions”; or “where [the] off-label drug use is exceptionally concerning . . . could prohibit the off-label use altogether.”<sup>88</sup> In response to the government’s assertion that these suggestions were not “feasible,” the court remarkably concluded that such an assertion was “conclusory” and that the government—which of course during the democratic legislative process and with input from regulatory experts had considered many options and come up with the regulatory scheme currently in place—had to demonstrate that the “proposed alternatives”—thrown out in briefs by pharmaceutical companies and their supporters—“are less effective than its construction of the FDCA in furthering the government interests identified.”<sup>89</sup>

In a scathing dissent, Judge Livingston criticized the majority’s finding that the misbranding prosecution implicated the First Amendment and also asserted that, even assuming it did, all the *Central Hudson* factors were met. First, Judge Livingston pointed out that Caronia was not prosecuted for off-label promotion, but for misbranding. His statements about the off-label uses of Xyrem were entered as evidence of intent, and the Supreme Court has held—in a hate crimes case—that the “First Amendment . . . does not prohibit the evidentiary use of speech to establish the elements of a crime or to prove motive or intent.”<sup>90</sup> Thus, Judge Livingston asserted, “[c]onsistent with the First Amendment . . . otherwise permissible conduct may become impermissible if undertaken with a prohibited motive, and speech may be used as evidence of such a motive. An employer, for example, is generally free to refuse to promote an employee simply because he does not like the employee’s attitude, but he may not refuse to promote the employee because of her sex. . . . The First Amendment does not bar using the employer’s speech to demonstrate his discriminatory motive.”<sup>91</sup> Thus, under Judge Livingston’s analysis, the prosecution of Caronia did not even raise First Amendment concerns.

Nevertheless, Judge Livingston addressed whether, assuming that using Caronia’s speech as evidence of his intent was not necessarily constitutionally permissible, it met the requirements of *Central Hudson* and *Sorrell* and found that it met the scrutiny required by those cases.<sup>92</sup> Judge Livingston noted that

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<sup>88</sup> *Id.* at 168.

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

<sup>90</sup> *Id.* at 171 (citing *Wisconsin v. Mitchell*, 508 U.S. 476 (1993)).

<sup>91</sup> *Id.* at 175 (internal citations omitted).

<sup>92</sup> *Id.* at 177.

without the ability to prosecute drug companies and their employees for misbranding, the FDA would be unable to encourage participation in the drug approval process. After all, “[i]f drug manufacturers were allowed to promote FDA-approved drugs for non-approved uses, they would have little incentive to seek FDA approval for those uses.”<sup>93</sup> Thus, the ability to prosecute drug companies for misbranding when they promote drugs for off-label uses is essential to the entire scheme of drug approvals, the very scheme that the Supreme Court found to be “clearly an important governmental interest” in *Western States*.<sup>94</sup>

Judge Livingston found this scheme to be narrowly tailored to its objectives. She pointed to the fact that the prohibition on off-label promotion is limited to drug manufacturers, rather than all speakers, as evidence that the statute is narrowly drawn, since it targets “the precise group that the government must encourage to participate in the new drug approval process.”<sup>95</sup> And she noted that the prohibition on off-label promotion is thus not simply an act of paternalism “meant to shield physicians and patients from truthful information.”<sup>96</sup> Instead, “it is a necessary tool for the effective functioning of a regulatory system that the Supreme Court has endorsed as legitimate.”<sup>97</sup> Judge Livingston also asserted that the alternatives that the majority asserted as being less restrictive ways of advancing the government’s interests were not as effective, and with respect to a total ban on off-label promotion, more concerning under the First Amendment.<sup>98</sup> Ultimately, Judge Livingston concluded that the system of drug regulation that allows prosecution for misbranding for off-label promotion of a drug was constitutional under *Central Hudson* and *Sorrell*:

Our system of drug regulation developed to protect consumers from misleading and unsubstantiated claims about drugs’ safety and efficacy, and the prohibition on off-label promotion by drug manufacturers is essential to maintaining the effectiveness of that system. Therefore, even if such a prohibition is considered a direct regulation of speech, it is a regulation that directly advances a substantial government interest in a manner not more extensive than necessary to serve that interest.<sup>99</sup>

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<sup>93</sup> *Id.* at 178.

<sup>94</sup> *Id.* at 178; *supra* note 50.

<sup>95</sup> *Id.* at 178–79.

<sup>96</sup> *Id.* at 179.

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

<sup>98</sup> *Id.* at 180.

<sup>99</sup> *Id.* at 181.

## II. ATTACKING *CARONIA*

*Caronia* was wrongly decided for many reasons, including those laid out by Judge Livingston. There is a strong argument that misbranding prosecutions, which rely on off-label statements to show intent, do not even implicate the First Amendment because they seek to punish conduct, not speech. The D.C. Circuit had already held as much prior to *Caronia*, and even after *Caronia*, the Seventh Circuit in an unpublished decision in *United States v. LeBeau*<sup>100</sup> held that a misbranding prosecution did not raise First Amendment concerns.

The *Caronia* majority opinion also arguably failed to properly analyze the *Central Hudson* factors. Namely, the majority opinion assumed, without further inquiry, that promotional speech about off-label indications is truthful, when, in fact, it differs substantially from the previous types of commercial speech protected by the Supreme Court in its ability to be verified, and therefore to mislead. First Amendment commercial speech restrictions make clear that “false and misleading” information does not receive First Amendment protection. Of course, what the FDA’s regulatory regime ensures is that the information drug companies provide to physicians about off-label uses is not misleading—that it is fully truthful. Thus, to the extent that pharmaceutical companies and their employees provide information outside of the safe harbors, the information they provide is inherently misleading, and does not deserve First Amendment protection. The *Caronia* court therefore erred in assuming that the information *Caronia* provided to his physicians was neither false nor misleading.

The majority opinion also did not give enough weight to the substantial interest furthered by the FDA’s regulatory regime and wrongly substituted its own judgment as to what policies would be more narrowly tailored to further those interests. The FDA’s January 2017 memorandum goes a long way to bolstering these arguments. Moreover, the broadening of the safe harbors in the FDA’s 2014 guidance—released two years after *Caronia*—and amendments to the FDCA made by the 21<sup>st</sup> Century Cures Act give the FDA even more evidence to show that its regime in fact properly balances the need to protect the public from unsafe and ineffective drugs with the ability of the pharmaceutical companies to provide accurate, reliable, and fully truthful information about off-label uses of their products to the physicians who can write prescriptions for those products, and thus is as least restrictive as possible.

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<sup>100</sup> 654 Fed. App’x 826 (7th Cir. 2016).

Given the weaknesses in the *Caronia* court’s reasoning, the strong arguments the FDA has, and the fact that at least one other Circuit Court has found a misbranding prosecution not to implicate the First Amendment—albeit in an unpublished opinion—the FDA should not be concerned about, as Kesselheim and Mello, “taking another run”<sup>101</sup> at *Caronia* and continuing to protect the public by aggressively prosecuting misbranding cases when drug and device companies promote their products for unapproved uses.

#### A. *Speech May Be Used as Evidence of Intent in Misbranding Cases*

As Judge Livingston pointed out in her dissent, a prosecution for misbranding involves showing that a drug company or its employee promoted a drug for a use different from a use that the company intended be approved by the FDA. In order to provide evidence that the drug company put the drug in the stream of commerce without a sufficient label for the use, it must show what use the company or employee intended. Of course, the only way to prove such use is to put into evidence the written or oral statements of the company or its employee. FDA regulations make clear that for the purposes of making out a misbranding claim, the intended use of a drug is determined by taking into account “the objective intent of the persons legally responsible for the labeling of the drugs.”<sup>102</sup> “Objective intent” may be shown through “oral or written statements by such persons or their representatives.”<sup>103</sup>

In holding that the utilization of such evidence violated the First Amendment, the *Caronia* decision ignored Supreme Court precedent and put at risk a whole host of laws that regulate conduct in which *intent* makes all the difference. As Judge Livingston noted, the difference between a permissible employment termination and an impermissible one is intent.<sup>104</sup> And since no one can get into the head of any person, evidence of that intent is likely to come in written or spoken form. This is also true for hate crime legislation. In that context, the Supreme Court has been clear that use of speech to show that a crime was motivated by racial animus does not raise First Amendment concerns.

In *Wisconsin v. Mitchell*,<sup>105</sup> the Supreme Court considered whether a criminal penalty enhancement for hate crimes violated the First Amendment.

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<sup>101</sup> Aaron S. Kesselheim & Michelle M. Mello, *Prospects for Regulation of Off-Label Drug Promotion in an Era of Expanding Commercial Speech Protection*, 92 N.C. L. REV. 1539, 1584 (2014).

<sup>102</sup> 21 C.F.R. § 201.128 (2012).

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

<sup>104</sup> 703 F.3d at 175.

<sup>105</sup> 508 U.S. 476 (1993).

Mitchell, who was African-American, was convicted of aggravated battery for beating a white boy. Prior to the beating, Mitchell asked the group of young men who assisted him in the beating, “Do you all feel hyped up to move on some white people?”<sup>106</sup> Mitchell claimed that the penalty enhancement violated the First Amendment because it would chill speech. The Court rejected his argument, holding that the First Amendment “does not prohibit the evidentiary use of speech to establish the elements of a crime or to prove motive or intent.”<sup>107</sup>

In 2004, the D.C. Circuit applied this reasoning in a pharmaceutical marketing case. In *Whitaker v. Thompson*,<sup>108</sup> Whitaker sought to market saw palmetto—an extract from the pulp of the dwarf American palm—as a dietary supplement to “improve urine flow, reduce nocturia and reduce voiding urgency associated with mild benign prostatic hyperplasia (BPH).”<sup>109</sup> The FDA denied his petition, finding that he was not intending to market saw palmetto as a dietary supplement, but instead was making “drug claims.” Thus, saw palmetto could not be marketed to treat BPH without being approved as a drug. Whitaker sued, arguing that the FDA’s refusal to allow him to market saw palmetto using his proposed label violated the First Amendment’s protections for commercial speech. The court rejected his argument, noting that at issue was whether Whitaker intended to market the saw palmetto as a dietary supplement or a drug. Since his speech was integral to divining intent and thereby the proposed uses of the product, the FDA’s reliance on it did not violate the First Amendment. Specifically, the court held, relying on *Mitchell*, that “it is constitutionally permissible for the FDA to use speech, in the form of labeling, to infer intent for purposes of determining” whether the proposed sale of the product “would constitute the forbidden sale of an unapproved drug.”<sup>110</sup>

Even after *Caronia*, the Seventh Circuit has recognized that it is constitutionally permissible for speech to be used as evidence to show the intended uses of a product. In *United States v. LeBeau*,<sup>111</sup> LeBeau was convicted

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<sup>106</sup> *Id.* at 480.

<sup>107</sup> *Id.* at 489.

<sup>108</sup> 353 F.3d 947 (D.C. Cir. 2004).

<sup>109</sup> *Id.* at 948.

<sup>110</sup> *Id.* at 953; see also *Holistic Candles & Cons. Ass’n v. U.S. Food & Drug Admin.*, 770 F. Supp. 156, 160 n.8 (D.D.C. 2011) (“It is well established that the FDA may evaluate speech contained in labeling to determine whether sale of a regulated product is lawful.”); *United States v. Livdahl*, 459 F. Supp. 2d 1255, 1268 (S.D. Fl. 2005) (overruling defendant’s attempt to challenge his indictment as violating the First Amendment and recognizing that the offense defendant is charged with “entail[s] proof of statements or other communications made by the accused in furtherance of the illegal agreement or scheme to defraud,” thus the indictment seeks to punish defendant “not for his speech, but for the underlying crime evidenced by that speech.”).

<sup>111</sup> 654 Fed. App’x 826 (7th Cir. 2016).

under the misbranding provisions for introducing into interstate commerce four products that he claimed would treat certain allergies and diseases, without gaining FDA approval for the drugs. Mr. LeBeau had advertised that these four products could “mitigate certain food allergies, Lyme disease, colds, influenza, and H1N1 flu.”<sup>112</sup> He pled guilty, but reserved his right to challenge, among other things, the constitutionality of the misbranding provisions.<sup>113</sup> He argued that the provisions violated his First Amendment right to commercial speech by limiting his ability to make truthful claims about his product. The Court of Appeals for the Seventh Circuit rejected LeBeau’s claims, recognizing that the statements LeBeau made about the efficacy of his products to treat certain conditions constituted evidence to show how LeBeau intended consumers to use the products, and thus whether the products were “drugs” under 21 U.S.C. § 321(g)(1). Thus, LeBeau was not prosecuted for his speech, but for his acts—“his attempt to profit from the sale of a product—which he represented to have palliative properties—without having received approval to do so.”<sup>114</sup> The Court recognized, citing *Mitchell* and *Whitaker*, that it is constitutionally permissible to use speech as evidence to establish the elements of a crime.<sup>115</sup>

Likewise, in *Caronia*, the government was not prosecuting Caronia for his speech, but rather for promoting Xyrem for uses for which Orphan did not have FDA approval. The majority summarily rejected this argument, finding categorically that “the government has treated promotional speech as more than merely evidence of a drug’s intended use—it has construed the FDCA to prohibit promotional speech as misbranding itself.”<sup>116</sup> But this makes no sense. How else is the government supposed to prove whether a drug company or its employee intended physicians to use a product in a manner for which the company has not received approval? It can only rely on the statements made or the information provided to those physicians.

“Misbranding” is putting a drug into the stream of interstate commerce without adequate labeling. The only way to know whether or not the labeling is “adequate” is to understand what use the person or entity that put it into the stream of commerce intended for it. This is because directions are only adequate if they include, for example, “[s]tatements of all . . . uses for which such drug is intended,” and “usual quantities [of dose] for each of the uses for which it is

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<sup>112</sup> *Id.* at 828.

<sup>113</sup> *Id.*

<sup>114</sup> *Id.* at 830.

<sup>115</sup> *Id.* at 831.

<sup>116</sup> *Caronia*, 703 F.3d at 155.



intended.”<sup>117</sup> And so in *Caronia*, the only way to prove what “use” the drug was being provided for and whether its labeling was adequate for that use was to discuss and put into evidence Caronia’s promotional statements. But the government was prosecuting Caronia for an act—for conduct—not speech.

Certainly, in a discrimination case or even a hate crime case, the act and the statements that show intention may have more light between them. In a discriminatory termination case, you have the conduct—the termination—and then the question of whether or not it was permissible. In a hate crime case, you have the crime—the conduct—and then the question of whether it was motivated by racial animus. In a misbranding case where the drug has already been approved and therefore is already in the stream of commerce, the act and the intention are more closely tied because the actual communications can be construed as misbranding.

When Caronia made statements about the off-label use of Xyrem, the problem was that he was allowing the drug to be put into the stream of commerce for a use for which it was not approved. But because in a misbranding case involving a drug that has already been approved, the drug is already in the stream of commerce, there is no separate physical act that is easily disconnected from the statements that show intent. Thus, the statements themselves seem to be the target of the prosecution. In *Whitaker* and *LeBeau* the separation between the act and the statements showing intent was clearer, because in those cases the defendants were accused of putting a drug into the stream of commerce that had never been approved. But because the FDA requires a supplemental new drug application when a product considered a “drug” is put on the market for a specific use, regardless of whether it has previously been approved for another use, there is no difference between these prosecutions except that it is harder to see the conduct as separate from the speech in a case involving an already approved drug. Nevertheless, even in cases involving the off-label promotion of an already approved drug, the statements themselves are not the subject of the prosecution, even though those statements and the impermissible act are arguably more closely tied and more capable of confusion, than, say, a beating—which is a clearly physical act—and the words that explain the motive for that beating.

Given the lack of easily recognizable, maybe even physical, conduct in a misbranding case involving a drug that has already been approved for use, it is easy to see why a court may consider the off-label communication itself as

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<sup>117</sup> 21 C.F.R. § 201.5(a).

misbranding and therefore find that the prosecution involves speech itself. However, this view—the one taken by the majority in *Caronia*—has no basis in the statute and regulations under which *Caronia* was prosecuted. Instead, the use of statements to show the “intended use” of a product in a misbranding prosecution is constitutionally permissible under *Mitchell*. The FDA has a strong argument to continue to take this position in misbranding prosecutions.

*B. Prosecutions for Misbranding Involving the Promotion of an Approved Drug for an Unapproved Use Meet the Central Hudson Factors*

*1. Off-Label Promotion Is Inherently Misleading*

Even assuming that misbranding prosecutions involve speech, there are also compelling arguments for why they constitute a constitutionally acceptable restraint on speech. As explained above, the analysis of whether commercial speech meets First Amendment strictures is governed by the factors set forth in *Central Hudson*. When applying the *Central Hudson* test, a court first determines whether the commercial speech that is banned concerns unlawful activity or is false or misleading.<sup>118</sup> The *Caronia* court did not engage in an in-depth analysis of this element, assuming that “promoting off-label drug use concerns lawful activity (off-label drug use), and the promotion of off-label drug use is not in and of itself false or misleading.”<sup>119</sup> But this is not an inevitable conclusion. The Supreme Court held in *Central Hudson* that communications can be “misleading” and therefore permissibly prohibited if they are “more likely to deceive the public than inform it.”<sup>120</sup> In *Friedman v. Rogers*, the Court held that Texas’ prohibition on optometrists’ use of trade names did not violate the First Amendment because trade names *could* be misleading. The Court noted that the trade names did not *have* to be misleading in order to be regulated. Rather, trade names could properly be regulated because they facilitate “large-scale commercialization which enhances the opportunity for misleading practices.”<sup>121</sup> In *Virginia State Bd. of Pharmacy*, the Court recognized that commercial speech can be regulated, especially if it is deceptive or misleading.<sup>122</sup> The Court noted that it would not violate the First Amendment to ensure that commercial information “flow cleanly as well as freely.”<sup>123</sup>

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<sup>118</sup> 535 U.S. at 367 (citing *Central Hudson*, 447 U.S. at 566).

<sup>119</sup> *Caronia*, 703 F.3d at 165.

<sup>120</sup> *Central Hudson*, 44 U.S. at 563.

<sup>121</sup> 440 U.S. 1, 13 (1979).

<sup>122</sup> 425 U.S. at 771.

<sup>123</sup> *Id.*

Off-label promotion falls into the category of commercial speech that is highly likely to be misleading. In general, a specific piece of information about an unapproved use of a product may not be misleading, but when physicians are given incomplete information about an unapproved use, it certainly can be said to be “more likely to deceive” physicians than inform them. Indeed, many observers have noted that off-label promotion is *inherently* misleading, and is certainly so when unbounded—when pharmaceutical companies are allowed to provide physicians with whatever information the company wants. Former U.S. Representative Henry Waxman, who was a ranking member of the House Committee on Government Reform and a senior member of the House Committee on Energy and Commerce, both of which have jurisdiction over the FDA, wrote that prior to the Kefauver-Harris Amendments—and the FDA’s ability to ensure safety and effectiveness of drugs including through misbranding prosecutions—drug companies’ promotional claims about unproven uses were “inherently misleading” for several reasons: promotional information from manufacturers often fails to provide information about negative studies, data may be presented as if it is of high scientific quality when it is not, cited studies may be from low quality or foreign publications, and statements or findings in studies may be taken out of context or interpreted more favorably than the data show.<sup>124</sup>

Indeed, a 2006 study found that 21% of prescriptions were for uses not approved by the FDA, and that 73% of those unapproved uses had little or no scientific support.<sup>125</sup> A more recent study shows that when medical trainees interact with pharmaceutical representatives, the medical trainees that have positive associations with these interactions are more likely to prescribe branded drugs rather use evidence-based prescribing for their patients.<sup>126</sup> In other words, pharmaceutical marketers’ interactions with physicians (and would-be physicians) generally lead physicians to move away from making decisions based on accurate, fulsome scientific information. This is because promotional information provided to physicians has a marketing purpose and when it is not limited by rules that ensure its accuracy and truthfulness, can be said to be inherently misleading.

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<sup>124</sup> Waxman, *supra* note 1, at 307.

<sup>125</sup> David C. Radley, et al., *Off-label Prescribing Among Office-Based Physicians*, 166 ARCH. INTERN. MED. 1021–26 (2006); *see also* Tewodros Egale et al., *Association of Off-Label Drug Use and Adverse Drug Events in an Adult Population*, 176 JAMA INTERN. MED. 55–63 (Jan. 2016) (Canadian study showing that almost 12% of prescriptions were for off-label use and 80.9% of the off-label uses lacked strong scientific evidence).

<sup>126</sup> Kristen E. Austad, et al., *Association of Marketing Interactions With Medical Trainees’ Knowledge About Evidence-Based Prescribing*, 174 JAMA INTERN. MED. 1283 (2014).

Even when information provided to physicians is not promotional, but reflects preliminary research into the safety and effectiveness of a drug for a certain use, it may be misleading. In order to assess the safety and effectiveness of a drug or device for a particular use, the FDA requires data from completed clinical trials and results keyed to specific identified endpoints.<sup>127</sup> This is because many devices and drugs that initially appear promising based on early stage research ultimately fail to show clinical benefit in later phase research.<sup>128</sup> In one study, the authors found that more than half of drugs entering late-stage clinical development fail during or after pivotal clinical trials, mainly because they turn out not to be effective, safe, or both.<sup>129</sup> Thus, at a preliminary phase, scientific data may show some evidence of a link between a drug and some positive effect, but may not be sufficient to draw inferences or conclusions that the drug is safe and effective.<sup>130</sup> For this reason, such early stage information may be considered misleading. As the FDA has put it, “A firm communication that conveys scientific information that is not truthful, complete, or balanced or that lacks scientific validity has at least the potential to mislead the audience and does not contribute meaningfully to the marketplace of ideas.”<sup>131</sup>

The *Caronia* case is instructive. The “data” that Caronia provided to his physicians was not published, never mind in a reputable, peer-reviewed journal, and was, to say the least, highly preliminary. Caronia told one physician that because of Xyrem’s “properties,” “it’s going to insomnia, Fibromyalgia[,] periodic leg movement, restless leg.”<sup>132</sup> He also discussed studies that presumably the company was just then undertaking and had not completed: “also looking at . . . Parkinson’s and . . . other sleep disorders are underway such as MS.”<sup>133</sup> Other information Caronia and his partner relayed to doctors was completely anecdotal: “I’ve had people under thirteen and I’ve certainly talked

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<sup>127</sup> See generally 21 C.F.R. §§ 312.21, 314.

<sup>128</sup> FDA Memorandum, *supra* note 19, at 12.

<sup>129</sup> Thomas J. Hwang et al., *Failure of Investigational Drugs in Late-Stage Clinical Development and Publication of Trial Results*, 176 JAMA INTERN. MED. 1826–33 (2016).

<sup>130</sup> FDA Memorandum, *supra* note 19, at 7; Christopher T. Robertson, *When Truth Cannot Be Presumed: The Regulation of Drug Promotion Under an Expanding First Amendment*, 94 B.U. L. REV. 545, 560–61 (2014); Jerry Avorn et al., *Forbidden and Permitted Statements about Medications—Loosening the Rules*, 373 NEW ENGL. J. MED. 967 (2015) (“[F]or both claims of efficacy and statements about side effects, the results of individual studies can be incomplete or misleading while not being outright fraudulent; publication in a peer-reviewed journal does not in itself protect against this. Poorly designed or conducted clinical trials or observational studies can readily overstate benefits or minimize risks; unorthodox or inept statistical analyses can create the impression of efficacy or of safety even when more rigorous assessments would come to a different conclusion.”).

<sup>131</sup> FDA Memorandum, *supra* note 19, at 18.

<sup>132</sup> *Caronia*, 703 F.3d at 156.

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

to neurologists that have narcoleptics . . . between eight and ten . . .”<sup>134</sup> None of this information was *per se* false; it may be true that Xyrem’s properties make it promising for the indications Caronia mentioned; that the company was looking into new indications; that other physicians were using it for children even when it had not been approved for that use. But the information provided does not show that Xyrem is safe and effective for any of these uses and does not allow the doctor to fully evaluate and decide for himself whether the drug was, in fact, safe and effective for these uses. Caronia’s intent was to convince the physicians that Xyrem was safe and effective for the non-approved uses, when, in fact, he provided no scientifically reliable information to show that it was. So, while his statements were literally truthful, they had a high probability of misleading. Since misbranding prosecutions prevent such statements, they do not offend the First Amendment, and the *Caronia* court erred in finding otherwise.

The quality of the truthfulness of the information that is being curtailed makes a misbranding case like *Caronia* distinguishable from *Virginia Bd. of Pharmacy*, *Western States*, and *Sorrell*. The speech that misbranding prosecutions impinge upon indirectly is not of the same “truthful” quality as the speech at issue in these Supreme Court cases. In *Virginia Bd. of Pharmacy*, the information that was banned was drug pricing information. This information is either true or false—an advertised price either is or is not the price the pharmacist will charge the consumer for the drug—and is verifiable. When it is true, the information necessarily contributes to consumers’ ability to make rational economic decisions (compare and contrast pharmacy prices) without any risk of misleading. In *Western States*, the information that was essentially banned concerned what drugs the pharmacist compounded (or the fact that a certain pharmacist was compounding a certain drug). Again, this information is either truthful or is not, and is verifiable. If a pharmacist advertises that she compounds Drug X, she either does or doesn’t. In *Sorrell*, the data compilations showing physicians’ drug prescribing habits are also inherently truthful; they merely report the drugs and quantities physicians have actually prescribed, and again, are verifiable. While access to the information may lead to “bad” behavior, like harassing physicians, the information itself is not misleading.

This is not so with promotional information concerning the unapproved uses of drugs. This information is complicated, nuanced, and capable of manipulation. It is also not always, or even usually, verifiable. This is because it is the pharmaceutical company that has access to all of the positive and negative scientific information about the drug, making it difficult for the government, or

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<sup>134</sup> *Id.* at 157.

a physician, to ascertain whether the information provided is accurate and reliable.<sup>135</sup> As one commentator has noted, “To prove the truth or falsehood of any one claim about drug-disease efficacy would cost millions of dollars and years of research by dozens of investigators and many thousands of patients taking the drug and/or placebo, at real risk of side effects and often at real opportunity cost, compared to other treatments the patients could have tried instead.”<sup>136</sup>

Thus, promotional information about off-label uses of drugs does not inherently “flow cleanly.”<sup>137</sup> For this reason, the FDA’s safe harbors allow dissemination of the most accurate, reliable information, but promotional information that falls outside of the safe harbors—information that is not supported by independent, scientifically valid studies, medical research or well-established clinical practice guidelines—the type of information that Caronia was providing to physicians—is prohibited. “[T]he FDA’s current regulatory approach does not impose a blanket prohibition on off-label promotion, but instead focuses on those forms of communication that are most amenable to corruption.”<sup>138</sup> Thus, to the extent that misbranding prosecutions, and the FDA’s provision of safe harbors, ensures that off-label information provided to physicians is “clean,” meaning it is accurate, reliable, and truthful, such prosecutions should not—and do not—raise First Amendment concerns.

For the *Caronia* court to assume that the first *Central Hudson* factor was satisfied—that the speech indirectly affected by misbranding prosecutions is truthful and not misleading—was wrong. In fact, the FDA has a strong argument that misbranding prosecutions, if they implicate speech at all, implicate a type of speech that has a strong probability of misleading. As such, they meet the first *Central Hudson* test and are permissible under the First Amendment.

## 2. *The FDA’s Current Regulatory Scheme Advances the Government’s Interests in Protecting the Public Health & Safety by Ensuring the Safety and Effectiveness of Pharmaceutical and Medical Device Products*

The second and third parts of the *Central Hudson* test look at whether there are substantial government interests underlying the law or regulation at issue and

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<sup>135</sup> Greene & Noah, *supra* note 6, at 243.

<sup>136</sup> Robertson, *supra* note 130, at 559 (referencing Michael Dickson & Jean Paul Gagnon, *Key Factors in the Rising Cost of New Drug Discovery and Development*, 3 *Nature Reviews Drug Discovery* 417 (2004)).

<sup>137</sup> *Virginia State Bd. of Pharmacy*, 425 U.S. at 771.

<sup>138</sup> Kesselheim & Mello, *supra* note 101, at 1593.

whether those interests are furthered by the law or regulation. The *Caronia* court summarily noted the substantial interest underlying the FDA's regulatory regime. It said: "[T]he government's asserted interests in drug safety and public health are substantial. Specifically, the government asserts an interest in preserving the effectiveness and integrity of the FDCA's drug approval process, and an interest in reducing patient exposure to unsafe and effective drugs."<sup>139</sup> But the Court held that the government's construction of the FDCA to prohibit off-label promotion did not advance those interests because physicians are allowed to prescribe drugs for off-label uses, and "prohibiting off-label promotion by a pharmaceutical manufacturer while simultaneously allowing off-label use 'paternalistically' interferes with the ability of physicians and patients to receive potentially relevant treatment information; such barriers to information about off-label use could inhibit, to the public's detriment, informed and intelligent treatment decisions."<sup>140</sup> The court noted that "in the fields of medicine and public health, 'where information can save lives,' it only furthers the public interest to ensure that decisions about the use of prescription drugs, including off-label usage, are intelligent and well-informed."<sup>141</sup> Finally, the court concluded that "[i]f the government's objective is to shepherd physicians to prescribe drugs only on-label, criminalizing manufacturer promotion of off-label use while permitting others to promote such use to physicians is an indirect and questionably effective means to achieve that goal."<sup>142</sup>

The court's reasoning is flawed for numerous reasons. First, it assumes that the government's main purpose is to "shepherd physicians to prescribe drugs only on-label." This construction of the government's interest not only is overly simplistic, but is wrong. Second, the court assumed, following Supreme Court precedent, that in the realm of drug promotional activity and medical prescribing, more information equals more truth and that the "marketplace of ideas" helps physicians become better decisionmakers. But, as explained below, this reasoning is incorrect in a marketplace where all the actors do not have equal access to information and the decisionmaker has no way to properly verify the accuracy or reliability of the information being provided. It may be that medicine and drugs "save lives," but in an inefficient market, off-label prescribing actually leads to more adverse events, not life saving. The FDA's regulatory scheme ensures that patients get life-saving treatments and guarantees that purported life-saving medicines do what they promise to do.

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<sup>139</sup> *Caronia*, 703 F.3d at 166.

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

<sup>141</sup> *Id.* at 167 (quoting *Sorrell*, 564 U.S. at 566).

<sup>142</sup> *Id.*

The *Caronia* court's notion that the government's main interest is to encourage physicians not to write off-label prescriptions is incorrect. The government's purpose in the way it interprets and enforces the FDCA is to ensure that drugs that are placed on the market are safe and effective and that information provided for uses of those drugs that have not yet been proven safe and effective, but which may nevertheless help patients, is accurate, reliable, and not misleading. As the FDA explained in its recent memo, the FDA has "sought to strike a careful balance, supporting medical decision-making for patients in the absence of better options, but doing so without undermining the measures designed to incentivize the development and approval/clearance of medical products that would reduce the need to rely on unapproved use, in light of its risks."<sup>143</sup>

By myopically focusing on a supposed governmental interest in "shepherding" physicians towards prescribing on-label, the *Caronia* court ignored the complex, multi-faceted interests that the FDA seeks to protect. While it is true that the FDA "prefers" on-label prescriptions because those prescriptions are for uses that have been proven to be safe and effective, and thus do not put at risk the public health, on the other side of the coin, the FDA wants to incentivize drug companies to do the clinical trials that are necessary to show a new use is safe and effective. To do so, the FDA uses both a carrot and a stick. The carrot is patent protection: not only do drug manufacturers get five years of patent exclusivity when the FDA approves a new drug, but every time the manufacturer receives approval for a new use of the drug, the patent exclusivity is extended for three years.<sup>144</sup> The stick is misbranding prosecutions. Without both, the government's interest in ensuring that all medically helpful uses of a drug are explored fully and properly in clinical trials is illusory.

The FDA has articulated its interests to include: (1) motivating the development of "robust scientific data on safety and efficacy"; (2) protecting against fraud, misrepresentation, and bias and preventing the diversion of limited health care resources towards ineffective treatment; (3) ensuring drug and device labeling is accurate and informative; (4) protecting human subjects receiving experimental treatments; (5) ensuring informed consent; (6) maintaining incentives for clinical trial participation; (7) promoting development of products for underserved patients; and (8) supporting informed decision-making for patient treatment.<sup>145</sup> Any court that evaluates the

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<sup>143</sup> FDA Memorandum, *supra* note 19, at 20.

<sup>144</sup> 21 U.S.C. § 355(j)(5)(B) and (F); 21 C.F.R. § 314.108.

<sup>145</sup> FDA Memorandum, *supra* note 19, at 4–20.



government's substantial interests and whether they are furthered by the FDA's regulatory scheme must take into account *all* of these various factors. The *Caronia* court paid lip service to "the government's asserted interests in drug safety and public health," its interest "in preserving the effectiveness and integrity of the FDCA's drug approval process, and an interest in reducing patient exposure to unsafe and effective drugs."<sup>146</sup> But when it came down to analyzing whether the regulatory regime advanced that interest, the court actually defined the interest very narrowly, ignoring the number and complexity of the interests involved.

The *Caronia* court also erred by assuming, as most First Amendment cases do, that more information is better. Indeed, in *Sorrell*, the Supreme Court credited the testimony of a Vermont physician who said "information is power. And the more you know, or anyone knows, the better decisions can be made."<sup>147</sup> And the Court characterized Vermont's law as being motivated by an impermissible "fear that people would make bad decisions if given truthful information."<sup>148</sup> But when it comes to pharmaceutical company marketing of drugs for off-label uses, information is not necessarily power because the market is inefficient: the decisionmakers do not have access to all the information necessary to make a well-informed decision. Moreover, the issue is not the government's fear that physicians would make bad decisions (e.g. a decision to prescribe a drug off-label) if given truthful information, but whether the information can really be considered "truthful" when it is not inherently so and is not capable of being verified or tested.

As stated above, unlike drug prices, or information related to whether a compounding pharmacist compounds a specific drug, pharmaceutical companies' communications about off-label promotion are neither inherently truthful nor verifiable. When promotional information about an off-label use is provided to a physician, it is not one piece of information that adds to other information available to the physician about that use to provide a complete picture and allow rational decision-making. Instead, while there may be other published information about the off-label use that can help a physician decide whether she ought to prescribe the drug in that manner, more often than not, there is no complete, scientifically reliable picture available to the doctor. Physicians are provided off-label information by the drug companies, but often do not even know what the approved indications are, and have a hard time

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<sup>146</sup> *Caronia*, 703 F.3d at 166.

<sup>147</sup> *Sorrell*, 564 U.S. at 578.

<sup>148</sup> *Id.* at 577.

keeping up with “rapidly changing medication information.”<sup>149</sup> As one commentator has explained:

This is not a transparent, efficient market, where buyers evaluate the value of products themselves. Even learned and earnest physicians are little help on their own when the underlying science is missing. After all, no individual physician could find it rational to perform . . . a randomized trial of the drug merely to assess its utility in her own practice. This is a classic collective action problem.<sup>150</sup>

Thus, misbranding prosecutions do not constitute a paternalistic effort to protect physicians from bad decision-making; they are part of a regulatory scheme that protects physicians from “bad”—incomplete, inaccurate, unverifiable—information.

The *Caronia* court’s notion that “information saves lives” is also not borne out by the evidence when it comes to off-label marketing and prescribing. First, because off-label uses are not proven to be safe and effective, they are, predictably, more strongly associated with adverse events than on-label use. A Canadian study that analyzed three years of physician-prescribing data from 2012-2015 showed that 11.8% of the prescriptions were for off-label use.<sup>151</sup> In 80.9% of these cases, the off-label uses lacked strong scientific evidence.<sup>152</sup> The researchers found that the adverse event rate—the rate at which drug use was terminated due to an adverse or allergic reaction—for on-label use drugs was 12.5 per 10,000 person-months, while the adverse event rate for off-label use was 19.7 per 10,000 person-months, which represents a 44% increase in the risk for adverse events with off-label use.<sup>153</sup> The study concluded that “[o]ff-label drug use, and particularly off-label use without strong scientific evidence, is a risk factor for [adverse drug events].”<sup>154</sup>

Further, the FDA’s safe harbors ensure that physicians are not completely barred from getting information that could help save their patients’ lives. By allowing pharmaceutical companies to provide information about off-label uses from independent, peer-reviewed journals, medical reference texts, and even clinical practice guidelines, the FDA ensures that physicians do have accurate, reliable, evidence-based information about off-label uses of products so that patients who have no other options can be provided possibly life-saving cures.

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<sup>149</sup> Egualé, *supra* note 125, at 60.

<sup>150</sup> Robertson, *supra* note 130, at 562.

<sup>151</sup> Egualé, *supra* note 125, at 58.

<sup>152</sup> *Id.*

<sup>153</sup> *Id.*

<sup>154</sup> *Id.* at 61.

Finally, the FDA's regulatory scheme—now aided by the 21<sup>st</sup> Century Cures Act—seeks to aid patients in need of last-resort treatment to get the drug approvals they need and works toward making the clinical trial and subsequent approval process more efficient. One argument for allowing off-label promotion suggests that patients cannot get access to treatment because the costs of engaging in clinical trials to support the approval of new uses is prohibitive. For example, Lars Noah has argued that it seems unfair to prohibit drug manufacturers from sharing information that “substantiates an appropriately limited claim of safety and effectiveness” when an NDA would require “a substantial investment of time and resources, averaging on the order of a dozen years and over \$1 billion.”<sup>155</sup> He posits a hypothetical in which an anticoagulant could be used off-label to treat Alzheimer's, and claims it makes little sense for the manufacturer to go through the expensive process of submitting a supplemental new drug application in order to “await the Agency's imprimatur.”<sup>156</sup> But real-world examples show how weak this argument is. Eliquis, an anticoagulant, made its manufacturer Bristol-Myers Squibb \$602 million in the last quarter of 2015.<sup>157</sup> BMS' total revenue for the period was \$4.29 billion and for that year, close to \$17 billion.<sup>158</sup> A similar drug, Xarelto, earned its manufacturers \$3.7 billion in 2014<sup>159</sup> and brought in \$819 million in revenue in the first quarter of 2017.<sup>160</sup> The notion that if, hypothetically, either of these drugs could cure Alzheimer's, it would be prohibitive for these manufacturers to expend \$1 billion over the course of 12 years to do the clinical trials necessary to gain FDA approval for the use is laughable. The reality is that investing \$1 billion on clinical trials in order to support a new drug application is not, relatively speaking, a huge investment for these companies. Such investments are often recovered within just a few years of a new drug (or a new use) coming to market.

Further, the FDA has several programs that expedite the approval process for life-saving treatments so that there is not, in fact, a 12-year wait for approval: the Orphan Drug Designation program, the Rare Pediatric Disease Priority

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<sup>155</sup> Greene & Noah, *supra* note 6, at 249 (citing Lars Noah, *Law, Medicine, and Medical Technology* 260–674, 270–71 (3d ed. 2012)).

<sup>156</sup> *Id.* at 250.

<sup>157</sup> See <http://www.fiercepharma.com/special-report/18-eliquis> (last visited July 16, 2007).

<sup>158</sup> Bristol-Myers Squibb, Press Release, Bristol-Myers Squibb Reports Fourth Quarter and Full Year 2015 Financial Results, available at <https://news.bms.com/press-release/financial-news/bristol-myers-squibb-reports-fourth-quarter-and-full-year-2015-financia> (last visited July 16, 2017).

<sup>159</sup> See [http://www.pmlive.com/top\\_pharma\\_list/Top\\_50\\_pharmaceutical\\_products\\_by\\_global\\_sales](http://www.pmlive.com/top_pharma_list/Top_50_pharmaceutical_products_by_global_sales) (last visited July 16, 2017).

<sup>160</sup> Ludwig Burger, *Stroke drug Xarelto, plastics lift Bayer earnings*, Reuters, Apr. 27, 2017, available at <http://www.reuters.com/article/us-bayer-results-idUSKBN17T0OE> (last visited, July 16, 2017).

Review Voucher program, the Humanitarian Use Device program, and three extramural grant programs.<sup>161</sup> The 21<sup>st</sup> Century Cures Act also aims to drive down the costs of clinical trials by pharmaceutical companies by incentivizing the FDA to modernize and improve efficiency in clinical trial design. And it establishes new channels for pharmaceutical companies to more quickly and efficiently have life-saving products approved. For example, it establishes a Limited Population pathway, which streamlines development programs for certain antibacterials and antifungals intended to treat targeted groups of patients suffering from serious or life-threatening infections where there is a lack of available therapies.<sup>162</sup>

In short, the *Caronia* court was incorrect in asserting that the FDA’s primary goal is to stop off-label prescribing and to therefore assume that the agency’s construction and enforcement of the FDCA fails to further that goal. In doing so, it failed to fully credit the Supreme Court’s finding that “[p]reserving the effectiveness and integrity of the FDCA’s new drug approval process is clearly an important governmental interest, and the Government has every reason to want as many drugs as possible to be subject to that approval process.”<sup>163</sup> The FDA has strong arguments for why the structure of its regulatory regime furthers its substantial interest, meeting the second and third *Central Hudson* factors.

### 3. *The FDA’s Regulatory Scheme Is Tailored to Protect and Effectuate the Government’s Interests*

Once the *Caronia* court narrowly characterized the government’s interest as limiting off-label promotions, it was easy enough for it to conclude that misbranding prosecutions were not a good fit for effectuating that purpose. But given that the FDA’s purposes are both broader and more complex than the *Caronia* court’s construction, it is difficult to argue that there is some better, more narrowly tailored way to adequately balance all of the relevant competing interests.

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<sup>161</sup> See FDA, Guidance for Industry, Expedited Programs for Serious Conditions – Drugs and Biologics (May 2014), available at <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm358301.pdf>; FDA, Developing Products for Rare Diseases & Conditions, at <http://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/ucm2005525.htm> (last updated Jan. 5, 2017).

<sup>162</sup> Robert M. Califf, *21st Century Cures Act: Making Progress on Shared Goals for Patients*, FDA Voice, Dec. 13, 2016, available at <https://blogs.fda.gov/fdavoices/index.php/2016/12/21st-century-cures-act-making-progress-on-shared-goals-for-patients/> (last visited July 16, 2017).

<sup>163</sup> *Western States*, 535 U.S. at 369.

Generally, when a court finds that a law, statute, or regulation is not adequately tailored to a government purpose, it is because it can think of other, more narrow, less constitutionally offensive means to effectuate the purpose. The *Caronia* court came up with its own suggestions for policies that it believed would better fit the government's purposes. The majority suggested that the government "could guide physicians and patients in differentiating between misleading and false promotion, exaggerations and embellishments, and truthful or non-misleading information."<sup>164</sup> Or it "could develop its warning or disclaimer systems, or develop safety tiers within the off-label market, to distinguish between drugs."<sup>165</sup> The majority also suggested that the government could "require pharmaceutical manufacturers to list all applicable or intended indications when they first apply for FDA approval."<sup>166</sup> It also proposed that the government could include ceilings or caps on off-label prescriptions.<sup>167</sup> And, the majority noted that "where off-label drug use is exceptionally concerning, the government could prohibit the off-label use altogether."<sup>168</sup> But as Judge Livingston pointed out in her dissent, none of the majority's alternatives would be "similarly effective" in advancing the government's interests.<sup>169</sup>

The majority's suggestion that the government could provide guidance to physicians and patients in differentiating between misleading and false promotion, exaggerations and embellishments, and truthful or non-misleading information is flawed because, as stated above, even the government does not have enough information to necessarily know what information is accurate and reliable, and what information is not. Indeed, this suggestion is marred by the assumption that off-label promotional claims can necessarily be verified. Until randomized clinical trials are complete, the safety and effectiveness of a drug cannot be established. Thus, providing "guidance" to help physicians and patients differentiate is neither logical nor feasible.

The FDA has also argued that the proposal is not feasible and would not further the agency's interest in assuring that drug uses get adequate premarket review because it would "replace the FDA's thorough and rigorous scientific review process with a review of promotional materials by health care providers and patients."<sup>170</sup> The agency has also pointed out that health care providers and

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<sup>164</sup> *Caronia*, 703 F.3d at 168.

<sup>165</sup> *Id.*

<sup>166</sup> *Id.*

<sup>167</sup> *Id.*

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

<sup>169</sup> *Id.* at 179.

<sup>170</sup> FDA Memorandum, *supra* note 19, at 31.

patients “cannot be expected to acquire the tools, background, and specialized expertise in statistics, pharmacokinetics, biomedical engineering and other fields that are necessary to conduct a thorough evaluation of the risks and benefits of a new intended use that even roughly approaches that provided by FDA review (assuming that adequate data exist and that all the data are made publicly available).”<sup>171</sup> Further, “it is unrealistic to suggest that a government-sponsored education campaign would provide this kind of multi-discipline expertise.”<sup>172</sup>

Likewise, a warning or disclaimer system would “provide manufacturers much less incentive to submit their drugs for FDA approval, and in turn [would] encourage promotion based on data much less reliable than the clinical investigations required” by the FDA’s regulations.<sup>173</sup> Warnings are also not very effective. In a study of disclaimers on dietary supplements, the researchers found “ample evidence that such disclaimers are often misunderstood or ignored by consumers and had no effect on consumers’ ability to understand messages about health care products and critically evaluate potentially unsupported statements about effectiveness or safety.”<sup>174</sup>

As for requiring pharmaceutical manufacturers to list all applicable or intended indications when they first apply for FDA approval,<sup>175</sup> the FDA has noted that “it is not possible to divine all potential uses of a medical product from an initial study; data and information develop over time through scientific study before and after product approval, as well as [through] product use.”<sup>176</sup> Moreover, implementing this requirement would likely mean that initial applications would be significantly delayed while new indications were explored, and once a drug was approved, there would be no incentive for manufacturers to continue important research that could lead to the development and approval of new treatments.<sup>177</sup>

Putting in place ceilings or caps on off-label prescriptions would “not align with any discernable government interest and would adversely affect the public

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<sup>171</sup> *Id.*

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

<sup>173</sup> *Caronia*, 703 F.3d at 179.

<sup>174</sup> Aaron S. Kesselheim et al., *Mandatory Disclaimers on Dietary Supplements Do Not Reliably Communicate the Intended Issues*, 34 HEALTH AFFAIRS 438, 445 (2015); see also Aaron S. Kesselheim, *Off-label Drug Use and Promotion: Balancing Public Health Goals and Commercial Speech*, 37 AM. J.L. & MED. 225, 250–51 (2011).

<sup>175</sup> *Caronia*, 703 F.3d at 168.

<sup>176</sup> FDA Memorandum, *supra* note 19, at 28.

<sup>177</sup> *Id.* at 29.

health.”<sup>178</sup> As the FDA points out in its Memorandum, it is unclear how a ceiling or cap would be determined, and by what public health rationale:

If the unapproved use is thought to be potentially harmful for patients, how would one ascertain and justify the number of patients who can be exposed to the unapproved use? And if the unapproved use is thought to be potentially positive, how would one justify denying all other patients access to the product for the unapproved use after the cap is reached?<sup>179</sup>

Indeed, this suggestion is so arbitrary and capricious, it would likely not even pass rational basis review, much less the heightened scrutiny standard required by *Central Hudson*.

Finally, the *Caronia* majority’s suggestion that the government could prohibit off-label use altogether also raises constitutional concerns. As Judge Livingston noted, “it would constitute an unprecedented intrusion into the practice of medicine, and would result in perhaps an even greater restriction on speech.”<sup>180</sup> While the approach would be “extremely effective in protecting the government interests in motivating scientifically robust research into unapproved uses and ensuring that new uses of approved/cleared medical products are proven safe and effective before they are used to treat patients,” it would not “take into account the public health interests behind allowing health care providers and patients to work to determine the best treatment options for each patient in specific circumstances.”<sup>181</sup> There are certain populations of patients for whom there are few, or even no, approved uses for their condition.<sup>182</sup> These patients would be left with no options under the court’s proposed “solution.”

In sum, *none* of the *Caronia* majority’s suggestions adequately addresses the government’s interests as the current regulatory system. The court’s willingness to judge the system not to be tailored to the government’s interest by substituting the court’s own judgment for the agency’s experience and expertise illustrates how problematic such judicial activism can be with respect to a complex regulatory environment. A court only has the briefs before it—it

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<sup>178</sup> *Id.* at 27.

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

<sup>180</sup> *Caronia*, 703 F.3d at 180.

<sup>181</sup> FDA Memorandum, *supra* note 19, at 26.

<sup>182</sup> See, e.g., John E. Osborn, *Can I Tell You the Truth? A comparative Perspective on Regulating Off-Label Scientific and Medical Information*, 10 YALE J. HEALTH & POL’Y L. & ETHICS 299, 304 (2010) (“[T]here is little doubt that in oncology and pediatrics off-label prescribing is exceedingly common. . . . [I]n some therapeutic areas off-label uses are the customary, preferred treatments.”).

does not have the expertise or the experience, the hours of testimony, or the help of experts to try to craft a complex system that balances many different interests while remaining constitutionally sound. This, of course, was one of Judge Rehnquist's concerns in his dissent in *Virginia Bd. of Pharmacy*.<sup>183</sup> And it was also Justice Breyer's concern in his dissents in *Western States* and *Sorrell*.<sup>184</sup> In *Sorrell*, Justice Breyer worried: "The Court reaches its conclusion . . . without taking full account of the regulatory context, the nature of the speech effects, the values these First Amendment categories seek to promote, and prior precedent. At best the Court opens a Pandora's Box of First Amendment challenges to many ordinary regulatory practices that may only incidentally affect a commercial message. At worst, it reawakens *Lochner*'s pre-New Deal threat of substituting judicial for democratic decisionmaking where ordinary economic regulation is at issue."<sup>185</sup>

*Western States* and its aftermath illustrate the consequences that ensue when a court substitutes its own judgment for that of the legislature and an expert agency. In *Western States*, Justice O'Connor insisted that the FDA could use "non-speech-related means of drawing a line between compounding and large-scale manufacturing"<sup>186</sup> and held that a provision in section 503A, which allowed compounding pharmacies to avoid the NDA process as long as they did not advertise, to violate the First Amendment. After *Western States* essentially invalidated prohibitions on compounding pharmacy advertising, the FDA determined that all of section 503A was invalid.<sup>187</sup> Thereafter, many compounding pharmacies grew to national scale.<sup>188</sup> In 2012, hundreds of people were sickened and dozens killed when they contracted fungal infections from unsafe compounded steroid injections made in a Massachusetts compounding

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<sup>183</sup> 425 U.S. at 787 (arguing that drawing the line between "truthful" and "false and misleading" speech is "too Procrustean to take into account the congeries of factors which I believe could, quite consistently with the First and Fourteenth Amendments, properly influence a legislative decision with respect to commercial advertising.")

<sup>184</sup> *Western States*, 535 U.S. at 389 (arguing that the majority's "overly rigid 'commercial speech' doctrine will transform what ought to be a legislative or regulatory decision about the best way to protect the health and safety of the American public into a constitutional decision prohibiting the legislature from enacting necessary protections."); *Sorrell*, 564 U.S. at 602–03.

<sup>185</sup> *Sorrell*, 564 U.S. at 602–03.

<sup>186</sup> *Western States*, 535 U.S. at 372.

<sup>187</sup> FDA, Dep't of Health & Human Servs., *Guidance for FDA Staff and Industry: Compliance Policy Guides Manual § 460.200 Pharmacy Compounding 2* (2002).

<sup>188</sup> Kesselheim & Mello, *supra* note 101, at 1557–58 (citing Staff of S. Comm. on Health, Educ., Labor & Pensions, 113th Cong., *The Case for Clarifying FDA Authority: Large-Scale Drug Compounding and the Ongoing Risk to Public Health 7* (Comm. Print 2013), available at <http://www.help.senate.gov/imo/media/doc/Senate%20HELP%20Committee%20Staff%20Report%20-%20Large-Scale%20Drug%20Compounding%20%202013.pdf>).



pharmacy that were sold and marketed nationwide.<sup>189</sup> *Western States* shows that the FDA's concerns about the public health and safety were valid, and that using nationwide advertising as a proxy for large-scale compounding in fact made sense. It also shows that courts do not have expertise in divining solutions to complex regulatory issues and may not be the best venue for deciding the quality of truthfulness in commercial speech. Instead, these decisions should generally be left to the legislature and the expert agency—here, the FDA.

In fact, the FDA's regulatory scheme is tailored to protect the government's interests in the least restrictive manner possible. It argued this in *Caronia*, but its argument is even stronger now, as the safe harbors for off-label promotion are broader, allowing not only journal articles, but medical texts and clinical practice guidelines with information about off-label uses of drugs to be shared with physicians. And, under the 21<sup>st</sup> Century Cures Act, the companies may also share health care economic data with certain entities related to an unapproved use of a drug.

The FDA's interpretation of the FDCA and its pursuit of misbranding prosecutions ensures that the public is protected from the tragedies of Mellaril and DES by incentivizing the drug companies to conduct thorough, scientifically sound clinical trials that prove both safety and effectiveness for a particular use of a drug before being able to market the drug for that use. But its decision not to prohibit all off-label uses also protects the doctor-patient relationship and ensures treatment for individuals with rare diseases. The safe harbors allow pharmaceutical companies to share scientifically sound, evidence-based, and therefore truthful, information about off-label uses with physicians, while ensuring that incomplete, non-verifiable, biased, and otherwise misleading information cannot be shared. This regime effectuates all of the government's substantial interests in a manner that is as least offensive as possible to the First Amendment.

## CONCLUSION

Although *Caronia* struck a harsh blow to the FDA's efforts to ensure that uses of drugs are proven safe and effective before they can be marketed, and although it is not an entirely surprising decision given the Supreme Court's commercial speech jurisprudence, "fighting to ensure that a regulatory regime is in place to promote accurate and unbiased promotional communications is a

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<sup>189</sup> *Id.* (citing Kevin Outterson, *Regulating Compounding Pharmacies after NECC*, 367 *NEW ENGL. J. MED.* 1969, 1971 (2012)).

public health imperative.”<sup>190</sup> Thus, while pharmaceutical and device companies and their defenders will continue to complain that the current system is broken and will use the First Amendment as a tool to try to further shatter it, the FDA should not be cowed. In fact, the current regulatory system is not in need of fixing, and certainly not of undoing. While the FDA could make some further tweaks to strengthen its ability to argue that it is narrowly tailoring its regime to be as least restrictive as possible,<sup>191</sup> there is no need to give up on misbranding prosecutions or False Claims Act cases.<sup>192</sup> And there is also no need for legislative “fixes” like the Medical Product Communications Act of 2017, which would broaden companies’ ability to promote for off-label uses based on information that is not evidence-based so as to undermine the premarket review approval and clearance process. Indeed, the Medical Product Communications Act of 2017 would take us back to the time before the Kefauver-Harris amendments. By contrast, the current regulatory regime and the FDA’s interpretation and enforcement of the FDCA, including through misbranding prosecutions, strikes the right balance between ensuring that the tragedies that took place prior to the Kefauver-Harris amendments do not recur and encouraging physicians to provide the best, evidence-based treatments for their patients. The FDA should stand by its regulatory regime and fight to ensure that neither the courts nor the legislature undo it.

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<sup>190</sup> *Id.* at 1604.

<sup>191</sup> *See id.* at 1597–1602 (making suggestions to even further expand safe harbors to “help bolster the argument that the FDA’s regulatory scheme is narrowly tailored to advancing the goal of protecting the public from unsafe prescribing.”).

<sup>192</sup> With respect to False Claims Act cases, not only do the government and whistleblowers have an argument that *Caronia* was wrongly decided, but their arguments are bolstered by the fact that even if the government cannot prosecute a pharmaceutical company for off-label marketing, it can constitutionally condition payment for those drugs on whether or not the claims were influenced by off-label marketing. False Claims Act off-label cases are based on the theory that the claims submitted for off-label prescriptions are “false” because Medicare and Medicaid do not pay for off-label uses, except in certain exceptional circumstances. The government is allowed to refuse payment and consider claims for off-label prescriptions that are due to impermissible off-label promotion “false” because under well-established Supreme Court jurisprudence, the government can condition payment in a way that may otherwise offend constitutional principles. *United States v. Am. Library Ass’n, Inc.*, 539 U.S. 194, 211 (2003); *Rust v. Sullivan*, 500 U.S. 173, 194 (1991).