

# OFF-LABEL PRESCRIPTION ADVERTISING, THE FDA AND THE FIRST AMENDMENT: A STUDY IN THE VALUES OF COMMERCIAL SPEECH PROTECTION

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**INTRODUCTION**

In order to protect the nation from harmful or worthless drug and devices, the Food and Drug Administration (FDA) is legislatively authorized to restrict the sale of prescription drugs or medical devices to those whose efficacy and safety have been reviewed and approved by the agency.<sup>1</sup> Drugs and devices are approved for a specific medical purpose. In numerous instances, however, the medical profession has discovered that treatments approved for one purpose may also serve other valuable medical purposes.<sup>2</sup> Indeed, on a number of occasions such “off-label” treatments have proven to be essential to the successful treatment of some very serious illnesses.<sup>3</sup>

In these off-label situations, the FDA is faced with a dilemma. On the one hand, off-label use of prescription drug and devices gives rise to a series of major problems for the FDA. While the drug and devices in question have been vetted and approved by the FDA for their designated purpose, at no point has the FDA reviewed the supporting scientific data to determine efficacy for the off-label purpose. It is therefore at least conceivable that if such off-label uses are permitted, the drug or device may in reality be worthless or even dangerous for its alternative use, yet doctors may be freely employing it for that purpose. Moreover, widespread off-label use of prescription drugs and devices conceivably undermines the FDA’s authority and deters manufacturers from seeking on-label FDA approval for even widespread alternative uses. The fear, then, would be that the FDA’s initial approval could serve as a wedge to permit the industry’s equivalent of the Wild West, where the rule of law was seen only rarely. On the other hand, were the federal government to categorically prohibit all off-label uses, instead requiring drug and devices to gain administrative approval for each use, potentially valuable treatments—often for the most serious of diseases—could at best be tied up in years of administrative red tape while they seek FDA approval and at worst could be completely lost because manufacturers decide that seeking and gaining FDA approval for the off-label use is simply not worth its costs. In any event, under the current regulatory framework, the FDA asserts that it lacks legal authority to restrict the ability of doctors to prescribe drugs or devices for off-label uses.

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<sup>1</sup> Federal Food, Drug, and Cosmetic Act, §§ 505(a), 510(k), 515.

<sup>2</sup> See discussion *infra* at xx.

<sup>3</sup> See discussion *infra* at xx.

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The FDA has sought to resolve this dilemma by effectively swimming half way across a river—thereby pleasing no one and avoiding none of its quite legitimate concerns. It has resolved its dilemma by leaving off-label uses essentially unregulated, but to make categorically illegal a manufacturer’s promotion of an off-label use. As a result, while the benefits of off-label use are roughly preserved, whatever dangers might accompany such uses are in no way avoided since off-label uses are still generally allowed. At the same time, while it is true that the ban on off-label promotion by manufacturers prevents false or misleading advertising, because the ban is all-inclusive it simultaneously prevents promotion of valuable off-label uses of which doctors otherwise may well be unaware. To be sure, those other than the manufacturer are still permitted to discuss the relative merits of off-label uses, and even manufacturers are authorized to speak about certain circumstances surrounding off-label use, such as accompanying dangers. But the FDA could not have stated more clearly that manufacturers are prohibited from advocating off-label uses in any way. This is so, even where the FDA in no way challenges the accuracy, truthfulness or completeness of that promotion.<sup>4</sup> As a result, in many instances doctors are likely to be deprived of valuable information about important off-label uses that are totally lawful and extremely beneficial to some very sick people. In short, the FDA’s policy, as well intentioned as it no doubt is, has made a shambles of off-label use, by simultaneously over-regulating and under-regulating the practice.<sup>5</sup>

Arguably even more important is the shambles the FDA’s categorical ban on off-label promotion makes of the First Amendment right of free expression. Indeed, the FDA’s treatment of off-label advertising amounts to a virtual how-not-to-do-it manual for reconciling the governmental interest in preserving drug and device safety and effectiveness on the one hand and the constitutional right of commercial speech, on the other hand. In short, the FDA’s ban on off-label promotion violates the First Amendment right of free expression. This does not mean that commercial speech must receive absolute protection, or that the FDA should be wholly deprived of authority to regulate drug and device advertising in the interests of public health. It means, simply, that governmental imposition of a categorical ban of truthful promotion of lawful commercial activity contravenes both established commercial speech doctrine and core notions of free speech theory. The First Amendment demands that government employ less sweeping means of achieving its legitimate goals.

In this Article, we seek to accomplish two complementary goals. Initially, we seek to establish the unambiguous unconstitutionality of the FDA’s current prohibition on off-label promotion as measured by controlling Supreme Court decisions concerning the First Amendment’s protection of commercial speech.<sup>6</sup> Secondly, we seek to glean from this analysis far more significant insights about the core premises of the constitutional protection of free expression. We point to four basic postulates of American constitutional and political theory that, we assert, underlie the social contract between citizen and government implicit in a societal commitment to liberal democracy.<sup>7</sup> These core premises, we believe, represent the normative foundations of the constitutional protection of not only *commercial* speech, but indeed *all* speech. By demonstrating this important philosophical overlap, we demonstrate the inherent

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<sup>4</sup> See discussion *infra* at xx.

<sup>5</sup> The situation is rendered even more bizarre by current FDA practices towards wholly unapproved drugs. See discussion *infra* at xx.

<sup>6</sup> See discussion *infra*, at xx.

<sup>7</sup> See discussion *infra*, at xx.

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linkage between commercial speech protection and the broader premises of the constitutional guarantee of free expression.

The first section of this Article provides a detailed description of the history and statutory framework of the FDA's regulation of off-label uses of prescription drugs.<sup>8</sup> In the section that follows, we demonstrate the inconsistency between the FDA's current practice and the existing doctrinal framework for the constitutional protection of commercial speech. In the final section, we explore the deep structure of commercial speech protection, and show how the FDA's prohibition of off-label advertising contravenes the core normative premises that make up that structure. In so doing, we will show that the core premises of commercial speech protection simultaneously rationalize *all* constitutional protection of free expression.

### I. THE FDA'S SUPPRESSION OF OFF-LABEL PROMOTION: DEVELOPMENT OF THE REGULATORY FRAMEWORK

#### A. Off-Label Use and Accepted Medical Practice

While the phrase "off-label use" may seem to imply dubious medical practice, the reality is quite the opposite. Two important points must be noted as we begin our analysis of the constitutionality of the FDA's prohibition on a manufacturer's ability to promote off-label use: (1) the prescription and use of approved drugs and medical devices for purposes not set forth in their FDA-authorized labeling is legal,<sup>9</sup> and (2) not only are such practices legal, they are quite common and, indeed, often accepted medical practice.<sup>10</sup>

Government officials have themselves often openly acknowledged the benefits of off-label uses. For example, as far back as 1992 the FDA's Deputy Commissioner for External Affairs conceded that "off-label drug use is often essential to good medical practice, and in some areas—oncology and pediatrics in particular—off-label uses are often considered necessary. In fact, it is on this edge that science and medicine move forward to benefit patients with intractable illness."<sup>11</sup> Several years later, the FDA noted that "[g]ood medical practice and the best interests of the patient require that physicians use legally available drugs, biologics and devices according to their best knowledge and judgment."<sup>12</sup> There

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<sup>8</sup> See Section II, *infra*.

<sup>9</sup> "Once a drug product has been approved for marketing, a physician may, in treating patients, prescribe the drug for uses not included in the drug's approved labeling." Proposed New Drug, Antibiotic, and Biologic Drug Regulations, 48 Fed. Reg. 26,720; 26,733 (proposed June 9, 1983). The FDA disclaims authority to interfere with a doctor's judgment to prescribe a drug for an unapproved use. *Id.* See also 21 C.F.R. § 312.3(d) (exemption from FDA regulations for "the use in the practice of medicine for an unlabeled indication of a new drug product approved" by the Agency"). The same is true for medical devices. 21 U.S.C. § 396.

<sup>10</sup> According to one authority, off-label uses are "common, and can be a source of innovation, and in some settings may represent the standard of care." Donna T. Chen et al., *U.S. Physician Knowledge of the FDA-Approved Indications and Evidence Base for Commonly Prescribed Drugs: Results of a National Survey*, 2009 *Pharmacoepidemiology & Drug Safety* (footnotes omitted); see also Susan G. Poole & Michael J. Dooley, *Off-Label Prescribing in Oncology*, 12 *Support Care Cancer* 302 (2004): "For some diseases, such as non-small cell lung cancer and cystic fibrosis, off-label uses either are the only therapies available, or are the therapies of choice."

<sup>11</sup> Carol Scheman, *Prescription Drug Marketing and Promotion—An FDA Perspective*, Address before the PMA Public Affairs Section, Mid-Year Meeting, April 15, 1992.

<sup>12</sup> FDA, *"Off-Label" and Investigational use of Marketed Drugs, Biologics, and Medical Devices—Information Sheet*, available at <http://tinyurl.com/mj3n37>.

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may well be instances in which off-label use is effectively required by the dictates of good medical practice. Under these circumstances the failure to prescribe off-label might well be deemed medical malpractice.<sup>13</sup> The conclusion is therefore inescapable that both patients and prescribers would often be aided by the dissemination of information to the medical profession about these valuable off-label uses—uses that health care practitioners may well be unfamiliar with absent such communications.<sup>14</sup>

Despite the indisputable value of off-label uses and the corresponding need for doctors and other prescribers to be informed about them, the FDA has categorically banned manufacturers of drugs and devices from promoting their use for unapproved purposes to the medical profession. This is so, despite the obvious reality that manufacturers are in a unique position to provide valuable information off-label uses to the medical profession. Manufacturers possess a combination of incentive and resources to disseminate information to doctors about off-label uses. As the FDA itself has long acknowledged, “[s]cientific departments within regulated companies generally maintain a large body of information on their products,”<sup>15</sup> including information about off-label uses. As the Seventh Circuit Court of Appeals has persuasively reasoned, “if a given use is lawful, and thus can be written about freely in newspapers or blogs, and discussed among hospitals... doesn’t it make a good deal of sense to allow speech by the manufacturer, which after all will have the best information? Why privilege speech by the uninformed?”<sup>16</sup> To be sure, instances may arise in which particular claims about off-label uses could be deemed false or misleading. The same could be said about the advertising of *any* product or service. But the FDA’s ban draws no such distinctions. Even totally truthful, valuable information provided in the form of promotion is banned. It is difficult to comprehend the logic of such a distorted system.

Equally puzzling is the limited judicial attention that has been devoted to the constitutional issue. While in limited contexts the ban has been found unconstitutional,<sup>17</sup> to this point there has been surprisingly little judicial attention to the constitutional implications of the FDA’s prohibition.<sup>18</sup> It is for these reasons that detailed and thoughtful consideration of the First Amendment’s applicability to the FDA’s ban is called for. The first step in that analysis must be an attempt to understand the origins, legal source, and rationale of the FDA’s actions. It is to those issues that our attention now turns.

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<sup>13</sup> *Buckman Co. v. Plaintiffs’ Legal Comm.*, 531 U.S. 341, 349-51 & n.5 (2001). See also Fran Kritz, *FDA Seeks to Add Drugs’ New Uses to Labels*, Wash. Post, March 29, 1994, at Z11: “In some cases, if you didn’t use the drug in the off-label way you’d be guilty of malpractice.”

<sup>14</sup> See Paul E. Kalb & Paul E. Greenberg, *Legal and Economic Perspectives Concerning U.S. Government Investigations of Alleged Off-Label Promotion by Drug Manufacturers*, 27 *Pharmacoeconomics* 623, 623 (2009): “Physicians’ decisions to prescribe off label are informed by the available scientific literature, and it stands to reason that the more truthful, non-misleading data available, the more informed their decisions will be.”

<sup>15</sup> 59 Fed. Reg. at 59,823.

<sup>16</sup> *United States v. Caputo*, 517 F.3d 935, 939 (7<sup>th</sup> Cir. 2008).

<sup>17</sup> [*Washington Legal Foundation*].

<sup>18</sup> One district court decision, on the basis of questionable reasoning (see note xxx, *infra*), upheld the ban. *United States v. Caronia*, 576 F.Supp. 2d 385 (E.D.N.Y. 2008). In a separate decision, the United States Court of Appeals for the Seventh Circuit ultimately avoided the constitutional issue, but nevertheless raised serious doubts about the ban’s constitutionality. *United States v. Caputo*, 517 F.3d 535 (7<sup>th</sup> Cir. 2008). On the basis of this scant data, it is reasonable to conclude that as a narrow doctrinal matter, at least, the issue remains an open one.

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### B. The Legal Source of the Off-Label Promotion Ban

Although the Federal, Food, Drug, and Cosmetic Act does not expressly prohibit “off-label promotion” in so many words, the FDA has relied on that statute to justify its ban of off-label promotion. First, the FDA asserts that such promotion violates the FDCA on the ground that it constitutes false or misleading labeling<sup>19</sup>; second, the FDA contends that it causes an approved new drug to become an unapproved new drug all over again, thus triggering the requirement of FDA approval anew;<sup>20</sup> and third, the FDA claims that off-label promotion misbrands the drug because it “is evidence of” a new “intended use” for which “adequate directions” necessarily would be lacking in labeling by virtue of the unapproved status of the use.<sup>21</sup> Although the details of the FDA’s theory in a particular case may vary according to the factual scenario presented, the basic point is that the FDA regards the dissemination of any information relating to off-label uses as an action prohibited by the FDCA.<sup>22</sup> The same is true for devices, although the statutory details vary somewhat.

Originally, the FDA invoked these provisions to protect the American consumer against quackery—fraudulent therapeutic claims about products that had never been submitted to the FDA for *any* kind of review. This approach was limited to the restriction of false or misleading statements in commercial promotion and therefore was generally thought not to raise any First Amendment issue.<sup>23</sup> In

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<sup>19</sup> Section 502(a) of the FDCA provides that “A drug . . . shall be deemed to be misbranded—. . . If its labeling is false or misleading in any particular.” 21 U.S.C. § 352(a). Section 502(a) has been invoked with respect to drugs bearing literally false statements as well as drugs marketed with unsubstantiated therapeutic claims. See, e.g., *United States v. 4 Cases Slim-Mint Chewing Gum*, 300 F.2d 144 (7th Cir. 1962) (affirming trial court denial of new trial in section 502(a) case in which jury found no false or misleading statements in labeling of diet gum); *United States v. Articles of Drug*, 442 F. Supp. 1236, 1241 (S.D.N.Y. 1978) (drugs violate section 502(a) when they are labeled “100 capsules” but contain only 6 capsules in each packet). For this provision to apply, a false or misleading statement must appear in a communication that qualifies as “labeling,” which is defined by statute to mean “all labels and other written, printed, or graphic matter (1) upon any article or any of its containers or wrappers, or (2) accompanying such article.” 21 U.S.C. § 321(m). Under *Kordel v. United States*, 335 U.S. 345 (1948), to “accompany” an article, matter must supplement or explain the product in connection with its distribution and sale. But “labeling does not include every writing which bears some relation to the product.” *United States v. 24 Bottles . . . “Sterling Vinegar and Honey,”* 338 F.2d 157, 158-59 (2d Cir. 1964).

<sup>20</sup> 21 U.S.C. § 355(a). According to FDA, “an approved new drug that is marketed for a ‘new use’ becomes an unapproved new drug with respect to that use.” 65 Fed. Reg. 14,286, 14,286 (2000). As with section 502(a), this theory would apply only where the off-label statement occurs in a communication that qualifies as “labeling” under the FDCA.

<sup>21</sup> 21 U.S.C. § 352(f)(1). In FDA’s view, virtually the only way to avoid violating this provision is to submit a use for FDA review. See 21 C.F.R. § 201.100(c)(2).

<sup>22</sup> E.g., 59 Fed. Reg. 59,820, 59,822 (Nov. 18, 1994) (“Information disseminated by companies in contexts such as scientific and educational meetings, symposia, books, and articles may provide evidence of a regulated product’s intended use.”); 65 Fed. Reg. 14,286, 14,286 (2000) (“an approved new drug that is marketed for a ‘new use’ becomes an unapproved new drug with respect to that use.”).

<sup>23</sup> Manufacturers did raise First Amendment arguments in enforcement actions during this period, to no effect. During the period in which much of modern food and drug law developed, commercial speech was thought to be without any constitutional protection at all. In the few cases arising under the FDCA in which First Amendment arguments were made, they were summarily rejected. See, e.g., *United States v. Articles of Drug*, 32 F.R.D. 32 (S.D. Ill. 1963); *United States v. 8 Cartons . . . “Plantation ‘The Original’ etc. Molasses,”* 103 F. Supp. 626 (W.D.N.Y. 1951). And legal practitioners did not seriously contend that FDA regulation of labeling and advertising might run afoul of the Free Speech Clause. The first serious examination of the issue in the principal food and drug law review did not appear until 1975, and it concluded: “Government regulation of misbranding and false advertising is clearly constitutional.” Thomas H. Christopher, *Free Speech and the Regulation of Labeling and Advertising*, 30

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the 1990s, however, the FDA dramatically increased its reliance on the FDCA in off-label promotion cases and sought increasingly severe penalties for alleged violations. The shift is attributable primarily to increasing concern over a sphere of activity over which the FDA now largely denies regulatory control: physicians' off-label prescribing decisions.

The FDA's current approach to the regulation of speech about off-label uses originated with physician decisions in the 1960s—right around the time the FDA was struggling to implement statutory amendments requiring robust scientific evidence of efficacy for all marketed drugs—to prescribe drugs for off-label uses despite the lack of information supporting the safety or efficacy of those uses. During this period, the FDA asked the author of a medical textbook to revise the book to warn against an unsafe dosage of a particular drug product, only to be roundly criticized by the medical community—even though the dosage had been linked to several deaths. In response, the FDA issued a public statement assuring physicians that the agency had no intention of regulating their prescribing decisions.<sup>24</sup> Toward the end of the decade, Congress turned its attention to the off-label use “problem,” focusing on the widespread off-label use of the highly toxic drug methotrexate to treat psoriasis.

Some Members of Congress became concerned by “the Methotrexate situation” as early as 1968, and in that year invited the FDA's attention to a medical journal article that encouraged the use of the drug to treat psoriasis despite the absence of FDA approval for that use. The FDA had approved the drug solely for treatment of certain cancers, and had authorized only the highly limited and tightly regulated investigational use of the drug in psoriasis and rheumatoid arthritis. The FDA's primary concern involved the risks of bone marrow suppression, leucopenia, thrombocytopenia, and anemia—side effects that might be considered to be justified for a patient with one of the indicated, or labeled, conditions, but not for a patient with a much less serious condition like psoriasis. The FDA was also influenced by the fact that methotrexate appeared to treat, but not “cure,” psoriatic disease. Further complicating matters from the agency's perspective, any action to remove the drug from the market would have interfered with the treatment regimens of the cancer patients for whom methotrexate was being used “on-label.”

A House subcommittee convened hearings in the summer of 1971 “to examine an anomalous and apparently dangerous situation in many respects, in which a new drug legally marketed for a restricted purpose has come into widespread use in the treatment of a different medical condition for which it has not been approved.”<sup>25</sup> FDA witnesses testified that the agency's ultimate decision was to avoid interfering in the treatment of cancer patients through enforcement action (e.g., a product seizure) and “to try to deal with it as an educational matter” instead.<sup>26</sup> FDA officials cooperated with key opinion leaders in the dermatology community to prepare an editorial that was published in the September 22, 1969, issue of the *Journal of the American Medical Association*. The editorial discussed potential risks of the drug and advised careful monitoring of patients being treated with methotrexate. The editorial was republished in the *Archives of Dermatology* in 1970, together with a companion editorial on the danger of cirrhosis

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Food Drug Cosm. L. J. 512, 525 (1975). The author did not even consider the scope of FDA authority to regulate the content of truthful and non-misleading commercial speech.

<sup>24</sup> Herbert Ley, FDA Papers (Letter to the Editor), 8 *Clin. Pharm. & Therapeutics* 749 (1967).

<sup>25</sup> New Drugs Used For Nonapproved Purposes (Methotrexate for Psoriasis), Hearings before a Subcomm. of the House Comm. on Gov't Operations, July 29-30, 1971, 92<sup>nd</sup> Cong., 1<sup>st</sup> Sess. 1 (1971).

<sup>26</sup> *Id.* at 26 (statement of William Goodrich, Chief Counsel, FDA).

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from the drug and possible need for liver biopsy to ascertain liver function.<sup>27</sup> Denying that the FDA’s “educational” approach had been adequate to address the problem and dissatisfied by the heterogeneity of FDA officials’ prior statements on the question, Members of Congress requested that the FDA develop a more coherent position on the agency’s ability to constrain prescriber decisions to order the off-label use of approved drugs.<sup>28</sup> FDA witnesses, for their part, asserted that the FDCA provided adequate authority for the FDA to constrain off-label uses but acknowledged that agency officials had not always spoken with one voice.<sup>29</sup>

Pressure from Congress to establish a clear policy on off-label use led the FDA to consider new regulations that would have given the agency the ability to interfere directly in medical practice by controlling particular off-label uses with which the agency disagreed. Even as Congress was pressuring the FDA to control indiscriminate prescription of off-label use, the medical community continued its vigorous campaign of resistance to any effort on the FDA’s part to constrain prescribers’ clinical judgments. Against this backdrop of conflicting influences, the FDA proposed sweeping new rules to constrain physician prescribing habits, despite the agency’s denial that it had any intention to interfere with medical practice. Under the proposed rule, issued in 1972, the FDA would have been “obligated” to take one or more enumerated actions to address an “unapproved use” that endangered the public health.<sup>30</sup>

The FDA sought to satisfy both constituencies—physicians and legislators—by explaining that its statutory authority to control the market introduction and labeling of new drugs did not encompass the power to restrict the uses to which approved drugs might be put. It was at this point in the development of the FDA policy on off-label use that the agency’s official policy began focusing on the dissemination of information about off-label uses by the product manufacturers, and not on the use itself. According to the explanatory statement accompanying the 1972 proposal, the FDA would allow prescribing decisions based on the information set forth in the agency-approved “labeling” for a drug product, and would even tolerate clinical decision making based on “other adequate scientific data.” But it would simply not allow a manufacturer to even hint to a prescriber or patient that an off-label use might be clinically indicated:

[W]here a manufacturer or his representative, or any person in the chain of distribution, does anything that directly or indirectly suggests to the physician or to the patient that an approved drug may properly be used for unapproved uses for which it is neither labeled nor advertised, that action constitutes a direct violation of the Act and is punishable accordingly.<sup>31</sup>

What began as an effort to control off-label prescribing by physicians thus shifted to the use of a federal statute to constrain manufacturer speech about such prescribing—purely, it would seem, because physicians so vociferously objected to any insinuation by the FDA into decisions relating to the circumstances in which lawfully marketed drugs would be used.<sup>32</sup>

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<sup>27</sup> Id. at 18.

<sup>28</sup> Id. at 58-70.

<sup>29</sup> Id. at 66, 67, 70.

<sup>30</sup> 37 Fed. Reg. 16,503 (Aug. 15, 1972).

<sup>31</sup> Id.

<sup>32</sup> According to David Kessler, FDA “was concerned” about “improper prescribing,” but “was under great pressure from the American Medical Association not to tell the doctor what he or she could prescribe.” David A. Kessler, Regulating the Prescribing of Human Drugs for Nonapproved Uses under the Food, Drug, and Cosmetic Act, 15

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The FDA's effort both to establish an off-label use policy in order to satisfy Congress and to avoid interfering in medical practice failed, largely because the 1972 proposed rule was fiercely opposed by physicians.<sup>33</sup> In the face of this opposition, the FDA chose not to issue the rule in final form.<sup>34</sup> What followed, instead, was a series of statements from the FDA calculated to soothe the medical community by denying that the agency's proposal represented any genuine threat to prescribing decisions.<sup>35</sup> The FDA went further, amending its regulations to make clear that the requirement for a regulatory authorization for a new drug did "not apply to the use in the practice of medicine for an unlabeled indication of a new drug product approved" by the FDA.<sup>36</sup> During this same period, the FDA even established "safe harbors" for certain types of manufacturer communications about off-label uses in an effort to facilitate off-label prescribing by physicians.<sup>37</sup> Shortly thereafter, however, the FDA, concerned that its liberalization of the environment through this series of measures went too far in allowing manufacturers to promote off-label uses, turned its attention to the regulation of manufacturer speech through a combination of policy refinements and increasingly aggressive enforcement actions.

### C. The FDA's Expansion of its Authority in the 1990s

During the 1990s, the FDA sought to crack down on manufacturer dissemination of information about off-label uses through energetic reliance on the agency's broad enforcement authorities. At the same time, the FDA also pursued policy solutions to the off-label promotion problem. In 1991, the FDA began developing a new written policy on off-label information dissemination in scientific and educational settings.<sup>38</sup> The following year, the FDA refused to allow a manufacturer to distribute free copies of a recognized, widely used oncology textbook at a major medical conference, on the ground that the textbook mentioned off-label uses of several of the manufacturer's drugs.<sup>39</sup> In response, the textbook's publisher, J.B. Lippincott, wrote the agency in protest, noting that publishers had begun to feel the effects of the FDA's crackdown on promotional and educational materials mentioning off-label uses.<sup>40</sup> According to Lippincott, Merck had declined to fund or distribute a supplement on benign prostatic hyperplasia in 1991 because of concern over the FDA enforcement. In another case, Squibb Diagnostics bought 4,000 copies of a textbook on magnetic resonance imaging but did not distribute them.<sup>41</sup>

In February 1993, the FDA announced that it was developing a policy to cover all industry-sponsored "enduring materials," loosely defined as materials of a lasting nature like books, audio, or

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Harv. J. on Legis. 693, 698 n.13 (1977). Kessler indicated that FDA "chose to deal with the problem [of off-label prescribing] as an educational matter."

<sup>33</sup> FDA's Growing Influence on Your Practice, *Med. World News*, Mar. 1, 1974, at 46; *Eternal Vigilance—The Price of Liberty*, 222 *JAMA* 1553 (1972).

<sup>34</sup> Letter from American Soc. of Hosp. Pharmacists to FDA Commissioner Donald Kennedy, at 5 (Aug. 9, 1977). In 1991, FDA considered and rejected withdrawing the 1972 proposed rule. *See* 56 *Fed. Reg.* 42,668, 42,669 (1991).

<sup>35</sup> A 1982 "drug bulletin" issued by FDA emphasized that the agency regarded off-label use as "accepted medical practice." 12 *FDA Drug Bull.*, Apr. 1982, at 4.

<sup>36</sup> This provision remains in effect, and is currently codified at 21 C.F.R. § 312.2(d).

<sup>37</sup> DDAL, Position on the Concept of Solicited and Unsolicited Requests, Apr. 22, 1982; 52 *Fed. Reg.* 19,466 (May 22, 1987); 52 *Fed. Reg.* 8,798, 8,833 (Mar. 19, 1987).

<sup>38</sup> "Drug Company Supported Activities In Scientific or Educational Contexts" (Oct. 26, 1991).

<sup>39</sup> *See* Amended Complaint at 11-15, *Washington Legal Found. v. Kessler* (D.D.C. 1995) (Civ. No. 94-1306) (listing examples of FDA refusal to allow distribution of major oncology texts).

<sup>40</sup> *The Pink Sheet*, July 13, 1992, at T&G-14.

<sup>41</sup> *Id.*

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video tapes, and software.<sup>42</sup> Concerned that the FDA would adopt a restrictive approach to enduring materials, the medical community formed a task force under AMA auspices and developed its own proposed guidelines.<sup>43</sup> The FDA also met with the American Medical Writers Association and the American Medical Publishers to address the groups' concerns that the FDA would establish a policy that "impede[s] . . . the free flow of information."<sup>44</sup>

On December 6, 1995, the FDA published two draft guidance documents<sup>45</sup> describing the circumstances in which the FDA would permit manufacturers to disseminate journal article reprints and reference texts containing off-label use information to health care professionals. The two guidance documents were published in final form on October 8, 1996, virtually unchanged.<sup>46</sup> In December 1997, the agency finalized the guidance on industry-supported scientific and educational activities.<sup>47</sup>

During this critical period in the development of FDA policy, enforcement actions brought under the FDCA took a new turn. Rather than focusing on quack products—wholly unregulated products for which false or fraudulent therapeutic claims were being made, largely to consumers—the federal government began invoking the FDCA to prohibit manufacturers of already-regulated drugs and medical devices from providing information about new uses to physicians. This shift in FDA behavior was significant because of the potential severity of the remedies available under the FDCA. Later, the consequences of the shift in enforcement became even more serious, as the government and private plaintiffs invoking *qui tam* provisions began advancing novel theories of treble damages under other statutory authorities never before used in off-label promotion cases.<sup>48</sup>

In May of 1991, the FDA announced that it had entered into an agreement with Bristol-Myers Squibb to settle allegations that the company had promoted several of its cancer drugs off-label by disseminating a scientific oncology publication to physicians.<sup>49</sup> According to the FDA's spokesperson, the agency's concern was not with off-label information dissemination *per se*; rather, it objected to the dissemination of promotional information under the guise of scientific information.<sup>50</sup> The following month, at a congressional hearing, FDA's commissioner pledged to exert the "full force of the law" to clamp down on pharmaceutical companies that promoted their products for off-label uses.<sup>51</sup> The commissioner might have had in mind the ongoing investigation of Ortho Pharmaceutical Corporation, a unit of Johnson & Johnson.<sup>52</sup> Ortho ultimately was referred to DOJ for possible criminal prosecution, based on the alleged off-label promotion of Retin-A, an approved anti-acne drug, for use in treating wrinkles.<sup>53</sup> Ultimately, obstruction charges were brought against Ortho, leading to a guilty plea in 1995.<sup>54</sup>

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<sup>42</sup> FDA to Target Scientific and Consumer Materials, FDA Advertising and Promotion Manual, Feb. 1993, at 1.

<sup>43</sup> The Pink Sheet, Sept. 19, 1994, at T&G-9.

<sup>44</sup> 59 Fed. Reg. 59,820, 59,823 (Nov. 18, 1994).

<sup>45</sup> 60 Fed. Reg. 62,471; 60 Fed. Reg. 63,384 (republication with omitted text).

<sup>46</sup> 61 Fed. Reg. 52,800.

<sup>47</sup> 62 Fed. Reg. 64,074.

<sup>48</sup> E.g., *United States ex rel. Franklin v. Parke-Davis*, 147 F. Supp. 2d 30, 44 (D. Mass. 2001).

<sup>49</sup> See The Pink Sheet, Nov. 27, 1995, at 3; Nancy Benac, FDA Getting Tough On Disguised Drug Promotions, AP, May 30, 1991 (wire) (available via Lexis/Nexis).

<sup>50</sup> [cite]

<sup>51</sup> [cite]

<sup>52</sup> [cite]

<sup>53</sup> [cite]

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The Ortho case was merely the first in what has become a long string of cases in which the FDCA has been invoked in an effort to prohibit manufacturer speech about off-label uses of lawfully marketed medical products. In virtually all of these cases, manufacturers have paid increasingly large monetary fines because of the government's reliance on the Federal False Claims Act with its treble damages provisions. More recently, FDA and Department of Justice officials have stepped up the level of rhetoric regarding the supposed need to "hold individuals accountable" for off-label violations—as though intransigence and not genuine ambiguity in the law (or the incentive for False Claims Act relators to initiate their own litigation under the *qui tam* provisions of the False Claims Act) provides the sole explanation for the continued proliferation of off-label promotion cases.

During this period of stepped-up enforcement, the FDA contended that its assertion of virtually plenary authority over manufacturer speech relating to off-label uses presented no First Amendment issue. According to the FDA, its regulation of speech was nothing more than an incidental consequence of its regulation of products themselves, and manufacturers could not be heard to complain because of the highly regulated nature of their activity. This theory appeared in defense of speech-restrictive regulatory initiatives across all product categories within the FDA's jurisdiction under the FDCA.<sup>55</sup> Starting in 2001, the FDA at least gestured in the direction of First Amendment values, but that period of greater circumspection proved short-lived.<sup>56</sup> Currently, the FDA's posture on off-label promotion remains much as it did in the 1990s—any manufacturer dissemination of information relating to an off-label use represents a presumptive statutory violation.

### D. The FDA's Rationale for the Suppression of Off-Label Promotion

Although the antecedents of the FDA's current stance on off-label promotion arose in the context of off-label use of methotrexate four decades ago, the FDA has generally not invoked the methotrexate example to justify its restrictive approach to manufacturer dissemination of off-label use information. Naturally, the FDA has relied on selected statutory provisions to assert that it is compelled to commence enforcement action against any manufacturer engaged in off-label promotion, but its efforts at justification have not ended there.

The FDA has bolstered its legal arguments against off-label promotion by reciting a "parade of horrors" that, agency officials assert, have resulted or will likely result as a consequence of such promotion. Since the first time the FDA published the "parade" in 1994,<sup>57</sup> FDA officials have reiterated

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<sup>55</sup> See, e.g., 63 Fed. Reg. 40,025, 40,038 (July 27, 1998) ("Because the regulation of [medical] devices is an area of extensive Federal regulation, the agency may regulate the communications at industry-supported scientific and educational activities without violating the First Amendment."); 62 Fed. Reg. 64,074, 64,077 (Dec. 3, 1997) ("As with securities regulation, the Federal Government exerts extensive authority over the sale and promotion of drugs and devices"); 58 Fed. Reg. 2,478, 2,525 (Jan. 6, 1993) ("As with securities, labor, and antitrust regulation, the Government exerts extensive regulatory authority over the economic activity surrounding food and its labeling.").

<sup>56</sup> See, e.g., 67 Fed. Reg. 34,942, 34,944 (May 16, 2002) (requesting public comment on "the extent of FDA's ability to regulate speech concerning off-label uses"); Letter from Margaret M. Dotzel, Assoc. Comm'r for Policy, FDA to Daniel J. Popeo & Richard A Samp, WLF 1 (Jan. 28, 2002), available at [http://www.fda.gov/ohrms/dockets/dailys/02/Jan02/013002/01p-0250\\_pdn0001\\_01\\_vol2.pdf](http://www.fda.gov/ohrms/dockets/dailys/02/Jan02/013002/01p-0250_pdn0001_01_vol2.pdf); 65 Fed. Reg. 14,286, 14,287 (Mar. 16, 2000).

<sup>57</sup> See 59 Fed. Reg. 59,820 (Nov. 18, 1994).

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these arguments, including as recently as May 2010.<sup>58</sup> As with methotrexate, these examples reflect the FDA's desire to constrain prescribing decisions themselves by regulating speech relating to those decisions. The FDA's regulation of speech is not the ultimate objective of the regulatory scheme, although that is surely its immediate target. Instead, the purpose of the off-label promotion ban is to regulate indirectly, through enforcement aimed at manufacturers, what the FDA has decided it cannot, for essentially political reasons, accomplish directly—that is, the regulation of the physician's decision to prescribe a drug for a particular off-label use. In any event, as we shall see, the examples cited by the FDA, fairly analyzed, do not support the current restrictive approach to off-label promotion.

The “parade” argues that off-label promotion (1) causes healthcare providers to avoid or delay using known, effective therapies or products in favor of unapproved products and (2) blurs the distinction between investigational and approved products and uses. In particular, the FDA asserted that two drugs used off-label in patients who had suffered from myocardial infarction were later shown to be harmful. First, the FDA stated that practitioners prescribed anti-arrhythmic agents for patients who had suffered from an acute myocardial infarction based on the unsubstantiated impression “that survival would be favorably affected by [ventricular premature beat] suppression,” but that subsequent studies showed increased mortality from use of the agents in this population. Second, the FDA stated that physicians had used calcium-channel blockers for patients after a myocardial infarction, although studies showed that the drugs did not provide benefit to this population and that the use might cause harm.<sup>59</sup> The FDA also raised concern that practitioners could view calcium-channel blockers as a substitute for beta-blockers, which had been shown to improve survival in post-myocardial infarction patients.<sup>60</sup> The FDA asserted that “several manufacturers of calcium-channel blockers” had previously sought to “encourage their use” in post-myocardial infarction patients, but the FDA “successfully rejected these attempts.”<sup>61</sup>

The FDA's description of events suggests that physicians were swayed by off-label promotion to make prescribing decisions to the detriment of their patients, but the scientific literature supports a different interpretation of events. During the 1980s, cardiologists debated the therapeutic benefit of prescribing anti-arrhythmic agents in the post-myocardial infarction setting. One article described a “decade of controversy” of the post-infarction use of such drugs, but the author still ultimately recommended “prophylactic antiarrhythmic drugs for all patients with acute infarction, especially in those undergoing early interventional therapy.”<sup>62</sup> Although the cardiac arrhythmia suppression trial (CAST) later showed that anti-arrhythmic agents lacked benefit post-infarction,<sup>63</sup> that information was not available to physicians who, before the study was conducted, had to determine how to treat patients

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<sup>58</sup> Margaret A. Hamburg, Commissioner of Food and Drugs, FDA, Remarks at the Massachusetts Medical Society's 2010 Shattuck Lecture (May 15, 2010); Linda A. Suydam, Senior Associate Commissioner, FDA, Keynote Address at the FDLI Conference on Advertising and Promotion in the New Millennium (Sept. 13, 1999); Hearing on Unapproved Uses of Prescription Drugs and Medical Devices, Before the S. Comm. on Labor and Human Resources, 105th Cong. (Feb. 22, 1996) (statement of William B. Schultz, Deputy Commissioner For Policy, FDA).

<sup>59</sup> It is not clear from the Agency's description whether physicians prescribed calcium channel blockers to post-myocardial infarction patients before or after the results of the studies showing lack of benefit had been released.

<sup>60</sup> *Id.*

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

<sup>62</sup> See Donald C. Harrison, Arrhythmia Prophylaxis After Acute Myocardial Infarction: A Decade of Controversy, 2 *CARDIOVASCULAR DRUGS & THERAPY* 783, 783 (1989).

<sup>63</sup> see Gerald V. Naccarelli et al., A Critical Appraisal of the Cardiac Arrhythmia Suppression Trial (CAST), 4 *APPLIED CARDIOPULMONARY PATHOPHYSIOLOGY* 9 (1991).

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suffering from myocardial infarctions. Thus, rather than demonstrating that doctors were inappropriately influenced by off-label promotion, this anecdote actually shows medical practice in action, with physicians trying to make the best decisions they could for their patients in a context of limited therapeutic options.

The calcium-channel blocker example is similarly nuanced. Although the FDA discusses all calcium-channel blockers as a class, medical literature up to the early 1990s reflects efforts to assess the efficacy of specific calcium-channel blockers in the post-infarction setting. Some calcium-channel blockers were shown not to be effective, but others were effective in lowering heart rate, preventing supraventricular tachycardia, and reducing ventricular premature complexes early after an acute myocardial infarction.<sup>64</sup> Again, the scientific literature shows that physicians could reasonably have made the decision to prescribe calcium-channel blockers based on the available medical literature and does not support the conclusion that they were misled by alleged off-label promotion.

The FDA also cited examples of allegedly-harmful off-label medical device promotion.<sup>65</sup> In particular, the FDA raised concern about “some entrepreneurs” (who may or may not have been medical device manufacturers) promoting the use of a “breast coil” as effective in detecting leakage of a silicone gel breast implant.<sup>66</sup> The FDA’s concerns appear to have been unfounded, however, as the FDA’s own guidance document now recommends the use of breast coils for this purpose.<sup>67</sup> Even in the mid-1990s, the medical literature reflected that breast coils were being developed and used in this manner.<sup>68</sup>

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<sup>64</sup> See, e.g., Peter H. Held & S. Yusuf, Calcium Antagonists in the Treatment of Ischemic Heart Disease: Myocardial Infarction, 5 CORONARY ARTERY DISEASE 12 (1994) (reviewing studies of six calcium-channel blockers and finding little benefit in their use post-myocardial infarction); Merete Vaage-Nilsen et al., Effect of Verapamil on Arrhythmias and Heart Rate During 16 Months Following an Acute Myocardial Infarction, 8 Cardiovascular Drugs & Therapy 147 (1994) (“Verapamil significantly lowered heart rate, prevented supraventricular tachycardia, and reduced VPC [ventricular premature complexes] early after an AMI [acute myocardial infarction].”); Chris L. Pashos, P.H. Held & S. Yusuf, Effects of  $\beta$ -Blockers and Calcium Channel Blockers in Acute Myocardial Infarction, 14 EUROPEAN HEART J. (SUPP. F) 18, 22 (1993) (“Subgroup analysis revealed that agents which decreased heart rate (verapamil and diltiazem) differed from agents that increased heart rate, which were associated with an excess of deaths and reinfarctions. Subgroup findings like these have to be very carefully interpreted, but subsequent data . . . appear to reinforce this observation.”).

<sup>65</sup> 59 Fed. Reg. at 59,825.

<sup>66</sup> See id.

<sup>67</sup> See FDA, Guidance for Industry and FDA Staff: Saline, Silicone Gel, and Alternative Breast Implants 28 (Nov. 2006) (“FDA recommends magnetic resonance imaging (MRI) as the current method of choice for detecting silent rupture of silicone gel-filled breast implants. . . . MRI of the breast should be performed with a dedicated breast coil, with a magnet of at least 1.5 Tesla, and preferably in centers experienced in performing and interpreting this type of examination.”); see also Anabel Medeiros Scaranelo et al., Evaluation of the Rupture of Silicone Breast Implants by Mammography, Ultrasonography and Magnetic Resonance Imaging in Asymptomatic Patients: Correlation with Surgical Findings, 122 SAO PAULO MED. J. (Mar.-Apr. 2004) (“[I]t can be concluded that magnetic resonance imaging with a dedicated breast coil had the highest sensitivity, while the specificity was similar to other methods.”).

<sup>68</sup> See Debra L. Monticciolo et al., MR Detection of Leakage from Silicone Breast Implants: Value of a Silicone-Selective Pulse Sequence, 163 AM. J. ROENTGENOLOGY 51, 52 (July 1994) (“A standard circular surface coil with a diameter of 24 cm was placed around each breast imaged.”); see also Christina Y. Ahn, Residual Silicone Detection Using MRI Following Previous Breast Implant Removal: Case Reports, 19 Aesthetic Plastic Surg. 361, 366 (1995) (“At the present time, the surface coil allows higher resolution and an increased signal to noise. Therefore, if a breast prosthesis rupture or leak is suspected in only one breast, a surface coil would be the coil of

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History similarly has not borne out the FDA's concern about off-label promotion of BOTOX® (onabotulinumtoxinA). The FDA raised concern that the drug, which was licensed at the time for the treatment of "strabismus and blepharospasm associated with dystonia," was being promoted off-label for cosmetic purposes, but did not identify any particular harms that had resulted from these communications.<sup>69</sup> This is perhaps not surprising, given that, in April 2002, BOTOX® was approved for cosmetic use.<sup>70</sup>

The FDA's list of horrors also includes the contention that "distinctions between approved and investigational products would be blurred, and the protections associated with the use of investigational products (such as obtaining informed consent from research subjects and institutional review board approval to ensure that the rights and welfare of research subjects are protected) would be easily circumvented."<sup>71</sup> Several FDA policies are inconsistent with the FDA's argument and in fact support "line blurring" to further public health objectives.

The FDA's first step came in the mid-1980s when, in response to the AIDS epidemic, it promulgated an interim regulation to establish a policy on expedited development of new drugs for life-threatening or severely debilitating conditions.<sup>72</sup> As part of the FDA Modernization Act of 1997 (FDAMA), Congress codified the FDA's initiative into law and termed it "fast track" approval.<sup>73</sup> Under Section 506, the FDA may approve an application for a fast track product where the agency finds that "the product has an effect on a clinical endpoint or on a surrogate endpoint that is reasonably likely to predict clinical benefit."<sup>74</sup> A fast track product thus may be approved before any clinical benefit has been shown, so long as a "surrogate endpoint" likely to predict clinical benefit has been affected.<sup>75</sup>

On May 31, 2002, the FDA promulgated a final rule, known as the "Animal Efficacy Rule," which was designed to permit approval or licensing of prescription drugs and biological products that are intended to reduce or prevent serious or life-threatening conditions caused by exposure to biological, chemical, radiological, or nuclear substances based on studies conducted on animals and any additional supporting data.<sup>76</sup> Specifically, the rule applies where adequate and well-controlled clinical studies in humans cannot be ethically conducted and field efficacy studies are not feasible.<sup>77</sup>

As these examples illustrate, the FDCA is not binary with respect to medical product marketing authorization decisions; it does not limit the FDA to either approval or rejection of proposed therapies. Rather, the legislation and the FDA's own policies, taken together, create a continuum of marketing authorization decisions in recognition of the need for patients to have varying degrees of access to drugs, biological products, and medical devices. Off-label promotion does not, as the FDA suggests, raise public health concerns because it "blurs" a distinction between approved and unapproved products or

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choice. Dedicated breast coils are being developed that will allow imaging of both breasts simultaneously as well as of specific areas of the breast for silicone.").

<sup>69</sup> Id.

<sup>70</sup> See Approval Letter, BOTOX® Cosmetic, BLA 103000/5000 (April 14, 2002).

<sup>71</sup> 59 Fed. Reg. at 59,825.

<sup>72</sup> See 53 Fed. Reg. 41,516 (Oct. 21, 1988).

<sup>73</sup> Federal Food, Drug, and Cosmetic Act (FDCA) § 506, 21 U.S.C. § 356.

<sup>74</sup> 21 U.S.C. § 356(b)(1).

<sup>75</sup> See also 21 C.F.R. Pt. 314, Subpt. H; 21 C.F.R. Pt. 601, Subpt. E.

<sup>76</sup> See 67 Fed. Reg. 37,988 (May 31, 2002).

<sup>77</sup> Id. at 37,989.

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uses. The FDA has itself established a more nuanced regulatory regime—one that is supported by the dissemination of information about off-label uses in carefully limited circumstances.

Finally,<sup>78</sup> the FDA's insistence that, for the sake of the integrity of the approval process, it must stringently regulate manufacturer speech about off-label uses of lawfully marketed medical products rings somewhat hollow given the agency's prolonged failure to implement fully the very statutory provisions that created that process. The contemporary system for FDA review of data demonstrating the safety and effectiveness of new drugs and medical devices dates to 1962 and Congress's enactment of the Kefauver-Harris Amendments to the FDCA. The central provision of that legislation amended the 1938 drug approval requirement by adding a mandate that each "new drug" be marketed only pursuant to an FDA finding not only of "safety"—which was included in the 1938 law—but also "effectiveness." Before the 1962 amendments, a manufacturer was permitted to go to market with a new drug based solely on the FDA's non-objection upon receiving a submission purporting to demonstrate product safety. Kefauver-Harris therefore augmented the demands on manufacturers by requiring efficacy data as well as requiring them to await affirmative FDA approval before product launch.

The FDA was given a two-year period in which to implement the new efficacy requirement, which applied not only to future-marketed drugs but also to those that had been introduced to the United States market before 1962. Yet the FDA still, nearly half a century after Congress directed the agency to bring all marketed "new drugs" under the safety and effectiveness requirements of the FDCA, has failed to implement those statutory commands. The FDA's abdication reflects, in part, the lack of resources available to the agency to apply the effectiveness requirement retrospectively to the thousands of products to which it applied within the two-year time given. But it also reflects, perhaps more so, the FDA's determination that the agency's mission to protect the public health simply does not require the agency to apply the drug approval requirements to all products.

The FDA's effort to comply with that requirement with respect to prescription drugs was called the Drug Efficacy Study Implementation (DESI). The volume of products covered by DESI was quite large, and the resulting process moved slowly. Even though the 1962 amendments became effective in October 1964, the FDA gave drug manufacturers until July 1967 to submit proof that their drugs were effective for their claimed uses. The resulting submissions were reviewed by panels convened under the auspices of the National Academy of Sciences-National Research Council (NAS-NRC), which made recommendations for categories of drug products according to intended use and active ingredient. After evaluating each NAS-NRC report, the FDA would announce whether each category was "effective," "probably effective," "possibly effective," or "lacking substantial evidence of effectiveness." If the

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<sup>78</sup> Also worth mention is the FDA's approach to drug shortages. Although not formalized in a policy as such, the FDA's general practice is to facilitate the importation of unapproved drugs when an approved counterpart has become unavailable, provided the agency has determined—outside the formal new drug approval process and on an expedited basis—that the substitute product is "safe and effective" and the active ingredient of the substitute is covered by an approved new drug application. See Valerie Jensen, et al., FDA's Role in Responding to Drug Shortages, *Am J Health Syst Pharm.* 2002; 59:1423-5; FDA, Questions and Answers on the Propofol Shortage (Apr. 23, 2010), <http://www.fda.gov/Drugs/DrugSafety/DrugShortages/ucm209227.htm>. This practice, like the agency's failure to implement DESI, gives the lie to the notion, so frequently articulated in defense of the off-label promotion ban, that the FDCA drug approval process must be applied without compromise or else risk jeopardizing the public's health. If the process were to crucial to patient safety, then the FDA would not simply ignore it in a shortage scenario.

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finding was anything other than “effective,” the FDA granted the manufacturer additional time to gather additional information before initiating the statutorily mandated action to remove the drug from the market.

The FDA’s policy at the time was to allow manufacturers to continue marketing their products during the entire DESI review process even though they, by definition, lacked the approval required by the 1962 amendments. In 1972, a federal district court granted mandamus against the FDA on the ground that the FDA’s policy of allowing unapproved drugs to remain on the market after the FDA had determined them to not be effective was a clear violation of the 1962 amendments.<sup>79</sup> Three years later, the court struck down a similar FDA policy of allowing “me-too” drugs (i.e., unapproved products that were identical, related, or similar to an approved product) to remain on the market without an approved application.<sup>80</sup>

In June 2006, the FDA announced a policy to bring any non-DESI unapproved drugs marketed in the United States into compliance with the FDCA.<sup>81</sup> A major theme of the policy is the FDA’s desire to avoid disrupting the market for unapproved new drugs. Although manufacturers of such products “have not provided the FDA with evidence demonstrating that their products are safe and effective,” the FDA wants to “encourage . . . manufacturers . . . to obtain the required evidence and comply,” but “without adversely affecting public health, imposing undue burdens on consumers, or unnecessarily disrupting the market.”<sup>82</sup> Although the FDA estimates that “several thousand drug products are marketed illegally without required FDA approval,” the agency asserts that it lacks the resources to “take action immediately against all of these illegally marketed products.” To make the “best use of scarce Agency resources,” therefore, the FDA will “prioritize” its efforts by focusing on a few products, while allowing the remainder to stay on the market.

The FDA has, to put it mildly, been highly selective in implementing the 2006 policy—a policy that itself, by design, falls far short of providing for complete or immediate implementation of the statutory scheme. The 2006 policy provides that the FDA will “giv[e] higher priority to enforcement actions” against potentially unsafe and ineffective drugs. Since the policy was published, the FDA has removed from the market only thirteen unapproved new drugs, and not all of these actions were undertaken by the agency *sua sponte*.<sup>83</sup>

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<sup>79</sup> See *American Public Health Assoc. v. Veneman*, 349 F. Supp. 1311, 1315 (D.D.C. 1972) (“[I]t could not be clearer that the Secretary must begin the procedures to withdraw a drug when he concludes that there is no substantial evidence of efficacy.”).

<sup>80</sup> See *Hoffman-LaRoche, Inc. v. Weinberger*, 425 F. Supp. 890 (D.D.C. 1975).

<sup>81</sup> Guidance for FDA Staff And Industry: Marketed Unapproved Drugs—Compliance Policy Guide, § 440.100 (June 2006), available at <http://bit.ly/5Bz5x2> (visited Aug. 6, 2010). Interestingly, in the CPG, FDA dials back its rhetoric about the importance of the new drug approval process, saying only: “The new drug approval . . . process[] play[s] an essential role in ensuring that all drugs are both safe and effective for their intended uses.” *Id.* at 2 (emphasis added).

<sup>82</sup> *Id.* at 2.

<sup>83</sup> “Some of the specific actions the Agency has taken have been precipitated by evidence of safety or effectiveness problems that has . . . been brought to our attention by outside sources.” *Id.* at 2. In at least two of these cases, FDA took action only after manufacturers of approved versions of the unlawful products threatened litigation and/or took other action to pressure FDA to implement the new drug approval requirements.

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Given the FDA's determination, often repeated in the context of off-label use, that new uses are by definition unsafe and ineffective because they lack FDA approval, the FDA's position in the unapproved new drugs context that not all such drugs are unsafe or ineffective is hard to comprehend. If FDA officials believe that unapproved products can remain on the market because their very history of marketing and their acceptance by physicians as part of clinical practice provide some evidence of safety and effectiveness, then they should likewise acknowledge the legitimacy of off-label uses with similar track records.

The gout drug colchicine is a case in point. Before the 2006 policy was announced by the FDA, numerous pharmaceutical companies manufactured and/or sold single-ingredient colchicine tablets without FDA approval. After the FDA announced the unapproved drugs policy in 2006, one manufacturer began to develop data to support approval for its single-ingredient colchicine tablets, and the manufacturer's drug was approved in 2009. As the FDA was well aware, the unapproved products were unsafe for use by gout patients. Indeed, the clinical investigations conducted by the manufacturer of the lone approved colchicine drug demonstrated that the labeling that had historically accompanied unapproved versions of the product contained dosing instructions that presented serious safety issues.

The studies revealed, among other things, that the historically-used dose of colchicine was far higher than necessary to achieve the intended therapeutic effect. According to both the FDA and World Health Organization adverse event reporting systems, unapproved colchicine drug products had resulted in at least 1,380 side effects ranging from nausea to acute renal failure, thrombocytopenia, leucopenia, and death. Indeed, a senior FDA official, recognizing the practice-changing importance of the new colchicine data published an open letter to practitioners emphasizing the importance of the new dosing instructions.<sup>84</sup> Despite the recognized need for the FDA to remove unapproved versions of colchicine-containing products from the market, the FDA for a time refused to do so on the ground that physicians treating gout patients preferred the lower-cost, unapproved versions, despite the obvious negative public health consequences.<sup>85</sup>

The FDA's assertion, in the "parade of horrors," that the public health demands strict application of the new drug approval requirements to new uses of approved products cannot co-exist with the agency's notorious refusal to implement those very requirements with respect to thousands of products currently on the market—some of which are frequently prescribed and may even represent the standard of care. Indeed, in some situations the FDA has appeared to turn the statutory scheme completely upside down in deference to the demands of physicians interested in preserving their access to the unapproved products.

Government lawyers representing the FDA in off-label promotion cases describe the history of the agency's efforts to address the harms it ascribes to such promotion into two periods: before enactment of the 1962 drug amendments and after. The 1962 date is, of course, pivotal in the development of the law because it began a period of greater scrutiny of the substantiation manufacturers had developed to support the information given to prescribers about the effectiveness of various drug products. And, as

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<sup>84</sup> Open Letter from Janet Woodcock, M.D., Director, Center for Drug Evaluation and Research, FDA (Mar. 3, 2010).

<sup>85</sup> Janet Woodcock & Sarah Okada, Incentives for drug development—the curious case of colchicine, *N Engl J Med.* 2010 Oct 7;363(15):1484.

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noted, 1962 began the two-year period Congress gave the FDA to require evidence of effectiveness for drugs introduced into commerce before enactment. As we have seen, the FDA has yet to complete its implementation of the 1962 amendments, and that lack of effort has enabled the continued marketing of thousands of products in flagrant disregard of that very legislation.

The FDA's failure of action undercuts the off-label promotion regime not only because it belies the notion that the new drug approval provisions of the FDCA must be enforced scrupulously for the sake of public health, but also because it permits the very disclaimer-based alternative regime that the government has rejected in off-label promotion cases. Brief discussion of one recent case illustrates the point.

In its most recent brief in the *Caronia* litigation,<sup>86</sup> filed October 20, 2010, the government responded to the argument, proffered by the Washington Legal Foundation as amicus curiae, that a manufacturer should be permitted to provide information about off-label uses as long as the information is accompanied by an adequate disclaimer—in this context, presumably meaning further information sufficient to assure that the off-label statement is not viewed by physicians as resting on a firmer foundation than the science indicates, or perhaps even an explicit statement that the use that is the subject of the information has not yet been FDA-approved. According to the government's brief in response, "Allowing drug manufacturers to promote drugs for off-label uses as long as they disclose that the uses are not FDA-approved would turn back the regulatory clock more than seventy years, to the regime of caveat emptor that prevailed before the FDCA was enacted in 1938, and would radically undermine the incentives for manufacturers to go through the new drug approval process." The brief continues: "WLF's suggestion that the manufacturer of . . . a dangerous product has a First Amendment right to promote it for unapproved uses, and to do without providing adequate directions (or, in this case, any directions) for use, is breathtaking." The government, finally, rejected as "risible" WLF's further assertion that including a statement that an off-label use has not been approved by the FDA would enable manufacturers to give physicians information they need to make informed decisions about such use.

In fact, the FDA had itself made almost that exact point in 1971, in a Federal Register notice accompanying regulations (which remain on the books) implementing the 1962 drug amendments. There, the FDA expressly endorsed—indeed, required—a disclaimer regime of the type advocated by WLF in its amicus curiae submission in the *Caronia* case. Using language strikingly consistent with that of WLF, the FDA rejected comments on the proposed rule asserting that physicians would not benefit from information regarding the lack of approval of off-label uses:

There is no real hardship in bringing the prescribers in on the fact that the medical data base upon which a claim of effectiveness is being made does not satisfy the requirements of adequate and well-controlled clinical investigations. . . . [F]ull disclosure . . . should lead to better patient care, rather than worse, and to better understanding by the physician of the drugs he prescribes. . . . [T]he requirement to include in the labeling and advertising of a prescription drug an authoritative conclusion regarding its usefulness is clearly within the authority and intent of the law to assure that the prescriber has adequate information on the drug for its safe and effective use . . . .<sup>87</sup>

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<sup>86</sup> See discussion *supra* at xx.

<sup>87</sup> 36 Fed. Reg. 11,022, 11023 (June 8, 1971).

## Off-label Promotion and Commercial Speech

Under the final rule, all package labeling, promotional labeling, and advertising for a drug that is included in the FDA program for implementing the 1962 drug amendments “shall include . . . an appropriate qualification of all claims evaluated as other than ‘effective’” by the expert panels convened by the FDA for the purpose of reviewing such claims.<sup>88</sup> Far from treating a proposed disclaimer regime as inconsistent with full and robust implementation of the drug effectiveness and approval requirements for the protection of the public health, the FDA in this rulemaking under the 1962 amendments went so far as to require disclaimers as to the lack of effectiveness of drugs then in commercial distribution. Although this approach fairly could be defended as an interim measure, it surely undercuts the FDA’s claims as to the public health necessity of unyielding enforcement of the new drug approval provisions for all “new drug” efficacy claims.<sup>89</sup>

### E. The History of the FDA’s Practice

A major defect in the FDA’s current restrictive approach to the regulation of off-label promotion is that it reflects the FDA’s decision to address conduct as to which it had repeatedly expressed concern by regulating speech endorsing that conduct—and doing so at a categorical level—rather than by regulating the underlying conduct itself. As noted, the FDA responded to the public health threat presented by the widespread off-label use of methotrexate to treat psoriasis through “educational” measures aimed at physicians, thereby abandoning its 1972 proposal to use a variety of regulatory techniques to constrain particular off-label uses of drugs that were harmful to patients or simply did not achieve the desired clinical benefit. Although the FDA repeatedly denies that it regulate the practice of medicine as such, it has consistently left room for the possibility that it could do so without any changes to its enabling statutes. Indeed, those statutes now clearly permit the FDA to address the public health concerns posed by off-label use through direct regulation of prescribing decisions rather than indirectly by commencing enforcement action against manufacturers who have engaged in speech about off-label uses. The central constitutional question arising out of these amendments is whether the FDA’s prohibition on off-label promotion can withstand First Amendment scrutiny given the agency’s clear statutory authority to regulate off-label prescribing itself.

To explore this key issue fully, a brief review of the history of the FDA’s efforts to regulate the clinical decisions of prescribers is necessary. Throughout the 1970s and 1980s, in the aftermath of the 1971 methotrexate hearings, the FDA occasionally sought to regulate the actual use of medical products. It did so at the same time that, at a policy level, it denied any intention to interfere with prescribers’ off-

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<sup>88</sup> 21 C.F.R. § 201.200(c).

<sup>89</sup> In an amicus brief submitted to the Supreme Court in a securities fraud case late last year, the FDA denied that efficacy data had to reach the level of statistical significance before providing meaningful information about a drug: “A study in which the cure rate for cancer patients who took a drug was twice the cure rate for those who took a placebo could generate meaningful interest even if the results were not statistically significant.” Brief for the United States as Amicus Curiae Supporting Respondents, *Matrixx Initiatives, Inc. v. Siracusano*, No. 09-1156, at 15 n.2. Just as the FDA, in the DESI context, recognized that efficacy data were clinically relevant even if they did not satisfy the standard applicable to efficacy assessments in the new drug approval context, so too did the agency in this case acknowledge that efficacy data could be relevant from an investment perspective. In both situations, the FDA’s approach undermines the agency’s assertion in the off-label promotion context that adequate protection of the public health requires unwavering enforcement of the high standards for efficacy data in the 1962 drug amendments.

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label use decisions. In the 1970s, FDA tried to control the use of methadone by limiting its distribution to FDA-approved maintenance treatment programs and pharmacies. The FDA also established requirements for regular blood testing and imposed patient registry and other restrictions on Clozaril (clozapine) in an effort to manage the risk of agranulocytosis (dangerously low white blood cell counts). Indeed, in the House hearings on methotrexate in 1971, FDA witnesses alluded to the prior experience with methadone in asserting that the FDA had statutory authority to regulate off-label prescribing and could choose to regulate such conduct by physicians as it deemed appropriate for the protection of the public health.

In the late 1980s and early 1990s, under pressure from the activist group ACT UP, the FDA developed new regulations that authorized the agency to restrict the distribution of approved prescription drugs and thereby control their actual uses. The stated premise of the initiative was that the FDA could permit the approval of a greater number of drugs for HIV/AIDS and other serious and life-threatening illnesses if it could control their use after approval and thereby assure a favorable risk:benefit ratio.<sup>90</sup> Thereafter, the FDA invoked these provisions to impose distribution restrictions, even for products that were not strictly within the scope of the regulations, where the agency believed restrictions on actual (i.e., off-label) use were necessary to manage risks. So, for example, in 1998, the FDA relied on Subpart H to restrict thalidomide by forbidding its off-label use.

Thalidomide is a drug indicated to treat, prevent and help suppress “cutaneous manifestations of moderate to severe erythema nodosum leprosum (ENL).”<sup>91</sup> The restrictions assuring safe use of the product under the manufacturer’s “S.T.E.P.S.” program included: (1) product labeling informing consumers of its risks and distribution restrictions; (2) registration of all prescribers, patients, and pharmacists who receive or dispense thalidomide; (3) six risk groups based on age, gender and reproductive status; (4) authorization validation for dispensing the drug; (5) a telephonic survey of patients and prescribers; (6) measures to prevent pregnancy in patients; (7) educational materials; (8) patient counseling; (9) limiting prescriptions to an 8-day supply in blister packs; (10) distribution to registered pharmacies; (11) immediate reporting of any suspected fetal exposures; and (12) quality assurance and ongoing evaluation of the S.T.E.P.S. program.<sup>92</sup> These restrictions were imposed to mitigate “the major specific safety concern [of] . . . teratogenicity” and fetal exposures.<sup>93</sup> Clearly, the FDA believed it then had broad authority under the FDCA to regulate thalidomide to prevent any prescriber from ordering its use in circumstances that the agency regarded as inconsistent with the protection of the public health.

The FDA furthered its effort at establishing its authority to restrict off-label use by issuing three guidance documents in 2004. In those documents, the FDA acknowledged that it had previously denied any intention to interfere in off-label use as part of medical practice, but described an array of “risk

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<sup>90</sup> See 21 C.F.R. Part 314, Subpart H.

<sup>91</sup> Approval Letter from Murray M. Lumpkin, M.D., Dep. Cnt. Dir., Review Management, Center for Drug Evaluation and Research (CDER) to Steve Thomas, Ph.D., Celgene Corp., Jul. 16, 1998 (available at [http://www.accessdata.fda.gov/drugsatfda\\_docs/applletter/1998/207851tr.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/applletter/1998/207851tr.pdf)).

<sup>92</sup> Memorandum from Carl Kraus, Med. Officer, CDER to Anne Trontell, Dep. Dir., Office of Drug Safety, Jan. 29, 2004 (available at <http://www.fda.gov/ohrms/DOCKETS/ac/04/briefing/4017B1-06b%20Overview%20STEPS%20Section%20C%20Tab%207.pdf>).

<sup>93</sup> Id.

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management” tools that it would impose as necessary to control the risks of medical product use.<sup>94</sup> In 2007, Congress effectively codified FDA’s approach, by enacting the FDA Amendments Act, which included provisions that gave the FDA authority to address drug risks—including risks associated with off-label uses—through the imposition of mandatory “Risk Evaluation and Mitigation Strategies.”<sup>95</sup>

Throughout this period, the FDA has repeatedly taken action with respect to specific drugs in an effort to address off-label use. To take but three examples, in September 1997, the FDA requested the voluntary withdrawal of fenfluramine and dexfenfluramine, frequently used off-label with phentermine to make the drug cocktail “fen-phen” to treat obesity. The FDA’s action was prompted by findings suggesting that fenfluramine and dexfenfluramine were the likely cause of heart valve problems in patients taking either drug alone or in conjunction with phentermine.<sup>96</sup> Second, in June 1998, the FDA announced that Wyeth-Ayerst Laboratories was withdrawing Duract, a popular prescription pain reliever, because of the risk of liver damage associated with an off-label dosing regimen.<sup>97</sup> Finally, in 2008, the FDA decided not to approve Injectafer (ferric carboxymaltose injection) due in part to concerns about off-label use.

FDA therefore does, whatever its protestations to the contrary, seek to regulate directly the off-label use of drugs when public health needs warrant. The availability of this regulatory option as an alternative to regulation of off-label promotion, like the other anomalies discussed above, make FDA’s ban on off-label promotion unconstitutional when measured according to the regnant standards.

## II. APPLYING COMMERCIAL SPEECH DOCTRINE TO THE FDA’S PROHIBITION OF OFF-LABEL PROMOTION

### A. The Existing Doctrinal Framework for Commercial Speech Protection

#### 1. The Evolution of the *Central Hudson* Test

Long excluded completely from the First Amendment’s scope,<sup>98</sup> commercial speech first received substantial constitutional protection in the Supreme Court’s 1976 decision in *Virginia State Board of Pharmacy v. Virginia Citizens Consumer Council, Inc.*,<sup>99</sup> where the Court invalidated the state’s prohibition on advertising of prescription drug prices. However, for many years thereafter, the Court afforded commercial speech only “a limited measure of protection, commensurate with its subordinate

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<sup>94</sup> See FDA, Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment (Mar. 2005) (available at <http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126834.pdf>); FDA, Guidance for Industry: Development and Use of Risk Minimization Action Plans (Mar. 2005) (available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071616.pdf>); FDA, Guidance for Industry: Premarketing Risk Assessment (Mar. 2005) (available at <http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm126958.pdf>).

<sup>95</sup> 21 U.S.C. § 355-1(f)(1)(a).

<sup>96</sup> See Press Release, FDA Announces Withdrawal Fenfluramine and Dexfenfluramine (Fen-Phen) (Sept. 15, 1997), available at <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm179871.htm>.

<sup>97</sup> See Questions and Answers for Withdrawal of Duract, available at <http://www.fda.gov/Drugs/ResourcesForYou/Consumers/QuestionsAnswers/ucm073043.htm>.

<sup>98</sup> For a history of Supreme Court protection of commercial speech in its early years, see generally [Ron Rotunda article on commercial speech].

<sup>99</sup> 425 U.S. 748 (1976).

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position in the scale of First Amendment values.”<sup>100</sup> The Court therefore upheld regulations of commercial speech on grounds that would never have been deemed acceptable had the speech being regulated been more traditionally protected non-commercial speech.<sup>101</sup>

In its 1980 decision in *Central Hudson Gas & Electric Corp. v. Public Service Commission*,<sup>102</sup> the Court adopted a four-part test to determine whether commercial speech is protected. This test continues to control, though as we will show a number of Justices have argued for a more protective test, and in any event in its modern application the test has taken a far more protective form than it did originally.<sup>103</sup> Under that test, the first inquiry asks whether the speech in question promotes the sale of an unlawful product or service, or is found to be false or misleading. Assuming the speech in question has passed this first hurdle, the remaining three questions scrutinize the nature of and justification for the speech regulation. For the regulation to be upheld, it must satisfy all three of the test’s remaining prongs. Failure to satisfy any one of the three results in a finding that the regulation is unconstitutional. For each of the three, the government bears the burden of establishing that the requirement is satisfied.

Under the test’s second prong, the government must demonstrate that its regulation of commercial speech serves a “substantial” governmental interest.<sup>104</sup> Once that test has been satisfied (and it has not proven to provide a significant constitutional barrier to regulation), the reviewing court must determine whether the regulation directly advances the governmental interest asserted. . . .”<sup>105</sup> The court will invalidate the regulation if it “only indirectly advance[s] the state interest involved.”<sup>106</sup> Moreover, the regulation must *materially* advance the state’s interest. Government has the burden of establishing, beyond mere speculation, that its regulation does in fact do so.<sup>107</sup> Even if this requirement is satisfied, the regulation must still be found to be “[no] more extensive than is necessary to serve [the substantial governmental] interest.”<sup>108</sup>

Although in the early years of the test’s application one might have been able to characterize the Court’s protection of commercial speech as far below the level afforded more traditionally protected varieties, over approximately the last 15 years the Court has extended commercial speech a level of protection that in many ways rivals full protection. It has consistently invalidated regulations of commercial speech for their failure to satisfy the third prong, the fourth prong, or a synthesis of the two.<sup>109</sup> Indeed, on occasion it has invalidated expressive restrictions even in the case of the FDA’s

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<sup>100</sup> *Ohralik v. Ohio State Bar Ass’n*, 436 U.S. 447, 456 (1978). For explication of the argument that commercial speech is deserving of full First Amendment protection, see Martin H. Redish, *Money Talks: Speech, Economic Power, and the Values of Democracy* 14-62 (2001).

<sup>101</sup> See, e.g., *Friedman v. Rogers*, 440 U.S. 1 (1979).

<sup>102</sup> 447 U.S. 557 (1980).

<sup>103</sup> See discussion *infra* at xx.

<sup>104</sup> 447 U.S. at 566.

<sup>105</sup> *Id.*

<sup>106</sup> *Id.* at 564.

<sup>107</sup> *Edenfield v. Fane*, 507 U.S. 761, 770-71 (1993) (“This burden is not satisfied by mere speculation or conjecture; rather a governmental body seeking to sustain a restriction on commercial speech must demonstrate that the harms it recites are real and that its restriction will in fact alleviate them to a material degree.”).

<sup>108</sup> 447 U.S. at 566.

<sup>109</sup> See, e.g., *Lorillard Tobacco Co. v. Reilly*, 533 U.S. 525, 565 (2001) (state’s restrictions of outdoor advertising of tobacco violate fourth prong of *Central Hudson*); *Greater New Orleans Broad. Ass’n v. United States*, 527 U.S. 173, 190 (1999) (invalidating federal law prohibiting “some, but by no means all, broadcast advertising of lotteries and

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regulation of drug advertising.<sup>110</sup> The Court has made clear that the government may not justify its regulations of truthful commercial speech simply by invoking sweeping and unsupported assertions of justification. The Court has found that commercial speech has significant value, and cannot be suppressed without strong and real justification.

### 2. The Move Towards a More Categorical Standard

On a number of occasions over the past 15 years, members of the Court have advocated or adopted an approach to commercial speech protection that, in certain instances, turns on more categorically established factors than does the interest balancing approach of even the more protective version of the *Central Hudson* test. In a number of opinions, Justices have argued that when the speech sought to be regulated or suppressed is truthful and advocates lawful purchase, governmental restriction of that speech is properly deemed categorically unconstitutional .

The first decision to openly advocate such a position was the plurality opinion of Justice Stevens in *44 Liquormart v. Rhode Island*.<sup>111</sup> Justice Stevens reasoned that bans of truthful advertising for lawful products or services when those bans are designed to protect consumers from commercial harms “rarely protect consumers from such harms. Instead, such bans often serve only to obscure an ‘underlying governmental policy’ that could be implemented without regulating speech.”<sup>112</sup> Such bans, Justice Stevens argued, “usually rest on the offensive assumption that the public will respond ‘irrationally’ to the truth. The First Amendment directs us to be especially skeptical of regulations that seek to keep people in the dark for what the government perceives to be their own good. That teaching applies equally to state attempts to deprive consumers of accurate information about their chosen products.”<sup>113</sup> In short, Justice Stevens was arguing that the First Amendment is designed to prevent government from manipulating citizen behavior, not through free and open debate but rather through the selective suppression of speech advocating lawful action. Where government is concerned about public health or safety, it is constitutionally authorized to regulate or even prohibit *the actual activity itself*, not merely the speech advocating the activity. Once government has made the activity itself illegal, it has full authority under the First Amendment to suppress speech advocating that now illegal activity. But it cannot achieve its regulatory goal furtively through suppression of information and opinion. If the First Amendment means anything, it means that much.

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casino gambling” because “[t]he operation of [the challenged statute] and its attendant regulatory regime is so pierced by exemptions and inconsistencies that the Government cannot hope to exonerate it.”); *44 Liquormart, Inc. v. Rhode Island*, 517 U.S. 484, 506 (1996) (emphasis in original) (invalidating prohibition of liquor price advertising as a means of promoting the government’s interest in temperance because “the State has presented no evidence to suggest that its speech prohibition will *significantly* reduce marketwide consumption.”); *Rubin v. Coors Brewing Co.*, 514 U.S. 476 (1995) (federal law prohibiting beer labels from displaying alcohol content held unconstitutional because under the law distilled spirits are permitted to display their alcohol content); *City of Cincinnati v. Discovery Network, Inc.*, 507 U.S. 410 (1993) (invalidating ban on commercial news racks on city streets in the city by an attempt to improve esthetics, because the remaining non-commercial newspaper racks rendered “marginal indeed” the esthetic benefits gained from the regulation).

<sup>110</sup> *Thompson v. Western States Medical Center*, 535 U.S. 357 (2002).

<sup>111</sup> 517 U.S. 484 (1996).

<sup>112</sup> *Id.* at 502-03 (citation omitted). Justice Thomas continues to adhere to a view similar to Justice Stevens’s. See [Justice Thomas’s concurring opinions in *44 Liquormart* and *Thompson*.]

<sup>113</sup> *Id.* (internal citation omitted).

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While a majority of the Court has never formally adopted this categorical approach in place of the *Central Hudson* test, on more than one occasion a majority opinion has expressed a similar sentiment. For example, in *Edenfield v. Fane*<sup>114</sup> the Court reasoned: “The commercial marketplace, like other spheres of our social and cultural life, provides a forum where ideas and information flourish. Some of the ideas and information are vital, some of slight worth. But the general rule is that the speaker and the audience, not the government, assess the value of the information presented.”<sup>115</sup> In its more recent decision in *Thompson v. Western States Medical Center*, the Court expressed similar thoughts, stating: “We have...rejected the notion that the Government has an interest in preventing the dissemination of truthful commercial promotion in order to prevent members of the public from making bad decisions with the information.”<sup>116</sup>

It is clear, then, that over the years this categorical approach to truthful advertising for a lawful product has gained a substantial following over the years. Most important to note, from a purely doctrinal perspective, is that at no point in recent years has a majority of the Court issued a holding on commercial speech protection that is in any way inconsistent with the categorical approach. While on occasion a majority has deferred the broader question about protection of truthful advertising, in at least the last 20 years it has never upheld a restriction that fails the categorical test.

It is, of course, true that commercial advertisements—much like the expression of political candidates and interest groups—are a form of advocacy. As such, they make no claim to total objectivity. Rather, they generally present only one side of an argument. But this fact, standing alone, does not automatically render them inherently misleading. Indeed, if advertising’s strategic selectivity were to render it inherently misleading, the entire concept of commercial speech protection would have to be rejected, since such a characterization automatically excludes commercial promotion from the First Amendment’s scope. In light of the Court’s vigorous level of protection of commercial speech in recent years, it is clear that the Court has surely not taken such a position. In those relatively few instances in which government properly concludes that, absent the provision of additional information, an advertisement is likely to give consumers a misimpression, it may require that the advertiser communicate whatever additional information is necessary to avoid such a result.<sup>117</sup> Moreover, unambiguously or affirmatively false claims may be suppressed consistent with the First Amendment. But the strategically selective nature of the arguments inherent in commercial advertising (or in *any* form of advocacy, for that matter) standing alone, does not provide a sufficient basis on which to justify the suppression of commercial speech.

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<sup>114</sup> 507 U.S.761 (1993).

<sup>115</sup> *Id.* at 767.

<sup>116</sup> 535 U.S. 357, 374 (2002).

<sup>117</sup> See, e.g., *Zauderer v. Office of Disciplinary Counsel*, 471 U.S. 616, xxx (1985).

## Off-label Promotion and Commercial Speech

### B. Measuring the FDA's Prohibition of Off-Label Promotion Under Supreme Court Commercial Speech Doctrine

#### 1. The Justifications for the Off-Label Prohibition: An Overview

There are, basically, three major constitutional justifications for the FDA's categorical prohibition on off-label advertising.<sup>118</sup> First, it is argued that the regulated activity is not "expression" at all but instead amounts to non-expressive conduct. Therefore the First Amendment is wholly inapplicable. Second, even if it were assumed that expression is being regulated, the government has a substantial interest in protecting the public against false or unsupported claims about off-label uses that could lead to unsafe or economically unjustified use, and absent formal FDA approval of the drug for that specific use there can be no assurance of the accuracy of the manufacturer's off-label claims. Finally, it is argued that for the very same reasons the government has a substantial interest in inducing manufacturers to seek FDA approval for off-label uses, and prohibition on manufacturer promotion of off-label uses does just that.

As superficially compelling as these arguments may seem, none of them justifies the FDA's prohibition of off-label advertising under existing commercial speech doctrine.<sup>119</sup> Equally important, we believe, is that these arguments reveal a fundamentally flawed understanding of core normative premises underlying the constitutional protection of free expression in general and the constitutional protection of commercial speech in particular. Their acceptance would therefore result in adoption of a foundationally pathological version of free speech theory.<sup>120</sup>

#### 2. The Off-Label Prohibition as Regulation of Non-Expressive Conduct

The FDA has argued that the prohibition of off-label promotion is not speech regulation at all, but rather simply the regulation of non-expressive conduct. Rather than myopically focus on the promotion itself, the argument proceeds, it is necessary to focus on the broader commercial transaction.<sup>121</sup> Though it is perfectly legal for a prescription drug to be prescribed for an off-label use, it is unlawful for a manufacturer of a prescription drug to sell its product with the intent that it be used for off-label purposes. Advertising an off-label use, then, is conclusive proof that the manufacturer is violating the lawful prohibition on its conduct. Any negative impact on expression is therefore merely incidental to the regulation of non-expressive behavior—a form of expressive regulation subjected to a far less protective constitutional standard.<sup>122</sup> If this argument were to be accepted, then all of the questions surrounding the protection of commercial speech would of course be rendered irrelevant. However, the argument must be rejected; it is manipulative and disingenuous on its face and inconsistent with controlling Supreme Court precedent.

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<sup>118</sup> Each of these constitutional justifications can be gleaned from the FDA's rationales for its treatment of off-label promotion. See generally Section I, *supra*.

<sup>119</sup> See discussion *infra* at xx.

<sup>120</sup> See discussion *infra* at xx.

<sup>121</sup> Brief for Appellants Food & Drug Administration, *Washington Legal Foundation v. Henney*, 202 F.3d 331 (D.C. Cir. 1999), 1999 WL 34834316, \*20 (Oct. 8, 1999).

<sup>122</sup> *U.S. v. O'Brien*, 391 U.S. 367 (1968).

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Under the FDA’s argument, the manufacturer’s promotion of off-label use is deemed to be nothing more than evidence of the broader illegal behavior of intentionally selling for off-label use. Initially, it is worth noting the bizarre incongruity of punishing the sale for the purpose of off-label use while simultaneously treating the prescription of the manufacturer’s drug for off-label use to be completely lawful. But more important is the fact that, contrary to its assertion, the FDA does *not* employ the fact of off-label promotion merely as *evidence* of the illegal act. Indeed, if the FDA were truly concerned with the manufacturer’s non-expressive act of sale with intent that the product be used off-label, it would logically prohibit *all* sales of a drug widely used off-label, because *any* time the manufacturer sells its drug, it would do so with knowledge that it will be used for off-label purposes. The fact that a manufacturer fails to promote off-label use surely does not imply that it is unaware that its product will be used off-label; a drug manufacturer is not an idiot. Indeed, reimbursement for specified off-label uses of prescription drugs is well established.<sup>123</sup> Yet there is no indication that the FDA has *ever* pursued a manufacturer for selling its drug with knowledge that it will be used for off-label purposes, absent off-label promotion. Where a manufacturer does not seek to advertise, the FDA makes no objection, *though there can be no doubt that the manufacturer is aware when it sells its product that it will be used off-label*. Any time a manufacturer sells its product, therefore, the “intent” to sell that product for off-label use must be imputed to it. Yet there is no evidence showing that the FDA ever seeks to punish a manufacturer for intentionally marketing its product for off-label use, absent manufacturer promotion of that use. Off-label promotion, then, constitutes both a necessary and sufficient condition for FDA action against a manufacturer. Contrary to the FDA’s argument, then, the FDA is not seeking to regulate the *act* of sale for the purpose of off-label use; it is, rather, seeking to regulate solely the expression itself—nothing more, nothing less. Surely, a reviewing court would not accept so strained an interpretation.

When the dust settles, then, it is clear that the FDA’s categorical prohibition of off-label use amounts to a classic suppression of commercial speech. What makes this prohibition so problematic, it should be recalled, is that the actual behavior being advocated is perfectly lawful; neither the FDA nor Congress has prohibited off-label uses themselves. Absent a showing that the suppressed promotion is false or misleading, it is by no means clear that, under current doctrine, suppression is *ever* constitutional. At the very least, suppression of truthful promotion of lawful use must satisfy increasingly demanding constitutional standards. As the following discussion will show, it is highly doubtful that current FDA practice can meet them.

A somewhat similar argument was rejected by the Supreme Court in *Thompson v. Western States Medical Center*.<sup>124</sup> The challenged statute in that case did not directly prohibit advertising of compounded drugs. Rather, it permitted such advertising, provided that any pharmacist who advertised his compounded drug would not be exempted from the new drug approval provisions of the Federal Food, Drug, and Cosmetic Act. Even though the statute did not directly restrict speech, the Court invalidated it as a violation of the First Amendment. In the words of one group of commentators, “[a]fter *Western*

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<sup>123</sup> [Get cite.]

<sup>124</sup> 535 U.S. 357 (2002).

## Off-label Promotion and Commercial Speech

States, [the] FDA can no longer assert that its use of speech as a proxy for conduct is exempt from First Amendment scrutiny.”<sup>125</sup>

### 3. Applying Commercial Speech Doctrine to the Prohibition of Off-Label Promotion

#### a. Applying the Categorical Standard

As previously noted,<sup>126</sup> a strong case can be made to support the proposition that, instead of using the four-part *Central Hudson* test to determine the constitutionality of commercial speech regulation, the Court would today apply a categorical standard which automatically invalidates suppression of truthful expression that advocates lawful consumer behavior. Justices who have advocated this position to date have reasoned that such paternalistic manipulation of consumer behavior is inconsistent with the very premises underlying democracy, let alone the constitutional guarantee of free expression, and no holding of the Court since at least the mid 1990s is inconsistent with this theory.<sup>127</sup> If one were to proceed on the assumption that this categorical standard would be applied, it is inconceivable that the prohibition on off-label promotion could survive.

Initially, it is important to emphasize that advertising is not automatically rendered false or misleading simply because it is used to promote off-label uses.<sup>128</sup> While it is of course conceivable that particular off-label promotion could be false or misleading, the same is true of advertising on behalf of any commercial product or service. Second, it is once again necessary to note that off-label uses of prescription drugs are in no way unlawful. The combination of these two indisputable assertions is that the prohibition of off-label promotion contravenes the categorical standard.

The argument that off-label promotion might convince doctors to prescribe drugs that would be ineffective or harmful and such promotion can therefore constitutionally be suppressed cannot survive scrutiny under this categorical standard. Indeed, the Supreme Court expressly rejected a parallel argument made by the FDA in *Thompson v. Western States Medical Center*.<sup>129</sup> There the Court held unconstitutional a statutory provision exempting “compounded drugs” from the FDA’s standard drug approval requirements as long as the providers agreed to abide by several restrictions, including that they refrain from advertising or promoting particular compounded drugs.<sup>130</sup> The Court there said that “[e]ven if the Government had argued that the [statute’s] speech-related restrictions were motivated by a fear that advertising compounded drugs would put people who do not need such drugs at risk by causing them to

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<sup>125</sup> A. Elizabeth Blackwell & James M. Beck, *First Amendment Right to Advertise and Promote Their Products for Off-Label Use: Avoiding a Pyrrhic Victory*, 58 Food & Drug L.J. 439, 445-46 (2003). See also *United States v. Wenger*, 427 F.3d 840, 846 n.1 (10<sup>th</sup> Cir. 2005) (“[T]he Supreme Court has rejected the idea that the power to extensively regulate in a certain area includes the authority to regulate speech without raising First Amendment concerns.”); *Washington Legal Foundation*, 13 F. Supp. 2d at 59 (“This court is hard pressed to believe that the agency is seriously contending that ‘promotion’ of an activity is conduct and not speech....”); *United States v. Caronia*, 576 F. Supp. 2d at 395-95. In the words of one commentator, “[t]he Supreme Court has never accepted the notion that truthful speech can be regulated in order to prevent harm where the sole embodiment of that harm is the speech itself.” Richard A. Samp, *Courts Are Arriving at a Consensus on Food and Drug Administration Speech Regulation*, 58 Food & Drug L.J. 313, 324 (2003).

<sup>126</sup> See discussion supra at xx.

<sup>127</sup> See discussion supra at xx; infra at xx.

<sup>128</sup> See discussion infra at xx.

<sup>129</sup> 535 U.S. 357 (2002).

<sup>130</sup> 21 U.S.C. s 353a; see 535 U.S. at 360.

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convince their doctors to prescribe the drugs anyway, that fear would fail to justify the restrictions.”<sup>131</sup> The Court rejected “the questionable assumption that doctors would prescribe unnecessary medications,”<sup>132</sup> and in any event dismissed the concern because it “amounts to a fear that people would bad decisions if given truthful information about compounded drugs.”<sup>133</sup>

### b. Applying the *Central Hudson* Test to the Prohibition of Off-Label Promotion

#### (1) First prong: is the speech false or misleading?

Even if we were to proceed on the assumption that the Court would apply the four-part *Central Hudson* test, rather than the categorical standard, there is little doubt that the FDA’s prohibition on off-label promotion would fail. It should be recalled that while in its original incarnation the test provided a level of constitutional protection far lower than that given more traditional form of expression, recent case law should disabuse us of this notion.<sup>134</sup>

For reasons already discussed, it would be incorrect to conclude that off-label promotion fails *Central Hudson*’s first prong because it is inherently false or misleading. It is true that while prescription drugs have necessarily passed rigorous FDA review of the scientific basis for the manufacturer’s claim of efficacy, no such review has ever been conducted for claims made on behalf of unapproved off-label uses. But it surely does not follow that *all* claims made on behalf of off-label uses are *inherently* false or misleading. Indeed, if such a sweeping, categorical assumption were true, it is inconceivable that government would allow off-label uses in the first place. Indeed, the FDA has itself conceded that off-label uses are often tremendously beneficial.<sup>135</sup> In any event, most commercial speech does not have to satisfy *ex ante* governmentally set standards of accuracy; yet it surely does not follow that for that reason it must be considered inherently misleading.

Of course, like any form of advertising protected by the commercial speech doctrine (or any fully protected advocacy, for that matter), off-label promotion is just that—promotion. For that reason, it is not likely to explore fully both sides of the issue. But as previously noted,<sup>136</sup> the strategic selectivity of expression designed to promote the interests of the speaker in no other context automatically renders the expression false or misleading. To the extent that the failure of commercial speech to include negative information has the potential to mislead the listener, under established doctrine government may require the speaker to communicate that information.<sup>137</sup> In the case of off-label promotion, for example, at the very least it would make sense for government to require that the manufacturer indicate that the FDA has never approved the particular use described in its promotion. But that does not mean that government may

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<sup>131</sup> Id. at 374.

<sup>132</sup> Id.

<sup>133</sup> Id.

<sup>134</sup> See discussion *supra* at xx.

<sup>135</sup> See discussion *supra* at xx.

<sup>136</sup> See discussion *supra* at xx.

<sup>137</sup> *Zauderer v. Office of Disc. Counsel*, 471 U.S. 626 (1985).

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suppress the communication completely when the danger can be avoided by the provision of more information, rather than less.<sup>138</sup>

### **(2) Second prong: what is the government’s “substantial interest”?**

Assuming the regulated speech is found not to be false or misleading, a reviewing court will proceed to an examination of the three remaining elements in the *Central Hudson* test. The first of those remaining inquiries—whether the regulation furthers a substantial governmental interest—is usually not very difficult to satisfy. That is equally true in the context of the suppression of the promotion of off-label use, at least to the extent that interest is defined in the broadest manner. No one could deny that government has a substantial interest in preserving the populace’s health and safety,<sup>139</sup> and to the extent the complete suppression of the promotion of off-label use furthers that interest in a material way and goes no further than necessary, then the *Central Hudson* test would be satisfied. But as the following discussion clearly demonstrates, neither of those final two requirements is met by the FDA’s prohibition.

In order to finesse the obvious problems under the third and fourth prongs, the FDA could attempt to redefine its interest more narrowly. For example, the FDA has argued that the prohibition on off-label promotion furthers its interest in inducing manufacturers to seek the FDA’s approval of the off-label use.<sup>140</sup> The inability of manufacturers to promote the off-label use, the argument proceeds, encourages them to obtain FDA approval for the use in question. To do so, the manufacturer would have to provide substantial scientific proof of the drug’s efficacy for that purpose—a burden it would not likely be willing to bear unless it stood to gain a substantial benefit as a result.

If the FDA were allowed to define its interest in so circular a manner, it likely would be successful in its constitutional defense. However, the interest itself is misleading, because it effectively circumvents the important constitutional protections embodied in the final two prongs of the *Central Hudson* test. It is therefore to application of those final two factors that our analysis now turns.

### **(3) Third prong: Does the regulation materially advance the government’s substantial interest?**

If one assumes that the FDA’s “substantial interest” under the second prong is to promote the safety and welfare of the populace by reducing the dangers of off-label drug use, it is purely speculative whether a ban on off-label promotion will achieve that goal. The FDA has conceded that not only are many off-label uses not only not harmful, but may in fact be quite beneficial.<sup>141</sup> It is presumably for this reason that the federal government has not categorically prohibited such off-label uses in the first place. The question then becomes, should we want prescribing doctors to be made fully aware of valuable off-label uses? The answer most assuredly must be yes; it would be wholly unacceptable for ill patients to be deprived of valuable and lawful treatments for the simple reason that their doctors were unaware of their existence. Yet the FDA’s categorical ban on manufacturer promotion will likely have this impact. It is therefore impossible to assert that public health and safety will be advanced by the categorical prohibition of off-label promotion.

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<sup>138</sup> For a discussion of FDA’s adoption of a disclaimer-based regime to assure that manufacturer speech about drug efficacy was truthful and non-misleading to physicians, see *supra* at xx.

<sup>139</sup> For a discussion of flaws in the FDA’s asserted justifications for the ban on off-label promotion, see *supra* at xx.

<sup>140</sup> See discussion *supra* at xx.

<sup>141</sup> See discussion *supra* at xx.

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Even more damning under the third prong is the FDA's accepted practice of permitting wholly unapproved drugs to remain on the market.<sup>142</sup> Such a practice is of course flatly inconsistent with the FDA's strategy in prohibiting off-label promotion. Inconsistency in governmental policy provides a classic basis for the Supreme Court's invalidation of commercial speech regulation under *Central Hudson*'s third prong.<sup>143</sup> In light of the fact that the FDA permits wholly unapproved and untested drugs to remain on the market, the agency's efforts to shut down lawful off-label promotion of drugs that have already been approved can hardly be said to "materially advance" the substantial interest in protecting public health and safety.

It is true, of course, that a good deal might turn on how at the outset one describes the government's "substantial interest." If one defines it narrowly to be the government's interest in encouraging manufacturers to put off-label uses on label by conducting the appropriate scientific tests and providing the agency with sufficient supporting data concerning the efficacy of the off-label use, then the analysis might be different. The government's argument here would be that if manufacturers were permitted to promote off-label uses, they would have no incentive to make the use on label. It is questionable, however, whether government should be permitted effectively to hold the First Amendment right for ransom. This argument effectively concedes that, when viewed on its four corners, the manufacturer's advocacy of off-label use is itself neither harmful nor illegal. Rather, the speech is being suppressed solely as an inducement to engage in a specific form of behavior. Allowing government to engage in such constitutional extortion amounts to imposition of an unconstitutional condition—a practice that the Court has deemed unacceptable.<sup>144</sup>

The most significant flaw in this argument leads logically to a discussion of the severe problems the regulation of off-label promotion incurs under *Central Hudson*'s fourth prong. The simplest response is that the government has available a means of achieving its goal that is far less invasive of free speech rights. The federal government has full constitutional authority under a synthesis of the Commerce Clause<sup>145</sup> and the Necessary and Proper Clause<sup>146</sup> to require that off-label uses be made on label. It may do so either by directly prohibiting the manufacturer from selling drugs for off-label uses, or by prohibiting doctors from prescribing drugs for off-label use. Such regulation would reach only conduct, not speech. As the following discussion will show, the *Central Hudson* test does not permit government to suppress commercial speech when its goal could be achieved instead by regulation of non-expressive behavior.

### **(4) Fourth prong: Does the regulation go further than necessary?**

As previously noted,<sup>147</sup> the fourth prong of *Central Hudson* requires that the regulation of commercial speech go no further than necessary to serve the government's substantial interest. While the Court noted early on that government does not necessarily have to employ the very least restrictive

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<sup>142</sup> See discussion supra at xx.

<sup>143</sup> *Greater New Orleans Broad. Ass'n, Inc. v. United States*, 527 U.S. 173 (1999); *Rubin v. Coors Brewing Co.*, 514 U.S. 476 (1995).

<sup>144</sup> [Get cites.]

<sup>145</sup> U.S. Const. Art. I, § 8, cl. 3.

<sup>146</sup> U.S. Const. Art. I, § 8, cl. 18.

<sup>147</sup> See discussion supra at xx.

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alternative in order to satisfy *Central Hudson*'s fourth prong,<sup>148</sup> in recent years it has significantly increased the burden that this requirement imposes on government, on more than one occasion invalidating the suppression of commercial speech because of its failure to satisfy its demands. The Court has invalidated commercial speech regulations under this prong either because alternative non-speech means of achieving the government's goal were available or because the regulation swept too far, impinging upon protected speech that failed to give rise to the harm sought to be prevented.<sup>149</sup> The off-label promotion prohibition violates both aspects of the fourth prong.

Initially, there can be no doubt that to the extent the government's goal is to prevent false or misleading advertising, the categorical prohibition contravenes the fourth prong. There is no way the FDA can establish, *ex ante*, that advertising is either false or misleading, merely because it promotes an off-label use. As already noted, many off-label uses are not only accepted, they are universally recognized as extremely valuable to the preservation of public health. The FDA's categorical ban subsumes manufacturer promotion of these uses, as well as any conceivably improper uses. The First Amendment does not permit the government to employ a hatchet when a scalpel is required. Secondly, we have already demonstrated that viable means of controlling non-expressive behavior are available to the government to prevent dangers to the public health arising from unjustified or dangerous off-label uses: simply prohibit off-label uses. Indeed, the fact that the federal government refuses to prohibit off-label use renders rather hollow its argument that promotion of such uses threatens the public health.

Our argument underscores the inconsistency of the off-label promotion ban with *both* versions of *Central Hudson*'s fourth prong. On the one hand, the goals of the ban could be achieved by non-expressive regulations. On the other hand, the ban sweeps much too far, including both expression that does give rise to the asserted danger and expression that does not do so.

### III. OFF-LABEL PROMOTION, COMMERCIAL SPEECH, AND THE FOUNDATIONS OF FREE EXPRESSION

#### A. Recognizing the Overlap between Commercial Speech and Traditional Categories of Protected Expression

We have already demonstrated how the FDA's prohibition of manufacturer's off-label promotion of prescription drugs unambiguously violates the controlling doctrinal framework for the constitutional protection of commercial speech. On one level, at least, our analysis should end the debate: the off-label promotion prohibition violates the First Amendment protection of commercial speech. On another level, however, there are interesting insights to be drawn from the constitutional travesty growing out of the prohibition of off-label promotion. By exploring the serious constitutional pathologies underlying the ban, we are able to grasp how suppression of commercial speech simultaneously undermines foundational precepts of American political and constitutional theory that underlie the First Amendment protection of

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<sup>148</sup> [*Fox* cite.]

<sup>149</sup> See, e.g., 44 *Liquormart, Inc. v. Rhode Island*, 517 U.S. 484, 507 (1996) (invalidating prohibition on price advertising of liquor because "[i]t is perfectly obvious that alternative forms of regulation that would not involve any restriction on speech would be more likely to achieve the State's goal of promoting temperance..."); *Lorillard Tobacco Co. v. Reilly*, 533 U.S. 525, 565 (2001) (state's restriction of outdoor advertising of tobacco, designed to prevent minors from being exposed to tobacco advertising, violate fourth prong because it unduly interferes with fully protected expression between manufacturers and adult consumers).

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*all* speech. In so doing, we are able to underscore the important theoretical overlap between the protection of commercial speech on the one hand and other more traditional categories of protected expression, on the other.

If we are correct in this suggested overlap, we will be able to draw out important implications for the First Amendment's currently accepted theoretical framework. A number of respected scholars have either categorically rejected extension of First Amendment protection to commercial speech<sup>150</sup> or proposed significant restrictions on its protection,<sup>151</sup> reasoning that the profit motivation of the speaker distinguishes it from more traditionally protected categories of expression. While in recent years the Supreme Court has extended a significant level of First Amendment protection to commercial speech,<sup>152</sup> it has long pointed to what it considers the "common sense differences" between that type of speech and the more traditionally protected forms of expression.<sup>153</sup> These conclusions have already been subjected to serious challenge.<sup>154</sup> The constitutional flaws that inhere in the FDA's suppression of off-label promotion, we believe, underscore the fallacies in the argument that commercial speech is less deserving of First Amendment protection.

Before we delve into the world of constitutional and political theory, we should emphasize that the FDA's ban on off-label promotion undoubtedly cannot survive scrutiny under well-established doctrinal standards for protection of commercial speech.<sup>155</sup> We believe, however, that the example of off-label promotion may also serve a broader purpose, by underscoring the important overlap between commercial and traditional expression, thereby casting significant doubt on the view of many scholars and jurists that commercial speech is significantly less deserving of constitutional protection than is the more traditional variety of expression.

### **B. The Underlying Postulates of the Theory of Free Expression**

There are many different, and often conflicting, theories of free expression. There are, however, certain core postulates of political theory without which any system of free expression would be incoherent. At some level, dispute may well exist as to the exact number and content of these postulates. But there are at least four such postulates that, we believe, are clearly contravened by the governmental suppression of off-label promotion. This is so, even though most or all of the expression suppressed by the FDA's prohibition is properly described as commercial speech.<sup>156</sup>

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<sup>150</sup> E. Baker, *Commercial Speech: A Problem in the Theory of Freedom*, 62 Iowa L. Rev. 1 (1976).

<sup>151</sup> Robert C. Post, *The Constitutional Status of Commercial Speech*, 48 UCLA L. Rev. 1 (2000).

<sup>152</sup> See discussion *supra* at xx.

<sup>153</sup> *Virginia Pharmacy Bd. of Pharmacy v. Virginia Citizens Consumer Council*, 425 U.S. 748 (1976).

<sup>154</sup> One of us has long been critical of opposition to commercial speech protection. See, e.g., Martin H. Redish, *Commercial Speech, First Amendment Intuitionism and the Twilight Zone of Viewpoint Discrimination*, 41 Loy. L.A. L. Rev. 67 (2008)

<sup>155</sup> See discussion *supra* at xx.

<sup>156</sup> Though at the margins the definition of "commercial speech" is subject to some confusion [see, e.g., Nike case in California Supreme Court], it is generally accepted that expression in the form of an advertisement by a profit-making seller that promotes sale of a commercial product or service falls within that definition. See, e.g., *Bolger v. Youngs Drug Prods. Corp.*, 463 U.S. 60 (1983). Whether *all* manufacturer discussion of its product is properly characterized as commercial speech is beyond the scope of this Article.

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The four core postulates of free speech theory that are indisputably contravened by the ban on off-label promotion are the following:

1. Government may not attempt to manipulate lawful citizen behavior by means of the selective suppression of truthful expression advocating lawful activity.
2. The self-motivated nature of expression does not automatically render it false or misleading, thereby removing it from the scope of constitutional protection.
3. Government has greater power to regulate conduct than it has to regulate expression.
4. Government may not hold fully protected expression hostage as a means of extortion.

When viewed in the context of non-commercial speech, presumably no educated observer could dispute the accuracy of these postulates, or their centrality to any coherent system of free expression. Indeed, if there existed a book entitled “Free Expression for Dummies,” these postulates would almost undoubtedly appear within the first few pages. Violation of any of these four postulates would correctly be deemed to undermine core notions of free speech theory. The social contract implicit in the relationship of citizen to government in a liberal democratic society would be undermined if government could disrespect the intellectual dignity of its citizens. Yet as the prohibition on off-label promotion illustrates, the exact same pathologies may occur when government violates these core postulates in the context of commercial speech, just as much as it does when other types of expression are suppressed; the same lines between government and citizen have been improperly crossed in both contexts. To demonstrate this point, we will consider each of the postulates separately.

### **1. Postulate one: Government may not attempt to manipulate lawful citizen behavior by means of the selective suppression of truthful expression advocating lawful activity**

In a democratic society, basic choices of policy are, ultimately, made by the populace—if only indirectly, through their elected representatives. To be sure, in certain instances the Constitution imposes limitations on majority choices, but even in those cases a super-majority of the populace may alter constitutional commands where it deems them to be no longer acceptable.<sup>157</sup> Government may of course prohibit certain behavior, but the inherent logic of democracy prevents it from prohibiting the populace from debating the merits of those prohibitions. Where government has left behavioral choices to the individual, the premises of liberal democracy prevent the government from attempting to influence those choices through selective suppression of one side of a debate.

The point can be made clearer by viewing it through the lens traditional political debate. If the First Amendment means anything, it prohibits government from suppressing one side of a political debate because it fears that the public might be convinced to make “the wrong” choice. For example, had the government sought to suppress opposition to the Iraq war because it feared that the public might be convinced to end that war, the suppression would undoubtedly have been found to infringe the First Amendment. In a democratic society, government may seek to influence the choices of the populace, not

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<sup>157</sup> U.S. Const. Art. V (authorizing amendment of the Constitution through super-majoritarian process).

## Off-label Promotion and Commercial Speech

by means of selective suppression, but rather by making its own contributions to that debate. Indeed, it is impossible to point to a single respected First Amendment scholar who would deem such a selective ban to be constitutional. The reason is that vesting such power in government would necessarily prove too much, for it would undermine the fundamental premise underlying the commitment to self-government in the first place—namely, the citizen’s ability to make lawful choices on the basis of free and open debate.

Given that no one could seriously challenge the constitutional pathology of paternalistically driven selective suppression in political debate, it is puzzling that so many have no difficulty authorizing such paternalism when the subject of the speech is commercial, rather than political. There is no way one may legitimately compartmentalize respect for citizens’ ability to make lawful choices on the basis of free and open debate. Either a democratic society trusts citizens to make such choices, or it does not—in which event it automatically transforms from a democratic society to an authoritarian one. The fact that a dictatorship is benevolent does not make it a democracy. Yet if citizens are deemed incapable of making lawful choices on the basis of free debate in the commercial realm, why all of a sudden do we deem them capable of making such choices in the political realm? When viewed through the lens of the relationship between government and citizen, the fact that in the commercial realm the speaker is seeking to make a profit is wholly irrelevant; the pathology in terms of democratic theory is not so much the suppression of the speaker’s right as it is the lack of respect for the citizen’s ability to make lawful choices—a lack of respect that inheres in the government’s selective suppression, regardless of the speaker’s purposes.<sup>158</sup>

Recognition of this fundamental element of the liberal democratic social contract between government and individual, then, leads to a rejection of the core distinction drawn between commercial and political speech. The FDA’s prohibition of off-label promotion, despite its concession that many off-label uses are extremely valuable and the fact that the promotion is not inherently false or misleading, serves effectively to underscore the point.

### **2. Postulate two: the self-interested nature of expression does not automatically reduce the level of constitutional protection.**

The FDA, it should be recalled, prohibits *manufacturer promotion* of off-label use; it does not, however, prohibit others from discussing such use.<sup>159</sup> The FDA, then, has necessarily made the decision that the harm it seeks to prevent derives exclusively from manufacturer promotion. The assumption implicit in that dichotomy is that the self-interested nature of the promotion somehow renders the expression both less worthy and more dangerous. As previously noted,<sup>160</sup> the logic of such a dichotomy, to the extent it were to justify categorical suppression, is inherently inconsistent with the Supreme Court’s commitment to the protection of commercial speech in the first place; under the Court’s definition, *all* commercial speech is manufacturer speech; yet under the Court’s doctrine it is extended a significant level of constitutional protection. Thus, the categorical suppression of speech for no reason other than the fact that it is made by an economically self-interested party is inconsistent with accepted Supreme Court jurisprudence.

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<sup>158</sup> It is worth noting that in the specific context of off-label promotion, the speech would be directed at trained members of the medical profession, rather than laymen. Under the logic of this premise of democratic theory, however, it is doubtful that that element should be deemed outcome determinative.

<sup>159</sup> See discussion *supra* at xx.

<sup>160</sup> See discussion *supra* at xx.

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Beyond its doctrinal difficulties, it is interesting to explore the consistency of the FDA's expressive discrimination against manufacturers from the broader perspectives of constitutional and political theory. In a democracy, it is generally understood that individuals will often act out of their own self-interest, and will employ expression as a means of convincing others to take actions to advance that self-interest. The long history and current power of political interest groups is conclusive proof of that political reality. In the world of non-commercial speech, no one would seriously suggest that the self-interested nature of expression somehow reduces the level of First Amendment protection it receives. When the unemployed urge others to support the extension of unemployment benefits, no one would ever contemplate the possibility that their expression receive reduced protection merely because they possess a self-interested economic motivation for their expression. When taxpayers urge others to oppose tax increases, once again no one would seriously think that their expression could be constitutionally banned because it will be shaped by the economic motive of the speaker.

One could easily come up with hundreds of similar examples. Yet in the case of off-label promotion the FDA appears to have made the wholly unsupported, *ex ante* assumption that manufacturer speech will be inherently distorted, and therefore suppressed, for no reason other than the self-interested economic nature of the speaker's expression.<sup>161</sup> Once again, when viewed through the lens of accepted political practice and modern democratic theory, the categorical discrimination against sellers for no reason other than the fact of the self-interested nature of their expression is rendered wholly incoherent. Few examples underscore this theoretically flawed dichotomy better than does the FDA's ban on off-label *promotion*, but not on off-label *discussion*.

### **3. Postulate three: the government has greater power to regulate conduct than it has to regulate speech.**

In the traditional world of free expression, no one would ever question that expression has considerably greater constitutional protection than most forms of conduct. For example, under certain circumstances, at least, one has the right to advocate unlawful conduct;<sup>162</sup> yet one surely has no constitutional right to engage in that unlawful conduct. While some scholars have challenged the conclusion that speech is truly "special",<sup>163</sup> it is not all that difficult to grasp the key differences. Expression deals more directly with the uniquely ability to think and reason on multi-dimensional levels—qualities that are essential in a democratic society.<sup>164</sup> Moreover, while of course expression can cause harm, as an *ex ante* matter it is reasonable to presume that the harm caused by expression will generally be less immediate and concrete than harm caused by physical conduct. For purposes of a constitutional protection in which broad judgments must be made, it is therefore reasonable to draw a categorical distinction between expression and conduct. By providing special protection to expression, this is exactly what the First Amendment does.

In the area of commercial speech, the distinction has not always been so clearly understood. For a time, the Court proceeded on the wholly misguided assumption that government's greater power to

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<sup>161</sup> It should be emphasized that, even were one to assume the correctness of the FDA's concern, under controlling commercial speech doctrine the problem could be solved by the far less invasive use of required disclaimers, rather than direct suppression. See discussion *supra* at xx.

<sup>162</sup> See, e.g., *Brandenburg v. Ohio*, xxx U.S. xxx (1969) (*per curiam*).

<sup>163</sup> Frederick Schauer, *Is Speech Special?*,

<sup>164</sup> See Martin H. Redish, *The Value of Free Speech*, xxx Univ. of Pa. L. Rev. xxx (1982).

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regulate conduct subsumed the “lesser” power to regulate expression advocating that conduct, even where the conduct is not prohibited.<sup>165</sup> This “logic,” of course, completely ignores the fact that because the First Amendment extends greater protection to expression than to conduct, it is, in reality, the regulation of the expression that is the “greater” power. Indeed, acceptance of this logic outside of the commercial speech context (and there is no logical basis for confining it in such a manner) would overturn over eighty years of Supreme Court jurisprudence in the constitutional protection of unlawful advocacy.<sup>166</sup> In his opinion announcing the judgment of the Court in the 1996 decision in *44 Liquormart v. Rhode Island*,<sup>167</sup> Justice Stevens categorically and vigorously rejected the specious logic of prior Supreme Court jurisprudence.<sup>168</sup> The Court’s vigorous protection of commercial speech since that decision<sup>169</sup> confirms that the Court as a whole has concurred in Justice Stevens’ rejection of the “greater includes the lesser” logic.

The FDA’s ban on off-label promotion runs directly counter to this core First Amendment premise, and in doing so highlights its importance. Whether the federal government in general or the FDA in particular wishes to control or even prohibit off-label uses is an issue on which the First Amendment is wholly agnostic. This is so, because such actions would regulate conduct, not expression. Yet while categorically prohibiting *promotion* of off-label use, the government has for the most part not restricted off-label use. Indeed, as we pointed out earlier,<sup>170</sup> the FDA has gone so far as to permit the use of drugs that have not been approved for any purpose at all. Instead of allowing the advocacy and restricting the conduct, the FDA has prohibited the advocacy but permitted the conduct, leaving doctors to fend for themselves in finding out about potentially life-saving off-label uses. In following this policy, the FDA has turned the First Amendment on its head, creating an Alice-in-Wonderland world in which speech receives less protection than the conduct it advocates. Such an inversion of constitutional values would surely not be permitted when traditionally protected non-commercial speech is involved; there is no basis in logic or experience to justify it in the context of commercial speech.<sup>171</sup>

#### **4. Postulate four: government may not hold fully protected expression hostage as a means of extortion.**

Recall that one of the conceivable justifications turns not at all on the constitutional unworthiness of the off-label promotion itself. It turns, rather, on the asserted need for the FDA to be able to coerce drug manufacturers into making off-label uses on label.<sup>172</sup> Doing so requires the manufacturers to prepare expensive and detailed scientific studies supporting the efficacy and safety of the off-label use, something they understandably may often not be inclined to do. By prohibiting their ability to promote off-label use, the FDA is able to pressure them into undertaking the necessary steps to make the uses on-label. In effect,

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<sup>165</sup> *Posadas de Puerto Rico Associates v. Tourism Co. of Puerto Rico*, 478 U.S. 328 (1986).

<sup>166</sup> For a description of that jurisprudence, see Martin H. Redish, *Freedom of Expression: A Critical Analysis* 173-212 (1984).

<sup>167</sup> 517 U.S. 484 (1996).

<sup>168</sup> *Id.* at xxx: “[O]n reflection, we are now persuaded that *Posadas* erroneously performed the First Amendment analysis....[T]he advertising ban [in that case] served to shield the State’s...policy from the public scrutiny that more direct, nonspeech regulations would draw.”

<sup>169</sup> See discussion *supra* at xxx.

<sup>170</sup> See discussion *supra* at xxx.

<sup>171</sup> As explained early, see discussion *supra* at xx, it appears that the rationale for suppressing promotion while simultaneously failing to regulate the activity being promoted originally was grounded largely in political rather than regulatory, considerations.

<sup>172</sup> See discussion *supra* at xx.

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the government is asserting that it is constitutionally authorized to suppress speech that it readily concedes, if only for purposes of argument, is on its four corners fully deserving of protection, in order to extort certain actions out of private entities that have absolutely no legal obligation to undertake such action.

It is hard to imagine government even attempting such outrageous actions when the speech in question is non-commercial, but if it did so there can be little doubt that its actions would be held unconstitutional. By much the same reasoning, government could presumably prohibit individuals from attending religious services unless individuals engaged in specified behavior, despite the existence of the First Amendment's Free Exercise Clause. One shudders to think what might result if government sought to achieve the same result by suspending citizens' Eighth Amendment right against cruel and unusual punishment.

Where citizen behavior on its face falls within the scope of a constitutional protection, it would be absurd to permit government to suppress that behavior in order to induce citizens to engage in behavior in which they have no legal obligation to engage. Yet that is exactly what the FDA is doing when it seeks to justify the suppression of off-label promotion on the grounds that it is seeking to induce manufacturers to make the uses on-label. The surreal aspect of such extortive behavior is underscored by the fact that the federal government has full constitutional authority to directly require the manufacturers to transform the off-label uses into on-label form, *simply by directly prohibiting the prescription of approved drugs for off-label use*.<sup>173</sup> Whether it would be simpler—or simply more expedient—for the government to achieve its goal indirectly by suppressing protected speech is irrelevant to the constitutional inquiry. The suppression of fully protected, potentially valuable expression is far too high a price to pay for governmental convenience.

### CONCLUSION

In light of the Supreme Court's vigorous protection of commercial speech rights in recent years, the FDA's continued suppression of off-label promotion is—as a constitutional matter, at least—quite puzzling. There is no basis to support the assumption that all off-label uses are harmful. To the contrary, off-label uses are generally legal; moreover, they are often extremely valuable to the preservation of public health, a fact which government officials have readily conceded. There is absolutely no basis to support the assumption that all manufacturer promotion of off-label uses is inherently false or misleading, and the FDA makes no such assumption. Indeed, it is quite conceivable that manufacturer promotion could inform doctors of life-saving or improving off-label uses of which they would not otherwise have been aware. Thus, we are dealing with a situation in which the suppressed speech truthfully advocates

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<sup>173</sup> U.S. Const. Art. I, s 8, cl. 3; cl. 18 (the commerce and necessary-and-proper clauses). While the court in *United States v. Caronia*, xxx F. Supp.2d xxx, xxx (xxD.20xx) reasoned that the federal government lacked such constitutional authority, such a conclusion preposterously ignores the last 60 years of Commerce Clause jurisprudence. See, e.g., *Gonzales v. Raich*, xxx U.S. xxx (2005) (upholding federal power to criminalize sale of drugs traveling in interstate commerce); *Katzenbach v. McClung*, 379 U.S. 294 (1964) (upholding Title II of 1964 Civil Rights Act, which prohibited discrimination in restaurants which sell food that traveled in interstate commerce). Whether the FDA itself, under the current regulatory framework, possesses such authority is wholly irrelevant to the constitutional analysis. If the federal government, as an entity, wishes to require that a prescribed drug be on-label, there is no doubt of its constitutional authority to do so. The government therefore cannot be permitted to suppress expression as an indirect means of achieving its goal, when it has available a perfectly legitimate direct means of achieving the same end.

## Off-label Promotion and Commercial Speech

lawful action which might well maximize the welfare of all involved. Yet an agency of the federal government has categorically prohibited such expression.

Under current Supreme Court commercial speech doctrine, truthful commercial advertising for a lawful product or activity is extended substantial First Amendment protection. Government must show beyond the level of mere speculation that the suppression of such speech materially advances a substantial interest, and goes no further than necessary to achieve that end. The Court has regularly invalidated regulations of commercial speech because of their failure to satisfy those requirements. Moreover, there is strong indication in modern Supreme Court doctrine that *any* suppression of truthful advertising for a lawful activity designed to protect the listener from making a lawful choice is categorically unconstitutional. The FDA's prohibition on off-label promotion unambiguously violates every one of these doctrinal directives.

When viewed on the more foundational levels of American political and constitutional theory, the ban on manufacturer promotion of off-label use becomes even more bizarre. The suppression of truthful commercial advertising promoting lawful activity does far more than contravene the First Amendment rights of the seller. Far more invidious to the foundations of the liberal democratic social contract is the government's lack of respect the ban demonstrates for the citizenry's ability to make lawful choices on the basis of truthful advocacy.

For all of these reasons, the ban on the promotion of off-label use must—and, at some point in the near future, almost certainly will—be held to violate the First Amendment. To be sure, individual situations may arise in which off-label promotion—or, indeed, *any* promotion—will properly be found to be false or misleading. In those instances, government agencies may appropriately take action to protect the public. But as we have attempted to show throughout this Article, in its ban on off-label promotion the FDA has employed a hatchet, when the First Amendment requires use of a scalpel. It is unfortunate that those vested with governmental power have not themselves recognized this fact. But rest assured that at some point, the judiciary will educate them.