Drug Manufacturers’ First Amendment Right to Advertise and Promote for Off-Label Use: Avoiding a Pyrrhic Victory

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I. OVERVIEW

Current Food and Drug Administration (FDA) regulation and enforcement policies prohibit drug and medical device manufacturers from promoting off-label uses for their approved products, except in narrowly defined circumstances. The constitutionality of those policies has long been questioned, and the Supreme Court’s recent decision in Thompson v. Western States Medical Center1 raises to new heights doubts regarding FDA’s ability to withstand First Amendment challenge in this area. Future invalidation of FDA’s current regime restricting manufacturer speech promoting off-label use seems a realistic possibility—as FDA itself recognized in calling for public comment on this question shortly after Western States was decided.2

At the same time, few would question that FDA’s current speech-restrictive off-label use policies were intended to advance regulatory interests that the agency regards as significant. These include FDA’s professed goal of protecting consumers from misleading safety and efficacy claims concerning off-label uses, as well as the agency’s overall mission to maintain the mandatory nature of its approval requirements for “new” drugs and devices. The importance of these interests ensures that, should FDA’s current speech-restrictive policies be invalidated, the agency will continue to pursue these interests, though through alternative regulatory policies. Thus, the maxim “be careful what you ask for, you just might get it” comes to mind. Before pressing a First Amendment legal argument that has an excellent chance of success, drug and device manufacturers should carefully consider the nonspeech regulatory alternatives available to FDA, the likelihood of their adoption by FDA, and whether those alternatives would be more or less desirable than the present regulatory scheme.

This article begins with explication of the First Amendment argument, not only to highlight the impact of the Western States decision, but also because understanding the specific constitutional infirmities of current FDA policy is critical to predicting how FDA might shape its future regulatory policy, if the current regulatory scheme is invalidated. As demonstrated below, FDA might respond to invalidation of its current speech-restrictive policies using one of two general approaches. First, FDA may attempt to salvage the existing regulatory policies by eliminating and/or modifying certain of their speech restrictions to avoid unconstitutional encroachment on regulated manufacturers’ First Amendment speech rights. Second, FDA might abandon its speech-restrictive approach altogether and identify nonspeech-restrictive means of advancing its important regulatory interests.

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1 122 S. Ct. 1497 (2002).
The writers believe that FDA is unlikely to respond to invalidation of its current policies by simply narrowing its speech restrictions and permitting more speech about off-label use. At least three factors militate against such an approach. First, the narrower speech restrictions permitted by the First Amendment are not likely to advance the regulatory interests of FDA, because maintaining control over new uses of regulated products is not dependent upon the actual truth or falsity of promotional speech. Second, FDA lacks the resources necessary to enforce narrower speech restrictions that require consideration of truth or falsity. Third, even a modified speech-restrictive regime would leave FDA with the intractable problem of distinguishing commercial speech from core scientific expression in its enforcement efforts.

Thus, invalidation of FDA’s current speech-restrictive policies regarding off-label use may lead to the adoption of alternative nonspeech-restrictive policies designed to further the agency’s regulatory interests. As shown below, drug manufacturers are likely to consider some of these alternative policies even less desirable than the speech-restrictive policies currently in place. Hence, regulated manufacturers should take seriously the task of identifying, and suggesting to FDA, desirable new policies designed to advance the agency’s important interests. Regulated manufacturers also should consider the most effective strategies for encouraging FDA to adopt one of these more desirable policy alternatives.

II. BACKGROUND—THE CURRENT REGULATORY FRAMEWORK

A. Off-Label Use

Once FDA has approved a regulated product, a physician may prescribe it for any use, even uses not approved by FDA (off-label use). Prescription of FDA-approved products for off-label use “is an accepted and necessary corollary of the FDA’s mission to regulate in this area without directly interfering with the practice of medicine.”3 As one court explained: “A physician may prescribe an approved drug for any medical condition, irrespective of whether FDA has determined that the drug is safe and effective with respect to that illness.”4 In short, “[o]nce a drug has been approved by the FDA for marketing for any use, the actual prescription choices regarding those drugs are left to the discretion of the physician.”5

“[U]sing an approved drug to treat a disease that is not indicated on its label, but is closely related to an indicated disease, treating unrelated, unindicated diseases, and treating the indicated disease, but varying from the indicated dosage, regimen or patient population can all be considered off-label use.”6 According to some estimates, between twenty-five and sixty percent of prescriptions are written for an off-label use.7 In some

5 Id. (emphasis added).
7 See Shane M. Ward, WLF and the Two-Click Rule: The First Amendment Inequity of the Food and Drug Administration’s Regulation of Off-Label Drug Use Information on the Internet, 56 Food & Drug L.J. 41, 45-46 (2001) (noting also that “[t]he percentages of prescriptions that are off-label are notoriously high among some patient populations: over 30% for cancer patients, 40% for AIDS patients, 80% for children, and 90% for patients with rare diseases (those affecting 200,000 people or fewer in the United States.’’); Beck & Azari, supra note 6, at 80 (citing similar statistics).
instances, off-label use actually reflects the standard of care. Indeed, as the court noted in Washington Legal Foundation v. Friedman, “[e]ven the FDA acknowledges that in some specific and narrow areas of medical practice, practitioners consider off-label use to constitute the standard of good medical care.”

B. Prohibition of Manufacturer Speech Promoting Off-Label Use

FDA restricts manufacturer speech promoting off-label use in two different ways. First, FDA may restrict speech by enforcing the federal regulations that explicitly prohibit regulated manufacturers from suggesting an off-label use in any advertisement for a prescription medical product. Second, FDA may restrict manufacturer speech about off-label use by using that speech as a basis for finding that the manufacturer either placed an unapproved, and thus “adulterated,” “new” drug or device in interstate commerce, or that the product is “misbranded.” Both bases for restricting speech are discussed below.

1. Direct Prohibition of Advertising Recommending or Suggesting Off-Label Uses for Approved Products

Advertising that recommends or suggests an off-label use for an approved drug is directly prohibited by 21 C.F.R. section 202.1(e)(4)(i)(a), which states: “An advertisement for a prescription drug . . . shall not recommend or suggest any use that is not in the labeling accepted in such approved new-drug application or supplement.” FDA interprets “advertising” to capture a significant amount of speech not typically considered advertising. According to FDA, “the legislative histories of the 1938 act and the 1962 amendments to the act support a broad construction of what constitutes ‘advertising.’” Thus, the agency interprets the term ‘advertisement’ to include information (other than labeling) that originates from the same source as the product and that is intended to supplement or explain the product. In short, other than labeling, FDA may treat any manufacturer speech explaining one of its products as an “advertisement” for the product and, thus, subject to the prohibitions in 21 C.F.R. section 202.1(e)(4)(i)(a). Thus, as interpreted by FDA, 21 C.F.R. section 202.1(e)(4)(i)(a) prohibits virtually any statement by a manufacturer “recommend[ing] or suggest[ing]” an off-label use for one of its products.

2. Indirect Prohibition of Manufacturer Speech Promoting an Off-Label Use by Using Manufacturer Speech to Determine When an Approved Drug Becomes a “New Drug” for Purposes of Enforcement Actions

a. Enforcement of “New Drug” Approval Requirements

As noted above, FDA also restricts manufacturer speech promoting off-label use through its enforcement of nonspeech-related conduct regulations. The first source of
FDA’s “indirect” speech restrictions is section 505(a) of the Federal Food, Drug, and Cosmetic Act (FDCA), which provides: “No person shall introduce or deliver for introduction into interstate commerce any new drug, unless an approval of an application filed [with the Food and Drug Administration] . . . is effective with respect to such drug.”12 This provision does not directly address advertising or promotion, but rather requires that any “new drug” placed in interstate commerce first be approved by FDA.13 The agency has adopted an enforcement policy for this provision that effectively prohibits manufacturers from providing information regarding off-label uses of their products except under certain narrowly-defined circumstances.

FDA has used this provision to prevent manufacturer promotion of off-label uses, by characterizing an approved drug, once promoted by its manufacturers for off-label use, as a “new drug” within the meaning of this provision. That is, if a manufacturer promotes an already approved drug for an off-label use, FDA has stated that, for that use, the approved drug is a “new drug”—and thus requires new FDA approval before it can be placed in interstate commerce. FDA justifies this construction as follows:

[A new drug] application must identify the particular use or uses to which the new drug will be put, and an approval of such an application for interstate distribution can become effective only with respect to such use(s). See 21 U.S.C. § 355(b), (d), (j). Thus, an approved new drug that is marketed for a “new use” [off label use] becomes an unapproved new drug with respect to that use.14

Through this reasoning, FDA concludes that a drug marketed for an off-label use is a “new drug” requiring FDA new drug approval before it can be placed in interstate commerce. FDA applies similar reasoning to medical devices marketed for “intended uses” not approved by FDA.15

By statute a “new drug” is defined as “[a]ny drug . . . not generally recognized . . . as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof . . . .”16 Thus, under the statute, an approved drug should be regulated as a “new drug” only if its “labeling” suggests uses not approved by FDA. The agency has sought to avoid this limitation by defining “labeling” to include all manufacturer statements regarding uses of the product. According to FDA, although the FDCA “defines the term ‘labeling’ to include all ‘written, printed, or graphic’ materials ‘accompanying’ a regulated product,” “this definition is not limited to materials that physically accompany a product. If the material supplements, explains, or is otherwise textually related to a product, it is deemed to accompany the

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12 21 U.S.C. § 355(a) (FDCA § 505(a)).
13 Similar provisions exist for medical devices, although approval requirements vary by device classification. See 21 U.S.C. §§ 360c, 360e (FDCA §§ 513, 515). See also 62 Fed. Reg. 64,074, 64,075 (“A sponsor who wishes to market a new medical device must either demonstrate to FDA that there is a reasonable assurance that the device is safe and effective for each of its intended uses or that it is substantially equivalent to . . . another device for which such a showing is not required.”).
15 Id. at 14,286 (FDCA “generally prohibits the manufacturer of a new drug or medical device from distributing the product in interstate commerce for any intended use that FDA has not approved as safe and effective . . . . The intended use or uses of a drug or device may also be determined from advertisements, promotional material, oral statements by the product’s manufacturer or its representatives, and any other relevant source.”).
16 21 U.S.C. § 321(p) (FDCA § 201(p)).
product for purposes of section 201(m) of the act.” FD
A therefore interprets “labeling” quite broadly.18

**b. Enforcement of Prohibition Against Misbranding**

The second source of FDA’s “indirect” speech restrictions is the prohibition against misbranding. FDA enforces this prohibition in such a way as to preclude manufacturers of regulated products from engaging in speech that promotes off-label use of those products. The relevant statute provides: “A drug or device shall be deemed to be misbranded . . . unless its labeling bears (1) adequate directions for use; and (2) such adequate warnings against use in those pathological conditions or by children where its use may be dangerous to health, or against unsafe dosage or methods or duration of administration or application, in such manner and form, as are necessary for the protection of users . . . .”19

Interpreting this provision, FDA has stated: “The courts have agreed with the agency that section 502(f)(1) of the act requires information not only on how a product is to be used (e.g., dosage and administration), but also on all the intended uses of the product.”20 As support for this proposition, FDA cites *Alberty Food Products Co. v. United States*, 185 F.2d 321 (9th Cir. 1950).21 Thus, FDA explains:

> “[A]ll drugs and devices must bear labeling with adequate directions for each intended use. If labeling for a drug or device fails to contain adequate directions for each intended use, the drug or device is deemed to be misbranded (section 502(f)(1) of the act) and subject to seizure or other enforcement actions.”

Once the leap from “use” to “all intended uses” is made, FDA can regulate manufacturers’ off-label speech, by declaring that:

> The intended use of a drug or device refers to the objective intent of the persons legally responsible for the labeling of the product. The intent is determined by such persons’ expressions or may be shown by the circumstances surrounding the distribution of the article, … [including,] for example, … labeling claims, advertising matter, or oral or written statements by such persons or their representatives.22

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17 62 Fed. Reg. at 64,075-76. Notably, the case FDA cites to support this proposition is *Kordel v. United States*, 335 U.S. 345 (1948), which predates the Supreme Court’s decision in *Virginia State Bd. of Pharmacy v. Virginia Citizens Consumer Council*, 425 U.S. 748, 772 (1976), in which the Court first recognized First Amendment protection for commercial speech.

18 See 21 C.F.R. § 202.1(k)(2) (including as regulated “labeling” “[b]rochures, booklets, mailing pieces, detailing pieces, file cards, bulletins, calendars, price lists, catalogs, house organs, letters, motion picture films, film strips, lantern slides, sound recordings, exhibits, literature, and reprints and similar pieces of printed, audio, or visual matter descriptive of a drug and references published (for example the “Physician’s Desk Reference”) for use by medical practitioners . . . containing drug information supplied by the manufacturer, packer, or distributor of the drug . . .”).

19 21 U.S.C. § 352(f) (FDCA § 502(f)). Another provision states: “A drug or device shall be deemed to be misbranded … [i]f it purports to be a drug the name of which is recognized in an official compendium, unless it is packaged and labeled as prescribed therein.” Id. § 352(g) (FDCA § 502(g)).

20 62 Fed. Reg. at 64,075 (emphasis added).

21 Id. at 64,075. The decision in *Alberty Food* predates the Supreme Court’s decision in *Virginia State Bd. of Pharmacy v. Virginia Citizens Consumer Council*, 425 U.S. 748, 772 (1976), where the Court first recognized First Amendment protection for commercial speech.

22 62 Fed. Reg. at 64,076 (emphasis added).

23 Id.
Indeed, FDA may use virtually any promotion of off-label use as a basis for finding the existence of an “intended use” for which instructions are not included in the product labeling, thus rendering the product misbranded. Thus, through broad interpretation of its statutory authority, FDA asserts authority over virtually all manufacturer speech regarding off-label uses.

C. Third-Party Speech Promoting Off-Label Use

As noted above, FDA has not sought to restrict doctors’ prescription of approved products for off-label uses. In addition, while FDA prohibits manufacturers from promoting off-label uses, FDA freely permits third parties to publish or otherwise disseminate scientific information promoting off-label uses. As the court in *Washington Legal Foundation v. Friedman* explained:

The FDA acknowledges that physicians need reliable and up-to-date information concerning off-label uses. “[M]ore generically, we certainly believe it’s very appropriate for physicians to get information about off-label uses from the many sources that they get them. And, of course, they get them from CME [Continuing Medical Education]; they get them from on-line databases; they get them through textbooks; they get them through discussions with colleagues; they get them through going to a medical center and grand rounds . . . . FDA does not desire or intend to interfere with that process . . . .”

Thus, FDA has not sought to restrict third-party dissemination of scientific information regarding off-label use. FDA has developed guidelines, however, for determining whether such third-party sources are independent of a manufacturer, or whether the third-party’s statements “promoting” an off-label use should be attributed to the manufacturer.

III. THE CONSTITUTIONAL ANALYSIS

Predicting how FDA may react to invalidation of its current speech-restrictive policies requires some understanding of the likely bases for such invalidation. If the constitutional infirmities of existing policy are slight, easily remedied, and not essential to accomplishing the agency’s purposes, FDA might respond to invalidation by simply
making slight modifications to existing speech restrictions. If, on the other hand, correcting the constitutional infirmities would be difficult, or would leave FDA with policies unlikely to advance its interests, there is a far greater chance that FDA policy will undergo more drastic revision.

A. Regulation of Speech or Regulation of Conduct?

The first step in the constitutional analysis is to determine which FDA policies are subject to First Amendment challenge. FDA may assert that its use of speech to prove that a manufacturer is engaging in prohibited conduct is not susceptible to First Amendment scrutiny. According to FDA, “the regulation of drugs and devices has an unavoidable effect on speech.”27 This “unavoidable effect” results because “oral statements and materials . . . may provide evidence of a product’s intended use.”28 FDA has argued previously that conduct regulations having an incidental effect on speech are not subject to First Amendment scrutiny.29 Specifically, FDA has asserted this argument to defend its use of manufacturer speech promoting an off-label use to prove that the manufacturer is in violation of the prohibition against drug misbranding, and/or the prohibition against placing in interstate commerce a new drug unapproved by the agency.30 FDA claims that it does not regulate manufacturer speech—which would raise First Amendment concerns—but rather, simply uses speech to characterize conduct—which it claims does not.31

The Supreme Court rejected a parallel argument in Western States, where FDA sought to justify restricting the speech of drug compounders by “argu[ing] that advertising . . . [was] ‘a fair proxy for actual or intended large-scale manufacturing,’ and that Congress’ decision to limit the FDAMA’s [Food and Drug Administration Modernization Act’s] compounding exemption to pharmacies that do not engage in promotional activity was ‘rationally calculated’ to avoid creating ‘a loophole that would allow unregulated drug manufacturing to occur under the guise of pharmacy compounding.’”32 The challenged regulations “use[d] advertising as the trigger for requiring FDA approval,”33 and, thus, the Supreme Court’s First Amendment analysis focused specifically on FDA’s use of advertising as a “trigger.”

After Western States, FDA can no longer assert that its use of speech as a proxy for conduct is exempt from First Amendment scrutiny. Its use of speech to determine when a regulated drug or device will be treated as “new” for purposes of approval requirements such as 21 U.S.C. section 355(a), or as “misbranded” for purposes of enforcing 21

28 Id. at 64,076-077.
31 To support the claim that its broad construction of statutory terms, which results in burdens on speech, does not implicate First Amendment values, FDA cites the following cases: Home Box Office, Inc. v. FCC, 567 F.2d 9 (D.C. Cir. 1977); United States v. Articles of Food ** Clover Club Potato Chips, 67 F.R.D. 419 (D. Idaho 1975); United States v. 8 Cartons Containing ‘Plantation ‘The Original’ etc. Molasses,” 103 F. Supp. 626, 628 (W.D. N.Y. 1951); United States v. Articles of Drug. 32 F.R.D. 32 (S.D. Ill. 1963); United States v. 24 Bottles ** “Sterling Vinegar and Honey,” 338 F.2d 157 (2d Cir. 1964). See 62 Fed. Reg. at 64,074, 64,077. These cases were all briefed and argued without the benefit of the Supreme Court’s opinion in Virginia State Board of Pharmacy, where the Court first recognized First Amendment protection for commercial speech. (Briefing and argument were completed in Home Box Office before the Supreme Court’s opinion in Virginia State Board of Pharmacy was handed down, though the Home Box Office opinion was handed down after Virginia State Board of Pharmacy.)
32 Western States, 122 S. Ct. at 1505.
33 Id.
U.S.C. section 352(f)—rather than some other benchmark—must survive exacting First Amendment standards. FDA's realization that its current structure may not pass muster has prompted its current re-evaluation.

B. Classifying the Speech—Commercial Speech or Scientific Expression

The next step in the constitutional analysis is to identify the type(s) of speech that are restricted by the FDA regulation and enforcement policies identified above, as the extent of First Amendment protection depends on the type of speech at issue. As the Supreme Court has explained: “[T]he Constitution accords less protection to commercial speech than to other constitutionally safeguarded forms of expression.”34 Indeed, unlike commercial speech, scientific expression is entitled to full First Amendment protection.35 As Justice Frankfurter stated, almost a half century ago:

Leveling the discourse of medical men . . . is a deadening influence . . . . The State has no power to put any sanctions of any kind on [a physician] for any views or beliefs that he has or for any advice he renders. These are his professional domains into which the State may not intrude . . . . Freedom working underground, freedom bootlegged around the law is freedom crippled.36

Because the extent of First Amendment protection depends on whether the regulated communication constitutes commercial speech or scientific expression, determining the nature of the speech restricted by FDA’s enforcement activities is critical to First Amendment analysis.

As noted above, in its enforcement of 21 C.F.R. section 202.1, FDA “interprets the term ‘advertisement’ to include information (other than labeling) that originates from the same source as the product and that is intended to supplement or explain the product.”37 This definition captures some speech that cannot be classified as commercial speech under the definition of commercial speech operative in First Amendment jurisprudence. The Supreme Court has defined “the core notion of commercial speech” as “speech which does no more than propose a commercial transaction.”38 Not even all “advertisement” constitutes “commercial” speech:

The mere fact that these pamphlets are conceded to be advertisements clearly does not compel the conclusion that their speech is commercial. Similarly, the reference to a specific product does not by itself render the pamphlets commer-

35 See, e.g., Miller v. California, 413 U.S. 15, 22-23 (1973) (“[I]n the area of freedom of speech and press the courts must always remain sensitive to any infringement on genuinely serious literary, artistic, political or scientific expression.”) (emphasis added); Universal City Studios, Inc. v. Corley, 273 F.3d 429, 446-47 (2d Cir. 2001) (“It is . . . settled . . . that the First Amendment protects scientific expression and debate just as it protects political and artistic expression”); Bd. of Trustees of the Leland Stanford Junior Univ. v. Sullivan, 773 F. Supp. 472, 474 (D.D.C. 1991) (“It is equally settled . . . though less commonly the subject of litigation, that the First Amendment protects scientific expression and debate just as it protects political and artistic expression.”). See generally James M. Beck, Constitutional Protection of Scientific and Educational Activities From Tort Liability: The First Amendment as a Defense to Personal Injury Litigation, 37 Tort & Ins. L.J. 981, 982-83 (Spring 2002).
38 Bolger, 463 U.S. at 66 (citing Virginia State Bd. of Pharmacy, 425 U.S. at 762).
cial speech. Finally, the fact that [the speaker] has an economic motivation for mailing the pamphlets would clearly be insufficient by itself to turn the materials into commercial speech. The combination of all these characteristics, however, provides strong support for the District Court’s conclusion that the informational pamphlets are properly characterized as commercial speech.39

Under this definition of commercial speech, it is likely that FDA policies restrict not only commercial speech, but also a great deal of core scientific expression regarding off-label use. The U.S. District Court for the District of Columbia held, however, that “manufacturer dissemination of enduring materials and sponsorship of CME seminars is properly classified as commercial speech”40 “because this information is supplied by the manufacturer, and because the primary purpose for supplying the information is to encourage the purchase of the featured product.”41 A similar analysis might be applied to the dissemination of the same material by third parties FDA might consider “representatives” of manufacturers.

Whether speech may be deemed commercial solely because of the economic motivations of the speaker is now an open question.42 The Supreme Court recently granted certiorari in *Nike, Inc. v. Kasky*, No. 02-575, to determine whether a corporation’s public statements in the context of a political controversy concerning its business practices43 may be regulated as “commercial speech” under the First Amendment simply because they were intended to or might influence consumers’ purchasing decisions. Resolution of this issue may impact whether current FDA policy is deemed to restrict only commercial speech, or some combination of commercial speech and core scientific expression. Similarly, as discussed below, resolution of this issue will influence whether FDA may respond to invalidation of its existing restrictions on speech regarding off-label use simply by narrowing those restrictions to satisfy constitutional requirements.

### C. Regulation of Commercial Speech

Assuming for purposes of analysis that FDA policy restricts only commercial speech and not core scientific expression, that policy is still subject to strong First Amendment challenge. Indeed, in *Western States* the policy at issue was invalidated as an impermissible commercial speech restriction. Restrictions on commercial speech are unconstitutional under the First Amendment unless the proponent of the speech restriction can satisfy its burden under the standard of constitutional scrutiny established in *Central Hudson Gas & Electric Corporation v. Public Service Commission of New York*.44 *Central Hudson* requires analysis of four elements: 1) the commercial speech “must concern lawful activity and not be misleading;” 2) the proposed speech restriction must be supported by a “substantial” governmental interest; 3) the restriction must advance

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39 Id. at 66-68 (citations and footnotes omitted).
40 See *WLF v. Friedman*, 13 F. Supp. 2d at 64-65.
41 Id. at 65.
42 As one court stated: “So, a compelling question is raised: does speech that would be fully protected as scientific and/or educational speech become transformed into commercial speech, with its reduced level of protection, by the mere fact that a commercial entity seeks to distribute it in order to increase sales of the product addressed in the speech?” *WLF v. Friedman*, 13 F. Supp. 2d at 64.
43 *Kasky* is an appeal from a 4-3 California Supreme Court decision subjecting the Nike Corporation to liability under the state consumer protection statute for its statements concerning working conditions in certain of its Asian factories. Kasky v. Nike, Inc., 27 Cal. 4th 939, 946, 45 P.3d 243, 246 (2002). [Authors’ Note: Since this article was written, the Court, *per curiam*, dismissed the writ in *Nike* as improvidently granted. 539 U.S. _____ (2003) (slip opinion).]
the asserted governmental interest in a direct and material way; and 4) the proposed speech restriction must be narrowly tailored and “not more extensive than is necessary” to serve the asserted governmental interest. FDA bears the burden of showing that the restrictions FDA imposes on manufacturer speech regarding off-label use—whether through direct speech regulation, or using speech to prove violation of a conduct regulation—survive this test.

1. To Be Entitled to Any First Amendment Protection, the Speech Must Concern Lawful Activity and Not Be Misleading

   a. Speech Concerning Lawful Activity

Under Central Hudson’s first prong, to be entitled to any First Amendment protection, the regulated speech must concern lawful activity and not be misleading. As noted above, off-label prescription and off-label use of approved drugs is entirely lawful. Thus, FDA regulation of speech suggesting or promoting off-label use cannot avoid First Amendment scrutiny in reliance on the “lawful activity” requirement of Central Hudson’s first prong. For a speech-restrictive regulation to avoid First Amendment scrutiny on this ground, the speech being prohibited must propose an unlawful commercial transaction. “The proper inquiry is . . . whether the conduct that the speech promotes violates the law.” Here it does not. Thus, FDA’s speech restrictive policies cannot avoid First Amendment scrutiny in reliance on the “lawful activity” requirement of Central Hudson’s first prong.

   b. Nonmisleading Speech

Central Hudson’s first prong also provides that, if the regulated commercial speech is false or inherently misleading, no First Amendment protection applies. Because FDA restrictions on manufacturer speech regarding off-label use are not limited to restricting false or inherently misleading speech, FDA also cannot avoid First Amendment scrutiny under the “nonmisleading” requirement of Central Hudson’s first prong. The Supreme Court has held that where communication of truthful and useful information “will be snared along with [allegedly] fraudulent or deceptive commercial speech, the State [or proponent of speech restriction] must satisfy the remainder of the Central Hudson test . . . .” FDA’s restraints on manufacturer speech regarding off-label use capture all forms of such speech, including its communication of truthful and nonmisleading information. Thus, for its speech-restrictive policies to survive constitutional scrutiny, FDA must prove that they satisfy the remainder of the Central Hudson test.
2. The Asserted Governmental Interest Must Be Substantial

The second prong of the Central Hudson test requires that the governmental interest allegedly furthered by the speech restriction must be “substantial.” In Western States, FDA offered three separate interests in support of its restriction on pharmacy advertisements of particular compounded drugs. They were: 1) “preserving the effectiveness and integrity of the FDCA’s new drug approval process and the protection of the public health it provides;” 2) “preserving the availability of compounded drugs” for patients who need them; and 3) “achieving the proper balance between those two independently compelling but competing interests.” The Supreme Court easily found that these asserted interests satisfied Central Hudson’s second prong.

The interests that FDA would offer in a constitutional challenge to its off-label use regulations would likely be quite similar to those it offered in Western States. FDA likely will assert that its use of speech as a proxy for determining when a product is treated as “new” for purposes of requiring further FDA approval, or as “misbranded”/“adulterated” for purposes of enforcement actions, is motivated by analogous interests. Specifically, FDA may argue that its current policies directed to off-label promotion are designed to advance the following interests: 1) preserving the effectiveness and integrity of FDA’s new drug approval process; 2) preserving the availability of off-label prescriptions for patients who require them; and 3) achieving the proper balance between the foregoing interests. FDA also may argue that the advertisement and labeling restrictions found in 21 C.F.R. sections 202.1(4)(i)(a) and 202.1(4)(i)(m) are motivated by an interest in preventing consumer deception or confusion regarding drug safety and efficacy, and/or the lack of FDA approval. Such interests should meet the constitutional requirement.

3. The Speech Restriction Must Directly Advance the Interest Asserted and Alleviate the Harms Alleged to a Material Degree

FDA’s off-label use regulatory scheme is unlikely to survive scrutiny under Central Hudson’s third prong. The third prong of Central Hudson requires the proponent of a speech regulation to demonstrate that the regulation will “directly advance the state interest involved,” and will “alleviate [the harms alleged] to a material degree.” A speech-restrictive regulation “may not be sustained if it provides only ineffective or remote support for the government’s purpose.” FDA may not rely on “mere speculation or conjecture” to satisfy Central Hudson’s third prong.

As noted above, FDA’s decision to use speech as the trigger for enforcement actions—i.e., for determining when a drug constitutes a “new drug” for purposes of enforcing 21 U.S.C. section 355(a), or a “misbranded” drug for purposes of enforcing 21 U.S.C. section 352(f)—is itself a speech-restrictive policy subject to First Amendment scrutiny. As also discussed above, FDA is likely to assert that this policy was adopted for purposes of preventing evasion of, or the creation of a “loophole” in, the “new drug” approval requirements.

In Western States, FDA sought to justify a similar regulatory policy on nearly identical grounds. At issue in Western States was a FDAMA provision that exempted from the “new drug” approval requirements pharmacists who refrained from advertising their

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49 Western States, 122 S. Ct. at 1498.
50 Central Hudson, 447 U.S. at 564.
51 Edenfield, 507 U.S. at 771.
52 Id. at 770 (emphasis added).
53 Id. at 770-71.
compounded drug products. Under the exemption, a pharmacist was permitted to introduce “new drugs” into interstate commerce without complying with the “new drug” approval requirements, so long as the pharmacist refrained from advertising his or her “new” compounded drugs. FDA’s policy of using speech to determine when a product is “new” or is “misbranded”/”adulterated” is functionally identical to the FDAMA compounding exemption invalidated in Western States—it directs enforcement of the new drug and device approval requirements to manufacturers who advertise/promote off-label uses for their products.

While the compounding exemption challenged in Western States was not invalidated under Central Hudson’s third prong, FDA’s off-label use enforcement policy may well be. A major factor will be the availability of factual evidence calling into question a fact Central Hudson’s third prong requires FDA to prove—that the policy effectively advances FDA’s asserted interests. As noted above, under prong three, a speech-restrictive regulation “may not be sustained if it provides only ineffective or remote support for the government’s purpose.” In Western States, with respect to prong three, the Court simply stated: “Assuming it is true that drugs cannot be marketed on a large scale without advertising, the FDAMA’s prohibition on advertising compounded drugs might indeed ‘directly advance[e]’ the Government’s interests.” Such an assumption is untenable, however, in the context of off-label use promotion. The fact that up to sixty percent of prescriptions currently are written for off-label uses undermines the argument that FDA’s present speech-restrictive enforcement policy “directly advances” FDA’s asserted interest in preventing manufacturers from avoiding the “new drug” approval requirements. The reality of physician prescription habits—the ubiquity of off-label use—undercuts arguments based on the effectiveness of FDA’s current regulatory regime.

Further, under prong three, a “challenged restriction on commercial speech ha[s] to be evaluated in the context of the entire regulatory scheme, rather than in isolation.” The Supreme Court has expressly held that where the purpose of a proposed speech restriction is undermined by exceptions to, or inconsistent requirements in, the overall regulatory regime, the regulation is incapable of satisfying the third prong of Central Hudson and cannot be sustained. For example, in Rubin v. Coors Brewing Company, the Supreme Court considered the constitutionality of a Federal Alcohol Administration Act (FAAAA) provision that prohibited beer labels from displaying the product’s alcohol content in either numerical or certain descriptive terms. The government asserted that such regulation was intended to advance its interest in preventing “strength wars” among beer brewers. The Court determined, however, that, because “brewers remain[ed] free to disclose alcohol content in advertisements” in many states, the regulation could not satisfy Central Hudson’s third requirement.

54 Id. at 770 (emphasis added).
55 Id. at 770-71.
56 FDA must introduce evidence proving the effectiveness of its speech-restrictive policies in promoting FDA’s asserted interests. See 44 Liquormart, Inc., 517 U.S. at 484 (“without any findings of fact, or indeed any evidentiary support whatsoever, we cannot agree with the assertion that the price advertising ban will significantly advance the State’s interest in promoting temperance”).
58 See, e.g., Greater New Orleans Broad. Assc., 527 U.S. at 195 (invalidating restrictions on casino advertisements because “the regulation distinguishes[d] among the indistinct, permitting a variety of speech that pose[d] the same risks the Government purport[ed] to fear”); Rubin, 514 U.S. at 488 (invalidating restriction because “[w]hile the laws governing labeling prohibit the disclosure of alcohol content . . . federal regulations apply a contrary policy to beer advertising;” (emphasis added)).
59 Rubin, 514 U.S. at 481.
60 Id. at 488.
Thus, where the surrounding regulatory scheme permits a variety of speech that poses the same risks as the speech sought to be prohibited, the prohibition cannot be sustained. Indeed, courts routinely have invalidated proposed commercial speech regulations where other aspects of the regulatory framework would prevent the proposed speech restriction from effectively advancing its asserted purpose. Because FDA permits third-party speech posing the same risks the agency allegedly seeks to prohibit through its off-label speech enforcement policies, those policies cannot survive Central Hudson’s third prong.

As explained above, the direct regulation of advertisements for prescription drugs, 21 C.F.R. section 202.1(4)(i)(a), provides an independent restriction on manufacturers’ ability to advertise their approved drug products for off-label use. This regulation also will fail under prong three, unless FDA can demonstrate that consumers—here, typically professional physicians, not lay patients—are more likely to be misled by manufacturer advertisements suggesting off-label uses for a prescription drug than they would be by third-party promotion of off-label uses for those drugs. Indeed, if the third-party speech permitted by FDA poses the same risks as the prohibited manufacturer speech, the prohibition on manufacturer speech is not capable of directly and materially advancing FDA’s interest in alleviating those risks.

Further, FDA cannot justify the prohibition on truthful promotion of off-label uses by asserting concern that physicians might misuse the information provided in making their prescription choices. The Supreme Court in Western States expressed great skepticism towards arguments that people, particularly medical professionals, should be deprived of truthful information “for their own good”:

Aside from the fact that this concern rests on the questionable assumption that doctors would prescribe unnecessary medications . . . , this concern amounts to a fear that people would make bad decisions if given truthful information about compounded drugs. We have previously rejected the notion that the Government has an interest in preventing the dissemination of truthful commercial information in order to prevent members of the public from making bad decisions with the information . . . . There is, of course, an alternative to this highly paternalistic approach. That alternative is to assume that this information is not in itself harmful, that people will perceive their own best interests if only they are well enough informed, and that the best means to that end is to open the channels of communication rather than to close them . . . . [B]ans against truthful, nonmisleading commercial speech usually rest solely on the offensive assumption that the public will respond “irrationally” to the truth. The First

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61 See, e.g., Pearson v. Edgar, 153 F.3d 397, 404 (7th Cir. 1998) (invalidating ban on real estate solicitation, the purpose of which was to protect privacy, where other kinds of solicitation which also intruded on homeowners’ privacy were permitted). Utah Licensed Beverage Assoc. v. Leavitt, 256 F.3d 1061, 1074 (10th Cir. 2001) (regulation could not directly advance asserted interest in promoting temperance due to its inconsistent treatment of different types of alcohol); Bad Frog Brewery, Inc. v. New York State Liquor Authority, 134 F.3d 87, 99 (2d Cir. 1998) (prohibition of “vulgar” displays on labels of alcoholic beverages could not directly advance interest in protecting children from such displays, in light of “the wide currency of vulgar displays throughout contemporary society”); Valley Broad. Co. v. United States, 107 F.3d 1328, 1335 (9th Cir. 1997) (“because section 1304 permits the advertising of commercial lotteries by not-for-profit organizations, governmental organizations and Indian Tribes, it is impossible for it materially to discourage public participation in commercial lotteries”); Missouri v. American Blast Fax, Inc., 196 F. Supp. 2d 920, 932, (E.D. Mo. 2002) (regulation could not materially advance asserted interest in protecting consumers from receiving unsolicited faxes because regulation prohibited only some unsolicited faxes but permitted others).
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.\textsuperscript{62}

Thus, both the direct prohibition of off-label promotion in advertisements, and FDA use of manufacturer speech to enforce conduct regulations, are likely to fail constitutional scrutiny under Central Hudson’s third prong.

4. The Speech Restriction Must Be Narrowly Tailored

a. Using Speech to Trigger Enforcement of New Drug Approval Requirements

FDA’s enforcement policy regarding off-label speech is likely to encounter similar problems with Central Hudson’s final prong, which requires the proponent of a commercial speech restriction to demonstrate \textit{additionally} that the proposed speech restriction is “‘narrowly drawn,’”\textsuperscript{63} and “‘is not more extensive than is necessary to serve [the governmental] interest’” asserted.\textsuperscript{64} To determine whether the fourth prong of Central Hudson is met, the Court must assess whether there is a reasonable fit between the means and the ends of the proposed speech restriction.\textsuperscript{65}

Under current policy mandates, FDA would characterize a drug or device as “new” if the manufacturer promoted it for an off-label use, regardless of whether the product was ultimately prescribed for any off-label use. At the same time, current FDA policy would not characterize a drug or device as “new” even if it were routinely prescribed off-label, provided the manufacturer did not promote it for off-label use. Thus, use of speech to determine when a regulated product should be subjected to approval requirements for “new” off-label uses is not reasonably related to FDA’s asserted interest in assuring that the new drug approval requirements serve their purpose.

Not only does FDA’s regulatory and enforcement policy lack the “fit” required by Central Hudson’s third prong, but it also is not narrowly tailored. In Western States, the Supreme Court reiterated:

\begin{quote}
In previous cases addressing this final prong of the Central Hudson test, we have made clear that if the Government could achieve its interests in a manner that does not restrict speech, or that restricts less speech, the Government must do so.\textsuperscript{66}
\end{quote}

Thus, if there are nonspeech-restrictive means of determining when a drug should be characterized as a “new drug” for purposes of the new drug approval requirements, those means must be used instead of FDA’s current speech-restrictive policy. The question, as in Western States, is whether such alternative means exist. Significantly, in Western States, the Supreme Court listed a number of examples of alternative, nonspeech-restrictive forms of regulation:

- FDA “could ban” pharmacies from using equipment that permitted “commercial scale manufacturing.”

\begin{footnotes}
\item\textsuperscript{62} Western States, 122 S. Ct. at 1507-08 (citations and quotation marks omitted).
\item\textsuperscript{63} Central Hudson, 447 U.S. at 565 (citation omitted).
\item\textsuperscript{64} Reilly, 533 U.S. at 554 (quoting Central Hudson, 447 U.S. at 569).
\item\textsuperscript{65} Id. at 561.
\item\textsuperscript{66} Western States, 122 S. Ct. at 1506.
\end{footnotes}
FDA “could prohibit” pharmacists from compounding drugs except “in response to prescriptions already received.”

FDA “could prohibit” the sale of compounded drugs “at wholesale to other state licensed persons or commercial entities for resale.”

FDA “could limit the amount of compounded drugs, either by volume or by numbers of prescriptions, that a given pharmacist or pharmacy sells out of state.”

FDA could “cap” sales of compounded drugs, “either by drug volume, number of prescriptions, gross revenue, or profit that a pharmacist or pharmacy may make or sell in a given period of time.”

That these nonspeech-restrictive alternatives were considered available in Western States to address FDA’s concerns regarding drug compounding strongly suggests that similar nonspeech alternatives may be available in the off-label use context. The question, which the remainder of this paper addresses, is what those nonspeech alternatives are and whether they might prove to be even more restrictive of off-label use than FDA’s current speech-based regime.

b. Direct Regulation of Prescription Drug Advertising

Central Hudson’s final prong likewise presents problems for the direct regulation of truthful advertising found at 21 C.F.R. section 202.1(4)(i)(a). As noted above, this provision prohibits virtually any manufacturer speech promoting an off-label use for a prescription medical product. Though the regulation ostensibly is intended to prevent consumer deception or confusion, it does not prohibit only false or inherently misleading speech, and is thus open to challenge as not narrowly tailored to serve the governmental interest asserted.

Further, even if it were accepted that any and all promotion of off-label use could be deemed “potentially misleading” to consumers who are medical professionals, there is still the issue of whether “narrower limitations” exist to “ensure that the information is presented in a non-misleading manner,”—such as requiring the “commercial message to ‘appear in such a form or include such additional information, warnings, and disclaimers, as are necessary to prevent its being deceptive.’” Commercial speech restrictions are not narrowly tailored where there are less restrictive means available to achieve the end sought: “[I]f the governmental interest could be served as well by a more limited restriction on commercial speech, the excessive restrictions cannot survive.” As one state supreme court has explained:

[T]he Court has held that a state may not place an absolute prohibition on certain types of potentially misleading information … if the information also may be presented in a way that is not deceptive. The Court has suggested that the remedy in the first instance is not necessarily a prohibition but preferably a requirement of disclaimers or explanation.

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67 Id.
69 Virginia State Bd. of Pharmacy, 425 U.S. at 772 n.24.
70 Central Hudson, 447 U.S. at 564. See also Rubin, 514 U.S. at 491 (“availability of these [other] options, all of which could advance the Government’s asserted interest in a manner less intrusive to respondent’s First Amendment rights, indicates that [the regulation] is more extensive than necessary” and, thus, unconstitutional); Cincinnati v. Discovery Network, Inc., 507 U.S. 410, 418 n.13 (1993) (when there are less burdensome alternatives to a restriction on commercial speech, the restriction does not have the constitutionally required reasonable fit between the ends and the means).
71 Desnick v. Dep’t of Professional Regulation, 171 Ill. 2d 510, 531 665 N.E.2d 1346, 1358 (1996) (internal citations omitted). See also Van Bremen v. Dep’t of Professional Regulation, 296 Ill. App. 3d 363, 367, 694 N.E.2d 688, 692 (2d Dist. 1998) (“potentially misleading information may not be absolutely prohibited if the information may also be presented in a way that is not deceptive”).
A clear and prominent disclaimer stating that the FDA has not approved the use being discussed, would appear sufficient to prevent consumers from being misled into believing the contrary. In short, FDA would have to demonstrate: 1) that all speech promoting off-label use is “potentially misleading” to consumers; and 2) that the addition of warnings or disclaimers could not eliminate the potential for consumer misunderstanding, in order for its prohibition of all commercial speech promoting off-label use to survive.

D. Government Regulation of Scientific Expression

It remains unclear whether FDA’s policies will be deemed to capture only “commercial” speech, or also some scientific expression. While FDA regulation and enforcement policies may well fail under even the less stringent standard governing regulations of commercial speech, the argument for their invalidity is strengthened if some scientific expression is restricted. Indeed, instead of the intermediate scrutiny applied to regulations of commercial speech, strict scrutiny applies to government regulation of core scientific expression.72

Under strict scrutiny, the government must demonstrate that its proposed speech-restriction is “necessary” to further a “compelling” state interest, and “narrowly tailored,”73 because it is the “least restrictive means” available.74 FDA regulation and enforcement policies cannot survive the more stringent strict scrutiny analysis for all of the same reasons that they cannot survive Central Hudson.

In addition, while FDA can impose an absolute prohibition on false or inherently misleading commercial speech, it cannot prohibit false scientific expression. The First Amendment does not protect only the expression of scientific opinions ultimately deemed correct. Rather, all genuine positions taken in scientific debate are entitled to the same protection under the First Amendment as literary, artistic, and political expression. “Under the First Amendment there is no such thing as a false idea.”75 “A rule requiring scientists and authors to guarantee the ‘truth’ of their hypotheses would inevitably lead to self-censorship and would stifle the very debate that leads to scientific knowledge.”76 The suppression of scientific opinions unless or until proven accurate would be inconsistent not only with the purposes of the First Amendment, but also with the scientific method itself. Thus, if FDA’s current off-label use regulation and enforcement policies are deemed to capture scientific as well as commercial expression, their chance of surviving constitutional challenge are slim.

IV. Alternative Means of Advancing FDA’s Interests

Invalidation of the current speech-restrictive enforcement policies of FDA, however, might prove to be a pyrrhic victory for regulated manufacturers. Currently, as long as a drug manufacturer refrains from promoting off-label uses of an approved product, the product actually may be sold extensively for off-label use, without the manufacturer being required to satisfy the “new drug” approval requirements. With as many as sixty percent of all current prescriptions being off-label—with much higher rates in many specialties—existing FDA regulatory policies are not particularly restrictive of off-label

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72 See supra note 35 and accompanying text.
74 Sable Comm. of Cal., Inc. v. FCC, 492 U.S. 115, 126 (1989).
use. If the current regulatory scheme is invalidated, however, FDA will have to re-evaluate its regulation of off-label use entirely. The outcome of that review could mean greater restrictions on prescription products that are sold extensively for off-label use, regardless of what their manufacturers choose to say or not say about such uses.

In general terms, FDA might respond to invalidation of its current regulatory policies in one of two ways. First, FDA might attempt to salvage the invalidated policies by eliminating or modifying certain of their speech restrictions, to bring the current regulatory regime in line with constitutional requirements. Second, FDA might stop attempting to advance its regulatory interests through speech restrictions altogether, and adopt new, nonspeech-restrictive policies designed to advance the agency’s significant regulatory interests. Apparently, FDA currently is considering both possible approaches.

In its May 16, 2002 Request for Comment on First Amendment Issues, FDA asked the following two questions, thereby demonstrating its consideration of both alternative approaches:

7. Would permitting speech by manufacturer, distributor, and marketer about off-label uses undermine the act’s requirement that new uses must be approved by the FDA? If so, how? If not, why not? What is the extent of FDA’s ability to regulate speech concerning off-label uses?

8. Do FDA’s speech-related regulations advance the public health concerns they are designed to address? Are there other alternative approaches that FDA could pursue to accomplish those objectives with fewer restrictions on speech?77

These two questions reflect the two different general approaches FDA might take in response to any future invalidation of its existing speech-restrictive policies governing off-label promotion. Question 7 asks whether, if FDA’s existing policies were modified to comport with constitutional requirements, those policies would continue to advance FDA’s interest in its maintaining control of the introduction of “new” uses of regulated products. Question 8, however, evinces FDA’s concern that it may need to move away from the current regulatory scheme’s “speech-restrictive regulations” and seek “alternative approaches” to advancing its interests.

FDA’s apparent concern that reliance upon narrower—i.e., constitutional—speech restrictions might not be a workable solution is entirely justified. Careful assessment of the narrower speech restrictions permitted by the First Amendment indicates that this type of restriction would not effectively advance FDA’s statutory interest in public health or its institutional interest in maintaining control over the introduction of new uses of regulated products. A “watered down” speech-based regulatory regime also would be extremely difficult for FDA to enforce. In addition, the ability of FDA to craft clear policies restricting speech only to the extent permitted by the First Amendment is unclear, given the different levels of constitutional protection applicable to commercial and scientific expression, and their interrelationship in the context of speech regarding off-label uses.

Thus, it is reasonable to predict that future invalidation of FDA’s current speech-restrictive policies regarding off-label use would result in FDA’s adoption of entirely new policies designed to promote the agency’s interests. A few examples of nonspeech-restrictive policy alternatives are considered below. Given that modified speech-restrictions are likely an untenable option for FDA, drug manufacturers should develop other, more desirable nonspeech-restrictive policy alternatives to suggest to the agency.

A. Modifying the Current Speech Restrictions to Comport With Constitutional Requirements

Many of those who responded to FDA’s request for comment on the two alternatives urged the agency to respond to any future invalidation of its current speech-restrictive policies by modifying those policies to permit more speech regarding off-label use.78 The three impediments to the viability of such an approach are discussed below.

1. Suggested Modification of the Current Speech-Restrictive Policies

Several respondents to FDA’s request for comment suggested that the agency should modify its current speech restrictions to prohibit only false or misleading speech promoting off-label use.79 Others suggested permitting promotion of off-label uses, but requiring that all such promotion be accompanied by appropriate warnings and/or disclaimers indicating the lack of FDA approval of the promoted drug for such uses.80 Other alternatives include: 1) permitting off-label promotion to physicians but not consumers; 2) permitting promotion through any means other than direct to consumer advertising; 3) permitting speech promoting off-label uses except on product labels; and 4) simply clarifying the boundaries between dissemination of off-label information that is considered promotional and, thus, prohibited, and dissemination that is considered nonpromotional and, thus, permitted.

Each of these proposals attempts to modify FDA’s existing speech-restrictive policies to satisfy the various constitutional requirements described in Section III. For example, Central Hudson’s first prong permits the government to prohibit all false and “inherently misleading” commercial speech without satisfying the remaining prongs of the Central Hudson test. A prohibition of false or inherently misleading commercial speech is not subjected to constitutional scrutiny because such speech is not entitled to any First Amendment protection. Likewise, where speech that is only “potentially misleading” to consumers would be restricted, Central Hudson’s fourth prong requires the government to require warnings and/or disclaimers, rather than ban the speech, unless the government can prove warnings and/or disclaimers would not be effective. Thus, the proposed narrower speech restrictions reflect a desire to keep FDA speech restrictions within constitutional bounds.

79 See, e.g., Comments of Schering-Plough, at 7 (Sept. 13, 2002) (“Schering-Plough believes that pharmaceutical manufacturers should be allowed to communicate truthful, nonmisleading information about prescription medications to all audiences.”); Comments of Johnson & Johnson, at 2 (Sept. 13, 2002) (“Companies should be allowed to present truthful and nonmisleading data about off-label uses of a product as part of legitimate scientific exchange.”); Comments of King & Spalding, at 2 (Sept. 13, 2002) (“FDA should permit manufacturers to disseminate truthful and nonmisleading information regarding off-label uses and unapproved products.”); Comments of PhRMA, at 19 (Sept. 13, 2002) (“the applicable test must be whether the materials are false or misleading”); and Comments of Medtronic, at 9 (Sept. 13, 2002) (“There is no evidence or reason to believe that prohibitions on truthful and nonmisleading speech are necessary . . . ”), available at http://www.fda.gov/ohrms/dockets/dockets/02n0209/02n0209.doc (last visited May 21, 2003).
80 See, e.g., Comments of Johnson & Johnson, at 2-3 (Sept. 13, 2002) (“companies should be able to distribute to healthcare providers and physicians reprints of articles from the medical literature that contain information considered to be off-label as long as: . . . (4) the article is accompanied by appropriate disclaimers informing the reader that the product has not been approved for the use discussed”); Comments of Schering-Plough, at 4 (Sept. 13, 2002) (“FDA might require affirmative disclosures of the lack of FDA approval of off-label messages”), available at http://www.fda.gov/ohrms/dockets/dockets/02n0209/02n0209.doc (last visited May 21, 2003).
In addition, each of the speech-based proposals identified takes seriously the need to identify policy alternatives that will advance FDA's asserted interest in protecting consumers from misleading speech promoting off-label uses. For example, prohibiting false or inherently misleading off-label promotion, or requiring the inclusion of warnings and/or disclaimers in all off-label promotion, reflects a real concern for preventing consumers from being misled by off-label promotion. So, too, does the proposal that would limit drug manufacturers to promoting off-label uses to physicians.

2. Problems With Adopting Narrower Speech Restrictions

Narrowing current speech restrictions to permit more speech regarding off-label use is an approach FDA is likely to reject for at least three reasons. First, while narrowing the current speech restrictions might cure the constitutional infirmities in the existing regulatory regime, doing so would produce a regulatory approach even less likely to advance the significant interests underlying FDA's current policies. Second, modifying FDA's current speech restrictions to comport with constitutional requirements would lead to regulatory policies FDA is ill-equipped to enforce. Finally, because the line between commercial speech and core scientific expression is difficult to draw in areas such as this, efforts to craft revised speech-restrictions that clear the constitutional hurdles may create additional headaches for FDA.

a. Inability to Advance Both Regulatory Interests

The narrower speech restrictions proposed by many commentators are reasonably calculated to advance FDA's asserted interest in protecting consumers from being misled by speech promoting off-label uses for prescription drugs. Either through the prohibition of false and inherently misleading speech promoting off-label use, and/or by requiring all off-label promotion to bear appropriate disclaimers or warnings, FDA could prevent consumer misunderstanding of off-label promotion, particularly if such promotion is limited to an audience of medical professionals. While the proposed speech restrictions likely would prevent consumer deception, if enforced effectively, they are unlikely to advance FDA's other important regulatory and institutional interest—preserving the integrity and effectiveness of FDA's “new” drug and device approval requirements.

In fact, permitting manufacturers a free hand at truthful promotion of approved products for off-label uses inevitably would undermine FDA's ability to enforce “new drug” and “new device” approval requirements. If restrictions on promotion of off-label uses of approved products were removed, manufacturers would have even less incentive than at present to go to the expense and effort of bringing such additional uses on-label through FDA approval. Furthermore, if the history of the “substantial equivalence” exception to premarket approval of devices is any guide, manufacturers can be expected to structure their regulatory strategy for yet-to-be-approved products to seek approval of only the cheapest and easiest initial labeled use, even if that use is quite narrow, knowing that they could promote broader off-label uses.

Thus, replacing FDA's existing speech-restrictive policies with narrower speech restrictions, while it might advance FDA's interest in preventing consumer deception, would leave FDA still in search of new policies designed to advance its interest in maintaining control over “new” uses of regulated products.

82 As discussed in Medtronic, Inc. v. Lohr, 518 U.S. 470, 479-80 (1996), device manufacturers seeking the easiest way to bring their products to market turned what was intended as a temporary exception into the avenue by which the overwhelming majority of devices come to market, even twenty years after the Medical Device Amendments were enacted.
b. Potential Enforcement Problems

Nor is it entirely clear that FDA could advance its interest in preventing consumer deception by adopting the narrower speech restrictions identified above. Any restriction on speech based on its “deceptive” quality requires creation of an administrative process to evaluate the actual truth or falsity of the speech. This requires an expenditure of resources and maintenance of scientific expertise that creates problems with FDA’s ability to enforce this type of regulation. While narrower speech restrictions based on falsity were the most popular with respondents to FDA’s request for comments, they largely failed to consider the important burden of proof allocation under existing First Amendment jurisprudence.

As noted in Section III, the Supreme Court has determined that the party seeking to impose a speech restriction must bear the burden of justifying it. Thus, if FDA adopted a policy of prohibiting only false and inherently misleading off-label promotion, the agency would be unable to restrict any speech under that policy without first marshaling sufficient evidence to prove the speech at issue was, in fact, false. Even though the revised policy should survive constitutional scrutiny, it would reverse completely the burden of proof allocation currently operative under existing FDA policy. Indeed, current FDA policy requires drug manufacturers to prove the truth, to FDA’s satisfaction, of the safety and efficacy claims they wish to make for their drug products, before those claims can be asserted. Under the proposed new policy, the burden would shift to FDA to prove the falsity of such claims before they could be prohibited. It is unclear whether FDA has the resources, human or monetary, to accommodate such a reversal.

c. Intractable Difficulties With Scientific Expression

The suggestion that FDA respond to any future invalidation of its current policies simply by adopting narrower speech restrictions faces one additional hurdle—the suggested policy revisions are designed to satisfy the constitutional requirements for regulations of commercial speech. As explained, supra, it is possible, if not likely, that a significant amount of manufacturer speech regarding off-label uses is properly characterized as core scientific expression, rather than commercial speech. Thus, for example, a policy prohibiting all false speech regarding off-label use would not survive constitutional scrutiny, because scientific expression cannot be regulated on the basis of its alleged falsity. Indeed, any effort to regulate scientific expression on the basis of falsity would produce “official scientific truths,” the very antithesis of First Amendment values.

Drug manufacturers’ statements regarding potential off-label uses for their products may take the form of commercial speech or scientific expression, or some combination of the two. Indeed, some might argue that virtually any statement promoting an off-label use includes some core scientific expression—i.e., the expression of an opinion on scientific matters, such as the drug’s safety and efficacy for unapproved uses. Where commercial speech and fully protected speech combine, the resulting combination must be judged by the stricter standards of fully protected speech:

[W]e do not believe that . . . speech retains its commercial character when it is inextricably intertwined with otherwise fully protected speech . . . . [W]here, as here, the component parts of a single speech are inextricably intertwined, we cannot parcel out the speech, applying one test to one phrase and another test to another phrase. Such an endeavor would be both artificial and impractical. Therefore, we apply our test for fully protected expression.83

The differing levels of First Amendment protection for core scientific speech and commercial speech, coupled with their frequent combination in speech regarding off-label uses, would make it difficult for FDA to draw clear lines regarding permissible and impermissible speech in this area, even on the basis of truth or falsity.

In sum, the narrower speech restrictions proposed to replace FDA’s current policies suffer at least three potential shortcomings. First, they advance, at most, only one of the important regulatory goals of FDA. Second, it is unclear that FDA possesses the administrative capabilities that would allow it to rely on the suggested narrower speech restrictions to advance any of its interests. Finally, it is unlikely that even the narrower speech restrictions suggested could be maintained, given the frequent confluence of commercial speech and core scientific expression, in this area. Accordingly, FDA may be expected to look for nonspeech-restrictive alternatives to advance its important regulatory interests.

B. Potential Nonspeech-Restrictive Alternatives

The most likely result of a successful challenge to FDA’s current regulatory regime on First Amendment grounds is to force FDA to establish new approval requirements that apply to off-label use itself, rather than to manufacturer speech about such uses. These nonspeech restrictions could well prove more onerous to many manufacturers than the extent limitations on their speech. There appear to be three general approaches FDA could adopt to further its interests in retaining control over uses of approved products and having those uses brought on-label. They are: 1) use a different (nonspeech) benchmark to determine when new drug approval is required for an off-label use; 2) limit physicians’ ability to write off-label prescriptions; and 3) increase the benefits of bringing additional uses on-label, while decreasing the burdens associated with doing so. Possible approaches in each area are discussed infra.

1. Identifying a Different Benchmark to Determine When New Drug Approval Is Required

If the courts invalidate FDA’s use of speech (off-label promotion by the manufacturer) as a “proxy” or “benchmark” for determining when a new approval is required for an off-label use, FDA may respond simply by identifying new nonspeech proxies or benchmarks along the lines suggested in Western States. Nothing in the First Amendment precludes FDA from requiring manufacturers to obtain information concerning the prevalence of off-label use of their products. FDA could require manufacturers to seek FDA approval of off-label uses if such uses reach specified statistical thresholds—either by pure volume of off-label prescriptions or by off-label use as a percentage of total product sales.\(^\text{84}\) Thus, instead of requiring submission of the off-label use for agency approval only when/if the product manufacturer promotes that use, FDA would require new drug approval whenever the statistics that it required manufacturers to keep showed that prescriptions for a particular off-label use had risen to a certain level.

Such an approach would force regulated manufacturers to obtain FDA approval for widespread off-label uses, to bring those uses on-label. This approach would effectively—arguably far more effectively than the current approach—promote FDA’s inter-

\(^{84}\) The authors have not attempted to predict the extent to which FDA currently possesses, or could obtain, statutory authority to adopt the alternative approaches discussed herein. Where obvious obstacles to the adoption of a particular alternative exist, however, they are noted.
est in ensuring that drug manufacturers comply with approval requirements for “new” uses, while neither interfering with beneficial but insignificant off-label use nor imposing speech-based requirements subject to First Amendment challenge. From the perspective of regulated manufacturers, the adoption of either of these policies by FDA would, as a practical matter, be much more onerous and less desirable than the current speech-restrictive regime, which allows widespread off-label use as long as the use is not promoted. Elimination of speech-based restrictions on promotion of off-label use could impact most seriously on companies with no intent to promote off-label use, by obligating them to act, not in response to their own conduct, but in response to physician prescribing practices that they cannot control.

2. Regulation of Physicians’ Ability to Write Prescriptions Off-Label

Alternatively, FDA may seek to advance its interest in ensuring manufacturer compliance with approval requirements by directly restricting the extent to which physicians can write off-label prescriptions. Such a policy would encourage drug manufacturers to obtain new drug approval for additional uses of their products essentially by harassing their customers. This route is considerably more problematic for FDA. First, the agency is statutorily restricted from regulating the practice of medicine. Second restricting the ability of physicians to prescribe for off-label uses would interfere with optimal healthcare decisions. As one court recognized:

New uses for drugs are often discovered after FDA approves the package inserts that explain a drug’s approved uses. Congress would have created havoc in the practice of medicine had it required physicians to follow the expensive and time-consuming procedure of obtaining FDA approval before putting drugs to new uses. Thus, Congress exempted the practice of medicine from the [FDCA] so as not to limit a physician’s ability to treat his patients.

In its comments to FDA, the American Medical Association (AMA) expressed its concern that FDA would consider the regulation of physicians a viable approach to advancing its interest in the new drug approval process, should the current regulatory regime be invalidated. The AMA stated:

The AMA is concerned, however, when the FDA attempts to extend its regulatory authority to include the practices of physicians and other health professionals. Since 1990, the FDA has attempted to exert its regulatory authority on . . . (4) which physicians can or cannot prescribe certain drug products under restricted distribution programs. The AMA does not believe the FDCA gives the FDA the authority to regulate medical practice and urges the Agency to avoid crossing this regulatory boundary.

If FDA had or, as a political matter, could obtain such authority, the agency might: 1) permit drugs to be prescribed off-label only for the treatment of certain diseases or

85 See 21 U.S.C. § 396 (FDCA § 906) (“Nothing in this Act shall be construed to limit or interfere with the authority of a health care practitioner to prescribe or administer any legally marketed device to a patient for any condition or disease within a legitimate healthcare practitioner-patient relationship”).


classes of patients; 2) impose onerous reporting requirements on physicians writing off-label prescriptions; 3) limit the amount of off-label prescriptions doctors can write; or 4) regulate which physicians can and which cannot prescribe certain drugs for off-label uses under restricted distribution programs.

3. Changing the Cost/Benefit Ratio for New Drug Approval

A third approach FDA might pursue, to advance its interest in its approval process for “new” uses, would be to increase the incentives for manufacturers to seek approval for off-label uses of their existing products. If FDA cannot condition the right to “promote” or speak about new uses for a drug on its approval, it could create new benefits that accrue upon receipt of new drug approval. One approach would be for FDA to create a preemption defense for drug manufacturers, and/or expand the existing preemption defense for device manufacturers in the context of civil lawsuits in which a prescription medical product was prescribed for an approved use. A regime in which prior FDA approval for the prescribed use constituted an effective or absolute defense to personal injury liability arising from the approved use, would be a strong incentive for manufacturers to seek FDA approval for as many potential uses of their drugs as possible.88 Even short of creating an absolute defense to liability, any strengthening of the preemption defense, or other available defenses, would increase drug manufacturers’ incentive to get additional uses of their drugs on-label.

The provision of new “incentives” for drug manufacturers to comply with the new drug approval procedures might be particularly effective in promoting FDA’s interest in enforcing the new drug approval requirements, if those incentives were coupled with a reduction in the burdens of the approval process. In short, FDA could more effectively advance its asserted interest in having new uses approved, by “decreasing the cost and delay involved in processing supplemental applications and by increasing the benefits to manufacturers arising from the approval of such applications.”89

To summarize, FDA’s current approach to enforcing the new drug approval requirements permits a great deal of off-label use and, thus, may be deemed ineffectual. By challenging the current regulatory regime, drug companies unwittingly may be asking for a system that more effectively limits off-label use, or more often requires new drug approval for existing drugs that routinely are being prescribed off-label. If the existing FDA regulatory regime were invalidated, it is impossible to predict the nature of the policies FDA would adopt to take its place—the stick, the carrot, or some combination of both. It does seem likely, however, that FDA would adopt some policy aimed at ensuring manufacturer compliance with the “new drug” approval requirements, and some of the options available to FDA are not appealing from the perspective of drug manufacturers.

V. Conclusion

The Supreme Court’s recent decision in Thompson v. Western States Medical Center suggests that FDA’s current prohibition on manufacturer promotion of off-label use for its approved drug products may be unconstitutional. Specifically, the Court’s decision

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88 Such an approach could have the unintended side effect of encouraging lawyers representing personal injury claimants to intervene in FDA approval proceedings.

89 Comments of Pfizer Inc., at 163 (Sept. 13, 2002), available at http://www.fda.gov/ohrms/dockets/dockets/02n0209/02n0209.doc (last visited May 21, 2003); see id. at 163-64 (suggesting specific methods of increasing the benefit to drug manufacturers of obtaining supplemental approvals).
is useful in challenging FDA’s current off-label speech restrictions under prong four of the *Central Hudson* test. It also should be useful in responding to FDA’s argument that its use of speech as the trigger for enforcing new drug approval requirements does not implicate drug manufacturers’ First Amendment rights.

The Supreme Court’s discussion in *Western States* of the alternative means FDA might adopt to advance its interests in enforcing the new drug approval requirements suggests, however, that drug manufacturers should think carefully before challenging FDA’s rather ineffectual current regulatory approach.