

**FIRST AMENDMENT IMPLICATIONS OF THE FDA’S
PROHIBITION AGAINST PROMOTION OF OFF-LABEL USE**

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THE CURRENT REGULATORY FRAMEWORK

The FDA has authority over drugs and medical devices under the Federal Food, Drug & Cosmetic Act, and the 1976 Medical Device Amendments, 21 U.S.C. §§301 *et seq.* (collectively “FDCA”). The FDCA requires new drugs or Class III medical devices to be proven safe and effective for each marketed use. *See* 21 U.S.C. §§321, 355, 360c. The FDA approves such products under a “substantial evidence” standard. *Id.* §355(d). It is illegal to sell drugs or medical devices that are “adulterated” or “misbranded.” 21 U.S.C. §331. *See also* 21 U.S.C. §351 (defining “adulteration”); 21 U.S.C. §352 (defining “misbranding”).

FDA approval involves labeling, which includes the product’s risks and benefits, as well as adequate directions for use. *See, e.g., id.* §352. “Labeling” encompasses all written, printed or graphic material accompanying the drug or device. *Id.* §321(k), (m). While “package inserts” accompanying products are the most well-known labeling, the term broadly reaches nearly every form of promotional activity, including advertising. *See, e.g.,* 21 C.F.R. §202.1.

The FDA approves products only for specifically submitted “indications” or “intended uses.” Manufacturers may not promote other “intended uses.” 21 U.S.C. §§351-52. Advertising recommending or suggesting off-label uses – those not approved by the FDA – is banned. 21 C.F.R. §202.1(e)(4)(i)(a) (advertising “shall not recommend or suggest any use that is not in the labeling”); 59 Fed. Reg. 59821 (Nov. 18, 1994) (“listing of unapproved uses in the . . . advertising . . . results in an adulterated medical device”). Any manufacturer statement, true or not – *and even mere knowledge of use* – can create a new “intended use,” and thus a misbranded or adulterated product:

[I]ntent may, for example, be shown by labeling claims, advertising matter, or oral or written statements.... The intended uses of an article may change after it has been introduced.... [I]f a manufacturer knows, or has knowledge of facts that would give him notice that a device...is to be used for conditions, purposes, or uses other than the ones for which he offers it, he is required to provide adequate labeling ...for such other uses.

21 C.F.R. §201.128 (meaning of intended uses); *accord id.* §801.4 (same definition for prescription medical devices).¹ The FDA’s “intended use” regulations have not changed substantively since 1952, long before First Amendment protection extended to commercial speech. *See* 17 Fed. Reg. 6818, 6820 (FDA July 25, 1952) (text of then 21 C.F.R. §1.106(o)).

With respect to off-label use, the FDA’s regulations allow manufacturers to respond to a physician’s unsolicited request for information about an off-label use, however, manufacturers may not actively distribute such information. 21 C.F.R. §99.1(b).

OFF-LABEL USE

In contrast, so-called “off-label use” – the prescription of an FDA-approved product beyond what is stated in the label – including different applications, different dosages, different patient populations – is both perfectly legal and widespread. “[O]ff-label’ usage...is an accepted and necessary corollary of the FDA’s mission to regulate in this area without directly interfering with the practice of medicine.” *Buckman Co. v. Plaintiffs’ Legal Committee*, 531 U.S. 341, 350 (2001).² In 1997, Congress wrote off-label use into the FDCA. *See* 21 U.S.C. §396 (the FDA cannot “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”).

In various ways, the government underwrites off-label use. Medicare pays for many off-label uses, 42 U.S.C. §1396r-8(k)(6) (criteria for off-label use as a “medically accepted indication”), and sometimes mandates payment. *Id.* at §1395x(t)(2)(B)(ii) (cancer treatment). Manufacturers have even been sued for *not* disclosing information about off-label uses. *See New York v. GlaxoSmithKline, PLC*, Consent Order, 2004 WL 1932763 ¶¶3, 7 (S.D.N.Y. Aug. 26, 2004) (requiring manufacturer to disclose studies of off-label uses).

Off-label use is considered essential to good medical practice because the medical community’s knowledge about efficacy of drugs and devices inevitably outpaces the painstaking FDA approval process for label changes. In many circumstances off-label use is standard-of-care medicine. *E.g.*, Dov Fox, *Safety, Efficacy, & Authenticity: The Gap Between Ethics & Law In FDA Decisionmaking*, 2005 Mich. St. L. Rev 1135, 1165-66 (2005) (discussing examples). “Even 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.” *WLF v. Friedman*, 13 F. Supp.2d 51, 56 (D.D.C. 1998).

FDA does, however, recognize the important public policy reasons for allowing manufacturers to disseminate truthful and non-misleading [medical and scientific information] on unapproved uses of approved drugs and...medical devices to

¹*See* 65 Fed. Reg. 14286 (FDA Mar. 16, 2000) (the FDA “generally prohibits the manufacturer...from distributing a product...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, or oral statements by the product’s manufacturer or its representatives, and any other relevant source”).

²*Citing* James M. Beck & Elizabeth Azari, *FDA, Off-Label Use, & Informed Consent: Debunking Myths & Misconceptions*, 53 Food & Drug L.J. 71, 76-77 (1998).

healthcare professionals and healthcare entities. Once a drug or medical device has been approved or cleared by FDA, generally healthcare professionals may lawfully use or prescribe that product for uses or treatment regimens that are not included in the product's approved labeling. . . . These off-label uses or treatment regimens may be important and may even constitute a medically recognized standard of care. Accordingly, the public health may be advanced by healthcare professionals' receipt of [medical and scientific information] on unapproved or new uses of approved or cleared medical products that are truthful and not misleading.

Draft Guidance, "Good Reprint Practices for the Distribution of Medical Journal Articles and Medical or Scientific Reference Publications on Unapproved New Uses of Approved Drugs and Approved or Cleared Medical Devices," at 3-4 (FDA Feb. 2008).³

For physicians properly to use drugs and devices off-label, involves their accessing product-specific information about when such use is medically appropriate. Information concerning off-label uses is thus an extremely valuable tool to health care practitioners and leads to better patient care. *Friedman*, 13 F. Supp.2d at 56 ("As off-label uses are presently an accepted aspect of a physician's prescribing regimen, the open dissemination of scientific and medical information regarding these treatments is of great import").

Thus, on the one hand off-label use as an activity is generally not subject to legal (as opposed to medical professional) restrictions, while on the other hand FDA-regulated manufacturers are forbidden to make statements, even truthful statements, that would be considered "promotional" by the FDA.

THE GENERAL CONSTITUTIONAL FRAMEWORK

Commercial speech – "speech which does no more than propose a commercial transaction," – did not historically benefit from any First Amendment protection. *See Valentine v. Chrestensen*, 316 U.S. 52, 54 (1942). That changed in 1976, when *Virginia State Board of Pharmacy v. Virginia Citizens Consumer Council*, 425 U.S. 748, 760-61 (1976) ("*Virginia State Board*"), drew on society's "strong interest in the free flow of commercial information," to confer upon it protection upon commercial speech:

What is at issue is whether a State may completely suppress the dissemination of concededly truthful information about entirely lawful activity, fearful of that information's effect upon its disseminators and its recipients. Reserving other questions, we conclude that the answer to this one is in the negative.

Id. at 773 (footnote omitted). Commercial speech does not, however, enjoy "full" First Amendment protected status. Such speech remains subject to a number of caveats:

- Commercial speech, like other speech, may be subject to reasonable time, place and manner restrictions. *Id.* at 771.

³Available at <http://www.fda.gov/OHRMS/DOCKETS/98fr/FDA-2008-D-0053-gdl.pdf> (last visited May 6, 2008).

- False, misleading, or deceptive commercial speech may be prohibited. *Id.* at 771-72.
- Commercial speech pertaining to transactions that are themselves illegal may also be “completely suppressed.” *Id.* at 772-73.

Constitutional protection of commercial speech is thus “qualified but nonetheless substantial protection.” *Bolger v. Youngs Drug Products Corp.*, 463 U.S. 60, 68 (1983). Commercial speech receives less protection in order to “protect consumers from misleading, deceptive or aggressive sales practices.” *44 Liquormart, Inc. v. Rhode Island*, 517 U.S. 484, 501 (1996). “[W]here a State entirely prohibits the dissemination of truthful, nonmisleading commercial messages for reasons unrelated to the preservation of a fair bargaining process, there is far less reason to depart from the rigorous review that the First Amendment generally demands.” *Id.* The First Amendment “presum[es] that the speaker and the audience, not the government, should be left to assess the value of accurate and non-misleading information about lawful conduct.” *Greater New Orleans Broadcasting Ass’n v. United States*, 527 U.S. 173, 195 (1999) (“*Greater New Orleans*”).

Restrictions on commercial speech, are analyzed under the framework established in *Central Hudson Gas & Electric Corp. v. Public Service Comm’n*, 447 U.S. 557 (1980).⁴ Under *Central Hudson*, to invalidate a governmental prohibition under the First Amendment protection, commercial speech must first meet four criteria: (1) it must be about lawful activity and not be misleading; (2) the government can only restrict commercial speech to promote a “substantial” interest; (3) the restriction must directly advance the interest the government asserts; and (4) the restriction cannot be more extensive than necessary to serve that interest. *Id.* The burden of proving the *Central Hudson* criteria is on the government.

It is well established that the party seeking to uphold a restriction on commercial speech carries the burden of justifying it. 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.

Edenfield v. Fane, 507 U.S. 761, 770-71 (1993) (citations and quotation marks omitted).

APPLICATION OF FIRST AMENDMENT PRINCIPLES TO OFF-LABEL PROMOTION

Assuming that the particular speech in question is inherently truthful and non-misleading, a strong argument can be made that the FDA’s absolute prohibitions upon promotion of off-label use, without regard to truth or falsity, cannot survive First Amendment scrutiny under the *Central Hudson* test.

⁴Several justices of the Supreme Court have expressed reservations about *Central Hudson*, but it remains the test until the Court decides otherwise. *Thompson v. Western States Medical Center*, 535 U.S. 357, 367-68 (2002) (“*Western States*”).

1. Truthful Promotion Of Off-Label Use Concerns Lawful Activity And Is Not Inherently Misleading.

The first prong of the *Central Hudson* test “rest[s] on the assumption that the law allows the activity that the speaker seeks to promote.” *United States v. Caputo*, 517 F.3d 935, 940 (7th Cir. 2008). As long as an FDA-regulated product has a valid agency-approved intended use, then commercial speech about off-label use concerns lawful activity, since off-label use is within the professional discretion of physicians. *Friedman*, 13 F. Supp.2d at 66 (“[i]t is obvious that the off-label prescription of previously approved drugs by physicians is presently lawful activity”).⁵.

Friedman rejected an FDA argument that, because the speech violated FDA regulations, it *ipso facto* concerned unlawful activity. *Id.* at 66. Considering this argument “tautological,” the court held that speech did not become unlawful just because the government banned it.

[T]he tautological nature of this argument exposes its shortcomings. The proper inquiry is not whether the speech violates a law or a regulation, but rather whether the conduct that the speech promotes violates the law. . . . Were the FDA's characterization of what constitutes “lawful activity” accurate, First Amendment protections for commercial speech could be all but eviscerated by the government: First Amendment challenges to speech restrictions would be defeated by noting that Congress had made the speech illegal, and therefore unlawful activity is at issue. . . . [W]hen the Supreme Court declares that the First Amendment does not protect illegal activity, it is referring to the conduct that the speech is promoting (*e.g.*, prostitution, counterfeiting, narcotic use, and the like), and not the speech subject to the restriction. Therefore, only at such time as off-label prescriptions are proscribed by law could the FDA legitimately claim that speech at issue addresses “illegal activities.”

Id.; accord *WLF v. Henney*, 56 F. Supp.2d 81, 85 (D.D.C. 1999) (reaffirming holding), *vacated in part on other grounds*, 202 F.3d 331 (D.C. Cir. 2000) (mootness). Thus where off-label use of a product is itself lawful, discussion of such off-label use is not something that promotes unlawful activity in violation of the first prong of *Central Hudson*.

Nor is truthful speech about off-label use inherently misleading. “[S]peech that is merely ‘potentially misleading’ does not render it able to be proscribed under the commercial speech test without further analysis.” *Friedman*, 13 F. Supp.2d at 66. Rather, the *Central Hudson* test requires such speech to be inherently misleading, *i.e.*, “more likely to deceive the public than to inform it.” 447 U.S. at 563.

Much “promotion” of off-label use comes in the form of distributing scientific articles. Such articles cannot become inherently misleading just because a manufacturer distributed them. *Friedman*, 13 F. Supp.2d at 67 (“Obviously, the exact same journal article or textbook reprint cannot be inherently conducive to deception and coercion when it is sent unsolicited, yet of

⁵*Cf. Caputo*, 517 F.3d at 940 (recognizing principle; holding that product in question had no valid FDA-approved use at all because it could not be considered a “modification” of previously approved product).

significant clinical value when mailed pursuant to a request.”). Nor do scientific articles become “inherently misleading” solely because FDA did not evaluate them. *Id.*⁶

Finally, the FDA’s intended use prohibitions reach far beyond inherently misleading speech. Anything – however truthful – promoting off-label use, or even showing manufacturer knowledge of it, allows the FDA to find a changed “intended” use, and thus illegal conduct. 21 C.F.R. §§201.128, 801.4. Where communication of truthful information “will be snared along with fraudulent or deceptive commercial speech,” the restriction must pass all of the *Central Hudson* test. *Edenfield*, 507 U.S. at 768-69. As the FDA’s off-label speech restrictions facially capture non-misleading information, the Agency will not be able to avoid the rest of the *Central Hudson* test.

2. Substantial Governmental Interests Are Implicated By Promotion Of Off-Label Use.

The second prong of the *Central Hudson* test requires that the governmental interest allegedly furthered by the speech restriction be “substantial.” *Central Hudson*, 447 U.S. at 564. The interest that the government typically advances for prohibiting off-label promotion regardless of truth is that the prohibition encourages manufacturers to seek FDA approval of additional indications for regulated products. *See, e.g., Thompson v. Western States Medical Center*, 535 U.S. 357, 368-69 (2002) (hereafter “*Western States*”); *Friedman*, 13 F. Supp.2d at 69. This interest has been recognized as satisfying *Central Hudson*’s second prong. *Western States, supra* (“[p]reserving the effectiveness and integrity of the FDCA’s new drug approval process is clearly an important government interest, and the government has every reason to want as many drugs as possible to be subject to that approval process”); *Friedman, supra*.

One purported governmental interest that cannot satisfy *Central Hudson* requirements is any version of the “paternalistic” notion that doctors and patients need to be “protected” against truthful knowledge about off-label use so they will not make mistakes. *Friedman*, 13 F. Supp.2d at 69. “[T]his concern amounts to a fear that people would make bad decisions if given truthful information about [the] drugs. We have previously rejected the notion that [the FDA] 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.” *Western States*, 535 U.S. at 374. Suppression of truthful speech for the “good of the recipient” is even “more unsupportable than usual” where the recipient is a highly trained physician. *Friedman*, 13 F. Supp.2d at 70; *see Western States*, 535 at 374 (finding “questionable” the “assumption that doctors would prescribe unnecessary medications”).

“[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 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.”

⁶As discussed, *infra*, in the final section of this paper, scientifically-related off-label promotion may be entitled to full First Amendment protection.

44 *Liquormart*, 517 U.S. at 503; accord *Virginia State Board*, 425 U.S. at 772 (1976).

Even a substantial governmental interest, however, cannot establish constitutionality where it is inconsistently pursued and thus riddled with exceptions. The First Amendment does not permit suppression of truthful commercial speech in this fashion. *E.g.*, *Greater New Orleans*, 527 U.S. at 187-89; *Rubin v. Coors Brewing Co.*, 514 U.S. 476, 488-89 (1995). Manufacturers can (and sometimes must) discuss off-label uses in certain circumstances and to various audiences. While manufacturers are silenced, everyone else: physicians, patients, even federal and state governments, can discuss off-label uses without restriction. This makes relatively little sense because manufacturers – by virtue of their administratively-imposed obligation to monitor adverse events and the medical literature – can be expected to have the broadest and most up to date information about their products.

3. Banning Truthful Promotion Of Off-Label Uses Is A Problematic Way Of Advancing The Government’s Asserted Interest And Has Not Materially Alleviated The Asserted Problems With Off-Label Use.

The FDA’s restrictions on truthful speech about off-label is questionable under the third *Central Hudson* prong because they do not “directly advance the state interests involved,” nor have they “alleviate[d the harms alleged] to a material degree.” *Central Hudson*, 447 U.S. at 564. A claimed governmental interest cannot support speech-restrictive regulation where other interests directly contradict it, or when it is so inconsistently pursued as to “provide[] only ineffective or remote support for the government’s purpose.” *Id.*

In *Greater New Orleans*, a prohibition against truthful advertising concerning certain casinos and other gambling fell under this *Central Hudson* prong because, at the same time, other gambling advertising (including Indian casinos and state lotteries) were permitted. 527 U.S. at 177-79. Although the governmental interest was substantial, the “regulatory regimen [wa]s so pierced by exceptions and inconsistencies that the Government cannot hope to exonerate it.” *Id.* at 190. The ban reached only some truthful information from some sources “despite the fact that [the same] messages. . .[were] being conveyed over the airwaves by other speakers.” *Id.* at 191. As Congress allowed some speakers to speak while suppressing other, equally truthful, commercial speech on the same subject, a court “cannot ignore Congress’ unwillingness to adopt a single national policy,” and its “simultaneous encouragement of [other forms of] gambling.” *Id.* at 187, 189.

[T]he regulation distinguishes among the indistinct, permitting a variety of speech that poses the same risks the Government purports to fear, while banning messages unlikely to cause any harm at all.

Id. at 195.

Similarly, in *Rubin*, a statute prohibited advertisement of the alcoholic content of beer, while inconsistently mandating that labels for wine and distilled spirits contain this same information. 514 U.S. at 480-81. The “irrationality of this unique and puzzling regulatory framework” – simultaneously banning and requiring the same truthful commercial speech depending upon the speaker – “ensure[d] that the labeling ban will fail to achieve [its] end.” *Id.* at 489. The ban was “directly undermine[d]” by exceptions for similar products that “counteracted any effect the labeling ban had exerted.” *Id.* at 489-90. *See Pearson v. Edgar*,

153 F.3d 397, 404 (7th Cir. 1998) (invalidating ban on real estate solicitation intended to protect homeowner privacy when other solicitations that intruded on privacy were permitted).⁷

Restrictions on commercial speech failed First Amendment scrutiny in *Greater New Orleans* and *Rubin* where inconsistent and conflicting governmental policies permitted or required similar speech by other speakers. The FDA's regulations banning truthful promotion of off-label use present many of the same drawbacks noted in *Greater New Orleans* and *Rubin*. They are inconsistent with other governmental regulations that encourage, and sometimes mandate, off-label speech. In addition, the FDA's ban silences only manufacturers – while allowing other speakers to make identical statements with impunity.

Viewing the “challenged restriction on commercial speech...in the context of the entire regulatory scheme, rather than in isolation,” *Greater New Orleans*, 527 U.S. at 192, the FDA's prohibitions – shot through with exceptions, inconsistencies, and contrary mandates – cannot possibly advance the interest they purport to serve, and in fact have not.

If the FDA's intent is to deter off-label use, its speech prohibitions have failed. Source after source demonstrates high levels of off-label use in many fields. *E.g.*, David C. Radley, *et al.*, *Off-Label Prescribing Among Office-Based Physicians*, 166 *Arch. Internal Med.* 1021, 1023 (2006) (over 20% of all prescriptions off-label; 46% of cardio-vascular prescriptions off-label); Shane M. Ward, *WLF & the Two-Click Rule: The First Amendment Inequity of the Food & Drug Administration's Regulation of Off-Label Drug Use Information on the Internet*, 56 *Food & Drug L.J.* 41, 45-46 (2001) (off-label use over 30% for cancer, 40% for AIDS, 80% for children, and 90% for patients with rare diseases); Beck & Azari, *Debunking Myths & Misconceptions*, 53 *Food & Drug L.J.* at 80 (off-label use 25-60% generally; more in many specialties); United States, General Accounting Office, *Off-Label Drugs: Reimbursement Policies Constrain Physicians in Their Choice of Cancer Therapies*, at 13-14 (1991) (65% of cancer treatment off-label). The extent of off-label therapies demonstrates the futility of uniquely precluding manufacturers – often the best source of information – from discussing off-label use.

The inconsistencies in and exceptions to the FDA's off-label use promotion ban equal those in *Greater New Orleans* and *Rubin*. The identity of the speaker and the identity of the audience determine who has a right to speak about off-label use. The speaker's identity matters:

⁷See also *Pitt News v. Pappert*, 379 F.3d 96, 107 (3d Cir. 2004) (ban on alcohol ads in state-supported university newspapers did not materially reduce exposure of students to alcohol advertising); *Utah Licensed Beverage Ass'n v. Leavitt*, 256 F.3d 1061, 1074 (10th Cir. 2001) (interest in promoting temperance fatally undercut by 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” labels could not directly advance interest in protecting children, given “the wide currency of vulgar displays”); *Valley Broadcasting Co. v. United States*, 107 F.3d 1328, 1335 (9th Cir. 1997) (anticipating *Greater New Orleans*; partial ban on lottery advertising could not “materially discourage public participation,” given exceptions); *Metro Lights, L.L.C. v. City of Los Angeles*, 488 F. Supp.2d 927, 943-44 (C.D. Cal. 2006) (sign ordinance with exception for persons under contract with the city contained too many exceptions to directly advance traffic safety interest).

- Unlike unaffiliated colleagues, manufacturer-employed physicians are barred from presenting scientific information about off-label uses. 62 Fed. Reg. 64074, 64093 (Dec. 3, 1997).
- The government itself routinely publicizes off-label uses while denying manufacturers that right.⁸
- Producers of dietary supplements – like wine and liquor sellers in *Rubin* – may make health-related claims, as long as they disclaim FDA approval. 21 U.S.C. §343(s); see *Pearson v. Shalala*, 164 F.3d 650, 656, 658-59 (D.C. Cir. 1999) (dietary supplement health claims not “inherently misleading” where FDA approval disclaimed).

The audience likewise matters. The FDA allows manufacturers to discuss off-label use with investors, clinical researchers, and research subjects – but not ordinary physicians.⁹

Governing statutes contain numerous exceptions. The FDCA expressly recognizes off-label use, 21 U.S.C. §396, and permits manufacturer dissemination of off-label information under specific circumstances, while prohibiting identical speech beyond those limitations. 21 U.S.C. §§360aaa(b), 360aaa-1; 21 C.F.R. Part 99.¹⁰ Off-label information can be provided in response to a physician’s “unsolicited” request, but a manufacturer cannot initiate an identical discussion. 21 U.S.C. §360aaa-6(a); 21 C.F.R. §99.1(b). Other federal statutes mandate disclosure of data about certain off-label uses. 42 U.S.C. §§284m (studies of pediatric off-label use), 282(j) (studies of cancer/AIDS off-label use). As a major third-party payer of medical costs, the federal government finances, and thereby encourages, off-label use. 42 U.S.C. §§1396r-8(k)(6), 1395x(t)(2)(B)(ii). Finally, the FDA has proposed loosening the requirements concerning manufacturer distribution of medical textbooks and articles while continuing to ban

⁸The National Institutes of Health maintain <http://clinicaltrials.gov/> (last visited Jan. 7, 2007). Searching that site’s library for “off-label” produced ten studies. The National Cancer Institute publicizes off-label medical advances. *E.g.* <http://cancer.gov/newscenter/Pressreleases/starresultsapr172006> (discussing off-label use of raloxifene) (last visited Jan. 7, 2007).

⁹FDA regulations “do not. . .operate as a bar to disclosure of [off-label] study results...in reports with the SEC and in press releases.” <http://www.fda.gov/ohrms/dockets/dailys/01/Aug01/081301/m000001.pdf> (FDA Letter to WLF dated Mar. 19, 2001 (last visited May 7, 2008); 21 C.F.R. §50.25 (informed consent requirements for clinical investigations).

¹⁰Whether particular off-label information may be disseminated depends upon: (1) peer-review, (2) if the manufacturer has or will seek FDA approval of the off-label use, (3) use of disclaimers, and (4) the FDA’s prior review (this consideration being a facial prior restraint). *Id.*

dissemination of identical (and truthful) information contained in other formats. *See* 73 Fed. Reg. 9342 (FDA Feb. 20, 2008).

Other governmental regulatory bodies also require disclosure of off-label research data. Some states mandate disclosure,¹¹ and others recognize product liability duties to provide safety information about off-label use.¹² Many prestigious medical journals also require that authors publicly post off-label clinical data.¹³

First Amendment jurisprudence has not allowed the government to ban truthful speech about off-label uses in such an inconsistent and contradictory fashion. *Greater New Orleans* and *Rubin* preclude the government from prohibiting truthful commercial speech only when delivered by certain speakers or to certain audiences:

[The government's] true perception of the speech at issue here is revealed by their attitude toward the same speech disseminated under other circumstances. . . . [D]efendants have no concern over the exchange of [off-label information] among physicians; more telling, defendants do not even object to a manufacturer providing such information to a health care provider upon such person's request. Only when the manufacturer initiates the exchange does the FDA choose to label the speech false or inherently misleading. The Supreme Court has recently addressed this situation with the following observation: "Even under the degree of scrutiny that we have applied in commercial speech cases, decisions that select among speakers conveying virtually identical messages are in serious tension with the principles undergirding the First Amendment."

Henney, 56 F. Supp.2d at 85-86 (quoting *Greater New Orleans*, 527 U.S. at 194). *See generally* Ralph F. Hall & Elizabeth S. Sobotka, "Inconsistent Government Policies: How FDA Off-Label

¹¹New York successfully sued to force such disclosures. *See* Consent Decree, *supra*, at p.8. Maine has an off-label disclosure statute. 22 Me. Rev. Stat. Ann. §2700-A. At least sixteen states have considered disclosure legislation. Marc J. Scheineson & M. Lynn Sykes, *Major New Initiatives Require Increased Disclosure Of Clinical Trial Information*, 60 Food & Drug L.J. 525, 531 (2005).

¹²*Knowlton v. Deseret Medical, Inc.*, 930 F.2d 116, 122-23 (1st Cir. 1991); *Woodbury v. Janssen Pharmaceutica, Inc.*, No. 93 C 7118, 1997 WL 201571, at *8-9 (N.D. Ill. Apr. 10, 1997); *Anderson v. Sandoz Pharmaceuticals Corp.*, 77 F. Supp.2d 804, 808 n.4 (S.D. Tex. 1999); *Medics Pharmaceutical Corp. v. Newman*, 378 S.E.2d 487, 488 (Ga. App.), *cert. denied*, 493 U.S. 824 (1989).

¹³*See Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing & Editing for Biomedical Publication* §III(J) (Feb. 2006), *available at* <http://www.icmje.org/icmje.pdf> (last visited May 6, 2008). Participating journals include the New England Journal of Medicine, Lancet, and JAMA.

Regulation Cannot Survive First Amendment Review Under *Greater New Orleans*,” 62 Food & Drug L.J. 1, 41-43 (2007).

By “select[ing] among speakers conveying virtually identical messages,” the FDA’s selective ban on off-label statements violates the First Amendment. *Greater New Orleans*, 527 U.S. at 194. All the exceptions and contrary mandates undercut any argument that the FDA’s restrictions actually advance the interest of encouraging submission of off-label uses for approval – and statistics demonstrate consistently high levels of off-label use. Because: (1) third-parties can speak about off-label uses, (2) manufacturers can speak to some audiences, and (3) disclosure of off-label information is permitted or mandated in quite a few situations, the FDA’s selective ban on truthful commercial speech about off-label use is suspect under the third prong of the *Central Hudson* test.

4. Banning Truthful Promotion Of Off-Label Uses Is Not Narrowly Tailored And Restricts More Speech Than Necessary.

The FDA’s ban against manufacturers truthfully disseminating off-label information also runs into problems with the First Amendment because that restriction is not “narrowly drawn” and is more restrictive than necessary to achieve the stated goals. *Central Hudson*, 447 U.S. at 565. In rejecting similar FDA arguments, the Supreme Court “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.” *Western States*, 535 U.S. at 371; see *Rubin*, 514 U.S. at 490-91 (less speech-restrictive alternatives rendered prohibition against displaying alcohol content on beer labels unconstitutional).

The question under the final *Central Hudson* prong is whether there is “a reasonable fit between the means and ends” of the questioned speech restriction. *Lorillard Tobacco Co. v. Reilly*, 533 U.S. 525, 561 (2001). “[T]he preferred remedy is more disclosure, rather than less.” *Bates v. State Bar of Arizona*, 433 U.S. 350, 375 (1977).

As discussed, the FDA’s asserted interest has been to encourage manufacturers to seek FDA approval of off-label uses. In *Western States*, the Court examined a similar FDA rationale and found it wanting – that FDA could not ban truthful advertising of pharmacy compounding to preserve its authority over drug manufacturing. The FDA argued that, absent advertising, compounding could not grow large enough to amount to unregulated manufacturing. 535 U.S. at 371. The Court barred FDA from using speech as a proxy for manufacturing because its ban swept too broadly:

Forbidding the advertisement of compounded drugs would affect pharmacists other than those interested in producing drugs on a large scale. It would prevent pharmacists with no interest in mass-producing medications, but who serve clienteles with special medical needs, from telling the doctors treating those clients about the alternative drugs available through compounding.

Id. at 376-77. “The fact that [the FDA] would prohibit such seemingly useful speech even though doing so does not appear to directly further any asserted governmental objective confirms our belief that the prohibition is unconstitutional.” *Id.* at 377.

The same is true with the FDA’s regulations banning truthful promotion of off-label use. As held in *Henney*:

The problem...is not [the FDA's] effectiveness in encouraging supplemental drug applications, but rather the means by which it encourages such applications. The supplemental application requirement of the act amounts to a kind of constitutional blackmail – comply with the statute or sacrifice your First Amendment rights. . . . Congress and the defendants have chosen to condition the exercise of rights guaranteed by the United States Constitution upon the submission of a supplemental drug application. Such a gross imposition upon free speech is in clear violation of the First Amendment, and it cannot stand.

56 F. Supp.2d. at 87.

Nor can the FDA's prohibition be justified as a condition attached to a government benefit. Since there is no other way to market drugs and medical devices in this country except through obtaining FDA approval, such a condition would be unconstitutional.

The doctrine of unconstitutional conditions places limits on the promises that an agency may extract from those who seek approval. And if a given use is lawful, and thus can be written about freely in newspapers or blogs, and discussed among [customers] that already have purchased [the product], doesn't it make a good deal of sense to allow speech by the device's manufacturer, which after all will have the best information? Why privilege speech by the uninformed? The manufacturer has an incentive to slant the speech in its favor and may withhold bad news, but many listeners (especially professionals such as physicians) understand this and can discount appropriately. That, at any rate, is the anti-paternalist view of *Virginia Citizens Consumer Council* and the cases that followed in its wake.

Caputo, 517 F.3d at 939.

Thus it is doubtful that the FDA could condition exercise of First Amendment rights upon additional administrative submissions of new uses for agency approval. The FDA has been employing a blanket prohibition upon truthful speech as a proxy for "intended use." While 21 C.F.R. §§201.128 and 801.4 so state, *Western States* prohibits FDA from doing precisely this:

[F]orbidding advertising [must be] a necessary as opposed to merely convenient means of achieving [governmental] interests. . . . If the First Amendment means anything, it means that regulating speech must be a last – not first – resort. Yet here it seems to have been the first strategy the Government thought to try.

535 U.S. at 373.

Nor, given extensive publicity about off-label use, is it likely that any significant number of physicians equate truthful statements about off-label use with full FDA vetting of such uses. It is far more likely that physicians value FDA product approval for what it is – an affirmative finding of safety and effectiveness following intensive testing and study. That alone provides an inherent commercial advantage, and thus strong incentive to obtain FDA approval. *Friedman*, 13 F. Supp.2d at 73 (where "physicians look to FDA approval as an important (or the exclusive) indication of safety and effectiveness, . . . manufacturers will seek to obtain FDA approval to

make their products more appealing”). Under *Western States*, the FDA’s ban on truthful manufacturer speech about off-label uses is manifestly overbroad.

LESS SPEECH-BURDENSOME ALTERNATIVES

In *Western States* the Supreme Court discussed “[s]everal non-speech-related means” as less restrictive alternatives to FDA’s penchant for banning speech. 535 U.S. at 372. These included: (1) banning equipment needed for commercial-scale compounding; (2) prohibiting compounding beyond existing prescriptions; (3) limiting, by dollar value or volume, how much compounded product could be sold in a given period, and (4) limiting the percentage of sales revenue that could be earned through compounding. *Id.* at 372.

These *Western States* examples find easy parallels in the off-label use context. Numerous alternatives are available to the FDA that would be less burdensome on the freedom of speech of FDA-regulated entities. Most obviously, the FDA’s goals could be achieved through “more disclosure, rather than less.” *Bates*, 433 U.S. at 375. The FDA could require disclaimers, as it already does with dietary supplements – “full, complete, and unambiguous disclosure by the manufacturer” when information concerns off-label use. *Friedman*, 13 F. Supp.2d at 73; see Hall & Sobotka, *Inconsistent Government Policies*, 62 Food & Drug L.J. at 32 nn.215-16 (discussing the FDA’s “inconsistent” disclaimer policies). Disclaimers highlight the distinction between approved and off-label uses. *Friedman*, 13 F. Supp.2d at 73.

In *Pearson v. Shalala*, the D.C. Circuit held that the First Amendment favors disclaimers over outright FDA suppression of speech. *Pearson* affirmed the unconstitutionality of a ban on health claims by manufacturers of dietary supplements. The court stated:

The government insists that it is never obliged to utilize the disclaimer approach, because the commercial speech doctrine does not embody a preference for disclosure over outright suppression. Our understanding of the doctrine is otherwise. . . . In more recent cases, the [Supreme] Court has reaffirmed this principle, repeatedly pointing to disclaimers as constitutionally preferable to outright suppression.

164 F.3d at 657 (citations omitted). “[W]hen government chooses a policy of suppression over disclosure – at least where there is no showing that disclosure would not suffice to cure misleadingness – government disregards a ‘far less restrictive’ means.” *Id.* at 658 (citation omitted).

If worried about safety, the FDA could require separate reporting and labeling of adverse events associated with off-label use to alert physicians specifically about off-label risks, where such uses are known.¹⁴ The Agency could also increase incentives for manufacturers to seek approval for off-label uses through any number of indirect economic means. The government could provide tax incentives for clinical research related to bringing off-label uses onto the label. It could provide manufacturers with a preemption defense in product liability cases involving

¹⁴Ultimately, FDA non-speech requirements could be more restrictive, in a practical sense, of off-label use than the current regime. Such restrictions may or may not be good public health policy, but they would not be subject to substantial First Amendment challenge.

off-label uses brought onto the label. Products with few off-label uses could receive faster and easier export authorization. Another approach would be to extend or reduce patent exclusivity depending upon the prevalence of off-label use. *See* Hall & Sobotka, 62 Food & Drug L.J. at 46. These or other changes to the existing regulatory scheme could increase submission of off-label uses for approval without burdening manufacturers' First Amendment free speech rights.¹⁵

However the FDA might choose to effectuate its goals, there are viable alternatives to the current speech-prohibitory regime. Whenever government would criminalize truthful commercial speech, the First Amendment is implicated. The Supreme Court's admonition in *Virginia State Board* remains as true now as thirty years ago: "It is precisely this kind of choice, between the dangers of suppressing information, and the dangers of its misuse if it is freely available, that the First Amendment makes for us." 425 U.S. at 770.

PROTECTED SCIENTIFIC SPEECH

The line between "commercial" speech and the various types of speech that enjoy full constitutional protection is often blurred. Certain aspects of speech, such as its being an advertisement, whether it expressly discusses specific product being sold, or and its role in advances the economic interests of the speaker, are factors in deciding its "commercial" status. *E.g.*, *Bolger*, 463 U.S. at 67-68. It also matters whether the speech is an "expression related solely to the economic interests of the speaker and its audience." *Central Hudson*, 447 U.S. at 561 (emphasis original). Courts invoke a "commonsense distinction between speech proposing a commercial transaction. . .and other varieties of speech." *E.g.*, *Ohralik v. Ohio State Bar Assn.*, 436 U.S. 447, 455-56 (1978). "The mere fact" that speech is "conceded to be [an] advertisement" or "propose[s] commercial transactions" does not require the speech to be downgraded to "commercial." *44 Liquormart*, 517 U.S. at 501 (1996); *Bolger*, 463 U.S. at 66.

For several kinds of manufacturer activity that the FDA has considered to be "promotion" – dissemination of articles from medical journals, providing free medical textbooks, and sponsoring continuing medical education – the question of whether the speech is "commercial" at all becomes critically important. Unlike commercial speech, scientific expression is entitled to full First Amendment protection.¹⁶ As Justice Frankfurter stated, a half century ago:

¹⁵Congress could, hypothetically, amend the FDCA and ban off-label use altogether – but that will never happen because off-label use is essential to the best medical treatment in too many areas. *Buckman*, 531 U.S. at 351 n.5 (off-label use "often is essential to giving patients optimal medical care. . . , which medical ethics, FDA, and most courts recognize") (quoting Beck & Azari, *supra*).

¹⁶*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 University v. Sullivan*, 773 F. Supp. 472, 474 (D.D.C. 1991) ("It is equally settled. . .though less commonly the subject of litigation,

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.

Sweezy v. New Hampshire, 354 U.S. 234, 263 (1957) (Frankfurter, J. concurring).

As alluded to previously, in enforcing 21 C.F.R. §202.1, the 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.”¹⁷ This definition captures some speech that cannot be classified as commercial speech under the definition of commercial speech operative in First Amendment jurisprudence. “[T]he core notion of commercial speech” is “speech which does no more than propose a commercial transaction.” *Bolger*, 463 U.S. at 66. 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 they are commercial speech. Similarly, the reference to a specific product does not by itself render the pamphlets commercial 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.

Id. at 66-68 (citations and footnotes omitted).

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. This issue is not clear cut, however, as the *Friedman* court held that “manufacturer dissemination of enduring materials and sponsorship of CME seminars is properly classified as commercial speech” “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.” 13 F. Supp. 2d at 64-65. Challenges to specific scientifically-related endeavors barred by the FDA as off-label promotion on the ground that they proscribe fully-protected scientific speech have yet to be litigated. *See generally E.g., Miller v. California*, 413 U.S. 15, 22-23 (1973); *see generally*, Glenn C. Smith, “Avoiding Awkward Alchemy – In the Off-Label Drug Context and Beyond: Fully-Protected Independent Research Should Not Transmogrify Into Mere

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).

¹⁷Final Guidance on Industry-Supported Scientific and Educational Activities, 62 Fed. Reg. 64074, 64076 (Dec. 3, 1997).

Commercial Speech Just Because Product Manufacturers Distribute It,” 34 Wake Forest L. Rev. 963, 1016-37 (1999).