Nos. 06-3612 & 06-3619 (consolidated)
IN THE UNITED STATES COURT OF APPEALS
FOR THE SEVENTH CIRCUIT

UNITED STATES OF AMERICA,	)	
	)	
Plaintiff-Appellee,	)	**Appeal from the Northern District of Illinois, Eastern Division**
	)	
vs.	)	**Nos. 03-CR-126-01, -02**
	)	**Honorable Ruben Castillo,**
ROSS A. CAPUTO, and	)	**Judge Presiding**
ROBERT M. RILEY,	)	
	)	
Defendants-Appellants.	)	

AMICUS CURIAE BRIEF OF WASHINGTON LEGAL FOUNDATION IN SUPPORT OF APPELLANT ROBERT RILEY

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RULE 26.1 DISCLOSURE STATEMENT

Amicus Curiae Washington Legal Foundation submits the following in compliance with FRAP 26.1 and Circuit Rule 26.1:

Washington Legal Foundation has no parent corporation and no company owns more than 10% of its stock.

The following are the law firms or lawyers who have appeared or are expected to appear for Washington Legal Foundation in this case:

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INTEREST OF THE *AMICUS CURIAE*

Washington Legal Foundation ("WLF") is a public interest law and policy center with members and supporters in all 50 states. It seeks to defend the rights of individuals and businesses against interference from excessive government regulation. WLF's members include physicians who seek to receive truthful information about potential "off-label" uses of FDA-approved products, and medical patients who want their doctors to have such information.

WLF has previously challenged FDA restrictions on the flow of truthful information about off-label uses. In 1993 and 2001, WLF filed citizen petitions with FDA asserting that prohibitions against dissemination of truthful information about off-label uses violate the First Amendment. After denial of the 1993 citizen petition, WLF brought suit against FDA in federal court to determine the constitutionality of FDA prohibitions against distribution to doctors of medical textbooks containing off-label information, and against manufacturer support of continuing medical education ("CME") that included off-label uses. WLF prevailed before the District Court. *See WLF v. Friedman*, 13 F. Supp. 2d 51, 56 (D.D.C. 1998);

WLF v. Henney, 56 F. Supp. 2d 81 (D.D.C. 1999), *appeal dismissed*, 202 F.3d 331 (D.C. Cir. 2000).[1]

STATEMENT OF THE CASE

Appellant Robert Riley was Vice President of Regulatory Affairs for AbTox, Inc., located in Mundelein, Illinois. AbTox developed and marketed a medical device, the Plazlyte hospital sterilizer, for surgical and other medical instruments. The Plazlyte sterilizer employed low temperature gas plasma as its sterilizing agent. FDA cleared the Plazlyte system as "substantially equivalent" to the ethylene oxide ("ETO") system, an existing FDA-cleared sterilizer.

In February 2003, Riley and other AbTox executives were indicted on offenses relating to marketing and sale of the Plazlyte system. Among other things, Appellants were charged with conspiracy, fraud, and introduction of an adulterated or misbranded device. The government claimed that Appellants never marketed or sold the FDA-cleared sterilizer, but only a modified version. The indictment charged that the modifications required separate FDA pre-market

[1]FDA mooted some of the injunction by conceding that "nothing in either of the provisions challenged. . .provides the FDA with independent authority to regulate manufacturer speech." *WLF v. Henney*, 202 F.3d 331, 336 (D.C. Cir. 2000). In partially vacating for mootness, the Court of Appeals "certainly d[id] not criticize the reasoning or conclusions of the district court. ...[W]e do not reach the merits of the district court's First Amendment holdings and part of its injunction still stands." 202 F.3d at 337 n.7.

approval ("PMA"). Because Appellants lacked PMA, the device allegedly was adulterated and misbranded.

Appellants moved to dismiss arguing, *inter alia*, that FDA prohibitions against truthful manufacturer discussion of off-label use of medical devices violated the First Amendment. The indictment's conspiracy count, Appellants contended, involved truthful statements about off-label uses. Appellants argued that, because FDA regulations unconstitutionally criminalized protected commercial speech, the conspiracy count should be dismissed.

District Judge Ruben Castillo of the Northern District of Illinois denied Appellants' motion, holding that prosecution for truthful statements about off-label use did not offend the First Amendment. *United States v. Caputo*, 288 F. Supp. 2d 912, 919-22 (N.D. Ill. 2003). At trial, the government asserted as criminal acts not only false or misleading statements, or those about unapproved products – but also undeniably truthful speech concerning off-label uses of FDA-approved products. Examples of truthful statements about off-label uses for the Plazlyte sterilizer that the government introduced at trial as evidence of "illegal" conduct include:

- Informing hospitals that they could conduct validation studies to establish effectiveness of the sterilizer for off-label uses, Tr. 2017, 2416, 2662-63;
- Encouraging hospitals to conduct such validation studies, Tr. 2414-15; 2758-2760;

- Offering reimbursement for instruments damaged during off-label use, Tr. 2049-51;[2] and

- Informing hospitals about risks of ETO sterilization and that Plazlyte was an alternative to an ETO system. Tr. 2482, 2591, 2753.[3]

REGULATORY FRAMEWORK

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. FDA approves such products under a "substantial evidence" standard. *Id.* §355(d).

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

[2]*See* Government Exh. 4B (letter from Defendant Mark A. Schmitt to Deaconess Medical Center). This letter stated: "AbTox Inc will reimburse customers for the repair of any functional damage to surgical instruments…when the damage is shown to be caused by the Plazlyte…."

[3]*See* Government Exh. 5K, Tab 2 (AbTox document quoting Associate Director of the American Hospital Association as stating that Plazlyte was "a viable alternative" to ETO sterilization); Government Exh. 15C (AbTox document referring to Plazlyte as "alternative" to ETO).

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.

FDA approves products only for specific submitted "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 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. §801.4 (meaning of *intended uses*); *see Id.* §201.128 (same definition for prescription drugs).[4] FDA's "intended use" regulations have not changed

[4]*See* 65 Fed. Reg. 14286 (Mar. 16, 2000) (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

substantively since 1952, long before First Amendment protection extended to commercial speech. *See* 17 Fed. Reg. 6818, 6820 (July 25, 1952) (text of then 21 C.F.R. §1.106(o)).

In 2002, the Supreme Court struck down similar FDA prohibitions against truthful advertising of pharmacy compounding services. *Thompson v. Western States Medical Center*, 535 U.S. 357 (2002) (hereafter "*Western States*"). Thereafter, FDA sought public comments on the constitutionality of prohibiting truthful promotion of off-label use. 67 Fed. Reg. 34942 (May 16, 2002). Over 4½ years later, FDA has neither responded to the comments it solicited nor altered its prohibitions against truthful promotion of off-label use.

For purposes of this brief, "off-label" use means only use of an FDA-approved product beyond what is stated in the label – including different applications, different dosages, different patient populations (*e.g.*, children, pregnant women), and different conditions (*e.g.*, rare diseases). A product without FDA approval for any purpose cannot be used "off-label," because there is no label. WLF is not addressing such products. Nor does WLF in any way

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may also be determined from advertisements, promotional material, or oral statements by the product's manufacturer or its representatives, and any other relevant source").

countenance dissemination of *un*truthful information about any product for any reason.[5]

ARGUMENT

Appellants were convicted on evidence that did not distinguish between false/misleading speech, speech concerning unapproved devices, and truthful speech about off-label uses of an FDA-approved device. Prior to trial, the District Court made clear its belief that the government could criminalize truthful speech about off-label uses. *Caputo*, 288 F. Supp. 2d at 922. Appellants may well have been convicted, in whole or in part, for engaging in protected commercial speech. WLF urges reversal because FDA's prohibitions against making truthful statements about off-label use – and thus Appellants' convictions for violating these prohibitions – violate the First Amendment by infringing upon protected commercial speech to a constitutionally impermissible degree.[6]

[5]WLF takes no position on the regulatory issue whether modifications to the Plazlyte sterilizer created a new, unapproved device.

[6]A criminal conviction for engaging in protected speech is a "restriction" on speech under First Amendment analysis – even fear of prosecution will support a First Amendment challenge. *E.g.*, *Los Angeles Police Dep't v. United Reporting Publishing Corp.*, 528 U.S. 32, 38-40 (1999).

I. INTRODUCTION

Off-label use is absolutely and entirely legal. "'[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), *citing* James M. Beck & Elizabeth Azari, *FDA, Off-Label Use, & Informed Consent: Debunking Myths & Misconceptions*, 53 Food & Drug L.J. 71, 76-77 (1998). Congress wrote off-label use into the FDCA. 21 U.S.C. §396 (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"). 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 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." *Friedman*, 13 F. Supp. 2d at 56.

For physicians properly to use drugs and devices off-label, they must have 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. *Id.* ("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"). Although manufacturers have both incentive and resources to provide off-label information, FDA regulations prevent them from disseminating it, even when undeniably truthful and non-misleading, except in very limited circumstances.[7] "[A] system that denies doctors and patients critically important information about the known [off-label] side-effects of a drug cannot be working as it should."

[7]Generally, manufacturers may respond to a physician's unsolicited request for information about an off-label use, but are forbidden from actively distributing such information. 21 C.F.R. §99.1(b).

Remarks by N.Y. State Attorney General Eliot Spitzer, at 10 (Nat'l Press Club Jan. 31, 2005).[8]

These restrictions undeniably limit manufacturers' commercial speech. Commercial speech is broadly defined as expression related to the economic interests of the speaker and its audience, generally as a commercial advertisement for sale of goods or services. *See Bolger v. Youngs Drug Products Corp.*, 463 U.S. 60, 66-67 (1983). Commercial speech enjoys less, but still powerful, constitutional protection than "pure" speech. *Id.* at 68 (applying the "qualified but nonetheless substantial protection accorded to commercial speech"). "[C]ommercial speech cannot lightly be singled out as 'less valuable' than other speech." *National Coalition of Prayer, Inc. v. Carter*, 455 F.3d 783, 786 (7th Cir. 2006).

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). FDA's regulations – long predating First Amendment protection of commercial speech – ignore this reason. Truthful and non-misleading information about off-label uses does not implicate the rationale for limiting protection of commercial speech; thus judicial review should be parti-

[8] *Available at* http://www.oag.state.ny.us/press/statements/Business_Ethics.pdf (last visited Jan. 5, 2007).

cularly exacting: "[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.* "[FDA] prohibitions of truthful commercial messages are 'particularly dangerous' and deserve 'rigorous review.'" *Western States Medical Center v. Shalala*, 238 F.3d 1090, 1096 (9th Cir. 2001) (citations omitted), *aff'd sub nom. Thompson v. Western States Medical Center*, 535 U.S. 357 (2002). 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*").

As restrictions on commercial speech, FDA prohibitions on promotion of off-label use are analyzed under the framework established in *Central Hudson Gas & Electric Corp. v. Public Service Comm'n*, 447 U.S. 557 (1980). *Goodman v. Illinois Dep't of Financial & Professional Regulation*, 430 F.3d 432, 438 (7th Cir. 2005).[9] Under *Central Hudson*, to obtain First Amendment protection, commercial speech must first "concern lawful activity and not be misleading." 447 U.S. at

[9]Several justices of the Supreme Court have expressed reservations about *Central Hudson*, but it remains the test until the Court decides otherwise. *Western States*, 535 U.S. at 367-68.

566; *Goodman*, 430 F.3d at 438. Commercial speech satisfying this threshold requirement cannot constitutionally be suppressed unless the government establishes that the restriction: (1) supports a "substantial" government interest; (2) "directly advances" that interest; and (3) is narrowly tailored and "not more extensive than is necessary" to serve the asserted governmental interest. *Central Hudson*, 447 U.S. at 566; *Pearson v. Edgar*, 153 F.3d 397, 401 (7th Cir. 1998). The government "carries the burden." *Pearson*, 153 F.3d at 401:

> 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).

II. APPELLANTS' COMMERCIAL SPEECH CONCERNED LAWFUL ACTIVITY AND WAS NOT MISLEADING.

The District Court correctly held that Appellants engaged (at least in part) in commercial speech meeting the threshold *Central Hudson* requirement in that their speech concerned lawful activity, and was not misleading. *Caputo*, 288 F. Supp. 2d at 920-21,

A. Appellants' Speech Concerned Lawful Activity.

Commercial speech about off-label use concerns lawful activity. *Id.* at 920. The District Court relied upon sound reasoning in *Friedman*, which answered the identical question, "[i]t is obvious that the off-label prescription of previously approved drugs by physicians is presently lawful activity," 13 F. Supp. 2d at 66, and held that FDA regulations prohibiting manufacturer distribution of peer-reviewed medical articles and CME sponsorship involving off-label uses violated the First Amendment. *Id.* at 72-73.

Friedman rejected the government's argument that, because the speech violated FDA regulations, it *ipso facto* concerned unlawful activity. *Id.* at 66. Recognizing this argument as "tautological," the court held that speech did not become unlawful just because the government banned it. *Id.* "The proper inquiry is not whether the speech violates a law or regulation, but rather whether the conduct that the speech promotes violates the law." *Id.* So it is here – off-label use of this device was lawful, therefore discussion of such off-label use cannot promote unlawful activity. *Caputo*, 288 F. Supp. 2d at 920.

B. Appellants' Speech Was Not Misleading.

The truthful speech for which Appellants were convicted (pp. 3-4, *supra*) was not 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. Appellants' truthful statements about validation, AbTox's reimbursement offer, ETO risks, and the Plazlyte alternative informed consumers and was not likely to deceive them.

Appellants were not charged with falsely claiming FDA approval for off-label uses, *Caputo*, 288 F. Supp. 2d at 921, and they directed their truthful off-label statements to an extremely sophisticated audience – "physicians who are familiar with the FDA approval process and able to independently evaluate the validity of [Appellants'] claims." *Id.* Thus, the government could not prove Appellants' speech was more likely than not misleading.

Further, Appellants were also prosecuted for 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 significant clinical value when mailed

pursuant to a request.").[10] Scientific/medical articles are pure speech – not commercial at all. *E.g.*, *Poe v. Ullman*, 367 U.S. 497, 514-15 (1961); *Universal City Studios, Inc. v. Corley*, 273 F.3d 429, 446-47 (2d Cir. 2001).[11]

Finally, 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 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 FDA's off-label speech restrictions facially capture non-misleading information – and were so applied here – the government must establish all of the elements of the *Central Hudson* test. That, it could not do.

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[10]*Friedman* further held that scientific articles do not become "inherently misleading" solely because FDA did not evaluate them. *Id.*

[11]Scientific expression receives full First Amendment protection. *E.g.*, *Miller v. California*, 413 U.S. 15, 22-23 (1973); *Universal City Studios, supra*.; *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 Commercial Speech Just Because Product Manufacturers Distribute It*, 34 Wake Forest L. Rev. 963 (1999).

III. 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 District Court held that "subjecting off-label uses to the FDA's evaluation process is a substantial government interest." *Caputo*, 288 F. Supp. 2d at 921. WLF agrees that, in and of itself, this interest can be substantial. *See, e.g.*, *Western States*, 535 U.S. at 368-69; *Friedman*, 13 F. Supp. 2d at 69.[12]

Even a substantial governmental interest, however, cannot establish constitutionality where it is inconsistently pursued and thus riddled with exceptions. The

[12]One purported governmental interest that cannot satisfy *Central Hudson* requirements is 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 [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." *44 Liquormart*, 517 U.S. at 503.

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.

The government's inconsistent and conflicting approach to truthful speech about off-label uses fatally undercuts the substantial interest that FDA's prohibitions purport to promote.

IV. PROHIBITING TRUTHFUL INFORMATION ABOUT OFF-LABEL USES NEITHER DIRECTLY ADVANCES THE GOVERNMENT'S ASSERTED INTEREST NOR MATERIALLY ALLEVIATES THE PURPORTED HARMS.

FDA's restrictions on truthful speech about off-label use violate the First Amendment because they neither "directly advance the state interests involved," nor "alleviate [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, courts "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 requir-

ing 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*, 153 F.3d at 404 (invalidating ban on real estate solicitation intended to protect homeowner privacy when other solicitations that intruded on privacy were permitted).[13]

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 same is true here. FDA's regulations banning truthful promotion of off-label use are inconsistent with other governmental regulations that encourage, and sometimes mandate, off-label speech. FDA's ban silences only manufacturers – while allowing other speakers to make identical statements with impunity.

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[13] *See also 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).

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, FDA's prohibitions – shot through with exceptions, inconsistencies, and contrary mandates – cannot possibly advance the interest they purport to serve.[14]

If 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*

[14]The District Court made no findings of fact and cited no evidentiary support for its conclusion that FDA's off-label use speech prohibitions survive this *Central Hudson* prong. *Caputo*, 288 F. Supp. 2d at 922.

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 FDA's off-label use information 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.[15] The speaker's identity matters:

- 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.[16]
- 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,

[15]Truthful statements concerning off-label use of the Plazlyte sterilizer were permissible under FDA rules under different circumstances. Physicians and hospitals could freely exchange among themselves information concerning Plazlyte as an alternative to an ETO system. *See*, *supra*, at p.4. AbTox could have provided the same information in response to an unsolicited physician request.

[16]The 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).

656, 658-59 (D.C. Cir. 1999) (dietary supplement health claims not "inherently misleading" where FDA approval disclaimed).

The audience likewise matters. FDA allows manufacturers to discuss off-label use with investors, clinical researchers, and research subjects – but not ordinary physicians.[17]

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.[18] 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). Finally, as a major third-party

[17]FDA 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 Jan. 7, 2007); 21 C.F.R. §50.25 (informed consent requirements for clinical investigations).

[18]Whether 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) FDA's prior review (this consideration being a facial prior restraint). *Id.*

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).

Other regulating bodies also require disclosure of off-label research data. Some states mandate disclosure,[19] and others recognize product liability duties to provide safety information about off-label use.[20] Many prestigious medical journals also require that authors publicly post off-label clinical data.[21]

Consistent with the First Amendment, FDA cannot 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:

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[19]New 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).

[20]*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).

[21]*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 Jan. 7, 2006). Participating journals include the New England Journal of Medicine, Lancet, and JAMA.

> [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) (emphasis added). *See generally* Ralph F. Hall & Elizabeth S. Sobotka, *Inconsistent Government Policies: How FDA Off-Label Regulation Cannot Survive First Amendment Review Under* Greater New Orleans, 62 Food & Drug L.J. ____ (2007) (forthcoming in February issue).

By "select[ing] among speakers conveying virtually identical messages," 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 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, FDA's selective ban on truthful commercial speech about off-label use cannot survive.

V. FDA'S OFF-LABEL PROMOTION BAN IS NOT NARROWLY TAILORED AND RESTRICTS MORE SPEECH THAN NECESSARY.

FDA's ban against manufacturers truthfully disseminating off-label information also violates the First Amendment because the restrictions are not "narrowly drawn" and are 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).

A. FDA's Speech Restrictions Are Overly Broad.

FDA's asserted interest is to encourage manufacturers to seek FDA approval of off-label uses. *Caputo*, 288 F. Supp. 2d at 921; *see Henney*, 56 F. Supp. 2d at 86. In *Western States*, the Court examined a similar FDA rationale and found it wanting – that FDA could ban truthful advertising of pharmacy compounding to preserve its authority over drug manufacturing. 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 [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 FDA's regulations banning truthful promotion of off-label use. As held in *Henney*:

> The problem…is not [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. The government convicted Appellants using the same argument rejected in *Henney* – conditioning their ability to speak truthfully about the Plazlyte sterilizer upon their submitting another application for approval to the FDA.

The District Court justified this prohibition by stating, "permitting Defendants to engage in **all** forms of truthful, non-misleading promotion of off-label use would severely frustrate the FDA's ability to evaluate the effectiveness of off-label uses." *Caputo*, 288 F. Supp. 2d at 922 (emphasis original). This reasoning flatly contradicts *Henney*'s holding that FDA may not condition exercise of First Amendment rights upon additional administrative submissions. Worse, it sanctions a blanket prohibition upon truthful speech as a proxy for "intended use." While 21 C.F.R. §801.4 so states, *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 (emphasis added).

Nor does the District Court's ruling have any record basis. No evidence shows that physicians equate truthful statements about off-label use with full FDA vetting of such uses. It is just as 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*, FDA's ban on truthful manufacturer speech about off-label uses is manifestly overbroad.

B. Less Speech-Burdensome Alternatives Are Available.

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 belie the District Court's professed inability here "to identify a less burdensome alternative that would advance the government's substantial interest." *Caputo,* 288 F. Supp. 2d at 922. Numerous alternatives are available to FDA that would be less burdensome on Appellants' freedom of speech. Most obviously, FDA's goals could be achieved through "more disclosure, rather than less." *Bates*, *supra*. 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 ____ nn.215-16 (discussing 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) (emphasis added). "[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, FDA could require separate reporting and labeling of adverse events associated with off-label use to alert physicians specifically about off-label risks, where they exist. 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 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, *supra*, 62 Food & Drug L.J. at ____. These or other changes to the existing regulatory scheme could increase submission of off-label uses for approval without burdening manufacturers' First Amendment rights.[22]

[22]Congress could, of course, 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

However FDA might choose to effectuate its goals, viable alternatives plainly exist to the current speech-prohibitory regime. Whenever government would criminalize truthful commercial speech, we must be mindful of the First Amendment. The Supreme Court's admonition in *Virginia State Board of Pharmacy v. Virginia Citizens Consumer Council Inc.*, 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. 748, 770 (1976).

VI. APPELLANTS' CONVICTIONS SHOULD BE VACATED

Appellants' convictions should be vacated because the jury's verdict may well have punished constitutionally protected commercial speech. Reversal would not implicate FDA's ban against false or misleading speech nor exonerate Appellants. The Court need only determine that the jury was allowed to convict partially on the basis of First Amendment-protected speech, and that it is impossible to tell if the convictions in fact rested upon that basis. "[W]here a provision of the Constitution forbids conviction on a particular ground, the constitutional guarantee is violated by a general verdict that may have rested on that ground." *Griffin v.*

"often is essential to giving patients optimal medical care…, which medical ethics, FDA, and most courts recognize") (quoting Beck & Azari, *supra*).

United States, 502 U.S. 46, 53 (1991); *see Yates v. United States*, 354 U.S. 298, 312 (1957) ("verdict [must] be set aside…where the verdict is supportable on one ground, but not on another, and it is impossible to tell which ground the jury selected"). *Accord*, *e.g.*, *United States v. Peterson*, 236 F.3d 848, 857 (7th Cir. 2001); *Feela v. Israel*, 727 F.2d 151, 154 (7th Cir. 1984).

CONCLUSION

For the foregoing reasons, WLF respectfully requests that the Court vacate Appellants' convictions and remand to the District Court for a new trial.

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CERTIFICATE OF COMPLIANCE

As required by Rule 32(a)(7)(B), I hereby certify that this brief is proportionally spaced and contains 6,869 words, excluding items listed as excludable under Rule 32(a)(7)(B)(iii), as calculated by my word processing software, Microsoft Word 2003. I certify that the information on this form is true and correct to the best of my knowledge and belief formed after a reasonable inquiry.

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ARNON D. SIEGEL

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As required by this Court, I hereby certify that the CD-Rom provided to this Court with a PDF version of this brief is virus-free.

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CERTIFICATE OF SERVICE

I hereby certify that two copies and one disk of the *Amicus Curiae* Brief Of Washington Legal Foundation In Support Of Appellant Robert Riley were served upon the persons listed below by First Class Mail on this sixteenth day of January, 2007. The original and 16 copies were also served on the Court on this date via Federal Express.

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