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The United States Court of Appeals for the Second Circuit concludes that the FDA's interpretation of the Food, Drug, and Cosmetic Act to ban the off-label promotion of approved prescription drugs violates the Free Speech Clause of the First Amendment.

United States v. Caronia: A Clear Victory for Free Speech

BY MICHAEL CARVIN AND ERIC MURPHY

On December 3, 2012, the United States Court of Appeals for the Second Circuit issued an important First Amendment decision prohibiting the federal government from punishing pharmaceutical companies and their representatives for truthfully speaking about ''off-label'' uses of prescription drugs approved by the Food and Drug Administration (''FDA'') under the Federal Food, Drug, and Cosmetic Act (''FDCA''). *See United States v. Caronia*, 09-5006-cr (2d Cir. Dec. 3, 2012) (10 PLIR 1525, 12/7/12). Because the United States has obtained (and continues to seek) billion-dollar settlements from pharmaceutical companies for allegedly engaging in such off-label promotion, the decision could have major ramifications for the pharmaceutical industry.

Michael Carvin is a partner in the Washington office of Jones Day. He can be reached at macarvin@jonesday.com. Eric Murphy is an associate in Jones Day's Columbus office, and can be reached at eemurphy@jonesday.com. Carvin and Murphy drafted an amicus brief in the Second Circuit's Caronia *case on behalf of the Washington Legal Foundation and Murphy participated in the oral argument. The views set forth herein are the personal views of the authors and do not necessarily reflect those of Jones Day.*

I. The Regulatory Background

The FDCA regulates the manufacture and distribution of drugs. *See* 21 U.S.C. § 301 et seq. Under the Act, a manufacturer cannot distribute a ''new drug'' unless it first files an application with, and obtains approval from, the FDA. *Id.* § 355(a). The manufacturer must include with its drug application ''the labeling proposed to be used for such drug,'' including the manufacturer's intended uses of the drug. *Id.* § 355(b)(1)(F).

Once the FDA approves a drug for a *particular* purpose, the agency permits physicians to prescribe the drug (and their patients to use it) for *any* purpose. In other words, a physician can prescribe the drug not simply for the uses identified in its approved labeling, but also for other uses that the physician believes appropriate. Since the Act does not regulate the practice of medicine, *see* 21 U.S.C. § 396, the FDA has interpreted it not to reach these ''off-label uses.'' The FDA has instead long indicated that a ''physician may . . . vary the conditions of use from those approved in the package insert, without informing or obtaining [its] ap-

 ISSN 1542-9547

proval.'' FDA, *Legal Status of Approved Labeling of Prescription Drugs; Prescribing for Uses Unapproved by the FDA*, 37 Fed. Reg. 16,503, 16,503 (Aug. 15, 1972).

These legal off-label uses are, as the Supreme Court has recognized, ''generally accepted'' in the medical community. *Buckman Co. v. Plaintiffs' Legal Comm.*, 531 U.S. 341, 351 (2001). ''For example, a 2006 study found that more than 20 percent of prescriptions written for 100 of the 500 most commonly used prescription drugs, and 60 prescription drugs chosen by random selection, in the United States were for off-label use.'' Government Accountability Office, *FDA's Oversight of the Promotion of Drugs for Off-Label Uses* 2 (July 2008) (6 PLIR 885, 8/1/08). Another study suggested that off-label uses made their way into the official drug compendia that physicians use when determining the drugs to prescribe, on average, two and a half years before they received FDA approval. *See* J.H. Beales III, *New Uses for Old Drugs, in Competitive Strategies in the Pharmaceutical Industry* (Robert B. Helms ed., 1996).

Indeed, off-label uses can represent the proper standard of care for a particular disease. *See* FDA, *Good Reprint Practices for the Distribution of Medical Journal Articles and Medical or Scientific Reference Publications on Unapproved New Uses of Approved Drugs* § III (Jan. 2009) (hereinafter ''*Good Reprint Practices*''). ''Examples of medical conditions whose standard treatments involve or have involved extensive off-label use include cancer, heart and circulatory disease, AIDS, kidney diseases requiring dialysis, osteoporosis, spinal fusion surgery, and various uncommon diseases.'' James M. Beck & Elizabeth D. Azari, *FDA, Off-Label Use, and Informed Consent: Debunking Myths and Misconceptions*, 53 Food & Drug L.J. 71, 80 (1998). Indeed, the federal government itself, in its Medicare program, reimburses many such off-label uses. *See, e.g.*, 42 U.S.C. §§ 1395w-102(e), 1396r-8(k)(6).

Despite the frequency with which physicians prescribe drugs for off-label uses, the FDA broadly restricts a drug manufacturer's ability to promote these lawful uses. As the FDA has noted in regulatory guidance, it ''has consistently prohibited the promotion of . . . unapproved uses of approved products'' by the products' manufacturers. FDA, *Final Guidance on Industry-Supported Scientific and Educational Activities*, 62 Fed. Reg. 64,074, 64,081 (Dec. 3, 1997). Accordingly, manufacturer advertisements cannot ''recommend or suggest any use that is not in the [drug's] labeling.'' 21 C.F.R. § 202.1(e)(4).

The FDA created this speech ban by expanding the Act's prohibition against the ''misbranding'' of a drug. 21 U.S.C. § 352. Specifically, the Act states that a drug is ''misbranded,'' and therefore unlawful, if its labeling lacks ''adequate directions for use.'' *Id.* § 352(f)(1). The FDA has turned this statutory requirement for ''adequate directions'' into a prohibition against manufacturers promoting off-label uses, by conclusively presuming that a drug's directions are automatically inadequate for all off-label uses, no matter what the directions actually indicate or whether they are ill-designed for the recommended off-label use. *See* FDA, *Good Reprint Practices* § III (''An approved drug that is marketed for an unapproved use (whether in labeling or not) is misbranded because the labeling of such drug does not include 'adequate directions for use.' '). Thus, as the Second Circuit found, ''the government has treated promotional speech as more than merely evidence of a drug's intended use—it has construed the FDCA to prohibit promotional speech as misbranding itself.'' *Caronia*, slip op. at 10.

In sum, the FDA broadly permits physicians to prescribe, and advise their patients to use, drugs for off-label use that the physicians find medically appropriate, but bars manufacturers from truthfully speaking about such off-label prescriptions with those same physicians.

II. Factual and Procedural History of Caronia

The *Caronia* case involved the criminal prosecution of Alfred Caronia, a pharmaceutical sales representative for Orphan Medical, Inc. *Caronia*, slip op. at 13. Orphan manufactured the drug Xyrem, ''a powerful central nervous system depressant.'' *Id.* at 11. Xyrem had been approved by the FDA initially in July 2002 ''to treat narcolepsy patients who experience cataplexy, a condition associated with weak or paralyzed muscles,'' and subsequently in November 2005 ''to treat narcolepsy patients with excessive daytime sleepiness.'' *Id.* at 12. The FDA required Xyrem's label to include a ''black box'' warning, the most serious warning on drug labels, indicating, among other things, that the drug's safety had not been proved for patients under sixteen and that there was limited experience among elderly patients. *Id.*

In March 2005, Orphan hired Caronia to promote Xyrem. *Id.* at 13. Around the same time, in the spring of 2005, the United States began investigating Orphan and its promotional practices for Xyrem. As part of that investigation, it had Dr. Stephen Charno, a government cooperator who had pleaded guilty to insurance fraud, pose as a prospective physician customer and tape record two conversations involving Caronia. *Id.* at 14. In the first, on October 26, 2005, the tape recording allegedly details Caronia speaking with Dr. Charno about unapproved uses. *Id.* at 15. In the second, on November 2, 2005, Caronia introduced Dr. Charno to Dr. Peter Gleason, a doctor knowledgeable about Xyrem who had been hired by Orphan to discuss Xyrem through Orphan's speaker programs. During that meeting, Gleason allegedly engaged in off-label promotion. *Id.* at 16.

In 2007, the United States charged Orphan, Gleason, and Caronia, among others, with various misbranding violations related to the marketing of Xyrem. Orphan ultimately pleaded guilty and agreed to pay $12,262,078 in restitution and a $5 million fine. *United States v. Caronia*, 576 F. Supp. 2d 385, 388 n.1 (E.D.N.Y. 2008). After Caronia refused to plead guilty, the United States filed a superseding information that deleted its prior references to fraudulent conduct and charged Caronia only with two ''misbranding'' misdemeanors. The information alleged that Caronia had (1) knowingly and intentionally conspired with others to misbrand Xyrem by marketing it for off-label uses, and (2) misbranded Xyrem while it was held for sale after shipment in interstate commerce. *Id.* at 389.

Caronia moved to dismiss the indictment. He initially argued that he had, in fact, given adequate directions for the off-label uses under the misbranding statute because he provided ''the black box warning outlining the dangers and side effects of Xyrem'' and because Xyrem is ''administered in the same manner and in the same dosage'' ''no matter whether Xyrem is prescribed for on or off-label indications.'' *Id.* at 391-92. The district court

  PLIR ISSN 1542-9547

found this argument ''utterly without merit,'' because, under the FDA's regulatory scheme, ''the promotion of a drug for an off-label use by the manufacturer or its representative is prohibited regardless of what directions the manufacturer or representative may give for that use.'' *Id.* at 392.

Given that legal regime, Caronia also argued that the United States could not constitutionally punish him for truthful, non-misleading promotion about Xyrem's off-label uses. The district court disagreed. *See id.* at 398-401. It initially rejected the United States' argument that it only sought to punish Caronia's conduct, and used his speech merely as evidence of his intent to sell Xyrem for off-label purposes. The United States' argument, the court determined, ''overlooks case law which has generally rejected the notion that promotion of an approved drug is conduct, as opposed to speech within the ambit of the First Amendment.'' *Id.* at 395.

The district court instead rejected the First Amendment challenge on the ground that the United States' ban on off-label speech survived the First Amendment test for commercial speech. *See Caronia*, 576 F. Supp. 2d at 396-401 (citing *Cent. Hudson Gas v. Pub. Serv. Comm'n of N.Y.*, 447 U.S. 557 (1980)). Under that test, the Government may only proscribe commercial speech in two ways. First, it may prohibit commercial speech that promotes unlawful activity or that inherently misleads its audience. *See Thompson v. W. States Med. Ctr.*, 535 U.S. 357, 367 (2002). Second, it may regulate such speech if it can prove that it has a substantial interest in restricting speech; that the speech restriction ''directly advances the governmental interest asserted''; and that the restriction ''is not more extensive than is necessary to serve that interest.'' *Id.* (internal quotation marks omitted).

Applying this test, the district court found that speech about off-label uses did not concern unlawful activity because those uses are entirely lawful under the FDA's regulatory regime. *See Caronia*, 576 F. Supp. 2d at 397. It also found that speech about off-label uses was not inherently misleading, especially considering the sophistication of the medical community to which this speech is directed. *Id.* at 397-98.

The district court held, however, that the United States had shown that its speech ban directly advanced a substantial government interest and was no more extensive than necessary to do so. *Id.* at 398-401. According to the district court, the United States had a ''substantial interest in compelling manufacturers to get off-label treatments on-label.'' *Id.* at 398. And the speech ban directly advanced this interest, the court suggested, because the speech ban ''constrain[ed] [manufacturer] marketing options'' and thereby incentivized them to proceed through the FDA's regulatory regime for unapproved uses of approved drugs. *Id.* Finally, the district court held that the speech ban was no more extensive than necessary to serve this purpose. It found that ''constraining the marketing options of manufacturers is one of the 'few mechanisms available' to the FDA to ensure that manufacturers will not seek approval only for certain limited uses of drugs, then promote that same drug for off-label uses, effectively circumventing the FDA's new drug requirements,'' and was ''unable to identify nonspeech restrictions that would likely constrain in any effective way manufacturers from circumventing that approval process.'' *Id.* at 401 (citation omitted).

At trial, ''[t]he government, in its summation and rebuttal, repeatedly asserted that Caronia was guilty because he, with others, conspired to promote and market Xyrem for off-label use.'' *Caronia*, slip op. at 21. And the district court's jury charge noted that a ''manufacturer, its agents, representatives and employees, are not permitted to promote uses for a drug that have not been cleared by the United States Food and Drug Administration.'' *Id.* at 22. On the verdict sheet, the district court split Count One into two subparts, asking whether Caronia had either conspired ''to introduce or deliver for introduction into interstate commerce a drug, Xyrem, that was misbranded'' or conspired ''to do an act with respect to a drug, Xyrem . . . result[ing] in Xyrem being misbranded.'' *Id.* at 23. Count Two of the verdict sheet asked the jury whether Caronia himself had done an act with respect to a drug, Xyrem, that would result in Xyrem being misbranded. *Id.* The jury found Caronia not guilty on the second subpart of Count One and on Count Two but found him guilty of the first subpart of Count One—conspiring to introduce a misbranded drug into interstate commerce. *Id.* at 24. The district court sentenced Caronia to one year of probation, 100 hours of community service, and a $25 special assessment. *Id.*

III. The Second Circuit's Decision Reversing

In a 2-1 decision written by Judge Chin and joined by Judge Raggi, the Court vacated Caronia's conviction. The Court initially rejected the United States' argument that it had punished Caronia merely for his conduct and not his speech. *Caronia*, slip op. at 27-31. It then held that the FDA's ban on off-label promotion was subject to heightened First Amendment scrutiny because the ban engaged in content- and speaker-based discrimination. *Id.* at 39-41. The Court went on to conclude that, regardless, the FDA's ban on off-label promotion could not even survive the intermediate scrutiny that applies to commercial speech under the test set forth in *Central Hudson Gas v. Public Service Commission of New York*, 447 U.S. 557 (1980). *Id.* at 42-51. Judge Livingston dissented from the ruling.

A. Speech v. Conduct

As in the district court, the United States initially argued to the Second Circuit that ''the First Amendment is not implicated in this case'' because it had merely used speech as evidence that the off-label uses were the intended uses for which Orphan sold Xyrem. *Id.* at 27. For a host of reasons, the Second Circuit flatly rejected this argument. Among other things, at trial, ''the Government repeatedly argued that Caronia engaged in criminal conduct by promoting and marketing the off-label use of Xyrem,'' and highlighted this promotion over forty different times. *Id.* at 28. The Government, by contrast, never argued that this speech was merely evidence of any illicit intent or evidence that Xyrem's labeling directions were somehow deficient. *Id.* at 29. The district court's instructions likewise made clear that ''Caronia's speech was itself the proscribed conduct.'' *Id.* at 30. Moreover, the prosecution in this case purely for speech was consistent with the FDA's longstanding view, as the agency had traditionally ''treated promotional speech as more than merely evidence of a drug's intended use—it has construed the FDCA to prohibit

promotional speech as misbranding itself.'' *Id.* at 10. The Second Circuit concluded that '' '[s]peech in aid of pharmaceutical marketing . . . is a form of expression protected by the Free Speech Clause of the First Amendment,' '' and so moved on to the constitutional question. *Id.* at 31 (quoting *Sorrell v. IMS Health, Inc.*, 131 S. Ct. 2653, 2659 (2011)).

B. The First Amendment

The Second Circuit held that the FDA's interpretation of the FDCA's misbranding provisions was unconstitutional because it would automatically ''criminalize the simple promotion of a drug's off-label use by pharmaceutical manufacturers and their representatives.'' *Id.* at 33. But ''such a construction—and a conviction obtained under the government's application of the FDCA—would run afoul of the First Amendment.'' *Id.*

In reaching that conclusion, the Court adhered to the two-step framework adopted by the Supreme Court in *Sorrell*, another case involving state-law speech restrictions on pharmaceutical marketing. *See id.* at 35-38. The Court first asked whether the United States' speech ban discriminated on the basis of content and speaker. It then asked whether the United States could even justify its speech ban under the commercial-speech test. Resolving both questions against the United States, the Court concluded ''that the government cannot prosecute pharmaceutical manufacturers and their representatives under the FDCA for speech promoting the lawful, off-label use of an FDA-approved drug.'' *Id.* at 51.

1. Heightened Scrutiny

The Court initially found that the United States' interpretation of the FDCA to ban off-label promotion was subject to heightened scrutiny because, like the state law struck down in *Sorrell*, it discriminated on the basis of content and speaker. *Id.* at 39-41. The ban was ''content-based because it distinguishes between 'favored speech' and 'disfavored speech on the basis of the ideas or views expressed.' '' *Id.* at 40. It favored speech about government-approved uses of drugs while prohibiting speech about unapproved (but legal) uses. ''[A]s in *Sorrell*, the 'express purpose and practical effect' of the government's ban on promotion is to 'diminish the effectiveness of [off-label drug] marketing by manufacturers.' '' *Id.* (quoting 131 S. Ct. at 2663). Likewise, the Court found the speech ban to be ''speaker-based because it targets one kind of speaker—pharmaceutical manufacturers—while allowing others to speak without restriction.'' *Id.* at 40. Physicians and academics could freely speak about off-label uses without any consequence, while the same exact speech could not be undertaken by manufacturers or their representatives. *Id.* at 41. The Court lastly concluded that heightened scrutiny was even more appropriate in this case than in *Sorrell* because it involved a *criminal* regulatory scheme. *Id.*

2. Commercial-Speech Test

The Court went on to find that the United States' speech ban could not survive under the normal commercial speech test set forth in *Central Hudson*. Like the district court, it found that ''promoting off-label drug use concerns lawful activity (off-label drug use), and the promotion of off-label drug use is not in and of itself false or misleading.'' *Id.* at 42. In doing so, it pointed out that the United States did not argue that Caronia's speech in this case was false or misleading, and that a defendant may, of course, ''be prosecuted for untruthfully promoting the off-label use of an FDA-approved drug, *e.g.*, making false or misleading statements about a drug.'' *Id.* at 42 n.11. Also like the district court, the Court next indicated that the United States had a substantial interest ''in preserving the effectiveness and integrity of the FDCA's drug approval process, and an interest in reducing patient exposure to unsafe and ineffective drugs.'' *Id.* at 42-43.

But, unlike the district court, the Court rejected the United States' position that its speech ban directly advanced these interests. To begin with, because the Government has not prohibited the off-label use of approved drugs, ''it [did] not follow that prohibiting truthful promotion of off-label drug usage by a particular class of speakers'' would further any interest in reducing patient exposure to unsafe and ineffective drugs. *Id.* at 44. In addition, ''prohibiting off-label promotion by a pharmaceutical manufacturer while simultaneously allowing off-label use 'paternalistically' interferes with the ability of physicians and patients to receive potentially relevant treatment information; such barriers to information about off-label use could inhibit, to the public's detriment, informed and intelligent treatment decisions.'' *Id.* The FDA itself recognizes that public health could be furthered through the dissemination of truthful information about off-label uses. *Id.* at 45. And once the United States has made the determination that off-label uses are lawful, ''it only furthers the public interest to ensure that decisions about the use of prescription drugs, including off-label usage, are intelligent and well-informed.'' *Id.* at 46. As such, ''the government's prohibition of off-label promotion by pharmaceutical manufacturers 'provides only ineffective or remote support for the government's purpose.' '' *Id.* at 47 (citation omitted).

The Court also found that the United States' speech ban was more extensive than necessary to serve any governmental purpose. The ''government could pursue several alternatives without excessive First Amendment restrictions.'' *Id.* at 48. If concerned about misleading physicians, the government could develop ''warning or disclaimer systems'' or ''safety tiers within the off-label market, to distinguish between drugs.'' *Id.* at 49. ''To minimize off-label use, or manufacturer evasion of the approval process for such use, the government could create other limits, including ceilings or caps on off-label prescriptions.'' *Id.* And where particular kinds of off-label uses were especially concerning, the United States could simply prohibit those uses. *Id.* at 49-50. As such, the Court found that ''[t]he government's interests could be served equally well by more limited and targeted restrictions on speech,'' and rejected the United States' ''conclusory assertions'' that all alternatives were administratively infeasible, noting that the United States failed to offer any evidentiary support for that position. *Id.* at 50-51.

In sum, the Court unequivocally ''conclude[d] simply that the government cannot prosecute pharmaceutical manufacturers and their representatives under the FDCA for speech promoting the lawful, off-label use of an FDA-approved drug.'' *Id.* at 51.

  PLIR ISSN 1542-9547

C. Judge Livingston's Dissent

In dissent, Judge Livingston suggested that ''the majority calls into question the very foundations of our century-old system of drug regulation.'' *Caronia*, slip op. at 1 (Livingston, J., dissenting). Judge Livingston first found that no First Amendment scrutiny applied at all because the misbranding provisions under which Caronia was convicted merely used speech as evidence of a manufacturer's intended use of the drug. *Id.* at 1-18. And even if the First Amendment had been triggered, Judge Livingston concluded that the regulatory scheme would survive the commercial-speech test on the same rationales that the district court had provided—because the prohibition on promotion of off-label uses was one of the few mechanisms to incentivize manufacturers to participate in the approval process and none of the potential alternatives that the majority discussed would be similarly effective at doing so. *Id.* at 19-27.

IV. The Legal Ramifications of the Decision

This decision has significant ramifications for the pharmaceutical industry. To begin with, the Second Circuit's decision is a clear repudiation of the FDA's longstanding interpretation of the FDCA and its implementing regulations. Consistent with the United States' trial arguments and the district court's jury instructions, the FDA has for years interpreted its regulatory regime flatly to prohibit speech about off-label uses as illegal ''misbranding.'' *See, e.g.*, FDA, *Promotion of Food and Drug Administration-Regulated Medical Products Using the Internet and Social Media Tools*, 74 Fed. Reg. 48,083, 48,087 (Sept. 21, 2009) (''Under the act, companies are *prohibited* from *promoting* approved . . . drugs . . . for unapproved uses.'' (emphases added)); 62 Fed. Reg. at 64,081 (The FDA ''has consistently *prohibited* the *promotion* of . . . unapproved uses of approved products.'' (emphases added)); 37 Fed. Reg. at 16,504 (''[W]here a manufacturer or his representative . . . does anything that directly or indirectly suggests to the physician . . . that an approved drug may properly be used for unapproved uses, that action constitutes a *direct violation* of the Act and is punishable accordingly.'' (emphasis added)). The Second Circuit found this interpretation unconstitutional—concluding ''that the government cannot prosecute pharmaceutical manufacturers and their representatives under the FDCA for speech promoting the lawful, off-label use of an FDA-approved drug.'' *Caronia*, slip op. at 51. The Second Circuit's decision would thus plainly require the FDA to change its interpretation and enforcement of its regulatory regime to make greater room for the First Amendment.

In addition, as the Second Circuit noted, ''[t]he government has repeatedly prosecuted—and obtained convictions against—pharmaceutical companies and their representatives for misbranding based on their off-label promotion.'' *Caronia*, slip op. at 8 (citing cases). In recent years, these prosecutions have involved billion-dollar settlements. *See, e.g.*, Katie Thomas, *Glaxo Agrees to Pay $3 Billion in Fraud Settlement*, N.Y. Times, July 3, 2012 (noting that several manufacturers had contemplated settling off-label promotion cases for billions of dollars). The Second Circuit's decision, by far, provides the most significant precedent in support of a First Amendment argument that can be used both in government prosecutions and in negotiations attempting to settle them.

That said, a word of caution is in order. The opinion is only binding in the Second Circuit, and the United States could seek further review of the decision either before the entire Second Circuit in en banc proceedings or before the Supreme Court. Moreover, of course, the United States may still prosecute companies and their representatives for ''false or misleading'' speech about off-label uses. Thus, the United States may seek to reframe any particular investigation as involving speech that is misleading. *See Caronia*, slip op. at 42 n.11. (But this is obviously much more difficult to prove than simple promotion of off-label uses.) Finally, because Caronia was convicted directly for his speech, the Second Circuit purportedly reserved for another day the question whether the government could actually use speech in other cases merely as ''evidence of a defendant's off-label promotion to prove a drug's intended use and, thus, mislabeling for that intended use'' (although, in the real world, this distinction between punishing intent and punishing speech is largely illusory). *Id.* at 27-28.