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Second Circuit Holds Food, Drug and Cosmetic Act Does Not Prohibit Off-Label Promotion

In a significant blow to the U.S. government's enforcement efforts against the pharmaceutical industry, a panel of the Second Circuit overturned the conviction of a pharmaceutical sales representative for conspiracy to promote an FDA-approved drug for off-label uses, holding that the Federal Food, Drug and Cosmetic Act ("FDCA") does not "prohibit[] and criminaliz[e] the truthful off-label promotion of FDA-approved prescription drugs." *United States v. Caronia*, No. 09-5006, slip op. at 51 (2nd Cir., Dec. 3, 2012). In reaching its decision, the majority opinion of the 2-1 decision concluded that permitting the government to prosecute someone for "speech promoting the lawful, off-label use of an FDA-approved drug" runs afoul of the First Amendment. *Id*. Although clearly a major defeat for the government, the practical implications of the decision remain unclear, both because the decision will most likely undergo further appellate review and because it makes clear the government can continue to pursue off-label cases where the off-label promotion involves false or misleading statements.

The Majority Opinion

Alfred Caronia, a sales representative with pharmaceutical company Orphan Medical, Inc. – later acquired by Jazz Pharmaceutical – was convicted after a jury trial of conspiracy to introduce a misbranded drug into commerce in violation of the FDCA, 21 U.S.C. §§ 331(a) and 333(a)(1). *Caronia*, slip op. at 3. Caronia had promoted Xyrem, a powerful central nervous system depressant FDA-approved to treat narcolepsy, to physicians for use in disease states and subpopulations for which the FDA has not approved use ("off-label" uses). *Id*.

The FDCA prohibits "[t]he introduction or delivery for introduction into interstate commerce of any … drug … that is …misbranded." 21 U.S.C. § 331(a). A drug is "misbranded" within the meaning of the FDCA if, *inter alia*, its labeling fails to bear "adequate directions for use," 21 U.S.C. § 352(f), which FDA regulations define as "directions under which the lay[person] can use a drug safely and for the purposes for which it is intended," 21 C.F.R. § 201.5. Misbranding carries a criminal penalty. 21 U.S.C. § 333(a)(2).

When the FDA approves a drug, it approves it for specific uses, although physicians are generally free to use their medical judgment to prescribe the drug for both approved and unapproved uses. As the Second Circuit held, however, "[t]he FDCA and its accompanying regulations do not expressly prohibit the 'promotion' or 'marketing' of drugs for off-label use." Caronia, slip op. at 10. Thus, the government has long prosecuted pharmaceutical companies and their representatives for off-label promotion on the theory that the drugs are "misbranded" because their labels do not contain adequate directions for those unapproved uses. In doing so, however, the government has not merely treated off-label promotion as evidence of the drug's intended use for purposes of determining whether the drug bears adequate directions for that use but rather has construed the FDCA as prohibiting off-label promotional speech as misbranding itself. *Id*.

Caronia appealed his conviction, arguing that the FDCA's misbranding provisions ran afoul of the First Amendment. "To avoid [the] serious constitutional question" of whether the FDCA restricted speech in violation of the First Amendment, the Second Circuit rejected the government's construction of the FDCA as criminalizing the truthful promotion of an FDA-approved drug for off-label use. Id. at 32-33, 51.

In reaching its decision, the Second Circuit relied on the Supreme Court's opinion last year in *Sorrell v. IMS Health*, 131 S. Ct. 2653 (2011). In *Sorrell*, applying "heightened" First Amendment scrutiny, the Court struck down the Vermont Prescription Confidentiality Law as a content and speaker-based restriction on the sale, disclosure and use of prescriber information by a particular group of speakers, namely drug manufacturers. The Supreme Court also concluded in *Sorrell* that Vermont's prescriber confidentiality law would have been invalid even if it had applied the less-strict standard for evaluating commercial speech restrictions first announced in *Central Hudson Gas & Electric Corp. v. Pub. Serv. Comm'n of N.Y.*, 447 U.S. 557 (1980). Id. at 2667. Significantly, the district court in *Caronia* had relied on *Central Hudson*'s analysis in denying the defendant's motion to dismiss the government's case, expressly finding the government's interpretation of the FDCA's restrictions on off-label promotion constitutional under the First Amendment. *See United States v. Caronia*, 576 F. Supp.2d 385, 402 (E.D.N.Y. 2008).

Following *Sorrell*'s roadmap, the *Caronia* majority first found that the government's construction of the FDCA's misbranding provisions is "content- and speaker-based, and, therefore, subject to heightened scrutiny." *Caronia*, slip op. at 39. In the view of the majority, the government's construction was content-based because it permitted speech about "government-approved" uses of prescription drugs, while prohibiting truthful speech about off-label uses that doctors – who are legally allowed to prescribe drugs off-label – might find useful. *Id*. at 40. The government's misbranding construction was found to be a speaker-based restriction because it "targets one kind of speaker – pharmaceutical manufacturers – while allowing others to speak without restriction." *Id*. For these reasons, the majority found this interpretation of the FDCA fatally flawed under *Sorrell* – indeed, they concluded that the defendant's claim to First Amendment protection in *Caronia* was, if anything "more compelling than in *Sorrell*" because his claim arose from the application of a criminal regulatory scheme, which warranted "more careful scrutiny." *Id*. at 41; *see also id*. at 34 (citing *Holder v. Humanitarian Law Project*, 130 S. Ct. 2705, 2724 (2010), for the proposition that criminal regulatory schemes are subject to more rigorous scrutiny under the First Amendment).

The majority then turned to its *Central Hudson* analysis. In *Central Hudson*, the Supreme Court set forth a four-prong test to determine whether commercial speech is protected by the First Amendment: (1) the speech must not be misleading and must concern lawful activity; (2) the asserted government interest must be substantial; (3) the regulation must directly advance the governmental interest asserted; and (4) the regulation must be "narrowly drawn," and may not be more extensive than necessary to serve the interest. *Caronia*, slip op. at 37-38 (citing *Central Hudson*, 447 U.S. at 566).

The Second Circuit noted that the first prong was easily satisfied because off-label drug use is a lawful activity and the promotion of a drug for off-label use is not in and of itself false and misleading. *Id*. at 42. As to the second prong, the Court stated that the government's asserted interests in drug safety and public health "are substantial." *Id*.

Turning, however, to the third prong, the Court found that the government's interpretation of the FDCA did not directly advance its interests because off-label drug use is not unlawful and, therefore, even if pharmaceutical companies are prohibited from promoting drugs off-label, "physicians can prescribe, and patients can use, drugs for off-label purposes." *Id*. at 43-44. Thus, the Court noted, prohibiting off-label promotion by a pharmaceutical manufacturer while allowing off-label use interferes with the free flow of relevant treatment information and could actually be to the public's detriment. *Id*. at 44. As the Court said, "[t]he government's construction of the FDCA essentially legalizes the outcome – off-label use – but prohibits the free flow of information that would inform that outcome." *Id*. at 47.

Analyzing the last prong, the majority found that the government's interpretation of the FDCA as imposing a criminal ban on off-label promotion was "more extensive than necessary to achieve the government's substantial interests." *Id*. at 48. The Court noted various alternative means of achieving those interests, such as developing warning or disclaimer systems to help educate and inform physicians and patients, requiring pharmaceutical companies to list all applicable or intended indications when they first apply for FDA approval, or, where off-label use is "exceptionally concerning," banning off-label use altogether. *Id*. at 48-50.

The Second Circuit thus "decline[d] to adopt the government's construction of the FDCA's misbranding provisions to prohibit [pharmaceutical] manufacturer promotion alone as it would unconstitutionally restrict free speech" and concluded that "[t]he 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.

The Dissent

Judge Debra Ann Livingston vigorously dissented from the majority opinion, arguing that it "calls into question the very foundations of our century-old system of drug regulation." *Caronia*, slip op., 1 (dissent). The dissent disagreed with the majority that Caronia was "prosecuted and convicted for promoting Xyrem off-label." *Id*. at 8. Noting that it is well-settled that the First Amendment does not prohibit the use of speech as evidence of the elements of a crime or to prove motive or intent, the dissent explained that Caronia's off-label promotion was evidence of his intent and that the jury was correctly instructed on all of the elements of conspiracy. *Id*. The dissent then performed its own analysis of the FDCA misbranding provisions and concluded that they withstood scrutiny under the Supreme Court decisions in *Central Hudson* and *Sorrell*. *Id*. at 19-27. The dissent concluded that the FDCA's prohibition on off-label promotion directly advanced the government interest in "preserving the effectiveness and integrity of the FDCA's new drug approval process." *Id*. at 21. It also questioned whether drug companies would have any incentive to seek FDA approval for nonapproved uses if they were allowed to promote FDA-approved drugs for any use. *Id*.

Implications

The Second Circuit's decision in *Caronia* strikes a significant blow to the government's enforcement efforts. However, its practical implications for pharmaceutical companies and their representatives remain less clear. At this point, the decision is binding only in the Second Circuit. Moreover, given the 2-to-1 decision with a vigorous dissent on an issue of great importance to both the government and industry, further appellate review, *i.e*., rehearing *en banc* by the Circuit and/or review by the Supreme Court, is almost certain. The First Amendment issues, which have continued to vex the courts since the *Washington Legal Foundation* litigation ended in inconclusive rulings a decade ago, remain unsettled.

In the meantime, the Court made clear that "off-label promotion that is false or misleading is not entitled to First Amendment protection." *Caronia*, slip op. at 42, n.11. Therefore, prosecutors will be free to pursue cases where they can show that the off-label promotion involved false or misleading statements about the drug. In light of these considerations, companies should proceed cautiously in authorizing their representatives to promote products for off-label uses as such activity may still bring a long and expensive government investigation.

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