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Second Circuit Vacates Off-Label Promotion Conviction on First Amendment Grounds in *U.S. v. Caronia*

On December 3, 2012, a panel of three judges on the U.S. Court of Appeals for the Second Circuit overturned the November 2009 conviction of Alfred Caronia for conspiracy to introduce a misbranded drug into interstate commerce by promoting the drug, Xyrem, for off-label use in violation of the federal Food, Drug, and Cosmetic Act (FDCA).[1] Caronia, a former Specialty Sales Consultant for Orphan Medical, Inc., appealed his conviction on the grounds that he was convicted for his speech when promoting Xyrem for off-label uses, in violation of the First Amendment. The Second Circuit agreed, holding that Caronia was convicted in violation of his right to free speech and vacating and remanding Caronia's judgment of conviction to District Court.

Factual Background

According to the opinion, the allegations against Caronia centered on his promotion of the drug, Xyrem, which was approved in July 2002 to treat narcolepsy patients who experience cataplexy. The drug's label contained a boxed warning stating that safety and efficacy were not established in patients under 16. As described in the Second Circuit's opinion, the federal government began an investigation of Orphan Medical and Dr. Peter Gleason, a paid physician speaker, in spring 2005 for alleged off-label promotion of Xyrem. The government obtained two tape-recorded conversations in which Caronia and Gleason promoted Xyrem for unapproved indications and subpopulations, including muscle disorders, chronic pain, daytime fatigue, excessive sleepiness, fibromyalgia, and patients under 16.

According to the Second Circuit, Caronia was indicted on July 25, 2007, and then again under a Superseding Information — the subject of Caronia's appeal — on August 19, 2008. The Superseding Information charged Caronia with two misdemeanor offenses: (1) a two-pronged conspiracy to introduce a misbranded drug into interstate commerce in violation of 21 U.S.C. §§ 331(a) and 333(a)(2) in which Caronia: (a) knowingly and intentionally conspired to introduce Xyrem into interstate commerce when the drug was misbranded, and (b) marketed Xyrem with others for medical indications that were not approved by the U.S. Food & Drug Administration (FDA) when he knew and believed that Xyrem did not contain adequate directions for and warnings against such uses;[2] and (2) introducing a misbranded drug into interstate commerce in violation of 21 U.S.C. §§ 331(a)

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and 333(a)(2). Orphan Medical and Gleason were also charged for misbranding offenses, and both pled guilty.

Prior to trial, Caronia moved to dismiss the charges against him on First Amendment grounds. The court denied his motion, recognizing that the issues he raised were "very much unsettled, not only in this circuit but nationwide" and that Caronia was charged with a crime, the *actus reus* of which was speech protected by the First Amendment, but concluding that the FDCA's criminalization of speech was constitutional under the commercial speech doctrine because it was not more extensive than necessary to achieve FDA's objective.

Caronia's case was tried to a jury in October 2008. On October 23, 2008, a jury found him guilty of charge 1(a), but not guilty as to charges 1(b) and 2. Caronia was sentenced to one year of probation, 100 hours of community service, and a $25 special assessment. He appealed his conviction, arguing that the First Amendment does not permit the government to criminalize truthful and non-misleading promotion of an FDA-approved drug for off-label uses where the promoted use itself is not illegal and others are permitted to engage in the same type of speech.

The Majority's Decision

In an opinion authored by Circuit Judge Denny Chin, the Second Circuit vacated Caronia's conviction. The court first examined whether it was constitutionally permissible to prosecute Caronia "only for promoting an FDA-approved drug for off-label use." The court assumed without deciding that evidence of off-label promotion could be used to prove a drug's intended use and mislabeling, citing *Wisconsin v. Mitchell*, 508 U.S. 476, 489 (1993) (concluding that the First Amendment did not prohibit the use of speech to establish intent). However, it rejected the government's argument that Caronia's promotion served merely as evidence of his intent to market a misbranded drug and determined instead that the government "clearly prosecuted Caronia for his words — for his speech" and that the district court's jury instructions "led the jury to believe that Caronia's promotional speech was, by itself, determinative of his guilt" despite the fact that "[s]peech in aid of pharmaceutical marketing . . . is a form of expression protected by the Free Speech Clause of the First Amendment." *Sorrell v. IMS Health, Inc.*, 131 S.Ct. 2653, 2659 (2011).[3] The court then engaged in the two-step inquiry used in *Sorrell* to determine the constitutionality of the restriction. The court first considered whether the restriction was content- and speaker-based, and, finding that it was both, the court then determined whether the restriction withstood "heightened" First Amendment scrutiny.

Following the analysis and reasoning in *Sorrell*, the court concluded that the government's construction of the FDCA misbranding provisions imposed content-based restrictions because the construction distinguished between favored speech about government-approved uses of a drug and disfavored speech about non-government approved, off-label uses of a drug. The court also found that the restriction was speaker-based because it only targeted manufacturers and their representatives, while other speakers, such as doctors and academics, were not subject to the restriction. Because the government's construction of the FDCA provisions was content- and speaker-based, the court concluded that the restriction was subject to heightened scrutiny.

The court then examined the restriction under the four-part *Central Hudson* test. Under the *Central Hudson* test, first, the speech in question must concern lawful activity and must not be misleading in order to be protected by the First Amendment. Second, the government interest asserted to justify the restriction on speech must be substantial. Third, the restriction must directly advance the governmental interest "to a material degree," and fourth, the restriction must be "narrowly drawn" and not more extensive than necessary to serve the government interest.

The court held that the first two prongs of the *Central Hudson* test were "easily satisfied" because promoting off-label drug use concerns the lawful activity of off-label drug use and promoting off-label use is not itself false or misleading. Also, the court agreed that the government's interest in "preserving the effectiveness and integrity of the FDCA's drug approval process, and [its] interest in reducing patient exposure to unsafe and ineffective drugs" is substantial.

With regard to the third prong, the court held that because off-label use is not illegal, "it does not follow that prohibiting the truthful promotion of off-label drug usage by a particular class of speakers would directly further the government's goals." The court described the government's position as "paternalistic[]," stating that it "essentially legalizes the outcome — off-label use — but prohibits the free flow of information that would inform that outcome." The court concluded that the government could not satisfy the third prong of the *Central Hudson* test because "if the government's objective is to shepherd physicians to prescribe drugs only on-label, criminalizing manufacturer promotion of off-label use while permitting others to promote such use to physicians is an indirect and questionably effective means to achieve that goal."

Turning to the last prong of the test, the court held that the government's imposition of a "complete and criminal ban" on off-label promotion by manufacturers was more extensive than necessary because numerous less restrictive alternatives were available, such as developing warning or disclaimer systems or safety tiers for the off-label market, capping off-label prescriptions, or banning off-label use, among other options. The court rejected as "insufficient" the government's "conclusory assertions" that the court's proposed alternatives were less effective than the proposed construction of the FDCA and concluded that the government did not establish a "reasonable fit" among its interests in drug safety and public health, the lawfulness of off-label use, and its construction of the FDCA.

In closing, the court noted that its decision was limited to "FDA-approved drugs for which off-label use is not prohibited," and the court summarized its holding, stating 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."

Judge Livingston's Dissent

Circuit Judge Debra Ann Livingston dissented from the majority's opinion. Judge Livingston would have affirmed Caronia's conviction because, in her opinion, the government had done nothing more than use Caronia's off-label speech as evidence of motive or intent, which the First Amendment does not prohibit. Judge Livingston also stated that she disagreed with the majority's application of the *Central Hudson* test. Unlike the majority, Judge Livingston would have held that the prohibition on off-label speech directly advanced a substantial government interest and was narrowly tailored to further that interest. Likewise, she would have concluded that the prohibition on off-label promotion was narrowly tailored because drug manufacturers "are the precise group that the government must encourage to participate in the new drug approval process." Thus, Judge Livingston concluded, even if the prohibition on off-label promotion directly regulates speech, it is constitutional because it does so in a manner that directly advances a substantial government interest and in a way that is not more extensive than necessary.

Implications of the Court's Decision

The Second Circuit's *Caronia* decision is the latest in a series of collisions between FDA's regulatory scheme and the First Amendment. Over the last decade, the government has collected billions of dollars in fines and penalties from pharmaceutical and medical device manufacturers by alleging truthful off-label promotion of FDA-approved products. According to the *Caronia* decision, the First Amendment prohibits the government from prosecuting these companies solely on their truthful off-label speech. While pharmaceutical and medical device manufacturers have long argued that the First Amendment shields truthful off-label speech from prosecution, that argument has now been further strengthened by the Second Circuit's decision.

However, manufacturers should still proceed with caution in this area because the decision in *Caronia* does not close the door on future enforcement actions based on off-label promotion. First, the decision does not preclude the government from pursuing enforcement action based on misleading off-label speech (*e.g.*, failure to adequately disclose risks, overstatements of efficacy, inadequate substantiation of claims). Second, because the court reserved the question of whether the government may use off-label speech as evidence of an intent to misbrand, the government will likely continue to take the position that it can pursue enforcement action in cases of off-label promotion by claiming that it seeks to use off-label speech only as evidence of intent to misbrand and not to prosecute the off-label speech itself, or by relying on other theories of adulteration or misbranding not directly addressed by *Caronia*. It may be difficult, however, for the government to succeed in reframing its position in that manner in cases where the only basis for the criminal charge is the existence of an off-label intended use and the only evidence of the off-label intended use is truthful speech about that use. Lastly, FDA may argue that the decision is binding only in the Second Circuit, which includes three states — New York, Connecticut, and Vermont — and that manufacturers can still be prosecuted in other jurisdictions using the theory that the Second Circuit rejected.

The *Caronia* decision could also raise new questions about the validity of certain FDA positions that depend on the same content- and speaker-based restrictions on speech that were at issue in *Caronia*. The last major round of First Amendment litigation regarding off-label speech by manufacturers — the *Washington Legal Foundation* litigation in the D.C. Circuit in the late 1990s — focused on manufacturers' distribution of medical journal articles and other enduring materials. After *Caronia*, manufacturers and FDA may look at regulatory guidance such as FDA's Good Reprint Practices Guidance and FDA's Guidance on Responding to Unsolicited Requests for Off-Label Information in a different light.

Caronia is not the only recent case that may impact the government's prosecution of off-label promotion by manufacturers. On December 6, 2012, three days after the Second Circuit decided *Caronia*, the Ninth Circuit heard argument in *U.S. v. Harkonen*, an appeal of the 2009 conviction of Scott Harkonen, former Chief Executive Officer of Intermune, Inc., for wire fraud based on a press release that proclaimed the success of a clinical study for the drug, Actimmune. In the press release, InterMune claimed that patients treated with Actimmune for idiopathic pulmonary fibrosis, an off-label use of the drug, experienced a survival benefit and reduced mortality, when neither outcome was a trial endpoint. On appeal, Harkonen argued that the press release "expressed a scientific view" protected by the First Amendment, while the government contended that false statements made with an intent to defraud the public were not immune from prosecution just because they were scientific information.

Both the *Caronia* decision and the argument in the *Harkonen* case underscore the need for more clarity in the area of off-label promotion and the dissemination of off-label scientific information that is not false or misleading. In its First Amendment analysis in *Caronia*, the court emphasized the importance to public health of "ensur[ing] that decisions about the use of prescription drugs, including off-label usage, are intelligent and well-informed" through appropriate discussion of off-label use. This emphasis, combined with the threat of litigation based on the *Caronia* decision, may encourage FDA to expand or clarify opportunities for sharing truthful, non-misleading information with the medical community about off-label uses, including its guidance on responding to unsolicited requests for off-label information and its ongoing evaluation of its policies on scientific exchange, which were opened for public comment in December 2011.[4]

Until the Supreme Court more conclusively decides what (if any) off-label promotion the First Amendment permits the government to prohibit, there is likely to be continued confusion in the area. While the *Caronia* decision further changes the landscape with regard to off-label promotion, manufacturers should continue to monitor their promotional efforts carefully for off-label promotion until this legal issue is resolved conclusively.

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[1] *United States v. Caronia*, No. 09-5006, slip op. (2d Cir. Dec. 3, 2012).

[2] 21 U.S.C. § 331(a) prohibits the introduction or delivery for introduction into interstate commerce of a misbranded drug and § 333(a)(2) describes the penalties for intentional misleading or fraud in violation of the FDCA.

[3] In *Sorrell v. IMS Health, Inc.*, the U.S. Supreme Court examined the constitutionality of a Vermont statute that prohibited pharmaceutical companies and similar entities from using prescriber-identifying information for marketing purposes. The Court held that "speech in aid of pharmaceutical marketing" was protected by the First Amendment, so the law was subject to "heightened scrutiny," which the Court determined the law could not withstand.

[4] *See* U.S. Food and Drug Administration, Communications and Activities Related to Off-Label Uses of Marketed Products and Use of Products Not Yet Legally Marketed; Request for Information and Comments, 76 Fed. Reg. 81,508 (Dec. 28, 2011).