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SECOND CIRCUIT RECOGNIZES SIGNIFICANT FIRST AMENDMENT PROTECTIONS FOR OFF-LABEL PROMOTION

On December 3, the United States Court of Appeals for the Second Circuit issued a significant opinion in *United States v. Caronia*,[1] concerning the application of the First Amendment to pharmaceutical promotion. Relying in part on the Supreme Court's opinion in *Sorrell v. IMS Health, Inc.*,[2] the court held that under the First Amendment, 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."[3] This decision raises significant questions about the government's ability to prohibit truthful, non-misleading off-label promotional speech.

BACKGROUND

The Federal Food, Drug, and Cosmetic Act (FDCA) does not expressly prohibit off-label promotion of approved drugs or devices. Nevertheless, the Food and Drug Administration (FDA) frequently issues Warning Letters and untitled letters citing off-label promotion of approved drugs as violations of the FDCA's misbranding provisions.[4] The FDCA imposes criminal penalties for misbranding, including fines and imprisonment.[5] Claims of off-label promotion also have featured prominently in criminal and False Claims Act cases brought by the Department of Justice and State Attorneys General against manufacturers, many of which have resulted in significant settlements.

THE FACTS AND ARGUMENTS AT ISSUE IN CARONIA

In *Caronia*, the government alleged that Alfred Caronia, a sales representative for Orphan Medical, Inc. (now Jazz Pharmaceuticals) actively promoted Xyrem for off-label uses. In doing so, the government alleged that Caronia conspired to introduce a misbranded drug into interstate commerce. At trial, the government highlighted Caronia's promotion of Xyrem for unapproved indications including insomnia, fibromyalgia, and restless leg syndrome.[6] Although Caronia argued that his promotional statements constituted speech protected by the First Amendment, the district court rejected this argument and Caronia was convicted under 21 U.S.C. §§ 331(a) and 333(a)(1) for conspiracy to introduce a misbranded drug into interstate commerce. Caronia appealed to the Second Circuit. While that appeal was pending, the United States Supreme Court issued its opinion

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[1] *United States v. Caronia*, No. 09-5006, slip op. (2d Cir. Dec. 3, 2012) (Slip Op.).
[2] 131 S. Ct. 2653 (2011).
[3] Slip Op. at 51.
[4] Such letters typically assert, among other things, that such promotion is false or misleading in violation of FDCA section 502(a), and/or creates a new intended use, thus rendering the drug's labeling misbranded on the ground that it does not contain "adequate directions for use" for all of the drug's intended uses, in violation of section 502(f)(1).
[5] FDCA § 303(a), 21 U.S.C. § 333(a).
[6] Slip Op. at 15-16.

in *Sorrell*. This opinion held that a Vermont statute that restricted pharmaceutical manufacturers from using prescriber-identifiable information for marketing purposes violated the First Amendment.[7]

On appeal, Caronia again asserted his First Amendment argument. Specifically, he argued that the government was prosecuting him solely for his truthful speech, which should be protected under the First Amendment.[8] He also argued that, under the *Central Hudson* test for commercial speech restrictions, a prohibition on off-label promotion is not narrowly tailored to meet the government's interests and protect First Amendment rights.[9] He argued that *Central Hudson* required the government to rely on more focused alternatives to accomplish these goals.[10] In response, the government argued that it was not prosecuting Caronia on the basis of his speech. Instead, it was using his promotional statements as evidence of the creation of a new intended use for Xyrem, for which its label did not contain adequate directions for use.[11] The government also argued that its restrictions on off-label promotion are necessary to meet the government's legitimate public safety interests.[12]

SECOND CIRCUIT OPINION

A majority of the Second Circuit panel (2-1) agreed with Caronia's First Amendment arguments and reversed his conviction. First, the court rejected the government's argument that it was using Caronia's speech merely as evidence of a new intended use. The court "assume[d], without deciding, that such use of evidence of speech is permissible," but concluded that "the government's theory of prosecution identified Caronia's speech alone as the proscribed conduct."[13] The court emphasized that the government had highlighted Caronia's off-label promotion of Xyrem "over forty times" in its summation and rebuttal at trial, and had failed to argue even once that his promotion was "evidence of intent."[14] Moreover, the court noted that the government never alleged that Caronia's speech was false or misleading, or that he had engaged in some other form of misbranding, such as placing deficient labeling on a drug.[15] Therefore, the court concluded that the government had prosecuted Caronia for his speech.[16]

The court determined that such a prosecution "would run afoul of the First Amendment."[17] Looking to recent Supreme Court precedent, including *Sorrell*, the court found that off-label promotional speech such as Caronia's, which is made "in aid of pharmaceutical marketing," should receive some form of protection under the First Amendment.[18] Therefore, the court analyzed the government's restriction to determine what type of scrutiny it warranted and whether it could pass constitutional muster.

For three reasons, the court concluded that government's restriction warranted "heightened scrutiny." First, the court concluded that the restriction is "content-based" in that it prohibits speech regarding off-label uses, but does not prohibit speech about "approved uses," which are favored by

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[7] 131 S. Ct. at 2659.
[8] *See* Slip Op. at 3, 25.
[9] Brief for Defendant-Appellant, at 38, *United States v. Caronia*, No. 09-5006 (2d Cir. April 15, 2010).
[10] *Id.* at 38-42.
[11] Supplemental Brief for the United States, at 1-2, *United States v. Caronia*, No. 09-5006 (2d Cir. Aug. 29, 2011).
[12] *Id.* at 8.
[13] Slip Op. at 32 & n.10.
[14] Slip Op. at 28, 29.
[15] Slip Op. at 29 & 42 n.11.
[16] Slip Op. at 10.
[17] Slip Op. at 33.
[18] Slip Op. at 31 (quoting *Sorrell v. IMS Health, Inc.*, 131 S. Ct. 2653, 2659 (2011)).

the government. Second, the restriction is "speaker-based:" it targets "one kind of speaker," pharmaceutical manufacturers and their representatives, while allowing others, such as physicians, "to speak without restriction."[19] Finally, because the regulation imposes criminal penalties, it warrants "even more careful scrutiny" than non-criminal statutes.[20]

The court then concluded that the government could not justify its speech restriction even under the four-part intermediate scrutiny standard established by *Central Hudson Gas & Electric Company v. Public Service Commission*.[21] *Central Hudson* directs courts to ask four questions in determining whether a speech restriction is lawful:

1. whether the speech at issue "concerns unlawful activity or is misleading," and therefore can be prohibited;
2. "whether the asserted government interest is substantial;"
3. whether the restriction "directly advances the government interest asserted;" and
4. whether the restriction is "not more extensive than necessary to serve that interest."

The court quickly concluded that the first two prongs of the *Central Hudson* test were satisfied. The court noted that "promoting off-label drug use concerns lawful activity" and that off-label drug promotion "is not in and of itself false or misleading."[22] The court also found that the government's interests in drug safety and public health clearly are substantial.[23] With respect to the third and fourth prongs, however, the court concluded that the restriction on speech did not directly advance the government's legitimate interests and swept much more broadly than necessary.[24] Specifically, the court found that prohibiting truthful promotion of off-label drugs does not directly advance the government's interests in safeguarding FDA's drug approval process and protecting patients, particularly given that FDA permits off-label use of drugs by physicians.[25] The court also criticized the restriction for interfering with potentially informative and useful communications between pharmaceutical companies and the public.[26] Finally, the court found that a "complete and criminal ban" on off-label promotion is "more extensive than necessary" and that less speech-restrictive alternatives are available.[27] For example, FDA could develop disclaimer systems or safety tiers within the off-label market, require manufacturers to identify all intended indications when initially applying for FDA approval, impose non-criminal penalties, or (where off-label use is "exceptionally concerning") prohibit off-label use entirely.[28] For these reasons, the court stated that construing the FDCA as prohibiting "the truthful off-label promotion of FDA-approved prescription drugs" violates the First Amendment.[29]

THE DISSENT

In dissent, Judge Debra Ann Livingston argued that the majority opinion departs from well-established precedent, and that Caronia was properly prosecuted for conspiring to misbrand Xyrem. Unlike the majority, the dissent found that the government had, indeed, used Caronia's speech

[19] Slip Op. at 40.
[20] Slip Op. at 34.
[21] 447 U.S. 557 (1980).
[22] Slip Op. at 42.
[23] Slip Op. at 42.
[24] Slip Op. at 43-51.
[25] Slip Op. at 43-47.
[26] Slip Op. at 44-47.
[27] Slip Op. at 48.
[28] Slip Op. at 48-50.
[29] Slip Op. at 51.

merely as evidence of a new intended use, and prosecuted based on a misbranding violation caused by that new intended use. The dissent then noted that "[i]t is well settled that 'the First Amendment does not prohibit the evidentiary use of speech to establish the elements of a crime or to prove motive or intent.'"[30] Further, even if this reliance on Caronia's speech implicates the First Amendment, and therefore requires analysis under *Central Hudson* and *Sorrell*, the dissent concluded that the misbranding provision should survive this scrutiny.[31] It agreed that the misbranding provision—like the law in Sorrell—targets particular types of content and speakers, but argued that this narrow focus is necessary to directly advance the government's interest in encouraging drug manufacturers to seek FDA approval.[32] It also concluded that prohibiting off-label promotion is the "least restrictive way of advancing the government's interests," and that the alternative means suggested by the majority would be ineffective.[33]

LOOKING FORWARD

Caronia represents a significant affirmation of First Amendment principles for speech related to pharmaceutical marketing. For the first time, a federal court has placed First Amendment limitations on the government's ability to criminally prosecute off-label promotion by pharmaceutical manufacturers. The case therefore has potentially far-reaching implications for government regulation in this area.

Precisely what the long-term impact of the case will be, however, remains to be seen. *Caronia* is currently binding only on courts in the Second Circuit, and the government is likely to appeal the decision to the *en banc* Second Circuit and/or seek certiorari in the U.S. Supreme Court. The *Caronia* court specifically limited its holding to "FDA-approved drugs for which off-label use is not prohibited," and declined to hold that "FDA cannot regulate the marketing of prescription drugs."[34] For example, the court "assume[d], without deciding," that the government can use off-label promotion as evidence of a new intended use, for which a drug's labeling lacks adequate directions.[35] The court also made clear that the government still can prosecute off-label promotional speech that is false or misleading. Nevertheless, the *Caronia* case has established a clear precedent in favor of First Amendment protection for truthful, non-misleading off-label promotion. The development of continued jurisprudence around *Caronia*, as well as the government's response, bears careful watching.

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[30] Slip Op. Dissent at 6 (quoting *Wisconsin v. Mitchell*, 508 U.S. 476, 489 (1993)).
[31] Slip Op. Dissent at 19.
[32] *See* Slip Op. Dissent at 20-25.
[33] Slip Op. Dissent at 24.
[34] Slip Op. at 51.
[35] Slip Op. at 32, n. 10.