Client Alert.

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Second Circuit Delivers Blow to Off-Label Promotion Prosecutions in *U.S. v. Caronia*

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In a much-anticipated decision, a federal court of appeals has ruled that the government cannot criminally prosecute pharmaceutical manufacturers and their representatives under the Food, Drug and Cosmetics Act ("FDCA") for truthful, non-misleading speech promoting the off-label uses of FDA-approved drugs. On December 3, 2012, the Second Circuit reversed the conviction of Alfred Caronia, a pharmaceutical sales representative, for conspiracy to introduce a misbranded drug into interstate commerce, in violation of the FDCA.[1] Over a strong dissent, the majority held that Caronia's conviction for off-label promotion of the drug Xyrem violated his constitutional right of free speech under the First Amendment. The *Caronia* decision seriously challenges the legal underpinnings of the government's prosecution of off-label promotion, but is unlikely to signal a retreat from ongoing aggressive enforcement by the government.

BACKGROUND

The FDA does not regulate the practice of medicine, and nothing prohibits physicians from prescribing drugs and devices off-label (i.e., for uses not approved by the FDA). In fact, physicians widely employ off-label uses, particularly in specialties such as oncology and pediatrics. In order to balance the risks and benefits of off-label uses, physicians need reliable and up-to-date scientific information concerning such uses. Drug and device manufacturers are an important source for such information. The government, however, fears that allowing the free flow of such information will encourage companies to bypass the regulatory approval process and undermine the FDA's mission to ensure the safety and efficacy of drugs and devices. In recent years, a steady stream of criminal prosecutions has been based on the premise that off-label promotion constitutes "misbranding" under the FDCA.[2] In short, the government considers drugs and devices marketed for an unapproved use to be misbranded because their labeling cannot include "adequate directions for use" for the off-label use. Precisely what manufacturers can and cannot say and do in connection with physicians' off-label uses of their products before crossing the line into "promotion" is often unclear. As a result, companies must resort to monitoring the latest multimillion dollar settlements to determine where the government is drawing those lines.

The legal theories under which off-label promotion becomes a criminal violation of the FDCA have received little judicial scrutiny. Although First Amendment challenges have been raised in off-label promotion cases, most have been withdrawn or resolved as part of the global settlement of charges against companies facing criminal healthcare fraud prosecutions.[3] Caronia's First Amendment challenge is one of the few to survive that process and result in a written opinion.

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[1] *U.S. v. Caronia*, No. 09-5006-cr (2d Cir. Dec. 3, 2012), *available online at* http://www.ca2.uscourts.gov/decisions/isysquery/e6fa2217-9e3d-46cb-a111-cf9756f39663/3/doc/09-5006_complete_opn.pdf.

[2] 21 U.S.C. §§ 331(a), 352(f).

[3] For example, in September 2010, Allergan, Inc. dismissed a challenge to the FDA's regulation of off-label speech as violating the First Amendment in order to resolve a civil and criminal investigation. In addition to dismissing the First Amendment case, Allergan agreed to pay fines totaling $600 million, and pled guilty to one misdemeanor charge related to its off-label promotion of the drug Botox.

CARONIA'S PROMOTION OF XYREM AND RESULTING PROSECUTION

Alfred Caronia was an employee of Orphan Medical, Inc. (currently Jazz Pharmaceuticals), the developer of Xyrem, a nervous system depressant. In 2002 and 2005, the FDA approved Xyrem for two specific uses related to the treatment of narcolepsy. Xyrem's active ingredient, gamma-hydroxybutryate (federally classified as the "date rape drug"), contributed to certain side effects that led to the inclusion of a "black-box" warning on Xyrem's label. The black box warning stated, among other things, that Xyrem's safety and efficacy had not been established in patients under 16, and that the drug had had very little experience in elderly patients. The FDA also regulated Xyrem's distribution by allowing only one Missouri pharmacy to distribute the drug nationally.

In 2005, a doctor acting as a government cooperator recorded two conversations with Caronia in which Caronia promoted Xyrem for unapproved uses, including muscle disorders and chronic pain. Caronia also offered to introduce the cooperator to a doctor hired by Orphan to promote Xyrem through its speaker program, and directed the cooperator to list specific insurance diagnosis codes when prescribing Xyrem. The government argued at trial that these conversations constituted off-label promotion that violated the FDCA's misbranding provisions. The government did not allege that Caronia's statements were false and misleading. The jury convicted Caronia, and he was sentenced to one year of probation. He then appealed to the Second Circuit.

THE SECOND CIRCUIT DECISION

The Second Circuit concluded that Caronia had been prosecuted for his statements about Xyrem's off-label uses, and that his conviction must be overturned because his speech was protected by the First Amendment.

Following the framework articulated by the Supreme Court last year in *Sorrell v. IMS Health*,[4] the Second Circuit held that the restriction on Caronia's speech was entitled to "heightened scrutiny." The court held that the government's interpretation of the FDCA's misbranding provisions to prohibit off-label promotion was an impermissible content-based restriction because speech about the government-approved use of the drug is permitted, while other speech about the drug (such as its unapproved uses) is prohibited, even though off-label use of the drug itself is not. The government's construction of the FDCA and its regulations was also found to be an impermissible speaker-based restriction because it targeted one type of speaker (pharmaceutical manufacturers) while allowing other speakers, such as doctors and scientists, to speak without restrictions or consequences. For these reasons, heightened scrutiny was appropriate.

Next, the court applied the *Central Hudson*[5] test used to analyze restrictions on commercial speech, and found that prosecuting Caronia for promotional speech did not pass constitutional muster. It determined that restricting speech regarding off-label uses did not directly advance the government's interest in preserving the effectiveness and integrity of the FDA's drug approval process, and that this restriction was not narrowly drawn. Other, less restrictive alternatives were available. The court noted that prohibition of off-label promotion "paternalistically" interferes with the free flow of relevant treatment information to physicians and patients and inhibits informed decision-making.

The court therefore declined the government's invitation to construe the FDCA's misbranding provisions as criminalizing the mere promotion of a drug's off-label use by pharmaceutical manufacturers and their representatives because this construction would violate the First Amendment. Rather, the court ruled that the government cannot prosecute

[4] 131 S. Ct. 2653 (2011).

[5] 447 U.S. 557 (1980).

pharmaceutical manufacturers and their representatives under the FDCA for speech promoting the lawful, off-label use of an FDA-approved drug.

SPEECH AS EVIDENCE OF INTENT – A LOOPHOLE IN THE COURT'S ANALYSIS?

The court considered, but did not decide, an alternative theory of misbranding that will surely be the focus of future litigation. The government argued that Caronia's speech regarding off-label uses was merely presented as evidence of Xyrem's intended uses, and that Xyrem's labeling failed to provide any directions for these intended uses. Under the FDCA and implementing regulations, a drug or device is misbranded if its labeling does not contain directions by which a lay person can safely use it for the purposes for which it was intended. Intended uses for the drug or device can be demonstrated by oral or written statements by the manufacturers and their representatives.

The majority assumed that such use of "speech as evidence" was permissible, but rejected the government's argument because "that was not what happened in this case." The court specifically cited the government's repeated arguments during summation and rebuttal that Caronia engaged in criminal conduct by promoting and marketing Xyrem's off-label uses. It also examined the jury instructions given by the trial judge. The *Caronia* majority held that the record made clear "that the government prosecuted Caronia *for* his promotion and marketing efforts."[6] The majority thus reasoned that it did not need to decide whether the First Amendment "permits the government to prove intended use by reference to promotional statements made by drug manufacturers or their representatives."

Although the majority disagreed with the government's position that Caronia's speech was only presented at trial as evidence of Xyrem's intended uses, the court did not foreclose the use of otherwise protected speech as evidence of a drug's or device's intended uses in future misbranding prosecutions.

ENFORCEMENT IMPLICATIONS

The *Caronia* decision squarely rejects the government's position that promotional speech itself constitutes misbranding under the FDCA, which has been a hallmark of off-label promotion prosecutions. In that sense, *Caronia* is a significant development. The impact of *Caronia* will depend, in part, on how the government responds to the decision. It may seek rehearing by the full Second Circuit and/or review by the Supreme Court. If the First Amendment analysis of *Caronia* survives, the government may have to adjust its prosecution theories to avoid the First Amendment issue. For example, it may employ the "promotion as evidence of intended use" theory that was left open by the Second Circuit, in which case the viability of that approach to misbranding prosecutions is likely to be the subject of litigation in future prosecutions. Or the government may focus on cases where the promotion is untruthful or accompanied by fraudulent conduct. In light of the Department of Justice's continued commitment to aggressive prosecution of healthcare fraud, while the *Caronia* decision may alter the government's theories and strategies, it is unlikely to result in a slowdown in prosecutions.

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[6] *U.S. v. Caronia*, No. 09-5006-cr (2d Cir. Dec. 3, 2012) (emphasis in original).

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