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Off-Label Marketing Questioned as a Viable Criminal Theory – But Stay Tuned

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On December 3, 2012, a divided Second Circuit held in *United States v. Caronia*¹ (“*Caronia*”) that the misbranding provisions of the Federal Food, Drug, and Cosmetic Act (“FDCA”) do not criminalize “the truthful off-label promotion of FDA-approved prescription drugs.” The two-judge majority based its holding primarily on last year’s Supreme Court decision in *Sorrell v. IMS Health, Inc.*,² which held that “[s]peech in aid of pharmaceutical marketing...is a form of expression protected by the Free Speech Clause of the First Amendment.”

The *Caronia* decision is a major blow to one of the government’s theories of criminal liability for off-label marketing – that promotion of a drug through commercial speech for a use that does not appear on the labeling approved by the Food and Drug Administration (“FDA”) for the drug is **itself** illegal under the FDCA. Because it may have such a major impact on the government’s strategy, we think it unlikely that *Caronia* will be the last word on the subject. The government may seek *en banc* review by the full Second Circuit or an appeal to the Supreme Court or both, especially given the dissent’s strongly-worded opinion that suggests the *Caronia* decision could undermine the FDCA’s entire regulatory scheme. Thus, while it remains to be seen whether *Caronia* is a watershed moment or a narrow departure from current law, it should embolden the pharmaceutical industry to continue to press the argument that providing factual information that is not false or misleading to physicians and patients about potential off-label uses of FDA-approved drugs should not be unlawful.

Case Summary

Background

Alfred Caronia was a pharmaceutical sales representative for Orphan Medical, Inc., a company that manufactured Xyrem, a powerful central nervous system drug approved by the FDA in 2002 to treat narcolepsy patients who suffer from weak or paralyzed muscles. In November 2005, Xyrem was approved by the FDA to treat narcolepsy patients with excessive daytime sleepiness. In 2005, Caronia was hired as a specialty sales consultant to promote Xyrem, and began marketing Xyrem with the assistance of physicians paid by Orphan to speak to other physicians about the drug. That same year, the federal government began an investigation of Orphan and its paid physician consultant and, in the process, recorded two conversations in which Caronia made unprompted promotional statements regarding “off-label” uses of Xyrem to a physician.

Caronia was tried and convicted by a federal jury in 2008 for conspiring to introduce Xyrem into interstate commerce for unapproved uses which render the drug “misbranded” under the FDCA, a misdemeanor.

¹ 2012 WL 5992141.

² 131 S.Ct. 2653, 2659 (2011).

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Caronia appealed his conviction on the basis that the misbranding provisions of the FDCA unconstitutionally restrict his speech by prohibiting and criminalizing off-label promotion in the form of truthful and non-misleading promotion of an FDA-approved drug to physicians for off-label use, where such use is not itself illegal.

Second Circuit Holding

A divided three-judge panel of the Second Circuit, in a 52-page majority opinion, found that the government's interpretation of the FDCA in charging and trying the case criminalized the "simple promotion" of a drug's off-label use in violation of Caronia's First Amendment right to free speech.

The majority rejected the government's contention that it did not prosecute Caronia for his speech itself, but rather that they used his speech as evidence of his intent to conspire to introduce Xyrem for an off-label purpose in violation of the FDCA. The Court reviewed the trial record and found "over forty times" where the government argued that Caronia's off-label promotion of Xyrem was **itself** a violation the FDCA, and that neither the government nor the lower court limited the use of the promotional statements to evidence of intent, rather than as evidence of violations of the FDCA themselves. The jury instructions were equally as unequivocal regarding the statements as violations of the FDCA: "the district court flatly stated to the jury that pharmaceutical representatives are prohibited from engaging in off-label promotion ... this specific instruction – together with the government's summation – would have led the jury to believe that Caronia's promotional speech was, by itself, determinative of his guilt."

Since it concluded that the government's theory criminalized Caronia's speech, the majority engaged in a lengthy First Amendment analysis, relying heavily on the Supreme Court's decision and holding in *Sorrell*, which was rendered during the course of Caronia's appeal. In *Sorrell*, the Supreme Court held that speech in aid of pharmaceutical marketing was protected First Amendment speech. Relying on *Sorrell*, the majority found that the government's restriction of Caronia's speech is subject to heightened scrutiny on the basis that it was both "content-based" and "speaker-based."

First Amendment Analysis

Without specifying whether it was applying strict scrutiny or heightened scrutiny in this case, the majority held that the government's interpretation of the FDCA criminalizing Caronia's speech did not pass either test because it was not directly advancing the FDA's "interest in reducing patient exposure to off-label drugs or in preserving the efficacy of the FDA drug approval process because the off-label use of such drugs continues to be generally lawful." The majority recognized that while doctors are free under the FDCA to prescribe a drug for any purpose, whether it be an on-label or off-label use, the government had historically sought to criminalize marketing which promoted off-label uses, even if doctors used the drug for such a purpose. The majority stated that prohibiting the off-label promotion by a pharmaceutical manufacturer while allowing off-label prescription by doctors "'paternalistically' interferes with the ability of physicians and patients to receive potentially relevant treatment information ... [that] could inhibit, to the public's detriment, informed and intelligent treatment decisions." Further, the prohibition against truthful and not misleading promotion of off-label uses of drugs was not narrowly-drawn to further the interests served by the restriction, listing various ways in which the government could inform, limit, or prevent off-label use of some or all FDA-approved drugs.

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Precedential Effect

The majority seemingly sought to minimize the impact of its extensive and broad ruling, stating: “we conclude 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.” That statement, however, would seem to undermine the government’s historically aggressive prosecutorial approach in off-label marketing cases.

In a 30-page, sharply-worded dissent, Circuit Judge Livingston strongly condemned the majority’s opinion and expressed concern that it could undermine the entire regulatory scheme for prescription drugs. “By holding ... that Caronia’s conviction must be vacated ... the majority calls into question the very foundations of our century-old system of drug regulation.”

Analysis

Statutory Scheme and its Historical Application

Off-label marketing of pharmaceutical products is not expressly prohibited under the FDCA. Rather, the government has historically addressed the marketing of unapproved uses of approved drugs by alleging that the manufacturer of the drug has violated FDCA Section 301(a) by introducing a “misbranded” drug into interstate commerce. Under this theory, the drugs are allegedly “misbranded” under FDCA § 502(f)(1) because they lack “adequate directions for use”, since the off-label use would not be included in the drug’s directions.³ FDA’s regulations define “adequate directions for use” as “directions under which the layman can use a drug safely and for the purposes for which it is intended.” 21 C.F.R. § 201.5. FDA’s regulations further define “intended use” to mean “the objective intent of the persons legally responsible for the labeling of drugs.” 21 C.F.R. § 201.128. The requisite intent to misbrand under the regulations can be demonstrated by “such person’s expressions or may be shown by labeling claims, advertising matter, or oral or written statements by such persons or their representatives.” *Id.*

Drugs labeled as “prescription drugs” are exempt from the requirement to be labeled with “adequate directions for use” (in part because they cannot be used safely by a layperson) **provided** the drug’s labeling contains “adequate information for its use, including indications, effects, dosages, routes, methods, and frequency and duration of administration, and any relevant hazards, contraindications, side effects, and precautions under which practitioners licensed by law to administer the drug can use the drug safely and **for the purposes for which it is intended, including all purposes for which it is advertised or represented.**” 21 CFR 201.100(c)(1) (emphasis added). Therefore, the FDA and Department of Justice have historically and routinely asserted that a manufacturer or distributor of a prescription drug can “misbrand” a drug by representing or advertising the drug for a use that is not adequately set forth in the drug’s labeling.

From a policy perspective, the FDA has aggressively pursued misbranding cases to protect the integrity of the preapproval process. The concern is that off-label promotion by drug companies creates a disincentive for the companies to pursue FDA approval of new indications which could lead

³ In contrast, the promotion of a medical device for an off-label use causes the device to be either “adulterated” under FDCA § 501(f) (Class III devices) or “misbranded” under FDCA § 502(o) (for Class II devices) of the FDCA.

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to wide use of drugs for indications that have not been studied, reviewed, or approved by FDA, thereby potentially jeopardizing public safety.⁴

Drug manufacturers facing allegations of misbranding due to a lack of adequate directions for an unapproved use frequently enter into consent decrees with the government in order to avoid possible collateral consequences to an enforcement action, including debarment from federal third party payor programs (e.g., Medicaid, Medicare Part D, Federal Supply Schedule, TRICARE, etc.). These consent decrees have often included an agreement on the part of the drug manufacturer to disgorge all profits gained as result of the sale of allegedly misbranded drug products, and may include fines and penalties paid to the government for violations of the FDCA or the False Claim Act, resulting from the submission of claims to Medicare or Medicaid for unapproved uses of the drug. The government has made headlines with record-setting fines in 2011 and 2012 on off-label marketing cases, including a \$3 billion settlement with another major drug manufacturer this past summer for, among other things, allegedly promoting an FDA-approved drug for unapproved uses. State governments are also getting in on these cases.

What does *Caronia* mean for the future of off-label marketing?

Will the *Caronia* decision stem the tide of these high-stakes cases? Does it mean that pharmaceutical sales representatives can – at least in those states comprising the Second Circuit – truthfully answer questions from physicians related to off-label uses of drugs without fearing criminal retribution? Does it go further, and permit companies and their agents to make affirmative statements about off-label uses of their drugs in the absence of unsolicited requests? If the answer to the second or third question is yes, does that, as the dissent suggests it could, begin to erode the broader purpose of the FDA's statutory and regulatory scheme, ultimately allowing pharmaceutical manufacturers to exert undue influence on physicians and leading to the sale of drugs for unapproved uses that could potentially harm patients?

The effect of the Second Circuit's ruling in *Caronia* remains to be seen. Assuming other courts embrace the majority's rationale, the government may have difficulty prosecuting pure speech-based claims that are not false or misleading, at least in instances where the marketer is responding to a question by a physician. That said, it is likely the government will continue to pursue these claims in such a way as to make clear that statements promoting off-label usage are simply evidence of the intent of the person standing accused of the violation. In other words, it may be a situation where the government attempts to avoid the First Amendment issues in the way it charges the violations and argues its cases. On the other hand, courts may broadly construe the *Caronia* opinion to allow companies and their representatives to speak openly – so long as the statements made are truthful and not misleading – to physicians and patients about off-label uses of FDA-approved drugs.

Because the ruling only applies in the Second Circuit, and most pharmaceutical companies market their drugs nationally and internationally, it is unlikely that pharmaceutical companies will or should change their behavior, or their compliance procedures for their off-label marketing at this point. While the government has not commented on whether it intends to appeal the decision to a full panel of the Second Circuit or the Supreme Court, that possibility remains.

⁴ Note that FDA has always recognized the ability of a health care provider to use a legally marketed product off-label in the practice of medicine. FDA has also recognized that there are certain circumstances where the discussion of unapproved uses is not promotional and supports legitimate scientific and educational purposes. See e.g., FDA Guidance for Industry: Industry-Supported Scientific and Educational Activities (1997) and FDA Guidance for Industry: Good Reprint Practices for the Distribution of Medical Journal Articles and Medical or Scientific Reference Publications on Unapproved New Uses of Approved Drugs and Approved or Cleared Medical Devices (2009).

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It should be noted that even if the *Caronia* decision is upheld, the government will not be without tools with which it can enforce the prohibition against the marketing and sale of drugs for unapproved uses. Nevertheless, while the sledgehammer of the federal health care regulatory scheme cannot be taken lightly, companies and individuals may be emboldened to look harder at impending or actual charges relating to off-label marketing when evaluating a case and considering settlement.

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