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THE RECORDER

IN PRACTICE

Off-label promotion: still a crime?

Federal appellate courts are poised to narrow the government's ability to prosecute under FDCA

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White-Collar Crime

On Dec. 3, 2012, the U.S. Court of Appeals for the Second Circuit issued a decision in *United States v. Caronia* that has the potential to turn the criminal enforcement scheme of the Federal Food, Drug and Cosmetic Act, or FDCA, on its head. A majority of the three-judge panel held that the FDCA cannot be construed to "criminalize the promotion of a drug's off-label use" because such a construction would be at odds with First Amendment free speech rights. As the dissenting panel member noted, the *Caronia* ruling "calls into question the very foundations of our century-old system of drug regulation."

Just three days later, on Dec. 6, a Ninth Circuit panel heard a similar First Amendment challenge to the wire fraud conviction of former InterMune Inc. CEO W. Scott Harkonen for allegedly false and misleading statements made in a press release regarding a clinical study for the drug Actimmune. Though Harkonen was not convicted under the FDCA (he was found not guilty of misbranding at trial), his appeal still stands to have a significant effect on determining what pharmaceutical companies and their sales representatives can and cannot say in promoting drugs.

With potential bicoastal ramifications, the *Caronia* decision and *Harkonen* case warrant further attention and comparison.

FDCA: THE REGULATORY SCHEME

The FDCA regulatory scheme is built upon the precept that a drug must be approved by the FDA before it can enter the stream of interstate commerce. When approving a drug, the FDA determines not only that the drug is safe for use by the public, but also the particular uses for which the drug is safe. These approved uses, and instructions for how to safely take or employ the drug for these uses, appear on what is known as the "label." Physicians are not bound by the label when prescribing drugs to patients, as such a requirement would improperly impinge upon a doctor's ability to exercise medical judgment, but FDA guidance and practice has heretofore restricted pharmaceutical companies and their sales representatives from promoting beyond the label. Any promotion of a drug that does not comport with the instructions and restric-

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tions on the label is considered "off-label," and has long subjected pharmaceutical companies to intense regulatory and enforcement scrutiny. Such scrutiny often has resulted in hefty settlements and fines with the government.

Significantly, nothing in the FDCA explicitly prohibits off-label promotion, although the statute does make it a crime to introduce a drug into interstate commerce that lacks adequate instructions for safe use for its intended purpose. Such a drug is considered "misbranded." A drug may also be misbranded if its label or container is false, misleading or otherwise defective, or if the drug is unsafe even if used in accordance with its label. One long-standing way the government has argued a drug is misbranded is by pointing to evidence that the drug was promoted to physicians or the public for unapproved uses, for which the label will lack instructions.

'UNITED STATES V. CARONIA'

Alfred Caronia was a specialty sales consultant promoting the drug Xyrem for Orphan Medical Inc. Xryem is approved to treat narcolepsy patients who experience cataplexy or who have excessive daytime sleepiness. Xyrem's label had a "black box" warning — a warning the FDA requires to be placed on the label inside a black box — stating that Xyrem's safety and efficacy has not been established in patients under age 16, and that there is "little experience" with the drug among the elderly. Not only did Caronia purportedly tell at least one physician, who was cooperating with the government, that Xyrem could be used to treat fibromyalgia, periodic leg movement, restless leg, daytime fatigue and Parkinson's disease, but in apparent contravention of the black box warning, he allegedly promoted the drug as "very safe" for patients as young as 14 and older than 65.

As a result, Caronia was charged with conspiring to introduce and introducing a misbranded drug into interstate commerce, in violation of the FDCA. A federal jury convicted Caronia only of the conspiracy charge, and he was sentenced to one year of probation and 100 hours of community service.

The Second Circuit found that the entirety of the government's prosecution theory was based on Caronia's "mere off-label promotion," i.e., his promotional speech. The court relied on statements made by the government at trial, particularly from its summation and rebuttal, arguing that Caronia engaged in criminal conduct by virtue of promoting Xyrem for off-label uses. Additionally, the court found no indication that the government meant for Caronia's speech to be considered anything other than the crime itself, such as evidence of intent or evidence of some other form of misbranding. The district court also instructed the jury that a drug manufacturer and its employees are prohibited from promoting a drug for off-label uses. Accordingly, the Second Circuit concluded the jury must have believed Caronia's promotional speech alone was enough to establish his guilt under the FDCA, and must have convicted Caronia on that basis. Turning next to the FDCA's misbranding provisions, the panel held that the only constitutionally permissible interpretation of the statute required that it not be held to criminalize mere off-label promotion. Any conviction under the FDCA based solely on promotion of a drug's off-label uses, therefore, violated the First Amendment's free speech guarantee.

The dissent agreed that Caronia could not be convicted for his speech alone, but was persuaded by the government's argument that Caronia's prosecution was not for his speech; rather, Caronia's speech was evidence of his intent to sell Xyrem for off-label purposes. Because the drug's label did not contain adequate instructions for these off-label uses, it was misbranded, and Caronia's conviction did not violate the First Amendment.

Importantly, the Caronia majority noted that false or misleading off-label promotion (of which

Caronia was not accused) remains unprotected by the First Amendment.

'UNITED STATES V. HARKONEN'

By contrast, InterMune's Harkonen was charged with making false and misleading statements in connection with the promotion of Actimmune, a drug approved by the FDA for the treatment of chronic granulomatous disease and severe, malignant osteopetrosis. As CEO of InterMune, Harkonen allegedly touted the results of an Actimmune clinical study as reducing mortality in patients with mild to moderate idiopathic pulmonary fibrosis, a fatal lung disease, by 70 percent. In the eyes of the FDA, however, the study was a failure and did not show a statistically significant effect of the drug.

Harkonen was tried on misbranding charges under the FDCA and wire fraud, but convicted only of the latter. On appeal, Harkonen argued that whether the results of a study demonstrate a certain effect is a hotly contested topic of scientific debate on which reasonable minds could disagree; convicting him of expressing a honestly held scientific viewpoint thus violated his First Amendment rights. The government, on the other hand, argued that it can criminally punish anyone who makes false and misleading statements about the statistical significance of a clinical study.

LOOKING FORWARD

The Second Circuit's ruling in *Caronia* likely represents a substantial victory for the pharmaceutical industry, from which the FDA has long exacted multimillion-dollar off-label promotion settlements. In the event that the Ninth Circuit issues a decision in *Harkonen* that echoes the limits on the FDCA apparently erected by the *Caronia* panel, the FDA's regulatory and enforcement powers will only further diminish, setting the stage for a final determination by the Supreme Court.

In the meantime, it is doubtful that the government will cease its off-label promotion investigations and prosecutions. This is especially true outside of New York, Connecticut and Vermont, the only states actually bound by *Caronia*. To change corporate and compliance policies with respect to off-label promotion now, in an immediate reaction to *Caronia*, would be premature. It may, however, be an opportune time to negotiate favorable settlements in pending off-label investigations and private lawsuits.

Nevertheless, even under *Caronia*, pharmaceutical companies and their counsel need to be particularly mindful of ensuring that sales representatives understand that liability for false or misleading promotional statements remains unchanged. And conveying an honestly held scientific viewpoint regarding a drug or medical device could turn into a *Harkonen*-like legal battle over whether such a statement was false and misleading commercial speech, and therefore unprotected by the First Amendment. Furthermore, the majority in *Caronia* did not explicitly decide whether speech may be used as evidence of intent to introduce a misbranded drug into interstate commerce, though the dissent made its position clear that doing so would not violate the First Amendment.

While a period of uncertainty will continue pending the Ninth Circuit's decision in *Harkonen* and potential Supreme Court resolution of *Caronia*, one thing is clear: The government has a great deal to lose in this potential narrowing of the FDCA, and it's not likely that regulators and enforcers will go down without a fight.

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