A landmark appeals court ruling that the government cannot prosecute pharmaceutical manufacturers under the FD&C Act’s misbranding provisions solely for off-label promotion likely will reshape the FDA and Justice Department’s approach to bringing such actions but will not foreclose them, industry attorneys say.

In a 2-1 opinion issued Dec. 3, a panel of the Second Circuit U.S. Court of Appeals said the government cannot prosecute manufacturers or their representatives under the FDCA for speech promoting the lawful, off-label use of an FDA-approved drug.

In so ruling, the court threw out the misdemeanor conviction of Alfred Caronia, a former Jazz Pharmaceuticals PLC sales representative. Caronia’s off-label promotion of the wakefulness drug Xyrem (sodium oxybate) led to a jury finding him guilty under the FDCA of conspiracy to introduce a misbranded drug into interstate commerce.

The decision appears to mark the first time that a criminal misbranding conviction under the FDCA has been overturned on First Amendment grounds.

The decision also could reduce the government’s leverage to extract large monetary settlements and corporate integrity agreements from pharmaceutical companies in cases brought under the FDCA, attorneys said. Such cases typically settle because if companies go to trial they face the risk of criminal conviction and exclusion from federal health care programs, such as Medicare and Medicaid.

The Caronia decision will have the effect of “shrinking the conduct that is the subject of settlements,” said Jennifer Bragg, a partner in the health care and life sciences group of Skadden, Arps, Slate, Meagher & Flom.

Impact On Future Enforcement

The impact of the Second Circuit’s decision on federal government enforcement under the FDCA will depend, in part, upon the government’s procedural response to the ruling. The effect of the court’s holding is technically limited to the three states within the Second Circuit: New York, Connecticut and Vermont. The government could seek further review of the decision, either by requesting a rehearing en banc by all the judges in the Second Circuit or filing a petition for certiorari to the Supreme Court. However, some observers suggest a cert petition would be unlikely, given recent Supreme Court decisions that have bolstered free speech protections under the First Amendment.

Beyond the immediate procedural questions, several attorneys said that although the majority holding does not foreclose the prosecution of cases related to off-label promotion, it could change the government’s approach to pursuing such actions. It also could cajole FDA to issue regulations or guidance clarifying issues surrounding off-label promotion.

Meredith Manning, co-director of Hogan Lovells’ pharma and biotech practice group, said the majority appeared concerned that the government was taking a shortcut in its burden of proof in misbranding cases. “It’s putting FDA to the test and saying you have to more clearly define what is false or misleading in these circumstances or you have to think twice about going to criminal penalties,” she said.
Manning said the government potentially could still make a case that promotional statements about off-label use are false or misleading. “I don’t think it means that prosecutions are impossible, I just think it means they’re harder,” she said.

Similarly, Coleen Klasmeier, who heads Sidley Austin’s food, drug and medical device regulatory practice, said the decision “ought to give the government pause” before pursuing such cases. Klasmeier represents a coalition of drug and medical device groups, known as the Medical Information Working Group (MIWG), that filed an amicus curiae brief in the Caronia case.

Several attorneys predicted the decision would affect cases in the investigation stage, forcing DoJ to move away from simple off-label promotion to focus more on whether there is evidence of false or misleading information or the withholding or concealment of information related to the off-label use that is being promoted.

Bragg said the decision might not reduce the number of settlements between pharmaceutical manufacturers and the government because companies must still consider the risks of taking a case to trial. However, it will change and reduce the scope of the cases and the potential monetary damages, and it could give companies more strength in their settlement negotiations, she said.

On the regulatory front, Manning said the Caronia decision might spur FDA to respond to industry’s requests for more clarity around issues related to off-label promotion.

In July 2011, several members of the MIWG submitted a citizen petition requesting FDA clarify regulations and policies in four areas of off-label communications: scientific exchange of information on investigational products; sharing information with formulary committees and payers; providing independent third-party clinical practice guidelines; and responding to unsolicited requests for information (“FDA Pressed To Clarify Permissible Formulary, Clinical Guideline Communications” – “The Pink Sheet” DAILY, Jul. 5, 2011).


However, Klasmeier said she worried that the Caronia decision would lead to greater FDA silence on issues surrounding off-label promotion. “The agency is going to want to avoid doing anything that’s going to create a litigation risk,” she said.

**Prosecuting Speech**

In March 2005, Caronia was hired by Orphan Medical Inc. (now Jazz) as a specialty sales consultant to promote Xyrem. During the course of a federal government investigation, Caronia was recorded on tape promoting Xyrem for unapproved uses and in unapproved subpopulations.

In November 2009, a jury in the U.S. District Court for the Eastern District of New York found Caronia guilty of conspiracy to introduce a misbranded drug into interstate commerce, a misdemeanor violation under the FDCA.

On appeal to the Second Circuit, Caronia principally argued that the FDCA’s misbranding provisions prohibit off-label promotion and, therefore, unconstitutionally restrict speech. “Caronia argues that the First Amendment does not permit the government to prohibit and criminalize a pharmaceutical manufacturer’s truthful and non-misleading promotion of an FDA-approved drug to physicians for off-label use where such use is not itself illegal and others are permitted to engage in such speech,” Circuit Judge Denny Chin said in the majority opinion. “We agree that Caronia’s conviction must be vacated, but for narrower reasons than he urges.”

Although the FDCA makes it a crime to misbrand or conspire to misbrand a drug, the statute and its implementing regulations do not expressly prohibit or criminalize off-label promotion, the court said. Rather, the law and regulations reference promotion only as evidence of a drug’s intended use.

In its arguments to the appeals court, the government contended that Caronia was not prosecuted for his speech, but that his statements served as “evidence of intent” that Xyrem be used for purposes not directed in labeling.

However, the majority flatly rejected this position, saying the trial court record makes clear that Caronia was prosecuted for promoting off-label use. Furthermore, “the government’s assertion now that it used Caronia’s efforts to promote Xyrem for off-label use only as evidence of intent is simply not true,” the court said. “Even if the government could have used Caronia’s speech as evidence of intent, the district court record clearly shows that the government did not so limit its use of that evidence.”

**Applying Sorrell And Central Hudson**

Having determined that the government clearly prosecuted Caronia for his speech, the court next considered whether such prosecution was permissible under the Supreme Court’s 2011 decision in Sorrell v IMS Health (“Sales Rep’s Free Speech Challenge Of Off-Label Regs Boosted By Sorrell Ruling” – “The Pink Sheet,” Sep. 5, 2011).

In Sorrell, the high court struck down a Vermont law that prohibited data mining companies and pharmaceutical manufacturers from using data about doctors’ prescribing practices for marketing purposes without their consent (“Rx Data Mining Opponents Will Need New Pitch After Supreme Court Strikes Down Vermont Law” – “The Pink Sheet” DAILY, Jun. 23, 2011).

The Sorrell decision involved a two-step inquiry. First the court determined that the Vermont law disfavored speech according to content (marketing) and speaker (pharmaceutical manufacturers), thereby subjecting the statute to a heightened level of scrutiny. The court then determined that the state had not shown that the speech restrictions were consistent with the First Amendment under this heightened
level of scrutiny. In making this latter determination, the court applied the four-part test in Central Hudson Gas & Electric Corp. v. Public Service Commission of New York for analyzing whether commercial speech is protected.

At the time the Sorrell opinion was handed down, drug law attorneys predicted the decision could create an opening by which to challenge FDA’s restrictions on off-label promotion (“FDA Off-Label Regs Face Cave-In Risk After Supreme Court Data-Mining Ruling” – “The Pink Sheet,” Jul. 4, 2011).

Applying Sorrell to the Caronia case, the majority said the government’s construction of the FDCA misbranding provisions impose content- and speaker-based restrictions on speech subject to heightened scrutiny. Specifically, the government distinguishes between “favored speech” about FDA-approved uses of a drug and “disfavored speech” about off-label uses. Furthermore, the government targets only one category of speakers, pharmaceutical manufacturers, while allowing others, such as physicians and academics, to speak about off-label use without consequences, the court said.

The court next moved to the four-part test under the 1980 Central Hudson case for evaluating commercial speech restrictions. To warrant First Amendment protection, the speech in question must not be misleading and must concern lawful activity. The Central Hudson test also requires an evaluation of whether the asserted government interest is substantial to justify regulations restricting speech, whether the regulations directly advance the government interest and whether they are narrowly drawn and not more extensive than necessary to serve that interest.

The court found that the first two prongs of Central Hudson were satisfied. “First, promoting off-label drug use concerns lawful activity (off-label drug use), and the promotion of off-label drug use is not in and of itself false or misleading,” the court said. “Second, the government’s asserted interests in drug safety and public health are substantial.”

However, the government’s construction of the FDCA as prohibiting off-label promotion does not withstand scrutiny under the third prong requiring that restrictions on speech directly advance the government’s interests, the court said. Crucial to the majority’s view on this point was the fact that off-label use of drugs is generally legal.

“As off-label drug use itself is not prohibited, 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 of preserving the efficacy and integrity of the FDA’s drug approval process and reducing patient exposure to unsafe and ineffective drugs,” the court said.

“Prohibiting off-label promotion by a pharmaceutical manufacturer while simultaneously allowing off-label use ‘paternalistically’ interferes with the ability of physicians and patients to receive potentially relevant treatment information; such barriers to information about off-label use could inhibit, to the public’s detriment, informed and intelligent treatment decisions.”

“The government’s construction of the FDCA essentially legalizes the outcome – off-label use – but prohibits the free flow of information that would inform that outcome,” the court said. “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 unquestionably effective means to achieve that goal.”

Furthermore, the government’s application of the FDCA “to impose a complete and criminal ban on off-label promotion by pharmaceutical manufacturers” is more extensive than necessary and fails Central Hudson’s fourth prong requiring that such restrictions on speech to be narrowly drawn, the court said.

The majority said there are less restrictive alternatives available to the government. These include guiding physicians and patients to distinguish between misleading and truthful information, as well as developing warning or disclaimer systems.

A Strong Dissent

In a dissent, Circuit Judge Debra Ann Livingston said the majority opinion “calls into question the very foundations of our century-old system of drug regulation.”

She said she would affirm Caronia’s conviction because the First Amendment does not prohibit the government from using speech as evidence of motive or intent. “Because Caronia’s speech was used simply as evidence of Xyrem’s intended uses, I agree with the government that Caronia’s conviction does not run afoul of the First Amendment.”

Judge Livingston said she disagreed with the majority’s view that the government prosecuted Caronia for his speech and not for conspiring to introduce a misbranded drug into interstate commerce.

Caronia, she said, does not have a First Amendment right to introduce into interstate commerce a drug for any intended purpose he wished. The fact that physicians can legally prescribe and patients can legally use Xyrem off label also is not enough to validate a First Amendment claim.
“The simple fact that one is generally allowed to sell something does not imbue one with a constitutional right to sell it for any intended purpose,” Judge Livingston said. “And the prohibition here on distributing drugs with the intent that they be used for purposes not supported by their labeling is entirely consistent with the broader purposes of the FDCA – namely, minimizing those occasions on which patients use drugs that have not been shown to be safe and effective.”

The dissenting judge said she believe the government’s application of the FDCA misbranding provisions survives scrutiny under Central Hudson because it advances a substantial government interest and is narrowly drawn.

The process of ensuring that drugs are safe and effective before they can be sold is central to the FDCA, she said. “The FDCA’s prohibition on off-label marketing directly advances this interest. If drug manufacturers were allowed to promote FDA-approved drugs for non-approved uses, they would have little incentive to seek FDA approval for those uses.”

Furthermore, the majority’s concern about manufacturers being singled out as a class of speakers prohibited from promoting off-label use is misguided because “drug manufacturers are the precise group that the government must encourage to participate in the new drug approval process.”

Judge Livingston also differentiated Sorrell from the case at bar. “The statute there did not directly advance Vermont’s interest in protecting patient privacy because it applied to only a small subset of those groups that could possibly compromise patient privacy,” she said. “Drug manufacturers, in contrast, form the entirety of those speakers that could possibly undermine the new drug approval process by not participating in it.”

The prohibition against off-label promotion is not simply a paternalistic attempt to shield physicians and patients from truthful information, Judge Livingston said, but rather is a necessary tool for the effective functioning of the drug regulatory system. “If drug manufacturers have a First Amendment right to distribute drugs for any use to physicians or even directly to patients, then the entire FDCA may well be unconstitutional.”

“If drug manufacturers were allowed to promote FDA-approved drugs for non-approved uses, they would have little incentive to seek FDA approval for those uses,” dissenting Judge Livingston said.