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Off-Label Promotion Is Not a Crime



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On December 3, 2012 (two years after the case was argued), the Second Circuit issued its decision in the much-anticipated case of *United States v. Caronia*.[1] Alfred Caronia, an Orphan Medical (now Jazz Pharmaceutical) drug sales rep, had been convicted of one count of misdemeanor conspiracy to introduce a misbranded drug. To the surprise of some, the Second Circuit vacated the conviction thanks to the First Amendment's protection of truthful non-misleading commercial speech.

Caronia, Dr. Peter Gleason (a paid physician consultant for Orphan) and Orphan were charged with misbranding Xyrem, a powerful central nervous system depressant approved for two specific narcolepsy conditions in patients over 16, by *promoting* it for other conditions like fibromyalgia and chronic fatigue and in patients under 16. Dr. Gleason and Orphan pleaded guilty before the trial. The jury acquitted Caronia of the underlying offense of introducing a misbranded drug, but convicted him for conspiring to introduce a misbranded drug contrary to the Food, Drug and Cosmetic Act (FDCA).

[1] *United States v. Caronia*, Docket No. 09-5006-cr (2nd Cir. Dec. 3, 2012) (10 PLIR 1525, 12/7/12).

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What is misbranding?

There is no crime of ''off-label promotion.'' As the Second Circuit noted, ''[t]he FDCA and its accompanying regulations do not expressly prohibit the 'promotion' or 'marketing' of drugs for off-label uses.'' Nor are doctors prohibited from using drugs ''off-label.'' Instead, the FDCA makes it a crime to introduce or deliver into commerce a misbranded or adulterated drug or medical device or to personally misbrand or adulterate a drug or medical device. There are many different ways that a drug or medical device might be ''misbranded'' or ''adulterated.'' For example, a drug is misbranded if its label does not accurately state the weight or quantity of the contents and a drug is adulterated if it is contaminated. Unfortunately, the government has fallen into the habit of describing the crime as ''off-label promotion.''

The FDCA provisions most commonly associated with the colloquial term ''off-label promotion'' comprise what some call ''intended use'' misbranding. To define the crime of ''intended use'' misbranding you have to read a number of statutory and regulatory provisions together. First, it is a crime to misbrand or introduce or deliver into commerce a misbranded drug. Second, a drug is misbranded if its labeling fails to bear ''adequate directions for use.'' Third, ''adequate directors for use'' are defined as ''directions under which the layman can use a drug safely and for the purposes for which it is intended.'' Fourth, a drug's ''intended uses'' are defined by ''the objective intent of the persons legally responsible for the labeling of drugs.'' The intended uses may

be determined by, among other evidence, ''labeling claims, advertising matter, or oral or written statements by [] persons or their representatives.''[2]

Thus, a drug may be misbranded when it is sold or delivered with the intention of being used for an unapproved use because its labeling fails to bear adequate directions for the unapproved but intended use. But in order to have a crime, there has to be an act. Until now ''intended use'' misbranding prosecutions predominantly have rested on the theory that the act of promoting an off-label use automatically renders the product misbranded.

The Caronia Decision

In a 2-1 decision, the Second Circuit vacated the conviction and remanded the case. The Court's rationale may be summarized as follows: (1) although off-label promotion is not expressly prohibited by the FDCA, Caronia was in fact prosecuted for his off-label promotion (i.e. speech), despite the government's protestations to the contrary on appeal; (2) the government's construction of the FDCA's misbranding provisions to permit prosecution on this basis imposes a content- and speaker-based restriction on speech subject to heightened scrutiny under the First Amendment; and (3) the government's construction of the FDCA's misbranding provisions is not narrowly drawn and runs afoul of the *Central Hudson*[3] First Amendment commercial speech test. In sum, the Court held that the First Amendment does not permit the government to prosecute pharmaceutical manufacturers and their representatives for truthful speech promoting the lawful, off-label use of a drug approved by the Food and Drug Administration (FDA).

The first holding, with which the dissenting judge disagreed, is a recognition of the fact that Caronia, like those who have been prosecuted for the same crime before him, was prosecuted based on the assumption that off-label promotion = ''intended use'' misbranding. Throughout the decision, the Second Circuit refers to this reality as the ''government's construction of the FDCA's misbranding provisions.'' Such language strongly suggests that the government's construction of the statute is not correct. The next two holdings flow directly from the recent Supreme Court decision of *Sorrell v. IMS Health*.[4]

In *Sorrell*, the Supreme Court struck down a Vermont law that prohibited pharmacies from selling and pharmaceutical manufacturers from using prescriber-identifying information for marketing purposes. Prescriber-identifying information (i.e. a physician's prescription history and practices) allows pharmaceutical manufacturers to better target doctors during sales calls, a process called ''detailing.'' Vermont's Prescription Confidentiality Law attempted to interfere in these marketing practices based on Vermont's view that detailing is an invasion of medical privacy and increases the likelihood that doctors will make prescription decisions that are not in the best interests of their patients or the State. The Supreme Court concluded that on its face the Vermont law imposed a content- and speaker-based restriction on speech. Such a restriction on speech – even commercial speech – is subject to heightened scrutiny under the First Amendment. The Court went on to find that, whether analyzed under the *Central Hudson* commercial speech test or the stricter scrutiny that applies when a law interferes with both commercial and non-commercial speech, neither of Vermont's purported justifications withstood scrutiny. Vermont never argued that detailing is false or misleading. According to the Supreme Court, the State simply burdened a form of protected expression because it found that speech too persuasive.

After concluding that the government's construction of the FDCA's misbranding provisions as prohibiting off-label promotion imposed a content- and speaker-based restriction on speech, the *Caronia* majority applied an equally non-deferential analysis of the government's purported justifications. The Second Circuit flat out rejected the government's argument that prohibiting the truthful off-label promotion by drug manufacturers would necessarily ''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'' since off-label drug use itself is not prohibited. Similarly, the Court held that ''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.'' Finally, the Court found that the government's construction was not narrowly drawn because it could have pursued several alternatives to advance the integrity of the FDA's drug approval process and increase the safety of off-label drug use without excessive First Amendment restrictions, such as developing its warning or disclaimer systems for off-label uses, requiring manufacturers to list all potential indications or uses when they first apply for FDA approval, creating ceilings or caps on off-label prescriptions, or even banning off-label use altogether for particular classes of drugs or medical devices (like the FDA did for human growth hormones).

First Amendment attacks on the FDA regime

The Second Circuit decision in *Caronia* is the culmination to date of attacks on the FDA's power to regulate the dissemination of off-label information by drug and medical device manufacturers dating back to at least the Washington Legal Foundation's challenges to FDA policies in the late 1990s.[5]

In 2000, the D.C. Circuit was set to address the Washington Legal Foundation's First Amendment challenge to a statute, which is no longer in effect, that authorized manufacturers to disseminate off-label safety and effectiveness information if it complied with several requirements and the FDA's Continuing Medical Education Guidance. The FDA changed its position at oral argu-

[2] 21 U.S.C. §§ 331(a), 333(a), 352(f)(1); 21 C.F.R. §§ 201.5, 201.128 (drugs); 21 C.F.R. §§ 801.4, 801.5 (medical devices).

[3] *Central Hudson Gas & Elec. Corp. v. Pub. Serv. Comm'n of N.Y.*, 447 U.S. 557 (1980).

[4] *Sorrell v. IMS Health*, 131 S. Ct. 2653 (2011) (9 PLIR 771, 6/24/11).

[5] *See, e.g., Washington Legal Foundation v. Friedman*, 13 F. Supp.2d 51 (D. D.C. 1998).

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ment mooting the appeal.[6] A First Amendment challenge also was raised in the Seventh Circuit in an appeal in *United States v. Caputo* by two individuals convicted of delivering misbranded medical instruments, wire fraud and other related charges. In its 2008 decision, however, the court held that it did not need to address the First Amendment question since the model of the medical instrument at issue was not FDA-approved and therefore could not be lawfully sold in the first place.[7] Most recently, Allergan, the manufacturer of Botox, raised First Amendment issues in a complaint for declaratory judgment in the U.S. District Court for the District of Columbia in 2009. While motions for summary judgment were pending, the FDA approved Botox for one of the off-label uses at issue and the government and Allergan reached a global settlement in which Allergan agreed to pay $600 million to resolve its criminal and civil liability arising from the company's unlawful promotion of Botox.[8]

At the heart of the First Amendment debate is a mismatched dichotomy: Physicians are free to discuss and prescribe FDA-approved drugs or medical devices for any use pursuant to their own medical judgment, but drug and medical device manufacturers (who often have the most information about their products) are prohibited from providing information about off-label uses except in certain limited circumstances construed by the FDA as safe harbors. For instance, the FDA has issued guidance permitting distribution of peer-reviewed medical and scientific journal articles and reference publications that discuss off-label use if the manufacturers follow a particular procedure.[9] Last year, the FDA also issued draft guidance describing how a manufacturer's medical or scientific officer (i.e. not the sales rep) may lawfully respond to unsolicited requests for off-label information with truthful, balanced, non-misleading, and non-promotional scientific or medical information that is responsive to the specific request.[10] Discrete safe harbors aside, the Second Circuit was clearly bothered by the problem with the status quo: ''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.''

FDA misbranding prosecutions

Despite a handful of failed First Amendment challenges, criminal prosecutions for so-called ''off-label promotion'' have become a priority (and money-maker) for the Department of Justice (DOJ) in recent years. In 2009, for instance, Pfizer and one of its subsidiaries agreed to pay $2.3 billion in a combination civil/criminal settlement. The criminal fine and forfeiture portion ($1.3 billion) resulted from pleading guilty to felony misbranding of Bextra (an anti-inflammatory drug that Pfizer pulled from the market in 2005) by ''promoting'' it for several uses and dosages that the FDA specifically declined to approve due to safety concerns.[11] In 2012, another pharmaceutical giant, GlaxoSmithKline, agreed to plead guilty and pay $3 billion to resolve its criminal and civil liability for a variety of violations, including the company's ''unlawful promotion'' of certain prescription drugs.[12] The criminal fine and forfeiture portion of that settlement ($1 billion) resulted from a guilty plea that included two counts of introducing misbranded drugs by promoting the anti-depressant Paxil to patients under 18 when it was not approved for pediatric use and by promoting the anti-depressant Wellbutrin for unapproved uses like weight loss and the treatment of sexual dysfunction.

The DOJ press release announcing the GlaxoSmithKline settlement states that ''[a]fter the FDA approves [a drug or medical device] as safe and effective for a specified use, a company's promotional activities must be limited to the intended uses that FDA approved. In fact, promotion by the manufacturer for other uses—known as 'off-label uses'–renders the product 'misbranded.' ''[13] If the *Caronia* decision stands, prosecutions for misbranding will no longer be as straightforward as this headline press release suggests. But before drug and medical device manufacturers rush out and undo all of the internal regulatory safeguards put in place to protect themselves from scrutiny for alleged ''off-label promotion,'' they must understand the limitations of the *Caronia* decision.

What is left after Caronia?

Given the stakes, there is a good chance that the government will seek review by the full Second Circuit and then possibly the United States Supreme Court so we may have to wait a few more years for the final answer. But even if the *Caronia* analysis becomes the accepted rule, there is arguably still room for the FDA to continue its battle against ''off-label promotion'' within the existing statutory and regulatory scheme.

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[6] *Washington Legal Foundation v. Henney*, 202 F.3d 331 (D.C. Cir. 2000) addressing the Food and Drug Administration (FDA) Modernization Act of 1997, Pub. L. No. 105-115, 111 Stat. 2296; 21 U.S.C. §§ 360aaa *et seq.*, which ceased to be effective Sept. 30, 2006; Guidance for Industry: Industry-Supported Scientific and Educational Activities, 62 Fed. Reg. 64 (1997).

[7] *United States v. Caputo*, 517 F.3d 935 (7th Cir. 2008).

[8] *Allergan, Inc. v. United States of America*, Docket No. 1:09-cv-01879 (D. D.C.); Allergan Agrees to Plead Guilty and Pay $600 Million to Resolve Allegations of Off-Label Promotion of Botox, Justice News, Sept. 1, 2010 (http://www.justice.gov/opa/pr/2010/September/10-civ-988.html) (8 PLIR 1131, 9/10/10).

[9] 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, Food and Drug Administration, Jan. 2009 (http://www.fda.gov/RegulatoryInformation/Guidances/ucm125126.htm) (7 PLIR 65, 1/16/09).

[10] Draft Guidance–Responding to Unsolicited Requests for Off-Label Information About Prescription Drugs and Medical Devices, Food and Drug Administration, Dec. 2011 (www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM285145.pdf) (10 PLIR 15, 1/6/12).

[11] Associate Attorney General Tom Perrelli at Pfizer settlement press conference, Justice News, Sept. 2, 2009 (http://www.justice.gov/asg/speeches/2009/asg-speech-090902.html); Justice Department Announces Largest Health Care Fraud Settlement in Its History, Justice News, Sept. 2, 2009 (http://www.justice.gov/opa/pr/2009/September/09-civ-900.html).

[12] GlaxoSmithKline to Plead Guilty and Pay $3 Billion to Resolve Fraud Allegations and Failure to Report Safety Data, Justice News, Jul. 2, 2012 (http://www.justice.gov/opa/pr/2012/July/12-civ-842.html) (10 PLIR 857, 7/6/12).

[13] *Id.*

Even if the *Caronia* analysis becomes the accepted rule, there is arguably still room for the FDA to continue its battle against ''off-label promotion'' within the existing statutory and regulatory scheme.

First, a fundamental premise underlying the *Caronia* decision is that the government did not argue at trial or on appeal that Caronia's off-label promotion was false or misleading. In an aside, the *Caronia* majority nonetheless confirmed that the First Amendment would not protect off-label promotion that is false or misleading. Accordingly, the government can avoid First Amendment issues in pursuing the related misbranding theory of introducing a drug with ''false or misleading labeling.''[14] False or misleading statements outside of a drug's ''labeling'' also might be prosecuted under wire fraud and related federal fraud statutes without running afoul of the First Amendment. It would also appear that the government might be able avoid dismissal of a felony ''intended use'' misbranding charge on First Amendment grounds if the government sufficiently alleges that the particular off-label promotional statements at issue were in fact false and misleading, not just off-label. Such charging language is arguably required by the additional ''intent to defraud or mislead'' element for felony misbranding charges in any event.[15] Where the *Caronia* holding leaves plain vanilla misdemeanor ''intended use'' misbranding prosecutions remains to be seen. In addition, prosecutions of the responsible corporate officer under the *Park* doctrine for traditional off-label promotion are clearly vulnerable to attack on First Amendment grounds, but such prosecutions may remain viable if there are false or misleading statements.[16]

To the extent the government attempts to prosecute a drug manufacturer for truthful off-label promotional statements on the theory that they were nonetheless misleading for failing to disclose information the government believes should have been disclosed, there will no doubt be a fight about what needs to be disclosed when a company or a sales rep talks about an off-label use. For example, in the failed prosecution of Stryker Biotech, its former President, and three of its sales managers, part of the government's theory of the case was that the company was promoting unapproved mixing instructions without disclosing adverse events associated with the mixture. The defendants' pre-trial motions, which were never definitely resolved given the abrupt termination of the prosecution, raised a number of challenges including the need for and absence of a duty to disclose.[17]

Second, the majority decision in *Caronia* also rests on the prosecutors' and the trial judge's description of Caronia's crime as ''off-label promotion.'' This was likely an attempt at simplicity and familiarity for the jury because off-label promotion is what has traditionally been understood as *the crime*. In the appeal, however, the government argued (and the dissenting Second Circuit judge agreed) that the First Amendment was not implicated because Caronia was not prosecuted for his speech; rather, his speech served merely as evidence of intent.

The logic behind this unsuccessful argument is based on the definition of ''intended use'' in the FDA regulations, which have essentially remained unchanged for sixty years. As noted above, the regulations do not expressly prohibit ''labeling claims, advertising matter, or oral or written statements'' about a drug outside of its FDA-approved label. Rather, the regulations state that a drug manufacturer's ''labeling claims, advertising matter, or oral or written statements by such persons or their representatives'' may be used as ''evidence'' of the drug manufacturer's intended use for the drug.

In ruling on Caronia's pre-trial motion to dismiss, the trial judge expressly rejected the government's argument that Caronia was being prosecuted for the unlawful *conduct* of misbranding and conspiring to misbrand a drug and not for his promotional *speech* (but nonetheless rejected the First Amendment challenge). The Second Circuit agreed, citing to the overt acts in the information and the government's summation and rebuttal, which highlighted Caronia's ''off-label promotion'' over forty times. Given this holding, a more carefully worded information and argument at trial might avoid the *Caronia* First Amendment problem altogether. Even the majority in *Caronia* assumed, without deciding, that use of promotional speech as evidence of an unapproved intended use would be permissible.

If the government adopts the speech-as-evidence-of-intent strategy going forward to avoid the First Amendment problem, an ''intended use'' misbranding enforcement action may still be vulnerable to other due process, statutory construction, and overbreadth challenges. No company, executive or sales rep has ever been prosecuted for ''intended use'' misbranding that was not based at least in large part on their speech. This despite the fact that the ''intended use'' regulations also say that a drug's intended use ''may be shown by the circumstances that the article is, with the knowledge of such persons or their representatives, offered and used for a purpose for which it is neither labeled nor advertised.'' Thus, as the *Caronia* majority notes, ''it still remains unclear how the government would identify criminal misbranding from communications between drug manufacturers and physicians authorized to prescribe drugs for off-label use. For example, would a manufacturer be guilty of misbranding if it ships Xyrem to a doctor who, in placing his order, reveals that he prescribes the drug for off-label use — on a theory that the manufacturer now knows that the drug is not properly labeled for that use — but not if the manufacturer ships to a doctor who does not reveal that he prescribes the drug off-label?''

Third, *Caronia* presupposes off-label promotion of an *approved* drug or medical device. If the drug or medical device is not approved (or it is sufficiently altered from a predicate drug or device that was approved such that a new approval was required, as found in the Seventh

[14] 21 U.S.C. § 352(a).
[15] 21 U.S.C. § 333(a)(2).
[16] *United States v. Park*, 421 U.S. 658 (1975).
[17] *United States v. Stryker Biotech*, Docket No. 09-cr-10330 (D. Mass.). Two of the authors of this article represented the former President of Stryker Biotech in this prosecution.

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Circuit *Caputo* decision), however, there may be no First Amendment protection.

Conclusion

Until recently, Caronia's First Amendment argument would have been laughed out of court. But with the Supreme Court's recent application of First Amendment principles to protect commercial and corporate speech, the industry's attacks against off-label prosecutions have yielded their first real victory in the *Caronia* decision. The battle is, however, far from over. Whether by new strategies within the existing statutory and enforcement regime or by revamping the rules, the FDA and the DOJ will no doubt continue trying to police off-label promotion.

While we should not expect the government to go gently into the night, one of the lessons of *Caronia* is that the fight is worth having. What the Washington Legal Foundation began in its efforts to ''defend[] the rights of individuals and businesses to go about their affairs without undue influence from government regulators,'' one sales rep achieved (at least for now) with the help of amici filings by the Washington Legal Foundation and the Medical Information Working Group. This is enlightening evidence that industry can fight back against what it sees as unfair or excessive governmental interference.