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**Off-Label Changes Coming? *Sorrell* Ruling Prompts New Legal Challenges**

**Pharmaceutical companies are unleashing fresh legal challenges to FDA’s restrictions on off-label promotion, arguing that they contain the same speaker- and content-based restrictions that were struck down by the Supreme Court in the Vermont data mining case *Sorrell vs. IMS Health.* The courts appear willing to listen. Is an end to off-label prosecutions on the horizon?**

 By Kate Rawson

In the sometimes hazy world of pharmaceutical marketing, industry has yearned for one thing: definitive rules from the Food & Drug Administration on off-label promotion.

Marketers have long complained about a lack of clarity from FDA on how to discuss unapproved uses of prescription drugs and biologics without running afoul of the Department of Justice. A statutory “safe harbor” for the dissemination of journal articles expired five years ago, and companies say current FDA guidance doesn’t outline clear boundaries on acceptable ways to provide information about unapproved uses—or offer protection from prosecution. (*See “*[*Off-Label Sales in Jeopardy*](http://therpmreport.com/EMS_Base/Agent.aspx?Page=/Content/2007500211.aspx)*,” The RPM Report, December 2007.*)

Drug manufacturers now see an opening to revisit the issue in the aftermath of the Supreme Court’s opinion in the Vermont data mining case *Sorrell vs. IMS Health*. In that case, the high court struck down as unconstitutional Vermont’s attempts to place restrictions on the use of physician prescribing data by pharmaceutical companies for marketing purposes. (*See “*[*Data Mining Case Struck Down by Supreme Court*](http://therpmreport.com/EMS_Base/Agent.aspx?Page=/Content/2011500104.aspx)*,” The RPM Report, July 2011.*)

The *Sorrell* [majority opinion](http://www.supremecourt.gov/opinions/10pdf/10-779.pdf) immediately prompted questions from the legal community about whether it made vulnerable certain FDA regulations, including the agency’s ban on most off-label promotion by pharmaceutical companies. Now, the appeal of a conviction of an Orphan Medical (now **Jazz Pharmaceuticals**) sales representative, Alfred Caronia, may provide an early test of whether off-label restrictions can withstand First Amendment scrutiny.

In *Caronia*, which is pending before the U.S. Court of Appeals for the Second Circuit, attorneys for the former sales representative argue that FDA’s restrictions on off-label promotion are a violation of the free speech provisions of the Constitution. And they say that the restrictions contain the same speaker- and content-based discrimination that was struck down by the Supreme Court in *Sorrell* as unconstitutional.

Many legal experts agree. Richard Cooper, a former FDA chief counsel and partner at **Williams & Connolly**, told the Food & Drug Law Institute’s Advertising & Promotion Conference on September 26 that like *Sorrell*, the off-label restrictions in *Caronia* apply only to a certain class of speakers (manufacturers of FDA-regulated products) and certain content (promotion of unapproved uses). As a result, Cooper says, *Sorrell* “puts FDA’s ban on off-label promotion in some jeopardy.”

Industry has also jumped into the fray. A coalition of 11 drug manufacturers filed an *amicus* brief with the Second Circuit arguing that the court should overturn Caronia’s conviction, because the FDA regulations on which it was based contain the same speaker- and content-based restrictions that were struck down in *Sorrell*. And they argue that existing FDA regulations lack the “coherence and clarity” to provide manufacturers with the guidance they need on off-label promotion.

The government dismisses that argument, saying in briefs to the Second Circuit that *Sorrell* has no bearing on *Caronia*. The off-label restrictions do not “tilt the playing field,” but rather ensure that the public receive “reliable information” about drug and biologics. Furthermore, the government says, FDA’s guidance document creates clearly defined safe harbors, and so long as manufacturers stay within those established boundaries, there is no danger of prosecution.

But a First Amendment argument in *Caronia* may be heard by sympathetic ears. It was the Second Circuit, after all, that reversed a lower court decision in *Sorrell* and deemed Vermont’s data mining restrictions to be a violation of the First Amendment—a decision the Supreme Court upheld. If the same logic can be applied to the *Caronia* case, major changes to off-label promotion may be on the horizon.

*Caronia:* A Rare Off-Label Prosecution

The ink was barely dry on *Sorrell vs. IMS Health* before legal pundits starting speculating on the implications of the majority opinion on FDA’s regulation of the pharmaceutical industry.

Now that the Supreme Court had deemed unconstitutional restrictions on the use of physician prescribing data, what might that mean for direct-to-consumer advertising? Or FDA’s Risk Evaluation & Mitigation Strategies? Or the federal anti-kickback statute? Or off-label promotion? Could the same logic that guided the Supreme Court’s decision in *Sorrell* prompt other First Amendment challenges? (*See “*[*Interpreting a Surprisingly Broad Decision*](http://therpmreport.com/EMS_Base/Agent.aspx?Page=/Content/2011500105.aspx)*,” The RPM Report, July 2011.)*

Indeed, Supreme Court Justice Stephen Breyer suggested that very possibility in his dissenting opinion in *Sorrell*: “The same First Amendment standards that apply to Vermont here would apply to similar regulatory actions taken by other States or by the Federal Government acting, for example, through Food and Drug Administration regulation.” The majority opinion “opens a Pandora’s Box of First Amendment challenges to many ordinary regulatory practices that may only incidentally affect a commercial message.”

An early test of that theory is playing out in the U.S. Court of Appeals for the Second Circuit. The court is considering the appeal of sales representative Alfred Caronia’s conviction for conspiracy to misbrand the narcolepsy drug *Xyrem* (sodium oxybate). A federal court convicted Caronia in 2008 after rejecting a motion to dismiss the case on First Amendment grounds. (*See “*[*The Super FDA: State Attorneys General Flex Their Muscles*](http://therpmreport.com/EMS_Base/Agent.aspx?Page=/Content/2009500006.aspx)*,” The RPM Report, February 2009.*)

Caronia’s prosecution was based on a sting operation during which Steven Charo, a government informant, met with Caronia and an Orphan medical expert, Peter Gleason, to talk about *Xyrem*, which was approved only for [cataplexy](http://en.wikipedia.org/wiki/Cataplexy) associated with [narcolepsy](http://en.wikipedia.org/wiki/Narcolepsy). Charo asked a number of questions about the off-label use for excessive daytime sleepiness; at the time, the indication was under review by FDA. The agency approved the excessive daytime sleepiness indication shortly after the sting operation.

Caronia was convicted in federal court of conspiring to distribute *Xyrem* without adequate directions of use—in essence, promoting the drug for the off-label indication of excessive sleepiness. He was sentenced in 2008 to one-year probation, 100 hours of community service and a $25 fine. According to “The Pink Sheet,” he is now trying to make a living as a carpenter. (*See “Sales Rep’s Free Speech Challenge Of Off-Label Regs Boosted By Sorrell Ruling,” The Pink Sheet,” September 5, 2011.*)

*Caronia* was the rare case in which prosecutors not only went after the drug marketer for off-label promotion, but also charged the individual sales representative with a crime. For industry, the case was an ominous indication of where the government might be taking off-label prosecutions. Indeed, in a later case, two sales managers for **Pfizer Inc.**’s valdecoxib (*Bextra*) were convicted for obstruction of justice in an off-label promotion investigation as part of a record-breaking $2.3 billion settlement. (*See “Bextra Settlement Coming Soon: Industry Should Brace For Impact,” The RPM Report, February 2009.*)

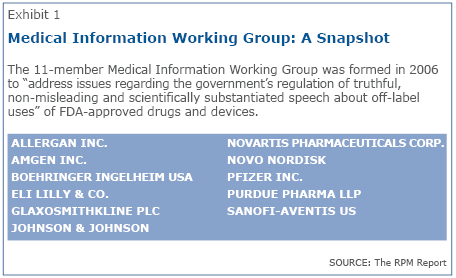
A New Off-Label Weapon?

After Caronia’s attorneys appealed his case to the Second Circuit, the court initially said it would issue a decision without hearing oral arguments—an indication that it was prepared to uphold the conviction. But then the court reversed that decision, and scheduled oral arguments to further examine both the constitutionality of FDA’s off-label restrictions, as well as questions about the validity of the verdict sheet during the federal court trial.

Oral arguments, which were heard on December 2, 2010, focused primarily on the constitutionality question and appeared to play in Caronia’s favor. The appeals court judges challenged the government on a number of points, including whether FDA is restricting speech (the government says no; the speech is merely evidence of intent to misbrand a drug), and whether the agency could find less restrictive ways to achieve the same ends (such as putting “timetables” on a manufacturer to seek approval).

*Caronia* was still pending at the Second Circuit when the Supreme Court issued the *Sorrell* opinion in June 2011, striking down Vermont’s data-mining restrictions as unconstitutional. In light of that decision, the Second Circuit asked the parties involved in the *Caronia* case to submit briefs on the relevance of the Supreme Court’s opinion on *Sorrell*.

The appeals court request yielded *amicus* briefs from the usual suspects, like the **Washington Legal Foundation**, which has been at the forefront of the off-label issue for years. But industry also got on board, with a brief from the **Medical Information Working Group**, a coalition of 11 drug manufacturers. (*See Exhibit 1.*) Both parties agree with attorneys for Caronia that *Sorrell* can be applied to FDA’s off-label promotion restrictions.



“Although they target a somewhat different subject matter, the FDA regulations at issue in this case are not less speaker- and content-based than was the law at issue in *Sorrell*,” the Medical Information Working Group’s brief states. “There is little question that the misbranding provisions…impose substantial limitations on speech (i) by particular speakers (manufacturers) and (ii) based on specific content (off-label uses of approved drugs and medical devices).”

The off-label restrictions restrict the speech of manufacturers, while payors and other parties can openly discuss unapproved uses, the coalition says. And the regulations are content-based in that they “do not prohibit dissemination of truthful, non-misleading speech about on-label uses, but do prohibit, in most circumstances, dissemination of information pertaining to off-label uses, regardless of how medically accepted such uses are.”

“In sum, the FDA’s regulations censor manufacturers: A manufacturer that speaks about the lawful off-label uses of its products subjects itself to potential enforcement action unless FDA and DOJ determine, in their sole discretion, that they will not treat the speech as evidence of an ‘intended use’ for the product.” This, MIWG says, creates a “chill on manufacturers’ speech, which has serious potential consequences for physicians, patients, and the public health.”

The Government’s Response

The government doesn’t see it that way. *Sorrell* “does not affect the constitutionality of Caronia’s conviction,” the government’s brief to the Second Circuit states. The Supreme Court’s decision to view the Vermont statute as a restriction on commercial speech (rather than regulation of conduct) and apply “heightened judicial scrutiny” does not set new legal precedent, the brief argues. “If the Court had actually meant to take such a drastic step, it surely would have said so.”

But even if *Sorrell* did raise the judicial scrutiny for restrictions on commercial speech, it would not affect *Caronia*, the government’s brief continues. “Caronia was not convicted for conspiring to promote off-label uses of *Xyrem*, but instead for conspiring to distribute *Xyrem* without adequate directions for use, and both the Second Circuit and the Supreme Court “have long employed a more relaxed standard of judicial review when the government requires disclosure of commercial information.”

The government also dismisses the argument that the restrictions are speaker-based. “To the extent that the Act’s misbranding provisions are effectively confined to manufacturers and others involved in drug distribution, that practical incidence reflects the realities of drug marketing, not a preference for one speaker over another. By their very nature, regulations of commercial speech ordinarily and unavoidably apply to persons engaged in particular commercial activity rather than to the world at large.”

Similarly, the restrictions are not content-based, the government’s brief continues. When the law “requires a drug manufacturer to provide adequate directions for the intended uses of its drugs, it does so not because of official hostility to the manufacturer’s message, but simply to ensure that physicians and patients receive the information they need to use the drug safely and effectively.”

The FD&C Act’s misbranding provisions “are not designed to favor one side of a public debate over the other side, but instead to provide the public with reliable information about the medicines they are using, in much the same fashion that securities laws provide the public with reliable information about the investments that they are making.”

“Unlike *Sorrell*, this is not a case in which the government is animated by ‘fear that people would make bad decisions if given truthful information,’” the brief states. Rather, off-label promotion “involves representations of safety and efficacy that are scientifically unproven and potentially false, and physicians and patients who rely on those representations may do so to the detriment of the patients’ health and even their lives. *Sorrell* casts no doubt on provisions that protect the public from these harms.”

Speech or Conduct?

There are some important distinctions between *Sorrell* and *Caronia* that may yield a different outcome in the Second Circuit. As the government points out in its brief, the Vermont law was designed to limit the promotion of brand-name drugs for approved uses. *Caronia*, in contrast, involves the promotion of drugs for unapproved uses.

That distinction, **Wiley Rein LLC** partner Bert Rein said at the FDLI conference, means that a reversal of *Caronia* is by no means a sure thing. “*Sorrell* comes up in a context where the pharmaceutical detailing is assumed to be truthful, non-misleading promotion,” namely, the on-label sale of drugs, Rein says. “In that framework, the court was very sensitive to the state trying to tip the balance of what it otherwise would allow to be a lawful consumer decision.”

With off-label use as seen in *Caronia*, the government’s rationale is somewhat different, he continues. The government argues that the off-label *speech* itself is not the crime, but the *conduct* of introducing a misbranded drug. The government, Rein says, is arguing: “We’re not punishing the speech, but we don’t want you to sell these drugs for which you have not provided an adequate evidence for safety and effectiveness.”

And that may well be a deciding factor in how the Second Circuit views *Caronia*. “It’s a real conundrum,” Rein says. “If you treat it all as speech restriction, then suddenly it’s very vulnerable. But if you start looking at, is the purpose here is to check the ideas or suppress an activity which in the public health interest ought to be suppressed, you may come to a different result.”

Cooper, the former FDA general counsel, agrees that the frame of reference matters, but thinks the Court will see it in free speech terms. “Perhaps the fundamental difference between the court and the dissenters in *Sorrell* was on whether the Vermont statute should be viewed as a restriction of speech, or merely as an incidental restriction in aid of general economic regulation,” he said. (*See “*[*A Case for Caronia*](http://therpmreport.com/EMS_Base/Agent.aspx?Page=/Content/2011500132.aspx)*.”*)

“Arguably, the same issue would apply to off-label promotion, and presumably, the same 6-3 split in the court would occur. FDA would argue that it is regulating conduct and regulating shipment of interstate commerce, and not regulating speech.”

But, he says, the Supreme Court “didn’t accept that argument in *Sorrell*, and I think it’s doubtful that the court would accept it in the context of off-label promotion.”

Incentivizing Supplemental NDAs

Cooper argues that the last defense that the government has in *Caronia* is the incentive that the off-label restrictions creates for companies to gain FDA approval of new indications. It’s a justifiable concern: Without restrictions on off-label promotion, the government fears that manufacturers would skip the supplemental approval process altogether—resulting in far less information about the safety and efficacy of drugs for patients and physicians.

But Cooper argues that the incentive simply doesn’t work. “The relatively small number of supplements that are submitted for additional uses, compared to the very large number of off-label uses that occur, suggest that the incentive isn’t particularly successful,” he says. “Given the volume of information about off-label uses that is available to speakers other than manufacturers, it is not surprising that the incentive is relatively weak.”

Besides, Cooper says, while the Supreme Court recognized in *Thompson vs. Western States* the importance of preserving the integrity of FDA’s new drug approval process, the government can reach that goal with less restrictive steps then a ban on off-label promotion.

The Washington Legal Foundation, in an *amicus* brief to the Second Circuit, agrees. The government’s interest in “providing incentives to submit approved drugs to the FDA for new uses is a legitimate one. But, as in Western States, the means of accomplishing that goal—regulating speech—is not narrowly tailored because that interest could be achieved by restricting other conduct or far less speech than the current ban.”

The appeals court seemed to hear that message. During oral arguments, Justice Reena Raggi pressed the government on that point, suggesting other ways that the off-label restrictions could be more narrowly tailored, such as setting a timetable for approval of the supplemental indication, or withdrawing the drug from the market if it is found to be unsafe. “The concept of precluding speech is one we look at with some concern,” Raggi said. “And so I’m not sure why this can’t be much more narrowly tailored.”

In the case of *Caronia*, there was no need for an incentive for Orphan Medical to file a supplemental application, since *Xyrem* was already under review for the use of excessive sleepiness. The Washington Legal Foundation makes this point in its *amicus* brief: “The FDA ban on speech about uses that are *already* going through the approval process if obviously overbroad and gratuitous, because there is no need to give the manufacturer an ‘incentive’ to do what it is already doing.”

“Clarity and Coherence”

In the absence of a court ruling striking down FDA’s restrictions on off-label promotion as unconstitutional, the pharmaceutical industry might be satisfied with more clearly defined rules about marketing drugs for unapproved uses. Industry has long complained that the current environment for pharmaceutical marketing is fraught with ambiguity, and leaves manufacturers without the necessary guidelines to market their products without fear of prosecution.

Indeed, some in industry wonder whether this is an area where regulators are deliberately vague, counting on uncertainty to do what regulation cannot: stop companies from making truthful statements about their own products.

A provision of the FDA Modernization Act of 1997 allowed manufacturers to disseminate peer-reviewed journal articles discussing off-label use of their medications, so long as the company has plans to submit a supplemental application to FDA covering the use of the drug. But that “safe harbor” expired on September 30, 2006, and while FDA issued a [guidance document](http://www.fda.gov/RegulatoryInformation/Guidances/ucm125126.htm) on its reprint policy in January 2009, companies have been left without statutory protection ever since.

Indeed, FDA guidance documents by definition “do not establish legally enforceable rights or responsibilities” but instead “describe the Agency’s current thinking on a topic, and should be viewed only as recommendations.” Those phrases, included in every FDA guidance document, underscore the fleeting protections that guidance documents afford manufacturers. *(See “*[*Revisiting WLF: Rules for Off-Label Promotion Could Change with the New Commissioner*](http://therpmreport.com/content/2006500207.aspx)*,” The RPM Report, November 2006*.)

In its brief to the Second Circuit on *Sorrell*’s significance in the *Caronia* case, the government dismisses any concerns that FDA guidance documents are not binding on the agency and are not embodied in formal rulemaking. “FDA and DOJ have *never* brought an enforcement action against a manufacturer on the basis of conduct that conforms to the guidances,” the government’s brief says. “The risk of liability for a manufacturer who engages in such conduct is nil.”

Still, MIWG, the industry coalition, argues that while the government has carved out exceptions where it will not pursue prosecution, “rather than creating any true ‘safe harbors,’ those asserted ‘exceptions’ to the general rule that manufacturers are prohibited from engaging in off-label speech are too narrow, too ambiguous, not rooted in and often inconsistent with the statutory language of the FDCA, generally not the products of formal agency rulemaking, and in most instance explicitly ‘non-binding.’”

For example, FDA’s guidance document on good reprint practices allows that if a manufacturer distributes a reprint of peer-reviewed journal article, the agency will not consider that action as establishing intent to promote an unapproved use. Yet, the industry brief says, “if a scientist working for the manufacturer drafts and disseminates an entirely accurate summary of the research on which that journal article was based, the manufacturer could be subject to prosecution.”

The result, as the Washington Legal Foundation argues in its *amicus* brief to the Second Circuit, has been a contradictory off-label promotion policy. Physicians can prescribe medications for unapproved uses for their patients—uses that are often paid for by the government through Medicare. But they cannot discuss those uses with other medical professionals (theoretically more sophisticated than most patients) if they are on the payroll of the drug marketer—unless they are answering a direct question about that use.

“That regulatory regime—which allows doctors to recommend that patients use *Xyrem* for off-label uses but prohibits manufacturers from encouraging those recommendations—cannot survive First Amendment scrutiny.”

The Citizen Petition Route

Manufacturers say it’s that sort of ambiguity that makes any off-label promotion treacherous. Immediately after the *Sorrell* opinion, a group of seven manufacturers (**Allergan Inc.**, **Eli Lilly & Co.**, **Johnson & Johnson**, **Novartis**, **Novo Nordisk**, **Pfizer Inc.**, and **Sanofi**) filed a citizen petition with FDA asking for clarification on communications about unapproved uses. (*See “*[*FDA Pressed To Clarify Permissible Formulary, Clinical Guideline Communications*](http://thepinksheet.elsevierbi.com/cs/Satellite?c=Page&cid=1216099165884&pagename=FDCReports/Page/PageNavigatorWrapper&autoLogin=yes&queryStr=resultpage*ArticleDetail:ArticleDetailWrapper/pii*110706p1/pubdate*20110706/qbax*sTbB2LA2KomiyWpHughAew==&jid=pink)*,” The Pink Sheet,” July 6, 2011.*)

The citizen petition asked for clarification on four areas: details on the standards for providing medical and clinical information on investigational products (often called “scientific exchange”); sharing information with formulary committees and payers; providing independent third-party clinical practice guidelines; and responding to unsolicited requests for information.

The “confusion” among those in industry with FDA’s policies in those areas “results in significant difficulties for companies in their day-to-day decision-making,” the citizen petition says. “That lack of clarity places manufacturers at risk of criminal or civil sanctions if they cannot correctly guess where the government would draw a line….Industry should not have to refer to the terms of DOJ settlements or informal statements of FDA officials to learn what is expected of them.”

Whether industry will get greater clarity from FDA on off-label promotion is uncertain: “Companies always do better with clarity,” **Pharmaceutical Research & Manufacturers of America** General Counsel Diane Bieri said at the FDLI conference. “Whether or not it’s possible to get to the level of clarity that the companies are asking for, I’m not certain. But I think the petition is a sincere attempt to try and get…a higher degree of clarity on some issues that have troubled the industry for a number of years.”

The Second Circuit may end the need for “clarity” from FDA on off-label promotion if it reverses the *Caronia* conviction. Until a decision comes down—perhaps as soon as this year—industry should play by the same rulebook. “As a practical matter, I don’t think that *Sorrell* changed the US Attorney’s world—certainly without further clarification from the courts,” Bieri says.

John Kamp, a partner at Wiley Rein LLC, agrees. “This is an information policy debate and a constitutional policy debate that is fascinating and important, but the law didn’t change,” he told the FDLI conference. The Department of Justice and the state AGs “are bringing those cases under the same authority they brought before this case was decided. So don’t go home and say, ‘Oh, we learned about the IMS case while we were at FDLI, and we don’t have to worry about those rules anymore. Yes, you do.’”

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