The significant implications of the *Caronia* off-label promotion decision for US FDA-regulated firms

Alan Bennett and *Douglas Hallward-Driemeier* analyze the landmark case.

A decade and a half after US litigation in *Washington Legal Foundation* first raised questions about the constitutionality of the Food and Drug Administration's regulation of promotion, a court of appeals in *United States v Caronia* held that "[t]he government cannot prosecute pharmaceutical manufacturers and their representatives under the [Food, Drug, and Cosmetic Act (FDCA)] for speech promoting the lawful, off-label use of an FDA-approved drug".

The Second Circuit Court of Appeals decision in *Caronia* was delivered on 3 December 2012. Although the full extent of the decision's reach is still uncertain, it will likely have significant implications for how the promotion of pharmaceuticals and medical devices is regulated. Until *Caronia*, criminal prosecutions, civil suits and FDA enforcement actions were often premised on a manufacturer or sales representative's promotional speech. Moving forward, the government, private plaintiffs and the FDA will likely change legal strategies to adapt to a landscape where truthful promotional speech can no longer be criminalized.

Five key features in *Caronia*

Alfred Caronia was a sales representative for Orphan Medical (now Jazz Pharmaceuticals). Mr Caronia was audiotaped by a government informant marketing Xyrem, an anti-narcolepsy drug for off-label uses and subpopulations. In October 2008, he was prosecuted in district court under the FDCA's prohibition against selling a "misbranded" drug.

A drug will be considered misbranded if, among other things, its labeling does not include "adequate directions" for the drug's "intended" uses. FDA regulations define the "intended" use of a drug by "the objective intent" of the drug manufacturer, which can be determined from "oral or written statements by [manufacturers] or their representatives" and the circumstances surrounding the drug's marketing and use.

Mr Caronia was found guilty of "conspiracy to introduce a misbranded drug into interstate commerce". His sentence was one year of probation, 100 hours of community service and a $25 "special assessment".

Mr Caronia appealed to the Second Circuit Court of Appeals, arguing that the FDA's restriction on off-label promotion unconstitutionally restricted his right to free speech. In a 2-1 opinion the Second Circuit agreed. The court explained that the misbranding provision would be unconstitutional if it criminalized truthful promotional speech about lawful off-label uses of an FDA-approved drug.

The holding in *Caronia* has five important features. First, the Second Circuit did not say that the FDCA misbranding provision was unconstitutional as written. Instead, it found that the way that the provision had been interpreted – to criminalize truthful speech about lawful off-label uses – would be unconstitutional, and so the statute should not be interpreted in that way.

Second, the Second Circuit applied "heightened" scrutiny – imposing a tough burden on the government to defend the law's speech restrictions because the prohibition specifically targets certain speakers for the restriction (drug manufacturers) while others, including doctors and academics, are free to discuss off-label uses. This holding was consistent with *Sorrell v IMS Health, Inc,* a recent Supreme Court decision that struck down a state statute that prevented drug firms from using information that identified which doctors prescribed which medications for marketing purposes.

Third, the Second Circuit held that "the promotion of off-label drug use is not in and of itself false or misleading", and so cannot be prohibited for that reason. The court did note, however, that "[o]f course, off-label promotion that is false or misleading is not entitled to First Amendment protection".

Fourth, the court explained that although the government has a "substantial" interest in ensuring drug safety and public health, prohibiting off-label speech neither "directly advances" the government's interest nor is "narrowly drawn" to avoid unnecessarily restricting speech. If the government is concerned that off-label drugs are unsafe, the court noted, there are more direct ways to address that problem.

Finally, in reaching its holding, the Second Circuit rejected the government's argument that Mr Caronia was prosecuted for "conduct" rather than speech, and that Mr Caronia's promotional statements were merely used as evidence of Xyrem's "intended use". The court noted that the prosecutor's closing and district court's jury instructions focused on Mr Caronia's "promotion" or "marketing" – ie his speech.

Government chooses not to appeal

Although the Second Circuit decision casts significant constitutional doubt over the FDA's off-label regulatory regime, the government chose not to seek further review. In public statements, the Department of Justice and the FDA have tried to characterize the decision as a narrow one, focused on the inadequacy of the district court's jury instructions (which the government itself requested). The government contends that it remains free to use promotional speech, as long as it is clear that the speech is merely evidence of the manufacturer's "intended use" and not the crime in itself.

The government may also have been concerned about its prospects before the Supreme Court. In *Sorrell,* at least five Justices agreed that "[s]peech in aid of pharmaceutical marketing… is a form of expression protected by the… First Amendment, and that restrictions on that speech are heavily scrutinized". Losing in the Supreme Court would make *Caronia* the law of the land, whereas the decision currently only applies to Connecticut, Vermont and New York.

Criminal and civil liability

In light of *Caronia*, the government is likely to alter its investigative and charging strategies to "*Caronia*-proof" its cases. Because the Second Circuit made clear that manufacturers and sales representatives can be prosecuted for false or misleading statements, the government will likely include such accusations in its charging documents. Proving that a statement is false or misleading is complicated, however, especially in comparison to the nearly strict-liability standard in a misdemeanor prosecution for off-label promotion. And, as discussed below, the Second Circuit's First Amendment holding may also affect the FDA's standard for deciding whether promotional claims qualify as false or misleading.

The government will, without question, be more careful to stress that promotional statements are offered as evidence of "intent", rather than the crime itself. It may also look to other forms of evidence to prove a drug's intended use, including internal company communications. But this may be a harder shift than the government wants to acknowledge. As the Second Circuit noted, the treatment of speech as the essence of the crime seems to be embedded in the FDA's regulations themselves, and not merely an isolated case of poor jury instructions.

Another likely consequence of *Caronia* is that the government will be less likely to prosecute individual defendants on an off-label

theory. One reason for the relative dearth of First Amendment precedent on off-label prosecutions before *Caronia* is that manufacturers who are found liable under health fraud laws can be excluded from participating in Medicare and Medicaid. These government health programs are a critical source of revenue and, as a result, manufacturers almost always must settle claims against them. For individual defendants, however, the calculus is different, and they have every incentive to fight the charges, subjecting the government's prosecution theories to much needed judicial review. It is possible that the strong First Amendment precedent in *Caronia* will lead companies subject to enforcement action to seek judicial review as well, whether through declaratory judgment actions or otherwise.

Although Mr Caronia was prosecuted criminally, much of the Second Circuit's reasoning applies with equal force to civil claims; if it is unconstitutional to prosecute criminally a manufacturer or sales representative for promotional speech, it is also likely unconstitutional to restrict speech through civil penalties, such as the treble damages and statutory penalties available under the False Claims Act (FCA). Whistleblowers who bring FCA suits seek theories of "false claims" that allow them to prove liability on a categorical, rather than claim-by-claim basis. Some whistleblowers asserted off-label promotion theories under the FCA in such a hope. To the extent that whistleblowers are forced to allege false and misleading promotion as the basis for FCA liability, their task will be considerably harder, and the requirement to plead falsity case-by-case can sometimes prove insurmountable.

Implications for FDA enforcement

The FDA's public position is that it "does not believe that the *Caronia* decision will significantly affect [its] enforcement of the drug misbranding provisions of the [FDCA]".

In the short term, it appears that the FDA will attempt to ignore the outcome of *Caronia* – and undoubtedly try to limit its impact – as *Caronia* was not a case directly involving the FDA, and the Second Circuit did not directly hold any FDA rule or policy to be unconstitutional. Nevertheless, *Caronia's* impact is likely to be felt in a number of areas.

The court in *Caronia* held that "pure" speech, without more, is constitutionally protected even if off label, so long as the underlying off-label use is legal. But many of the FDA's untitled and warning letters regarding off-label promotion are, in fact, based on speech alone. Unlike the DOJ, which has subpoena authority and can thus cite other "evidence" of intent to market a drug off label, such as sales force training or compensation materials, the FDA must rely on labeling or oral statements. Though it left the question for another day, the Second Circuit in *Caronia* expressed some skepticism that enforcement actions based on speech alone could withstand constitutional scrutiny.

As a result, as with the DOJ, the FDA may concentrate its enforcement efforts on cases where a manufacturer's speech is not merely inconsistent with approved labeling, but also "false or misleading" under the FDCA. However, this shift in focus will likely present significant challenges to the FDA for several reasons.

First, the "false and misleading" standard puts a greater evidentiary burden on the FDA because the agency cannot simply point to inconsistencies between product labeling and promotional language; instead, it must prove that the promotion is false or misleading or withholds or conceals information related to the off-label use. Second, this more rigorous evidentiary standard will necessarily raise transactional costs to the FDA, as it must dedicate additional time, money and resources to collecting evidence far more than is needed to demonstrate that an approved label and manufacturer's claim are inconsistent. Finally, the agency will likely face considerable debate over the meaning of "false or misleading" as applied to manufacturers' speech.

Although FDA regulations set forth select examples of "false or misleading" speech, there remain countless other examples where it is unclear whether the FDA would regard speech as "false or misleading".

For example, while there may be little debate that the FDA could cite a claim as false or misleading when there is no data supporting the claim, it is unclear how the agency might characterize off-label information contained in other sources – for example, information from government-approved third-party treatment guidelines. Similarly, where the FDA has not yet approved an indication for the product, but the manufacturer has strong evidence that supports the indication, *Caronia* raises doubt as to whether the FDA could successfully bring an enforcement action on the grounds that the information is "false or misleading".

The FDA has typically applied a strict "substantial evidence" standard to support a promotional claim. However, in light of *Caronia* (and some of the cases involving health claims for food), it will be difficult for the FDA to simply prohibit speech unless that standard is met; the FDA eventually may consider adopting one of several more flexible standards that also take into account appropriate disclaimers in assessing a product claim.

Implications for FDA guidance

Caronia may also spur a challenge to the validity of certain FDA guidance documents. *Caronia* and *Sorrell* apply a "heightened scrutiny" standard to content- and speaker-based speech regulations. FDA guidance documents governing reprint practices, unsolicited requests and continuing medical education (CME) may fail to survive heightened scrutiny as they arguably restrict speech based upon content, speaker and forum.

For example, the FDA's reprint guidance permits dissemination of literature about off-label uses only if it describes adequate and well-controlled studies about approved drugs. The agency's 2011 draft guidance on unsolicited requests also limits speech by both recommending that medical and scientific personnel, but not sales personnel, generate responses to unsolicited off-label requests and prohibiting manufacturers from responding to an unsolicited off-label request in public. Similarly, the CME guidance uses a multifactorial test to discern the legality of speech at an event that has received manufacturer support.

Legality of pre-approval promotion

Finally, *Caronia* may call into question the FDA's prohibition on pre-approval promotion of investigational new drugs (INDs) that have no approved use. The FDA sometimes cites manufacturers for statements made prior to approval for violating a regulation that prohibits commercializing IND drugs. Yet, for drugs that have not been approved, the agency cannot claim that speech is evidence of intent to misbrand a drug shipped in interstate commerce. Any enforcement action based upon promotion necessarily is grounded exclusively on the manufacturer's speech. While *Caronia* only applies to drugs that have at least one approved use, the case's holding could arguably restrict the FDA's ability to control speech for drugs not yet shipped into interstate commerce.

Summary

While *Caronia* leaves many questions unanswered, it is nonetheless a very significant case. After a half century of scant judicial review of the FDA's regulatory scheme, *Caronia* represents the beginning of a process to align the agency's policies and practices with First Amendment protections.

References for this article are available on the www.scripregulatoryaffairs.com website.

Alan Bennett and **Douglas Hallward-Driemeier** are partners in the Washington, DC, office of international law firm Ropes & Gray.
Emails: alan.bennett@ropesgray.com and douglas.hallward-driemeier@ropesgray.com.