



Drug Promotion in the Post-*Caronia* World

By Kellie Combs and Albert Cacozza

In its watershed decision in *United States v. Caronia*,¹ the United States Court of Appeals for the Second Circuit vacated and remanded the conviction of Alfred Caronia, a former sales representative for Jazz Pharmaceuticals accused by the government of promoting a drug off-label. The 2-1 majority held that the First Amendment prohibits the government from prosecuting a drug manufacturer or individual solely on the basis of off-label speech, and that as a result, the Food, Drug, and Cosmetic Act (“FDCA”) cannot be construed to restrict such speech. Because the *Caronia* decision is the first of its kind, industry has both lauded its holding and questioned its ultimate impact. This article

provides a brief overview of the decision and its immediate impact and highlights what industry should watch for once the dust from the decision begins to settle.

The Majority’s Analysis and Immediate Impact

Caronia challenged his criminal misbranding conviction on appeal by arguing 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



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Albert Cacozza is ...

such speech.”² Largely agreeing with this analysis, the *Caronia* majority invoked the principle of constitutional avoidance to conclude that the FDCA does not criminalize the “simple promotion” of a drug’s off-label use and went on to hold that because *Caronia* was a criminal defendant, and in light of Supreme Court precedents in *Central Hudson*³ and *Sorrell*,⁴ the government’s practice of penalizing him solely on the basis of off-label speech was unconstitutional.⁵

The immediate impact of the decision is settled. Because the government elected not to seek rehearing *en banc* in the Second Circuit and has decided not file a writ of certiorari to the U.S. Supreme Court, *Caronia* is now the law of the jurisdictions governed by Second Circuit—Connecticut, New York, and Vermont. In a public statement, FDA emphasized that it “does not believe that the *Caronia* decision will significantly affect [its] enforcement of the drug misbranding provisions of the Food, Drug & Cosmetic Act.”⁶ We nevertheless understand the Agency is marshaling internal resources to assess the impact of *Caronia* and may be wary of the litigation risks posed by certain enforcement actions. At least one senior FDA official has acknowledged that *Caronia* has the potential to upend the entire regulatory scheme.⁷ While it would be premature to arrive at such a drastic conclusion, and industry would be ill-advised to modify significantly its practices with regard to off-label communication, there are some potential long-term implications to consider.

Potential Effects of *Caronia* Shifting Focus Toward the “False and Misleading” Standard. From 2007 through 2012, FDA issued nearly 200 Warning and Untitled Letters to drug manufacturers, of which less than 20 percent allege off-label promotion. Thus,

the bulk of FDA promotional enforcement actions would appear not to be affected by *Caronia*. Unlike the Department of Justice’s enforcement actions against product manufacturers, which commonly rely on speech plus other indicia of intent (*e.g.*, call lists that target physicians likely to prescribe only for off-label uses, internal marketing plans), FDA’s allegations of off-label promotion have typically been grounded in speech alone—an approach that does not pass constitutional muster in light of *Caronia*. Because the majority opinion acknowledged that the First Amendment does not protect false or misleading speech,⁸ FDA may begin to focus its enforcement efforts on instances where a manufacturer’s speech is not only inconsistent with the approved product label, but is also false or misleading in violation of the FDCA. This change of purpose would, of course, raise the bar for the Agency. No longer would it be sufficient, as has long been FDA’s standard practice, to simply cite a manufacturer’s claim, compare it to the language of the product label, and conclude that the manufacturer has violated the law any time the Agency believes that the two are inconsistent. Instead, the Agency will likely need to demonstrate that the statement is false and misleading—a potentially difficult task. While the Agency has set forth in its advertising regulations detailed categories of claims that are or may be false or misleading,⁹ and likely would apply those categories to other forms of promotional speech, FDA has traditionally viewed itself as the arbiter of what scientific evidence is true based on its rigorous “substantial evidence” standard. In light of *Caronia* and perhaps after a lengthy dialogue with industry and the public, FDA may have to reconsider whether that is the only standard that can define

what “false and misleading” means in the context of product promotion or whether an FTC-like standard of “competent and reliable scientific evidence” could be applied as well. This much is certain: it will be critical for product manufacturers to ensure that any off-label statements are accompanied by disclaimers to clarify that the use at issue has not been approved by FDA and to qualify the type and quantity of evidence relied upon in making the statement.

Careful Reevaluation of FDA Policy and Guidance. Both the *Caronia* decision and the Supreme Court’s decision in *Sorrell* implicitly call into question recent FDA guidance that distinguishes permissible and impermissible speech on the basis of content, speaker, and audience. FDA’s 2011 draft guidance on unsolicited requests, for example, provides that medical rather than sales personnel should develop responses to unsolicited requests and indicates that manufacturers should censor internet responses on the basis that consumers, rather than physicians, might view them.¹⁰ Similarly, FDA’s reprints guidance permits dissemination of literature about off-label uses only if it describes adequate and well-controlled studies.¹¹ Such recommendations seem to run afoul of the *Caronia* court’s analysis and are deserving of close examination by the Agency and industry.¹²

Government Influence Over the Practice of Medicine. The crux of the *Caronia* court’s holding was that the regulatory regime improperly prohibited manufacturers from communicating off-label information while permitting physicians to prescribe drugs for off-label uses. The *Caronia* majority made clear that one way to resolve this disconnect would be to “prohibit the off-label use altogether.”¹³ If the government, on the one hand, provides manufacturers greater discretion to share truthful,

non-misleading information about off-label uses of their products, it may also begin to limit prescribing decisions by physicians on the other—especially where off-label use may be particularly risky or undesirable. There may be, for example, new restrictions or penalties that would prevent doctors from prescribing certain classes of products off-label, similar to the statutory ban on the off-label use of human growth hormone.¹⁴ FDA could also harness its REMS authority to curb off-label prescribing, refusing to approve a drug unless the manufacturer agreed to seek certification from every prescribing physician that the drug will be used on-label. Irrespective of the policy implications, limiting off-label use of products may allow the government to prohibit off-label promotion without implicating the First Amendment.

Increased Emphasis on Non-Speech-Based Activity. The *Caronia* court emphasized that its holding did not address the question of whether off-label speech could be used as evidence of intent to misbrand a product.¹⁵ As a result, FDA may begin to focus on manufacturer activity that could arguably evidence an intent to misbrand but that could not be characterized as “speech.” Marketing plans, incentive compensation programs, and directives to sales representatives that rely on off-label sales—though internal and not akin to promotion—may be of increased importance. Physician-directed activities may also provide a speech-free hook for FDA to regulate; if manufacturers provided drug samples to pediatricians when the label permitted use only in adult patients, the government may point to the sampling activity to demonstrate that the manufacturer intended an off-label use.¹⁶ Industry should also watch for future FDA enforcement actions based on a manufacturer’s knowledge that a product may be used off-label.

Although FDA has previously disavowed the notion of “knowledge as intent,”¹⁷ it has as recently as 2010 relied on a manufacturer’s knowledge of off-label use as justification to change the product label in a medical device case.¹⁸ In *Caronia* itself, the government reserved the right to use specific knowledge of off-label use as evidence to demonstrate an intended use, stating that while it does not establish intended use as a matter of law, “knowledge of how the product is being used ‘may’ be taken as evidence that the use is intended.”¹⁹ While *Caronia*’s First Amendment analysis likely will require a change in Agency practices, in other words, it would not prevent FDA from bringing misbranding charges altogether.

Conclusion

While it may be too early to discern whether the *Caronia* case will truly cause a sea change in the government’s policymaking and enforcement efforts, it undoubtedly will provoke important discussions about the constitutional concerns and practical considerations associated with FDA’s restriction of truthful, non-misleading off-label speech. The implications described above may represent just a handful of the many potential outcomes resulting from the decision, and future developments deserve industry’s rapt attention. ▲

1. *U.S. v. Caronia*, No. 09-5006-cr, slip op. 3 (2d Cir. Dec. 3, 2012).
2. *Id.* at 25.
3. *Cent. Hudson Gas & Elec. Corp. v. Pub. Serv. Comm’n of N.Y.*, 447 U.S. 557, 563-64 (1980).
4. *Sorrell v. IMS Health, Inc.*, 131 S. Ct. 2653 (2011).
5. *Caronia*, slip op. at 26-52.
6. See Ed Silverman, *FDA Declines to Pursue Hearing in Free Speech Case*, PHARMALOT (Jan. 22, 2013), available at <http://www.pharmalot.com/2013/01/fda-declines-to-pursue-hearing-in-free-speech-case/> (“The decision does not strike down

any provision of the FD&C Act or its implementing regulations, nor does it find a conflict between the act’s misbranding provisions and the First Amendment or call into question the validity of the act’s drug approval framework.”).

7. Brenda Sandburg, *Off-label Ruling’s Potential Fallout is “Terrifying,” FDA’s Temple Says*, THE PINK SHEET (Dec. 17, 2012) (noting that Robert Temple, FDA’s Deputy Director for Clinical Science in the Center for Drug Evaluation and Research, has called the *Caronia* decision “terrifying” and believes it has the potential to undermine the FDCA’s requirement that drugs must be proven safe and effective).
8. *Caronia*, slip op. at 42 n.11.
9. See 21 C.F.R. § 202.1(e)(6)-(7).
10. See FDA, *Draft Guidance for Industry: Responding to Unsolicited Requests for Off-Label Information About Prescription Drugs and Medical Devices* (Dec. 2011), at 8-9, 13.
11. See FDA, *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* (Jan. 2009), available at <http://www.fda.gov/RegulatoryInformation/Guidances/ucm125126.htm>.
12. Because FDA’s unsolicited requests guidance is still in draft form, the Agency could modify the recommendations to address these court decisions before finalizing.
13. *Caronia*, slip op. at 50.
14. 21 U.S.C. § 333(e).
15. See *Caronia*, slip op. at 32 n.10.
16. See Supp. Brief of the U.S. Gov’t at 20 n.3, *U.S. v. Caronia*, 09-5006-cr (Dec. 3, 2012).
17. See Decl. of Rachel E. Sherman, *Par Pharmaceutical, Inc. v. U.S.*, No. 1:11-cv-01820-RC-JMF (filed Jan. 11, 2012), at 7.
18. See Warning Letter from Alonza Cruse, FDA to Terrence Gregg, Dexcom, Inc. (May 21, 2010) (“Evidence collected during the inspection documented that your firm knows and has knowledge of facts that give notice that your device introduced into interstate commerce is being used for conditions, purposes, and uses other than the ones for which it is offered.”).
19. See Supp. Brief of the U.S. Gov’t at 19, *U.S. v. Caronia*, 09-5006-cr (Dec. 3, 2012).