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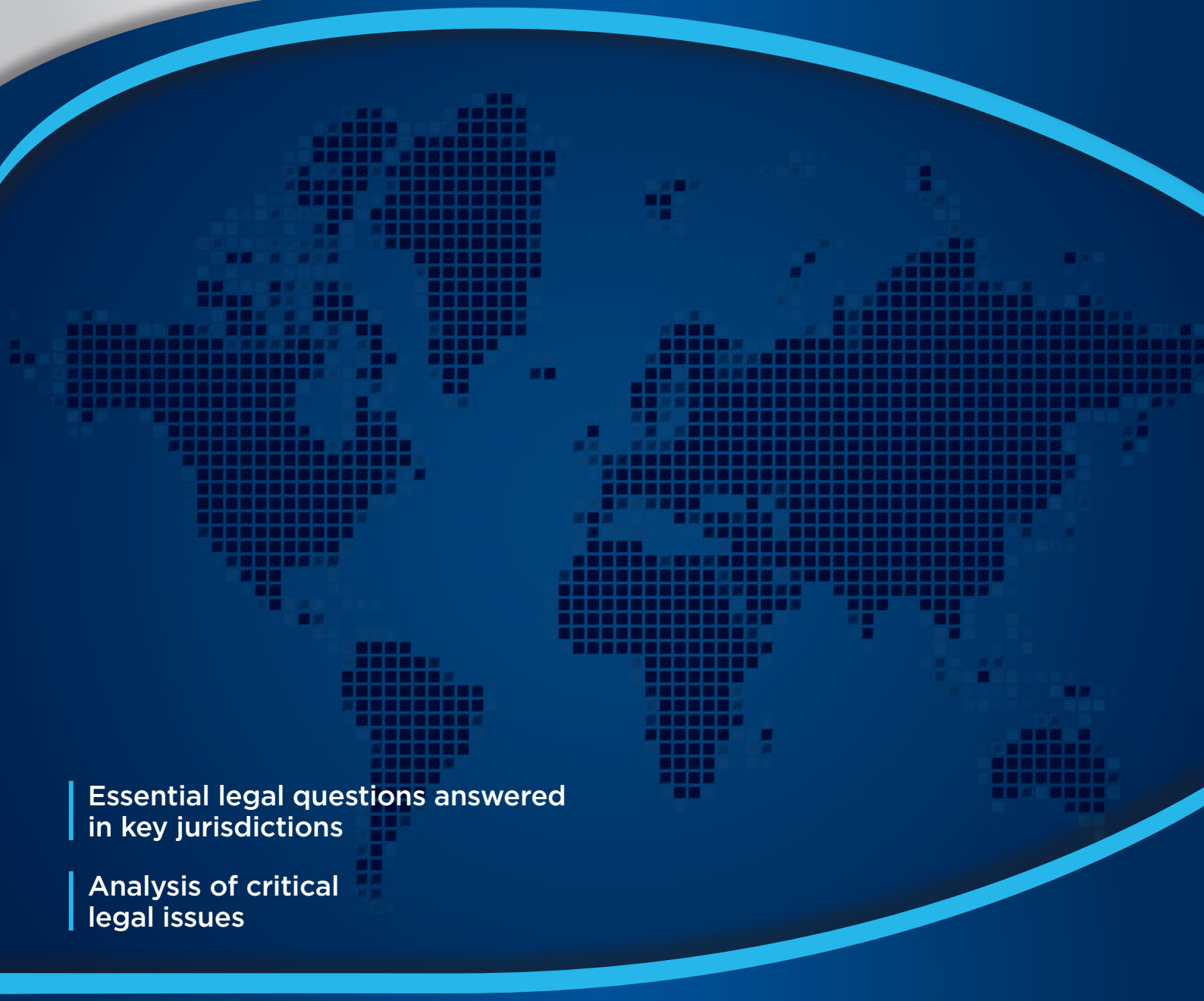

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The US Caronia case: truthful off-label communications by pharmaceutical companies

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On 3 December 2012, the US Court of Appeals for the Second Circuit issued an important and long-anticipated decision in *United States v. Caronia*, *No. 09-5006-cr*. The court held that construing the Federal Food, Drug, and Cosmetic Act (FDCA) and its implementing regulations to prohibit pharmaceutical companies from engaging in truthful and non-misleading speech regarding unapproved or off-label uses of Food and Drug Administration (FDA)-approved drugs violates the First Amendment to the US Constitution. This is a precedent that could have a significant impact on FDA regulations and US government enforcement moving forward.

Caronia is significant for at least three reasons:

- It is the first Court of Appeals decision holding that truthful and non-misleading off-label speech is protected under the First Amendment.
- It followed the US Supreme Court's 2011 decision in *Sorrell v. IMS Health Inc., 131 S. Ct. 2653 (2011),* which held that pharmaceutical marketing is a form of expression protected by the First Amendment. It concluded that the FDCA constitutes a content-based restriction on speech that is subject to heightened scrutiny.
- It found that criminalising off-label promotion fails to satisfy even the intermediate scrutiny test for commercial speech established by the Supreme Court in *Central Hudson Gas & Electric Corporation v. Public Service Commission of New York, 492 U.S. 469, 480-81 (1980)*. This requires that a restriction on commercial speech "directly advance the governmental interest asserted" and be "narrowly drawn".

The *Caronia* court found that interpreting the FDCA to restrict off-label promotion would not be narrowly tailored to further the government's interests, and it therefore interpreted the FDCA to avoid this result.

There are open questions after *Caronia*, including whether off-label speech can be used as evidence to support a failure to provide adequate directions for use charge under the FDCA (and, if so, what additional evidence beyond the speech would be necessary to prove the charge). However, *Caronia* will undoubtedly be cited by defendants in enforcement cases alleging off-label marketing, to support their position that truthful and non-misleading speech about an unapproved use of a drug is not illegal.

Against this background, this article examines the:

- Facts of the *Caronia* case.
- Second Circuit *Caronia* ruling.
- Rationale for the Second Circuit *Caronia* decision.
- Impact of the Second Circuit *Caronia* decision.

FACTS OF THE *CARONIA* CASE

The *Caronia* case began in 2005, when the US government launched an investigation into Orphan Medical, Inc. (Orphan), a wholly-owned subsidiary of Jazz Pharmaceuticals, and its sale of Xyrem®, a central nervous system depressant. A few months earlier, Orphan had hired Alfred Caronia and Dr Peter Gleason to market Xyrem®.

Although the FDA had approved Xyrem® for two medical indications relating to narcolepsy (cataplexy and excessive daytime sleepiness), the government obtained two audio recordings of Messrs Caronia and Gleason promoting Xyrem® to a physician for unapproved indications, including insomnia and fibromyalgia, and for unapproved patient populations, including patients under the age of 16.

Two years after the government began its investigation, Orphan pled guilty to felony misbranding and paid US$20 million in penalties (*Press Release, U.S. Department of Justice, Jazz Pharmaceuticals, Inc. Agrees to Pay $20 Million to Resolve Criminal and Civil Allegations in Off-Label Marketing Investigation (13 July 2007), (www.justice.gov/usao/nye/pr/2007/2007jul13a.html)*).

Dr Gleason pleaded guilty to misdemeanour misbranding (*United States v. Caronia, 576 F. Supp. 2d 385, 390 (E.D.N.Y. 2008)*). However, Caronia decided not to enter a plea and chose to proceed to trial. In a motion to dismiss before the trial court, Caronia argued in part that the FDCA's misbranding provisions as applied to him violated his speech rights under the First Amendment: "Reduced to its essence, Caronia's argument [was] that the government cannot restrict truthful, non-misleading promotion by a pharmaceutical manufacturer (or its employees) to a physician of the off-label uses of an FDA-approved drug" (*Caronia, at 393*).

Applying the *Central Hudson* test, the district court denied the motion, concluding that the government's interests in preserving the integrity of the FDA's drug approval process and public health and safety justified restricting Caronia's speech about unapproved uses of Xyrem® (*Caronia, at 394 to 402*).

The case proceeded to trial and, before it began its deliberations, the trial judge instructed the jury that "a misbranded drug may be shown by the promotion of the drug by a distributor for an intended use different from the use for which the drug was approved by

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the [FDA]". Additionally, the judge stated that a manufacturer and its agents and representatives "are not permitted to promote uses for a drug that have not been cleared by the [FDA]". The jury subsequently convicted Caronia of conspiracy to introduce a misbranded drug into interstate commerce.

SECOND CIRCUIT *CARONIA* RULING

Caronia appealed the conviction to the US Court of Appeals for the Second Circuit. After the appeal had been fully briefed and argued, the US Supreme Court issued its seminal decision in *Sorrell*, in which the Supreme Court held that pharmaceutical promotion is protected speech under the First Amendment, and that content-based or speaker-based restrictions on such speech are subject to "heightened judicial scrutiny".

In light of *Sorrell*, the Second Circuit ordered further briefing concerning its impact on the issues presented on appeal in the *Caronia* case, which was completed during the summer of 2011.

The Second Circuit issued its decision on 3 December 2012:

- Judge Denny Chin, joined by Judge Reena Raggi, held that applying the FDCA to restrict speech about unapproved uses fails to advance the government's interests in protecting public health and the integrity of the drug approval process in an appropriately tailored way.
- Because the First Amendment bars the government from prohibiting pharmaceutical companies from engaging in truthful and non-misleading speech about off-label uses, the majority interpreted the FDCA not to prohibit this speech.

This ruling calls into serious question the core theory used by the government to prosecute off-label promotion under the FDA's "intended use" regulations. It also may limit the ability of the government and private claimants to argue that off-label promotion leads to the submission of false claims.

Judge Debra Livingston dissented, arguing that the majority's decision "calls into question the very foundation of our century-old system of drug regulation" (*slip opinion, at 1 (Livingston, J, dissenting)*). In her view, the government was not prosecuting Caronia on the basis of his speech alone; rather, Caronia's speech was permissible evidence of his intent to violate prohibitions on misbranding: use of a prescription drug in ways the drug's labelling did not describe (*slip opinion, at 1, 7 to 15 (Livingston, J, dissenting)*). Notably, Judge Livingston cited a DC Circuit opinion authored by then Judge John Roberts, now Chief Justice of the Supreme Court, that similarly concluded that it was constitutionally permissible to infer criminal intent from speech (*slip opinion, at 17 (Livingston, J, dissenting) (citing Whitaker v Thompson, 353 F.3d 947, 953 D.C. Cir. 2004)*).

RATIONALE FOR THE SECOND CIRCUIT *CARONIA* DECISION

Impact of the *Sorrell* case

The Second Circuit's decision draws heavily from the Supreme Court's decision in *Sorrell*. There, the Supreme Court invalidated under the First Amendment a Vermont law that restricted pharmaceutical companies from using prescriber-identifying data for marketing purposes. It concluded that Vermont's law was subject to "heightened judicial scrutiny" because it imposed both content- and speaker-based restrictions on the speech of pharmaceutical companies (*Sorrell, at 2664*).

The Vermont law at issue precluded pharmaceutical companies, and only pharmaceutical companies, from promoting their products with prescriber-identifiable data. Others, such as insurance companies, academics, and the state, could use prescriber-identifiable data for promotion of products, such as generic drugs, without consequence. In the end, however, the *Sorrell* court ruled that the Vermont law could not survive even the less stringent intermediate scrutiny under the four-part *Central Hudson* test (*Sorrell, at 2667 to 2672*).

The court's response to the government's arguments

Before the Second Circuit, the government contended that Caronia's speech was merely "evidence" that a manufacturer's intended use of a drug was incompatible with the directions in its labelling, which by law are limited to approved uses (*slip opinion, at 27*). The *Caronia* majority quickly disposed of this argument, observing that the government had used Caronia's off-label speech at trial for more than mere evidentiary purposes. The court stressed that the government's closing arguments alone referred to "Caronia's off-label promotion of Xyrem[®]...*over forty times*" (emphasis added) (*slip opinion, at 28 (majority opinion)*).

Likewise, the court added, the government's summation and the jury instructions "led the jury to believe that Caronia's promotional speech was, by itself, determinative of his guilt" (*slip opinion, at 30*). No matter how brazen Caronia's promotional efforts were (excerpts of the audio recordings introduced at trial make clear that Caronia engaged in unequivocal off-label promotion), the court explained, Caronia's truthful off-label speech alone could not serve as the basis for prosecution (*slip opinion, at 31*): "Here, the proscribed conduct for which Caronia was prosecuted was precisely his speech in aid of pharmaceutical marketing".

The Second Circuit next addressed the government's view that the FDCA could be construed, consistent with the First Amendment, to criminalise truthful off-label promotion by drug companies and their representatives. Closely tracking the Supreme Court's analysis in *Sorrell*, the Second Circuit reasoned that criminally prohibiting such truthful speech would impose presumptively invalid content- and speaker-based restrictions (*slip opinion, at 39 to 41*). The court added that heightened scrutiny was even more appropriate than in *Sorrell*, because "this case involves a criminal regulatory scheme" (*slip opinion, at 41*).

Continuing to follow *Sorrell*, the Second Circuit explained that, although heightened scrutiny applied, prohibiting truthful off-label speech by drug manufacturers fails even intermediate scrutiny under *Central Hudson*. Under that test, the court observed (*slip opinion, at 37 to 38*):

- The speech at issue must be non-misleading and relate to lawful activity.
- The government must have a substantial interest in regulating the speech.
- The regulation must directly advance the government's asserted interest.
- The regulation must not impinge on any more speech than is necessary to achieve the governmental interest.

The *Caronia* court stated that off-label promotion is not inherently misleading, it concerns a lawful activity, and the government has substantial interests in "preserving the effectiveness and integrity of the FDCA's drug approval process, and...reducing patient exposure to unsafe and ineffective drugs" (*slip opinion, at 42 to 43*).

Furthering the government's interests

In a part of the holding that could have broader consequences, the Second Circuit said that construing the FDCA to prohibit truthful off-label promotion would not directly advance the government's interests, nor would it be the least-restrictive means available to achieve those interests.

Because physicians can and do lawfully write off-label prescriptions, the court did not see how proscribing truthful off-label communications by pharmaceutical companies furthered the government's interests in protecting public health. Indeed, mirroring the reasoning of *Sorrell*, the majority found 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; such barriers to information about off-label use could inhibit, to the public's detriment, informed and intelligent treatment decisions" (*slip opinion, at 44*).

Judge Livingston disagreed with the majority's conclusion that prohibiting off-label promotion is unconstitutionally "paternalistic", concluding that the prohibition was the least restrictive way of advancing the government's interests in both drug safety and effectiveness. In her view, "[i]f 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. Prohibiting such promotion is thus one of the few mechanisms available to encourage participation in the approval process" (*slip opinion, at 21 (Livingston, J, dissenting)*).

Further, the Second Circuit identified several ways in which the government could advance its interests without unduly restricting speech. Adopting a more robust system for warnings and disclaimers, requiring drug applications to include all intended uses, limiting the number of off-label prescriptions, or even prohibiting off-label prescriptions would all serve the government's interests "equally well" without impinging on protected speech (*slip opinion, at 48 to 50*). The court rejected as "conclusory" and unsupported the government's reply that such alternatives were not feasible or effective (*slip opinion, at 50 to 51*).

Applying the canon of constitutional avoidance, the Second Circuit construed the FDCA and its implementing regulations not to criminalise truthful off-label promotion. It accordingly vacated Caronia's conviction (*slip opinion, at 26, 51*). In so doing, the court recognised that false or misleading speech is not protected under the First Amendment and could, therefore, form the basis for a misbranding charge. The government has not sought rehearing of the *Caronia* decision by a full panel of the Second Circuit or by the Supreme Court.

IMPACT OF THE SECOND CIRCUIT *CARONIA* DECISION

To be sure, *Caronia* applies only to truthful and non-misleading speech. Shortly after *Caronia* was decided, the Ninth Circuit issued a highly anticipated decision in *United States v. Harkonen*, rejecting former InterMune Chief Executive Officer W Scott Harkonen's First Amendment defence because statements he made in a press release were false (*United States v. Harkonen, Nos. 11-10209 & 11-10242*).

The Ninth Circuit credited evidence, including the testimony of clinical personnel who stated the press release misrepresented the clinical trial's results, testimony indicating that Harkonen was "very apologetic" about the misleading nature of the press release, that Harkonen prevented clinical personnel from reviewing the press release before its publication, and that the press release was capable of influencing doctors and patients.

The court affirmed Harkonen's conviction for wire fraud because it concluded that the First Amendment requires deference to the jury's finding that the press release was false or fraudulent. Dr Harkonen has sought rehearing by a full panel of the Ninth Circuit on that aspect of the decision, which seems to conflict with prior Supreme Court precedent requiring appellate courts to review jury findings of constitutional fact on a new hearing basis (*see Snyder v. Phelps, 131 S. Ct. 1207 (2011), Bose Corp. v. Consumers Union, 466 U.S. 485 (1984), and New York Times Co. v. Sullivan, 376 U.S. 254 (1964)*).

The impact the *Caronia* decision will have on misbranding prosecutions and False Claims Act litigation involving truthful and non-misleading speech, and whether other circuits will adopt its reasoning, remains to be seen. The Second Circuit did not fully close the door on the possibility that the government could use a manufacturer's off-label speech as evidence of an intent to distribute a drug without adequate directions for use.

However, in two footnotes, the *Caronia* court questioned the viability of that approach, noting that it "remains unclear how the government would identify criminal misbranding from communications between drug manufacturers and physicians authorized to prescribe drugs for off-label use" (*slip opinion, at 32 n.10*).

The Second Circuit's reasoning in this regard is consistent with a line of Supreme Court precedents over the last decade rejecting government efforts to censor commercial speech, especially in the pharmaceutical context (*see Sorrell; Thompson v. W States Med. Ctr., 535 U.S. 357, 367 (2002); Virginia State Pharmacy Board v. Virginia Citizens Consumer Council, 425 U.S. 748 (1976); cf. Greater New Orleans Broadcasting Assn., Inc. v. United States, 527 U.S. 173 (1999); 44 Liquormart, Inc. v. Rhode Island, 517 U.S. 484 (1996)*).

Additionally, since a 2003 decision (*U.S. ex rel. Franklin v. Parke-Davis, Div. of Warner-Lambert Co., No. Civ.A. 96–11651PBS, 2003 WL 22048255 (D. Mass. Aug. 22, 2003)*), the government and relators have argued that off-label promotion of a drug causes the submission of false or fraudulent claims under the US False Claims Act. In light of the Second Circuit's holding that off-label speech without more is not unlawful, the viability of this theory of False Claims Act liability is subject to serious question.

Further, in December 2011, the FDA issued a draft guidance document regarding industry responses to "unsolicited requests" for off-label information from healthcare professionals (*see Draft Guidance, Responding to Unsolicited Requests for Off-Label Information About Prescription Drugs and Medical Devices (December 2011), available at www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM285145.pdf*).

The draft guidance proposed stringent requirements, including a requirement that requests occurring in a public setting (for example, a question at a speaker programme) must be answered only in a private setting to constitute permissible "scientific exchange". The government's ability to impose such restrictions on protected speech in this area and others, such as FDA's Good Reprint Practices Policy, is also suspect after *Caronia* (*see FDA* guidance, *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 (January 2009).*

Caronia may have already precipitated changes in the government's approach to truthful and non-misleading off-label communications. At a presentation on 26 February 2013 regarding pharmaceutical compliance issues, prosecutors from the United States Attorney's Offices for the Southern District of New York and for the District of New Jersey stated that they have declined to prosecute truthful off-label communications relating to off-label uses that are the medically accepted standard of care (*see, for example, Brenda Sandburg, Off-Label Prosecutions Hinge on Patient Benefits, Government Attorneys Say, The Pink Sheet, Vol. 13 No. 31 (11 March 2013)*).

Caronia may also affect the FDA's regulatory approach over time by, potentially, encouraging it to issue a more narrowly tailored set of restrictions on dissemination of reprints, responding to unsolicited requests for off-label information, and scientific exchange more generally. That change will take time. In the interim, *Caronia* represents an important step in the evolution of First Amendment jurisprudence with respect to truthful and not misleading pharmaceutical company communications in the US.

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