09-5006-CR

IN THE
UNITED STATES COURT OF APPEALS
FOR THE SECOND CIRCUIT

UNITED STATES OF AMERICA

Appellee

v.

ALFRED CARONIA

Defendant-Appellant

ON APPEAL FROM THE UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF NEW YORK

Amicus Curiae **Brief Of The Medical Information Working Group In Support Of Defendant-Appellant Alfred Caronia And Reversal Of The Decision Below**

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RULE 26.1 DISCLOSURE STATEMENT

Under Federal Rule of Appellate Procedure 26.1, *amicus curiae* states that the Medical Information Working Group (MIWG) is an informal working group of major manufacturers of prescription drugs and medical devices. The MIWG members submitting this brief are:

- Allergan, Inc., a corporation with publicly traded stock of which no publicly traded corporation owns more than 10%.
- Amgen Inc., a corporation with publicly traded stock of which no publicly traded corporation owns more than 10%.
- Boehringer Ingelheim USA Corporation, a wholly owned subsidiary of Boehringer Ingelheim Auslandsbeteiligungs GmbH.
- Eli Lilly and Company, a corporation with publicly traded stock of which no publicly traded corporation owns more than 10%.
- GlaxoSmithKline plc, a corporation with publicly traded stock of which no publicly traded corporation owns more than 10%.
- Johnson & Johnson, a corporation with publicly traded stock of which no publicly traded corporation owns more than 10%.
- Novartis Pharmaceuticals Corporation, a wholly owned subsidiary of Novartis AG.
- Novo Nordisk A/S, a corporation with publicly traded stock of which no publicly traded corporation owns more than 10%.
- Pfizer Inc., a corporation with publicly traded stock of which no publicly traded corporation owns more than 10%.
- Purdue Pharma, L.P., a privately held corporation of which no publicly traded corporation owns more than 10%.
- sanofi-aventis U.S. LLC, a wholly-owned subsidiary of sanofi S.A., a corporation with publicly traded stock of which no publicly traded corporation owns more than 10%.

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INTEREST OF *AMICUS*

The Medical Information Working Group (MIWG) is an informal working group of major manufacturers of prescription drugs and medical devices.[1] It was formed in 2006 to address issues regarding the Government's regulation of truthful, non-misleading, and scientifically substantiated speech about off-label uses of drugs and devices approved by the Food and Drug Administration (FDA). The MIWG has sought in particular to address concerns that, due to the absence of clear rules, the present regulatory framework fails to provide adequate notice of the line between permissible and impermissible speech. The MIWG has a strong interest in the issues presented in this case and specifically in the post-argument question that the Panel has raised regarding the First Amendment issues addressed by the Supreme Court in *Sorrell v. IMS Health Inc.*, 131 S. Ct. 2653 (2011).

ARGUMENT

In *Sorrell*, the Supreme Court held that Vermont's "Act 80" was a speaker- and content-based restriction on pharmaceutical manufacturers' speech. *See* 131 S. Ct. at 2663. Although they target a somewhat different subject matter, the FDA

[1] The MIWG members submitting this brief are: Allergan, Inc., Amgen Inc., Boehringer Ingelheim USA Corporation, Eli Lilly & Co., GlaxoSmithKline plc, Johnson & Johnson, Novartis Pharmaceuticals Corporation, Novo Nordisk A/S, Pfizer Inc., Purdue Pharma, L.P., and sanofi-aventis U.S. LLC. No party's counsel authored this brief in whole or in part, nor did any party, their counsel, or any other person other than *amicus* contribute money intended to fund the preparation or submission of this brief.

regulations at issue in this case are no less speaker- and content-based than was the law at issue in *Sorrell*. The Supreme Court's opinion in *Sorrell* resolves the question of the applicable standard of review: *Sorrell* made clear that where, as here, a law restricts truthful, non-misleading commercial speech on the basis of its content and the identity of the speaker, that law "must be subjected to heightened judicial scrutiny." 131 S. Ct. at 2659. The Court rejected the argument that a more lenient form of "intermediate" scrutiny should apply. *See id.* at 2664 (holding that "[c]ommercial speech is no exception" to the heightened judicial scrutiny applicable to speaker- and content-based speech restrictions); *id.* at 2667 (holding that if a law "imposes a speaker- and content-based burden" on commercial speech, "that circumstance is sufficient to justify application of heightened scrutiny"); *see also id.* at 2677 (Breyer, J., dissenting) (recognizing that this "'heightened' scrutiny" is "a standard yet stricter than *Central Hudson*"). *Sorrell* also made clear that content- and speaker-based restrictions on commercial speech will fail heightened judicial scrutiny "in the ordinary case." *Id.* at 2667.[2]

There is little question that the misbranding provisions in the Federal Food, Drug, and Cosmetic Act (FDCA) and the FDA's accompanying regulations

[2] In his dissent in *Sorrell*, Justice Breyer noted that the majority opinion implicated the FDA's regulatory framework because it, like "Act 80," imposes "speaker-based" restrictions on speech. 131 S. Ct. at 2678 (Breyer, J. dissenting).

(collectively, 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). There is significant ambiguity, however, regarding precisely what speech is proscribed by the Misbranding Provisions as construed and applied by the FDA and Department of Justice (DOJ). Manufacturers seek to conform their conduct to the law, but in the absence of clear rules they are unable to provide their employees and agents with the guidance they need. Because manufacturers often cannot know whether the Government will deem specific speech about an off-label use to be "evidence of an intended use" that will in turn trigger a criminal prosecution for misbranding, the Misbranding Provisions have the effect of broadly chilling manufacturer speech. As a result, physicians and patients are often deprived of valuable information about off-label uses, to the detriment of the public health.

Although the Misbranding Provisions effectively criminalize speech about off-label uses, it is important to note, as the Panel appeared to recognize at oral argument, that it is not a crime for physicians to prescribe a drug or device for an off-label use. To the contrary, off-label use is lawful, common, and—as the FDA itself has recognized—"may even constitute a medically recognized standard of care." FDA, *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, 74 Fed. Reg. 1694 (Jan. 13, 2009); *see also* Memorandum of the American Medical Association House of Delegates, Resolution 820, *Off-Label use of Pharmaceuticals*, Sept. 21, 2005 ("Up to date, clinically appropriate medical practice at times *requires* the use of pharmaceuticals for 'off-label' indications."). The FDA, Congress, and the courts have all recognized the public health necessity of off-label use. *See, e.g., Proposed New Drug, Antibiotic, and Biologic Drug Regulations*, 48 Fed. Reg. 26,720, at 26,733 (proposed June 9, 1983) ("Once a drug product has been approved for marketing, a physician may . . . prescribe the drug for uses not included in the drug's approved labeling."); 21 C.F.R. § 312.2(d) (providing an exemption from FDA regulations for "the use in the practice of medicine for an unlabeled indication of a new drug product approved" by the agency); 21 U.S.C. § 396 (providing that the FDCA does not "limit or interfere with the authority of a health care practitioner to prescribe or administer any legally marketed device to a patient for any condition or disease within a legitimate health care practitioner-patient relationship"); *Buckman Co. v. Plaintiffs' Legal Comm.*, 531 U.S. 341, 349-51 & n.5 (2001).

Off-label use is a necessary and common practice "[b]ecause the pace of medical discovery runs ahead of the FDA's regulatory machinery." *Richardson v. Miller*, 44 S.W.3d 1, 13 n.11 (Tenn. Ct. App. 2000). Recognizing the value of

developing medical science, Congress and CMS *mandate* federal reimbursement for certain off-label uses that are listed in medical compendia. *See* 42 U.S.C. § 1396r-8(k)(6) (Medicaid); 42 U.S.C. § 1395y(a)(1)(A); Medicare Benefit Policy Manual, Ch. 15, § 50.4.2 (Medicare). But even where the compendia support an off-label use, it could take months or even years before that use receives formal FDA approval. *See* J.H. Beales III, *New Uses for Old Drugs*, *in* COMPETITIVE STRATEGIES IN THE PHARMACEUTICAL INDUSTRY 281, 303 (Robert B. Helms ed., 1996) (finding 2.5 year average lag between compendia recognition and FDA approval). In the meantime, doctors—sophisticated consumers of medical and scientific information—want to make decisions with their patients on the basis of the most current and accurate information.

In addition, for many medical treatments, there is no natural or inevitable progression from "off-" to "on-" label use. For example, for certain rare diseases the "standard of care," and often the only, treatment is off-label. Because of the small number of potential patients and high costs associated with the FDA approval process, the treatment will likely remain off-label no matter how safe and effective or medically accepted it may be. FDA officials have recognized that off-label use provides a critical safety valve, allowing top-quality medical care before FDA approval—or when FDA approval will never come. *See No Regulatory Slack for Tough Supplemental Indications*, Pink Sheet, Sept. 7, 2009, at 21.

Notably, against this backdrop, the FDA has emphasized that physicians have a need for "objective, balanced, and accurate information on important unapproved uses of approved products." *Dissemination of Information on Unapproved/New Uses for Marketed Drugs, Biologics, and Devices*, 63 Fed. Reg. 64,556, at 64,579 (Nov. 20, 1998) (announcing final agency rule) (recognizing the "public health gains associated with the earlier dissemination" of such information). The FDA also has recognized that the public interest is best served when physicians have as much truthful, accurate, and non-misleading information as possible regarding these uses. *See id.*

At the same time, however, the Government has adopted a legal and regulatory framework that restricts, on the basis of content and the identity of the speaker, the dissemination of "objective, balanced, and accurate information" regarding off-label uses. The Misbranding Provisions indisputably constitute a speaker- and content-based restriction on speech. First, they are speaker-based: the regulations restrict only the speech of manufacturers and their agents, while all other classes of speakers remain entirely free to speak about prescribing FDA-approved products for off-label uses. Second, they are content-based: the regulations 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 creates a chill on manufacturers' speech, which has serious potential consequences for physicians, patients, and the public health. Physicians using a product off-label by definition must look beyond the FDA-approved label for the information they need to use the product safely and effectively. Yet, largely as a result of the present regulatory framework, physicians often have difficulty obtaining timely and relevant information regarding off-label uses, a problem that can be especially acute for physicians treating rare diseases or practicing outside centers of excellence, especially within underserved communities. Manufacturers are uniquely positioned to provide physicians with such information. *See, e.g.*, *Wyeth v. Levine*, 129 S. Ct. 1187, 1202 (2009) (recognizing that "manufacturers have superior access to information about their drugs, especially in the postmarketing phase as new risks emerge"). But given the FDA's regulatory framework (which is broad in its sweep but lacking in clear rules), the FDA and DOJ's enforcement policies, and the enormous potential penalties that manufacturers face for violations of the FDCA, they are chilled from doing so.

In response to Caronia's constitutional challenge, the Government has sought to avoid First Amendment scrutiny entirely by disavowing the idea that "off-label promotion" is a crime. *See* United States v. Caronia, 09-5006-CR (2d Cir.), Oral Argument (Dec. 2, 2010) (Government counsel stating "[p]romotion is not a crime" in response to question whether statute prohibits off-label promotion). The Government has argued instead that "speech" is merely "evidence of intended use," and that "intended use" is the core element of the alleged crime. *Sorrell* rejected, however, a similar argument that the law in question did not regulate speech, but only the conduct of selling data. *See* 131 S. Ct. at 2666-67. The Court made clear that courts must look beyond labels to the true nature and consequences of the prohibition: If a law "imposes more than an incidental burden on protected expression," it implicates the First Amendment. *Id.* at 2665.

As *Sorrell* instructs, it is immaterial whether the FDA's regulatory framework prohibits speech directly or restricts speech indirectly by treating certain types of speech as conclusive "evidence" that the manufacturer's product is "intended" for an off-label use. What matters is that, in practice, the Misbranding Provisions clearly impose more than an incidental burden on protected expression. There can be no serious question that this is the case here. If there is any lingering doubt that the Misbranding Provisions do, in fact, criminalize speech *qua* speech, that doubt is resolved by the Government's acknowledgement that the presence of

"off-label promotion" is both a necessary and sufficient condition to a misbranding prosecution in cases like this:

First, as the Government agreed at oral argument, a manufacturer would not be committing a crime merely by introducing into commerce a drug or device that the manufacturer *knew* the physician was going to use off label. *See* United States v. Caronia, 09-5006-CR (2d Cir.), Oral Argument (Dec. 2, 2010) (Government counsel agreeing with the Court's statement that it is not a crime for a manufacturer to arrange for pharmacies to sell a drug to doctors, knowing they are going to use it off label). And when asked whether the Government had ever "secured a conviction without speech," the Government's counsel stated that he was "not aware" of such a case. *Id.* In other words, the Government effectively acknowledged that the presence of "off-label promotion" is a necessary condition to conviction: if that speech is removed, there is no crime.

Second, the Government has consistently represented to courts that the presence of "off-label promotion" is a *sufficient* condition of a misbranding conviction. In this case, the Government's own proposed jury instructions provided that "[t]he manufacturer, its agents, representatives and employees are not permitted to promote uses for a drug that have not been cleared" by the FDA, United States v. Caronia, 1:06-cr-00229-ENV (E.D.N.Y.), Dkt. #77, at 17-19 (Sept. 2, 2008), and this is precisely what Judge Vitaliano ultimately charged the

jury, *see id.*, Dkt. #109, at 921:14-17 (Nov. 18, 2008). The Government's proposed instruction reflects the actual manner in which the Misbranding Provisions are understood and applied by the FDA and DOJ (*i.e.*, as a speech restriction). Indeed, the Government has taken a materially identical position in other litigation, stating that promotion of an off-label use *automatically* makes that use an "intended" one. *See* Allergan v. United States, No. 09-1879 (D.D.C.), United States' Reply in Support of Motion to Dismiss, Dkt. #37, at 7-8, (Mar. 29, 2010). This is no different than saying that "off-label promotion" is a crime.

To be sure, the Government has, in its discretion, identified certain limited circumstances in which it will choose not to initiate criminal enforcement proceedings even though a manufacturer disseminates off-label information about its products. But rather than creating any true safe harbors, these 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 product of formal agency rulemaking, and in most instances explicitly "non-binding." For example, non-binding FDA guidance provides that, if a manufacturer distributes to a physician a copy of a peer-reviewed journal article describing positive clinical trial results for an off-label use, the FDA will not consider such distribution "as establishing an intent that the product be used for an unapproved new use." Food

and Drug Administration, "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.[3] Yet, 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.

As another example, if a company pays a physician to provide an educational presentation to fellow doctors, the manufacturer is subject to criminal prosecution if that physician affirmatively discusses the off-label use of the manufacturer's product, but will not be subject to prosecution if the physician provides the exact same information in response to an audience member's "unsolicited request," *see, e.g.*, United States v. Stevens, No. CR-10-694 (D. Md. 2011), Tr. 90:10-22 (Apr. 27, 2011) (testimony of FDA official Sandeep Saini). As a final example, the Government previously has taken the litigation position that a manufacturer cannot expressly or implicitly promote the safety or efficacy of an off-label use but that it may disseminate "safety warnings" that discourage that use. *See* Allergan v. United States, No. 09-1879 (D.D.C.), United States' Reply in Support of Motion to Dismiss, Dkt. #37, at 7, (Mar. 29, 2010). Yet, the line that this position purports to draw is in practice an unclear one, given that safety and

[3] This narrow exception is subject to numerous qualifications. *See id.*

efficacy are not separate concepts but are instead intimately intertwined. *See United States v. Rutherford*, 442 U.S. 544, 555 (1979) (FDA "generally considers a drug safe when the expected therapeutic gain justifies the risk entailed by its use"). As a result, anything short of a blanket warning not to use a drug for an off-label use under any circumstances could potentially be deemed to implicitly suggest that the use is safe and effective in some circumstances. This broad, vague prohibition thus leaves manufacturers with little latitude to speak. They must not only avoid overt promotion but also must self-censor due to their uncertainty regarding whether and to what extent they may permissibly disseminate truthful information regarding potential safety issues with an off-label use.

As the above examples demonstrate, the FDA's overall regulatory framework not only burdens a broad array of protected speech, but also lacks the coherence and clarity required to provide manufacturers the guidance they need, which creates a First Amendment problem in its own right. At the most basic level, the FDA has never actually promulgated a formal rule that clearly delineates impermissible "promotion" from a permissible "scientific exchange" that may have the effect of encouraging physicians to engage in an off-label use. Manufacturers have thus had to rely on disparate Federal Register documents, non-binding guidance, letters, and other informal pronouncements in an effort to parse the agency's views as to what constitutes "promotion." While the FDA informally

recognized in guidance documents issued in 1982 that a manufacturer does not engage in "promotion" if it provides a physician with off-label information in response to an "unsolicited request," *see* DDAL, *Position on the Concept of Solicited and Unsolicited Requests* (Apr. 22, 1982), it has never issued a formal rule—let alone a clear and comprehensive one—that codifies that agency position. As another example, manufacturers have been left to guess what sorts of off-label information they can provide to formulary committees, payors, and similar entities that do not themselves prescribe FDA-approved drugs and devices. *See, e.g.*, Citizen's Petition, Dkt. #FDA-2011-P-0512 (submitted July 5, 2011) (asking FDA to clarify its regulations and policies with respect to manufacturer dissemination of information related to new uses of approved drugs and devices).

The lack of clarity in the FDA's regulatory framework is underscored in this very case by the Government's adoption of inconsistent positions on core elements of the alleged misbranding offense. Specifically, the Government represented to this Court at oral argument that off-label promotion is not a crime, while taking a different position at trial, asking the District Court to charge the jury that such promotion would support a criminal conviction. *Compare* United States v. Caronia, 09-5006-CR (2d Cir.), Oral Argument (Dec. 2, 2010) (Government counsel arguing that off-label promotion itself "is not a crime") *with* United States v. Caronia 1:06-cr-00229-ENV (E.D.N.Y.), Dkt. #77, at 19 (Sept. 2, 2008)

(Government's proposed jury instruction, later adopted by the district court, that a "manufacturer, its agents, representatives and employees are not permitted to promote uses for a drug that have not been cleared"). Similarly, and on an equally fundamental point, the Government stated at oral argument that a manufacturer would not be committing a crime by introducing into interstate commerce a drug or device without adequate directions for use merely because the manufacturer *knew* that its product was going to be used off label. *See* United States v. Caronia, 09-5006-CR (2d Cir.), Oral Argument (Dec. 2, 2010) (Government counsel agreeing that a manufacturer may lawfully ship a drug it knows will be used by the physician off label). At trial, however, the Government asked the District Court to charge the jury that such knowledge would alone suffice to support a criminal misbranding charge. *See* United States v. Caronia, 1:06-cr-00229-ENV (E.D.N.Y.), Dkt. #77, at 18 (Sept. 2, 2008) (Government's proposed jury instruction, adopted by District Court, that a manufacturer will have violated the Misbranding Provisions if it has "knowledge" that a drug it has introduced into commerce will be used off label by a physician).

That the Government's legal arguments differed so substantially between trial and appeal is arguably a direct consequence of the ambiguous and confusing nature of the Misbranding Provisions themselves. In the view of *amicus*, this case presents an opportunity to begin to resolve that problem. By making clear that the

Misbranding Provisions are subject to heightened First Amendment scrutiny, the Court will give the FDA the incentive to bring much needed clarity to its rules and regulations and to bring them into conformity with the First Amendment.

The Government has argued that the FDA's regulatory framework is narrowly tailored to advance the Government's interest in ensuring that manufacturers have an incentive to put new uses of their FDA-approved products through the rigors of the FDA approval process. But it is hard to see how this interest can withstand *Sorrell*'s "heightened scrutiny" and constitutionally justify a criminal prosecution where, as here: (i) the manufacturer already had filed a supplemental New Drug Application for the off-label use in issue; and (ii) the manufacturer's speech was directed exclusively to a sophisticated listener (namely, a licensed physician) rather than to a lay person or the public at large. This Court need not decide the broader question of the facial constitutionality of the FDA's speech restrictions because, at the very least, their application on these facts appears to be constitutionally indefensible.[4]

CONCLUSION

For the reasons set forth above, the decision below should be REVERSED.

[4] While this brief does not take a position on the precise limits that the First Amendment places on the Government's ability to regulate speech about off-label uses, it is clear that, where FDA's regulations seek to draw the line between permissible and impermissible manufacturer speech, they must do so with clarity.

Respectfully submitted,

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Certificate of Compliance

1. This brief is 15 pages in length and thus complies with the requirement of the Court's July 27, 2011 order that post-argument submissions regarding the effect of the Supreme Court's decision in *Sorrell* be no more than 15 pages in length.

2. This brief complies with the type-volume limitation of Federal Rule of Appellate Procedure 29(d) because it contains 4,123 words, excluding portions of the brief exempted by Federal Rules of Appellate Procedure 32(a)(7)(B)(iii).

3. This brief complies with the typeface requirements of Federal Rule of Appellate Procedure 32(a)(5) and the type style requirements of Federal Rule of Appellate Procedure 32(a)(6) because this brief has been prepared in a proportionally spaced typeface using Microsoft Word 2007 in Times New Roman size 14 font.

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Certificate of Service

I certify that this *amicus curiae* brief was served on August 22, 2011 by overnight mail and electronic mail on all parties who have filed notices of appearance in United States v. Caronia, 09-5006-CR (2d Cir.).

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