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First Amendment Off-Label Promotion Cases Work Their Way through the Courts

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Much Remains to Be Seen

The Food and Drug Administration (FDA) has long prohibited promotional statements by pharmaceutical manufacturers about drug uses not approved by the agency (referred to as off-label uses). Recently, however, a number of court cases regarding pharmaceutical promotional speech are working their way through the courts, and ultimately, the U.S. Supreme Court may be asked to again rule on the constitutionality of the FDA's regulation of pharmaceutical promotion under the First Amendment. Although these cases likely will not change the nature of drug promotion overnight, they will be cases to watch in the coming years.

REGULATION OF OFF-LABEL PROMOTIONAL SPEECH

Currently, pharmaceutical manufacturers are prohibited from promoting their drugs to health care professionals for unapproved "off-label" uses as this results in the marketing of both an unapproved and misbranded drug product, both of which are criminal offenses.[1] Under the Federal Food, Drug, and Cosmetic Act (FFDCA), all new drugs marketed in the United States must go through the FDA's drug approval process.[2] New drug status is determined based on the use "prescribed, recommended, or suggested" on the drug's labeling.[3] If a drug's labeling includes an indication that is not generally recognized as safe and effective, the drug is a new drug requiring FDA approval.[4]

Labeling is not confined only to what is on the drug container. It extends to all statements about the drug. Labeling, as defined by the FFDCA, is all material located on the container or accompanying the container.[5] Through its regulations, the FDA specifically has stated that labeling includes:

> Brochures, booklets, mailing pieces, detailing pieces, file cards, bulletins, calendars, price lists, catalogs, house organs, letters, motion picture films,

> film strips, lantern slides, sound recordings, exhibits, literature, and reprints and similar pieces of printed, audio, or visual matter descriptive of a drug and references published…for use by medical practitioners, pharmacists, or nurses, containing drug information supplied by the manufacturer, packer, or distributor of the drug and which are disseminated by or on behalf of its manufacturer, packer, or distributor…[6]

Accordingly, through the FDA's labeling regulation, off-label statements are prohibited in all forms.

The FDA has further ensured that there is no off-label promotion through the agency's advertising regulations. The regulations state, "An advertisement for [an FDA approved] prescription drug…shall not recommend or suggest any use that is not in the labeling accepted" by the FDA.[7]

Finally, the FDA has prohibited promotional off-label statements, including oral statements, through its misbranding authority.[8] FDA Untitled Letters have cited drug manufacturers for their sales representatives' off-label statements to health care professionals, stating that such statements cause pharmaceutical products to be misbranded.[9] The Department of Justice also has pursued False Claims Act cases against pharmaceutical manufacturers on the theory that off-label statements cause the promoted drug to be misbranded.[10]

Although the FDA has prohibited all off-label promotion of approved drug products, it has not prohibited all modes of disseminating off-label information. Rather, the FDA explicitly has recognized the permissibility of pharmaceutical manufacturers' dissemination of certain truthful and non-misleading scientific information pertaining to off-label drug uses. For instance, an FDA 2009 guidance document provided clear direction on when manufacturers may distribute scientific or medical journal articles and scientific or medical reference publications pertaining to off-label uses of approved drugs.[11] The FDA also has a long-standing policy of permitting the dissemination of certain off-label information in response to unsolicited requests for scientific information from health care professionals, which was recently reaffirmed through a December 2011 draft guidance document.[12]

Moreover, through its Investigational New Drug regulations, the FDA has permitted "the full exchange of scientific information concerning [Investigational New Drugs], including dissemination of scientific findings in scientific or lay media."[13] Accordingly, while the FDA allows the dissemination of certain off-label scientific information, it prohibits the dissemination of off-label promotional information.

The Need for Clarification

It is this line between scientific and promotional off-label information dissemination that has prompted a number of pharmaceutical companies to seek clarification through the courts and from the agency. In 2009, Allergan, Inc. challenged the FDA's regulation of off-label speech as a violation of the First Amendment.[14] In September 2010, however, as part of a criminal and civil investigation, Allergan dismissed its lawsuit.[15] Allergan stated:

> To resolve [a] criminal and civil investigation, Allergan was required by the Government to dismiss Allergan's First Amendment lawsuit pending in Washington, D.C., in which Allergan sought a ruling that it could proactively share truthful scientific and medical information with the medical community to assist physicians in evaluating the risks and benefits if they choose to use [Allergan's drug] off-label…Allergan is disappointed that the court was not afforded an opportunity to hear and rule on these important First Amendment issues, as Allergan believes that physicians, patients, manufacturers, payers, and ultimately the quality of evidence-based medi-

> cine itself would have benefited from a ruling clarifying the law.[16]

Allergan was not the only company that felt legal clarification was needed. On July 5, 2011, a citizen petition was submitted to the FDA on behalf of seven drug and device manufacturers asking the agency to clarify its regulations and policies concerning the permitted and prohibited off-label speech.[17] The petition explained that the "lack of clarity and vagueness surrounding the contours of permissible manufacturer speech has significant consequences to manufacturers, the government, physicians, and patients."[18] As a result of the uncertainty surrounding the FDA's regulations, "each individual manufacturer may either over- or under communicate clinically relevant information, with significant attendant consequences for the public health."[19]

Setting the Stage for Court Challenges

Further laying the groundwork for legal challenges to the prohibition on off-label promotion is a recent Supreme Court decision in *Sorrell v. IMS Health Inc,* a case that may bolster arguments that the regulation of off-label promotional speech is unconstitutional.[20] Although *Sorrell* did not directly address the question of off-label promotion, it did open the door for further First Amendment challenges.

The case decided whether a Vermont statute that prohibited the use of prescriber identifiable information for the marketing and promotion of prescription drugs was a violation of the First Amendment.[21] The Court held that Vermont's statute discriminated based on the content of the speech and the identity of the speaker, namely marketing speech by pharmaceutical companies.[22] Accordingly, the statute was subject to heightened scrutiny.[23] The Court struck down the statute using both strict scrutiny, which is applied to discriminatory statutes and is "all but dispositive[,]" as well as the slightly less stringent level of scrutiny applied to commercial speech.[24]

When coming to its conclusion, the Court made several statements that could have particular significance in a challenge to the FDA's off-label promotion policy. "A 'consumer's concern for free flow of speech often may be far keener than his concern for urgent political dialogue.' That reality has great relevance in the fields of medicine and public health, where information can save lives."[25] Particularly, the Court explained that:

> Those who seek to censor or burden free expression often assert that disfavored speech has adverse effects. But the "fear that people would make bad decisions if given truthful information" cannot justify content-based burdens on speech. "The First Amendment directs us to be especially skeptical of regulations that seek to keep people in the dark for what the government perceives to be their own good." These precepts apply with full force when the audience, in this case prescribing physicians, consists of "sophisticated and experienced" consumers.[26]

The Court went on, stating:

> There are divergent views regarding detailing and the prescription of brand-name drugs. Under the Constitution, resolution of that debate must result from free and uninhibited speech. As one Vermont physician put it: "We have a saying in medicine, information is power. And the more you know, or anyone knows, the better decisions can be made." There are similar sayings in law, including that "information is not in itself harmful, that people will perceive their own best interests if only they are well enough informed, and that the best means to that end is to open the channels of communication rather than to close them." The choice "between the dangers of suppressing information and the dangers of its misuse if it is freely available" is one that "the First Amendment makes for us."[27]

These statements likely will set the stage for a Supreme Court challenge to the prohibition of off-label promotion. In dissent, Justice Breyer acknowledged this, citing the FDA's promotional regulations and stating, "If the Court means to create constitutional barriers to regulatory rules that might affect the *content* of a commercial message, it has embarked upon an unprecedented task — a task that threatens significant judicial interference with widely accepted regulatory activity."[28]

Current Cases on Off-Label Promotion

Par Pharmaceuticals, Inc. or Alfred Caronia may provide the Supreme Court with the opportunity to reach the issue of the First Amendment implications of the FDA's off-label promotional policy and the government's related enforcement efforts. On October 14, 2011, Par sued the government in the United States District Court for the District of Columbia, seeking a court declaration regarding the legality of the FDA's off-label speech regulations.[29] Par produces Megace® ES, a drug for the treatment of AIDS-related wasting.[30] Although physicians frequently prescribe Megace® ES for its on-label use in AIDS patients, it is even more frequently prescribed off-label to treat geriatric and cancer patients.[31]

Par stated in its complaint that the majority of Megace® ES prescriptions are for such off-label uses.[32] According to Par, the off-label use of Megace® ES to treat cancer patients is so widely accepted by the medical community that Par was not able to conduct the placebo-controlled clinical studies required for FDA approval of a cancer indication.[33] Physicians would not agree to administer a placebo to cancer patients suffering from wasting because they felt that it would be contrary to the best interests of their patients.[34]

Par, however, does not seek to make off-label statements about the use of Megace® ES in cancer and geriatric patients. Rather, Par seeks to make on-label statements about Megace® ES to doctors who primarily treat cancer and geriatric patients.[35] Par asserts that physicians who treat cancer and geriatric patients reasonably may encounter patients suffering from AIDS-related wasting.[36]

However, if Par intends to market its AIDS drug for on-label purposes to oncology and geriatric specialists, it claims that it could be held criminally liable, as marketing to such practitioners could be viewed as evidence of intent to promote drugs for off-label purposes by the Department of Justice when enforcing the prohibition on off-label promotion.[37] In its complaint, Par cited recent cases in which the government prosecuted manufacturers "that spoke to physicians in settings where, in the government's view, there was insufficient likelihood of on-label use."[38] Accordingly, Par seeks a declaration that the government's prohibition of its speech is both unconstitutional and inconsistent with the FFDCA, as applied to its on-label statements to doctors who potentially could prescribe the company's drugs for off-label uses.

Relying heavily on the Supreme Court's *Sorrell* opinion, Par argues that the FDA's restriction on the company's on-label speech to physicians discriminates based on the content of the speech and the speaker.[39] The regulations only prohibit off-label speech and only prohibit such speech by drug manufacturers.[40] Accordingly, the regulations should be subject to the same heightened standard of review as *Sorrell*.[41]

Moreover, even if the heightened level of review does not apply, Par argues that the speech prohibition fails under the intermediate level of scrutiny used for commercial speech.[42] According to Par, the government does not have a substantial interest in restricting Par's proposed speech, and any interests the government may hold can be achieved through less restrictive means.[43]

Par proposes making truthful and non-misleading on-label statements.[44] As Par states, "the government's asserted interests in public safety and the integrity of the FDA approval process are at their lowest ebb when a manufacturer is engaged in speech about the FDA-approved, on-label use of its drug."[45] Further, any interest that the government may have in preventing the off-label use of Par's drug is

undermined by the facts that federal health care programs provide reimbursement for off-label uses of the medication and Par's communications would only be to licensed physicians.[46] Even if the government does have an interest in restricting the speech, it could be achieved through less restrictive means such as requiring manufacturers to confirm that the on-label use would be pertinent to the doctor's practice or disclose that the use is not FDA approved.[47] Finally, Par argues that not only has its Constitutional rights been violated but that the FDA overstepped its authority in promulgating the off-label speech regulations under the FFDCA.[48]

The government, however, has a different view of the regulatory scheme that Par faces. Chief among the government's arguments is that Par is not at risk for governmental enforcement action for making statements about approved drug uses to practitioners who might prescribe the drug for off-label purposes.[49] The government stated in a recent filing that "engaging in truthful and non-misleading speech about the approved use of [a drug] will not place [manufacturers] in danger of being charged with distributing a drug that was misbranded…because FDA would not regard that speech as establishing, by itself, [manufacturers'] objective intent that [a drug] be used for an unapproved use…."[50] At the same time, however, the government stated that "marketing a drug in settings where few if any patients come within the scope of the drug's approved indications may well prompt the government to inquire into the manufacturer's marketing activities."[51] Thus, while Par's proposed on-label statements to practitioners who might prescribe Par's drugs for off-label uses would not, on their own, prompt prosecution, it could prompt a governmental investigation.

Par's challenge to the FDA's regulations is not the only case making its way through the courts. The Supreme Court also may have the opportunity to review the FDA's regulation of off-label speech for drugs through *U.S. v. Caronia.* Alfred Caronia, a sales representative for Orphan Medical, Inc., now known as Jazz Pharmaceuticals, was convicted in September 2008 for conspiracy to misbrand as a result of arranging for alleged off-label statements by a promotional speaker.[52] In April 2010, Mr. Caronia appealed his sentence of one year probation, one hundred hours of community service, and a $25 fine in the Second Circuit Court of Appeals.[53]

His appeal included a challenge to the trial court's ruling that Mr. Caronia's First Amendment rights were not violated.[54] Mr. Caronia maintains that the FDA's misbranding position is "too restrictive and unconstitutional on the grounds that it was not narrowly tailored enough to protect" his constitutional rights.[55] Because the *Caronia* appeal commenced prior to the Supreme Court's *Sorrell* opinion, the parties submitted supplemental arguments regarding the impact of the *Sorrell* decision on Mr. Caronia's case.[56] The Medical Information Working Group, a coalition of medical and device manufacturers, also filed an *amicus curiae* brief in support of Mr. Caronia.[57] Both Mr. Caronia and the Medical Information Working Group argue that the *Sorrell* opinion applies to Mr. Caronia's speech, which, accordingly, should be protected by the First Amendment.[58]

The language used by the Supreme Court in *Sorrell* indicates that both Par and Alfred Caronia have strong arguments that the prohibition of promotional off-label speech violates the First Amendment. At the same time, however, these cases will not be heard in a vacuum. Both the Supreme Court and lower courts previously have addressed the constitutionality of the FDA speech regulation under the lower standard of review used for commercial speech. These courts have found that the FDA does have a significant interest in preventing the dissemination of off-label information by manufacturers, namely, encouraging manufacturers to seek FDA approval for all drug uses, and this interest is furthered by preventing manufacturer dissemination of information about unapproved drug uses.[59] The FDA laws and policies challenged, however, failed the constitutional test because there were less restrictive means that could have been used to achieve the same ends.[60] Thus, whether either *Par Pharmaceuticals*

Inc. or *Caronia* will prevail likely will turn on whether the FDA's prohibition of manufacturer off-label promotion is discriminatory and thus deserving of the highest level of scrutiny or, if not deserving of such scrutiny, whether the prohibition unduly burdens speech.

Whether *Par Pharmaceuticals Inc.* or *Caronia* will reach the Supreme Court is yet to be seen. And even if they are heard by the Supreme Court, a decision likely will not change the entire nature of off-label promotion. Rather, it is more likely that the Court will proceed incrementally, addressing discrete aspects of the government's off-label promotional policy. In the coming years, however, these will be cases to watch closely, as they could begin a course of events that impact how drugs are promoted in the United States.

Endnotes:

1. FFDCA §§301(a)-(b), (d) (2011).
2. FFDCA §505(a).
3. FFDCA §201(p).
4. FFDCA §§201(p), 505(a).
5. FFDCA §§201(k), (m) (emphasis added).
6. 21 C.F.R. §202.1(l)(2) (2011).
7. 21 C.F.R. §202.1(e)(4)(i)(a).
8. FFDCA §§301(a), 502.
9. *See e.g.,* Letter from the U.S. Food and Drug Administration to Forest Laboratories, Inc. (Apr. 28, 2011); *see e.g.,* Letter from the U.S. Food and Drug Administration to Astra Zenica LP (Dec. 1, 2008).
10. *See e.g.,* Information, *U.S. v. Pharmacia & Upjohn Co,* (2009); *see e.g.*, Information, *U.S. v. Merck Sharp & Dohme Corp.* (2011).
11. 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 (2009).
12. *See e.g.,* Citizen Petition Regarding the Food and Drug Administration's Policy on Promotion of Unapproved Uses of Approved Drugs and Devices; Request for Comments, 59 Fed. Reg. 59820, 59823 (Nov. 18, 1994); FDA, Draft Guidance for Industry: Responding to Unsolicited Requests for Off-Label Information About Prescription Drugs and Medical Devices (2011).
13. 21 C.F.R. §312.7(a).
14. Complaint, *Allergan v. United States*, No. 09-1879 (2009).
15. Allergan, News Release: Allergan Resolves United States Government Investigation of Past Sales and Marketing Practices Relating to Certain Therapeutic Uses of Botox® (Sept. 1, 2010).
16. *Id.*
17. FDA Citizen Petition (Jul. 5, 2011).
18. *Id.*
19. *Id.* In partial response to the 2011 Citizen Petition, FDA issued a draft guidance describing how manufacturers may respond to unsolicited requests for off-label information. FDA, Draft Guidance for Industry: Responding to Unsolicited Requests for Off-Label Information About Prescription Drugs and Medical Devices (2011). The FDA also opened a docket for comments regarding scientific exchange communications and activities related to off-label uses of drugs, biologics, and devices. Communications and Activities Related to Off-Label Uses of Marketed Products and Use of Products Not Yet Legally Marketed; Request for Information and Comments, 76 Fed. Reg. 81508 (Dec. 28, 2011).
20. No. 10-779 (U.S., June 23, 2011).
21. *Id.*
22. *Id.* at 8.
23. *Id.* at 8-15.
24. *Id.* at 15-25.
25. *Id.* at 11 (internal citations omitted).
26. *Id.* at 22 (internal citations omitted).
27. *Id.* at 23 (internal citations omitted).
28. *Id.* at Breyer Dissent 11.
29. Complaint for Declaratory and Injunctive Relief, *Par Pharmaceutical, Inc. v. U.S., et al.,* No. 1:11-cv-01820 RWR (D.D.C. Oct. 14, 2011).
30. *Id.* at 14.
31. *Id. at* 15.
32. *Id.*
33. *Id.* at 16.
34. *Id.*
35. Complaint for Declaratory and Injunctive Relief, *Par Pharmaceutical, Inc. v. U.S., et al.,* No. 1:11-cv-01820 RWR.
36. *Id.* at 18-21.
37. *Id.* at 24-26.
38. *Id.* at 25-26 (citing Information, *U.S. v. Eli Lilly & Co.,* No. 09-CR-020 (E.D. Pa., filed Jan. 15, 2009); Information, *U.S. v. Pharmacia,* No. 09-CR-10258 (D. Mass., filed Sept. 9,2009).
39. Plaintiff's Motion for Preliminary Injunction at 19-24, *Par Pharmaceutical, Inc. v. U.S., et al.,* No. 1:11-cv-01820 RWR (D.D.C. Oct. 14, 2011).
40. *Id.*
41. *Id.*
42. *Id.* at 24.
43. *Id.* at 24, 30-31.
44. *Id.* at 24-32.
45. *Id.* at 31.
46. *Id.*
47. *Id.* at 30-31.
48. *Id.* at 32-38.
49. Defendant's Memorandum in Support of Motion to Dismiss or for Summary Judgment and in Opposition to Motion for Preliminary Injunction at 17-18, *Par Pharmaceutical, Inc. v. U.S.. et al.,* No. 1:11-cv-01820 RWR (D.D.C. Jan. 11, 2012).
50. *Id.* at 17.
51. *Id.* at 28.

52. Brief and Appendix for Defendant-Appellant Alfred Caronia, *U.S. v. Caronia*, No. 09-5006-cr (L) (2d Cir., Apr. 15, 2010).
53. *Id.*
54. *Id.* at 34.
55. *Id*.
56. Supplemental Brief of Appellant Alfred Caronia, *U.S. v. Caronia,* No. 09-5006-cr (L) (Aug. 29, 2011); Supplemental Brief for the United States, *U.S. v. Caronia,* No. 09-5006-cr (L) (Aug. 29, 2011).
57. Amicus Curiae Brief Of The Medical Information Working Group In Support Of Defendant-Appellant Alfred Caronia And Reversal Of The Decision Below, *U.S. v. Caronia,* No. 09-5006-cr (L) (Aug. 22, 2011).
58. Supplemental Brief of Appellant Alfred Caronia, *U.S. v. Caronia,* No. 09-5006-cr (L) (Aug. 29, 2011); Amicus Curiae Brief of Med. Info. Working Group in Support of Defendant-Appellant Alfred Caronia and Reversal of the Decision Below, *U.S. v. Caronia,* No. 09-5006-cr (L) (Aug. 22, 2011).
59. *Thompson v. W. States Med. Ctr.*, 535 U.S. 357, 369-371 (2002); *Wash. Legal Found. v. Friedman,* 13 F. Supp. 2d 51, 70-72 (1999), *vacated in part*, *Wash. Legal Found. v. Henney*, 202 F.3d 331 (2000); *Wash. Legal Found. v. Henney*, 56 F. Supp. 2d 81, 86-87 (1999), *vacated, Wash. Legal Found. v. Henney*, 202 F.3d 331 (2000).
60. *W. States Med. Ctr.*, 535 U.S. at 371-373; *Wash. Legal Found. v. Friedman*, 13 F. Supp. 2d at 72-74; *Wash. Legal Found. v. Henney*, 56 F. Supp. 2d at 87.

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