UNITED STATES COURT OF APPEALS
FOR THE SECOND CIRCUIT

August Term 2010

(Argued: December 2, 2010 Decided: December 3, 2012)

Docket No. 09-5006-cr

UNITED STATES OF AMERICA,

Appellee,

v.

ALFRED CARONIA,

Defendant-Appellant.[*]

Before:

RAGGI, LIVINGSTON, and CHIN, *Circuit Judges*.

Appeal from a judgment of the United States District Court for the Eastern District of New York (Eric N. Vitaliano, *J.*) convicting defendant-appellant Alfred Caronia of conspiracy to introduce a misbranded drug into interstate

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[*] The Clerk of the Court is directed to amend the official caption in accordance with the above.

commerce in violation of the Federal Drug and Cosmetic Act. Caronia contends that he was convicted for his speech -- for promoting the off-label use of an approved prescription drug -- in violation of the First Amendment.

VACATED and REMANDED.

Judge LIVINGSTON dissents in a separate opinion.

DOUGLAS LETTER and MARTIN COFFEY (Jo Ann M. Navickas, Assistant United States Attorney, Scott R. McIntosh, Attorney, Appellate Division, United States Department of Justice, Anne K. Walsh, Associate Chief Counsel, Office of General Counsel, Food and Drug Division, *on the brief*), *for* Loretta E. Lynch, United States Attorney for the Eastern District of New York, Brooklyn, New York, *for Appellee*.

JENNIFER L. MCCANN (Thomas F. Liotti, *on the brief*), Law Offices of Thomas F. Liotti, Garden City, New York, *for Defendant-Appellant*.

ERIC E. MURPHY, Jones Day (Michael A. Carvin, Jones Day, Daniel J. Popeo, Richard A. Samp, Washington Legal Foundation, *on the brief*), *for Amicus Curiae Washington Legal Foundation*.

Joan McPhee, Ropes & Gray LLP (Douglas Hallward-Driemeier, Alan Bennett, Ropes & Gray LLP, and Paul Kalb, Coleen Klasmeier, Sidley Austin LLP, *on the brief*), *for Amicus Curiae The Medical Information Working Group.*

CHIN, *Circuit Judge*:

Defendant-appellant Alfred Caronia appeals from a judgment of conviction entered in the United States District Court for the Eastern District of New York (Eric N. Vitaliano, *J.*) on November 30, 2009, following a jury trial at which Caronia was found guilty of conspiracy to introduce a misbranded drug into interstate commerce, a misdemeanor violation of 21 U.S.C. §§ 331(a) and 333(a)(1). Specifically, Caronia, a pharmaceutical sales representative, promoted the drug Xyrem for "off-label use," that is, for a purpose not approved by the U.S. Food and Drug Administration (the "FDA"). Caronia argues that he was convicted for his speech -- for promoting an FDA-approved drug for off-label use -- in violation of his right of free speech under the First Amendment. We agree. Accordingly,

we vacate the judgment of conviction and remand the case to the district court.

STATEMENT OF THE CASE

1. ***The Regulatory Scheme***

Under the Federal Food, Drug and Cosmetic Act (the "FDCA"), before drugs are distributed into interstate commerce, they must be approved by the FDA for specific uses. 21 U.S.C. § 355(a). To obtain FDA approval, drug manufacturers are required to demonstrate, through clinical trials, the safety and efficacy of a new drug for each intended use or indication. 21 U.S.C. § 355(d); *see Weinberger v. Hynson*, 412 U.S. 609, 612-14 (1973).[1]

Once FDA-approved, prescription drugs can be prescribed by doctors for both FDA-approved and -unapproved uses; the FDA generally does not regulate how physicians use

[1] The FDCA provides: "No person shall introduce or deliver for introduction into interstate commerce any new drug, unless an approval of an application filed pursuant to subsection (b) or (j) of this section is effective with respect to such drug." 21 U.S.C. § 355(a). A "new drug" is defined as: "Any drug . . . not generally recognized . . . as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof." 21 U.S.C. § 321(p).

approved drugs. *See Buckman Co. v. Plaintiffs' Legal Comm.*, 531 U.S. 341, 350 (2001); *Weaver v. Reagen*, 886 F.2d 194, 198 (8th Cir. 1989); John E. Osborn, *Can I Tell You The Truth? A Comparative Perspective on Regulating Off-Label Scientific and Medical Information*, 10 Yale J. Health Pol'y L. & Ethics 299, 303 (2010) ("Physicians may prescribe FDA-approved drugs . . . for any therapeutic use that is appropriate in their medical judgment."); Randall S. Stafford, *Regulating Off-Label Drug Use: Rethinking the Role of the FDA*, 358 N. Engl. J. Med. 1427, 1427 (2008) (discussing 2003 study of 160 common drugs where off-label use accounted for approximately 21 percent of prescriptions).

Indeed, courts and the FDA have recognized the propriety and potential public value of unapproved or off-label drug use. *See Buckman*, 531 U.S. at 350 (Off-label use is an "accepted and necessary corollary of the FDA's mission to regulate in this area without directly interfering with the practice of medicine."); *Weaver*, 886 F.2d at 198-99 ("FDA[-]approved indications were not intended to limit or

interfere with the practice of medicine nor to preclude physicians from using their best judgment in the interest of the patient." (internal quotation marks omitted)); U.S. Food and Drug Administration, *Draft Guidance, 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* 3 (2009) ("[O]ff-label uses or treatment regimens may be important and may even constitute a medically[-]recognized standard of care.").[2] The FDA itself has observed:

> Once a drug has been approved for marketing, a physician may prescribe it for uses or in treatment regimens or patient populations that are not included in approved labeling. Such "unapproved" or, more precisely, "unlabeled" uses may be appropriate and rational in certain circumstances, and may, in fact, reflect approaches to drug therapy that have been extensively reported in medical literature.

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[2] *See also* James M. Beck & Elizabeth D. Azari, *FDA, Off-Label Use, and Informed Consent: Debunking Myths and Misconceptions*, 53 Food & Drug L.J. 71, 76-77 (1998); *cf.* 21 U.S.C. § 396 (protecting physician authority to prescribe or administer any legally-marketed device to patient).

U.S. Food and Drug Administration, *FDA Drug Bulletin*, 12 FDA Drug Bull. 1, 5 (1982).

The FDCA prohibits "misbranding," or "[t]he introduction or delivery for introduction into interstate commerce of any . . . drug . . . that is . . . misbranded." 21 U.S.C. § 331(a). A drug is misbranded if, *inter alia*, its labeling fails to bear "adequate directions for use," 21 U.S.C. § 352(f), which FDA regulations define as "directions under which the lay[person] can use a drug safely and for the purposes for which it is intended," 21 C.F.R. § 201.5.[4] FDA regulations define intended use by reference to "the objective intent of the persons legally responsible for the labeling of drugs," which may be demonstrated by, among other evidence, "oral or written statements by such persons or their representatives" and "the circumstances that the article is, with the knowledge of such persons or their

[4] A drug is also misbranded if, *inter alia*: its label is false or misleading; the label fails to display required information prominently; its container is misleading; or it is dangerous to health when used in the dosage, manner, frequency, or duration prescribed, recommended, or suggested on the label. *See* 21 U.S.C. §§ 352(a)-(n).

representatives, offered and used for a purpose for which it is neither labeled nor advertised." 21 C.F.R. § 201.128.

The consequences for misbranding are criminal. 21 U.S.C. § 333(a)(2) ("[I]f any person commits such a violation . . . such persons shall be imprisoned for not more than three years or fined not more than $10,000, or both."). Pharmaceutical manufacturers and their representatives can face misdemeanor charges for misbranding or felony charges for fraudulent misbranding. 21 U.S.C. § 333(a); *see* Osborn, *Can I Tell You The Truth?*, *supra*, at 328-29 (collecting cases). The government has repeatedly prosecuted -- and obtained convictions against -- pharmaceutical companies and their representatives for misbranding based on their off-label promotion. *See, e.g.*, Judgment, *United States v. GlaxoSmithKline, LLC*, 12-cr-10206 (RWZ), ECF Doc. No. 13 (D. Mass. July 10, 2012) (Information, *GlaxoSmithKline*, No. 12-cr-10206 (RWZ), ECF Doc. No. 1 (D. Mass. July 2, 2012)); Judgment, *United States v. Merck Sharp & Dohme Corp.*, No. 11-cr-10384 (PBS), ECF Doc. No. 30 (D. Mass. May 18, 2012) (Information, *Merck*, No.

11-cr-10384 (PBS), ECF Doc. No. 1 (D. Mass. Nov. 22, 2011)); Agreed Order of Forfeiture, *United States v. Abbott Labs.*, No. 12-cr-26 (SGW), ECF Doc. No. 7 (W.D. Va. May 7, 2012) (as a result of the guilty plea to the Information (Information, *Abbott*, No. 12-cr-26 (SGW), ECF Doc. No. 5-1 (W.D. Va. May 7, 2012))); Judgment, *United States v. Allergan, Inc.*, No. 10-cr-375 (ODE), ECF Doc. No. 20 (N.D. Ga. Oct. 7, 2010) (Information, *Allergan*, No. 10-cr-375 (ODE), ECF Doc. No. 1 (N.D. Ga. Sept. 1, 2010)); *see* Sentencing Transcript, *Merck*, No. 11-cr-10384 (PBS), ECF Doc. No. 27 (D. Mass. April 30, 2012) ("I want to emphasize that off-label marketing has been . . . a big problem . . . . I hope in a way that the . . . fact that all these cases are being pressed by the federal and state governments, the 44 state Attorney Generals, will be a signal that it isn't acceptable conduct."); *see also* Press Release, U.S. Department of Justice, *GlaxoSmithKline to Plead Guilty and Pay $3 Billion to Resolve Fraud Allegations and Failure to Report Safety Data, Largest Health Care Fraud Settlement in U.S. History* (July 2, 2012); Osborn, *Can I Tell You The Truth?*, *supra*, at 328-29.

The FDCA and its accompanying regulations do not expressly prohibit the "promotion" or "marketing" of drugs for off-label use. The regulations do recognize that promotional statements by a pharmaceutical company or its representatives can serve as proof of a drug's intended use. *See* 21 C.F.R. § 201.5. Off-label promotional statements could thus presumably constitute evidence of an intended use of a drug that the FDA has not approved. *See id.* The FDA, however, has concluded that "[a]n approved drug that is marketed for an unapproved use (whether in labeling or not) is misbranded because the labeling of such drug does not include 'adequate directions for use.'" *See* FDA, Draft Guidance, *supra*, at 2-3 (quoting 21 U.S.C. § 352(f)); *accord United States v. Caronia*, 576 F. Supp. 2d 385, 392 n.5 (E.D.N.Y. 2008); *see also* Gov't Br. 48 n.18 (contending no set of directions can constitute adequate labeling for drug's off-label use). Thus, the government has treated promotional speech as more than merely evidence of a drug's intended use -- it has construed the FDCA to prohibit promotional speech as misbranding itself.

2. *The Facts*[5]

a. *Orphan Medical and Xyrem*

Orphan Medical, Inc. ("Orphan"), now known as Jazz Pharmaceutical, was a Delaware-incorporated pharmaceutical company that primarily developed drugs to treat pain, sleep disorders, and central nervous system disorders. Orphan manufactured the drug Xyrem, a powerful central nervous system depressant. In 2005, after Jazz Pharmaceuticals acquired Orphan, Jazz continued to manufacture and sell Xyrem, grossing $20 million in combined Xyrem sales in 2005.

Xyrem can cause serious side effects, including difficulty breathing while asleep, confusion, abnormal thinking, depression, nausea, vomiting, dizziness, headache, bedwetting, and sleepwalking. If abused, Xyrem can cause additional medical problems, including seizures, dependence, severe withdrawal, coma, and death.

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[5] The facts are drawn primarily from the trial record. On appeal, this Court must view the evidence in the light most favorable to the government, drawing all reasonable inferences in its favor. *See United States v. Amico*, 486 F.3d 764, 780 (2d Cir. 2007).

Xyrem's active ingredient is gamma-hydroxybutryate ("GHB"). GHB has been federally classified as the "date rape drug" for its use in the commission of sexual assaults.

b. *The FDA's Regulation of Xyrem*

Despite the risks associated with Xyrem and GHB, the FDA approved Xyrem for two medical indications. In July 2002, the FDA approved Xyrem to treat narcolepsy patients who experience cataplexy, a condition associated with weak or paralyzed muscles. In November 2005, the FDA approved Xyrem to treat narcolepsy patients with excessive daytime sleepiness ("EDS"), a neurological disorder caused by the brain's inability to regulate sleep-wake cycles.

To protect against its serious safety concerns, in 2002, the FDA required a "black box" warning to accompany Xyrem. The black box warning is the most serious warning placed on prescription medication labels. Xyrem's black box labeling stated, among other things, that the drug's safety and efficacy were not established in patients under 16 years of age, and the drug had "very limited" experience among elderly patients.

To identify patients suffering side effects from the drug, the FDA also regulated Xyrem distribution, allowing only one centralized Missouri pharmacy to distribute Xyrem nationally.

c. *Caronia's Employment with Orphan*

In March 2005, Orphan hired Caronia as a Specialty Sales Consultant to promote Xyrem. Caronia primarily worked in Queens, Nassau, and Suffolk counties. Caronia's salary was based on his individual sales.

In July 2005, Caronia started Orphan's "speaker programs" for Xyrem. Speaker programs enlist physicians, for pay, to speak to other physicians about FDA-approved drug use. Orphan's speaker programs for Xyrem presented the benefits of the drug among patients with cataplexy and narcolepsy. Orphan hired Dr. Peter Gleason to promote Xyrem through its speaker programs.

Under Orphan's procedures, if Caronia, as a sales consultant for Xyrem, was asked about the off-label use of Xyrem, he was not permitted to answer; instead, when such questions were posed, Orphan sales consultants would fill out "medical information request forms" and send them to

Orphan, and Orphan would send information to the inquiring physician.[6] In contrast, physicians employed by Orphan as promotional speakers for Xyrem were permitted to answer off-label use questions; their responses were often informed by their own experiences with Xyrem.

d. *Caronia's Participation in the Conspiracy*

In the spring of 2005, the federal government launched an investigation of Orphan and Gleason. The investigation focused on the off-label promotion of Xyrem. Caronia and Gleason were audio-recorded on two occasions as they promoted Xyrem for unapproved uses, including unapproved indications and unapproved subpopulations. The first conversation was recorded on October 26, 2005 between Caronia and Dr. Stephen Charno, a physician who, as a government cooperator, posed as a prospective Xyrem customer. The second conversation was recorded on November 2, 2005; it taped a meeting arranged by Caronia to introduce Charno to Gleason.

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[6] In December of 2011, the FDA released recommendations for the pharmaceutical industry with respect to how manufacturers and their representatives can respond to "unsolicited requests for off-label information." *See generally* U.S. Food and Drug Administration, *Guidance for Industry, Responding to Unsolicited Requests for Off-Label Information About Prescription Drugs and Medical Devices* (2011).

On October 26, 2005, Caronia plainly promoted the use of Xyrem in unapproved indications with Charno:

> [Caronia]: And right now the indication is for narcolepsy with cataplexy . . . excessive daytime . . . and fragmented sleep, but because of the properties that . . . it has it's going to insomnia, Fibromyalgia[,] periodic leg movement, restless leg, ahh also looking at ahh Parkinson's and . . . other sleep disorders are underway such as MS.
>
> [Charno]: Okay, so then so then it could be used for muscle disorders and chronic pain and . . .
>
> [Caronia]: Right.
>
> [Charno]: . . . and daytime fatigue and excessive sleepiness and stuff like that?
>
> [Caronia]: Absolutely. Absolutely. Ahh with the Fibromyalgia.

(October 26, 2005 Recording Tr. (I) at 4-5). Caronia further directed Charno to list different "diagnosis codes" when prescribing Xyrem, for insurance purposes, including Fibromyalgia, chronic fatigue, or chronic pain.

On separate occasions, Caronia and Gleason each explained to prospective physician-customers that Xyrem could be used with patients under age sixteen, an unapproved Xyrem subpopulation:

> [Caronia]: Um, the youngest patients we have are sixteen in the studies as old as sixty-five. Ahh there have been reports of patients as young as fourteen using it and obviously greater than sixty-five. It's a very safe drug.

(October 26, 2005 Recording Tr. (I) at 7).

> [Gleason]: Well, it's actually approved for sixteen and above um, I've had people under thirteen and I've certainly talked to neurologists that have narcoleptics . . . between eight and ten . . . [but] I start at two-thirds the dose, but [if] they're real frail I only start with one-third the dose.

(November 2, 2005 Recording Tr. (II) at 51).

3. *Proceedings Below*

a. *The Charges*

On July 25, 2007, a grand jury returned its first Indictment against Caronia. The charging document at issue on this appeal, however, is the Superseding Information filed by the government on August 19, 2008, which charged Caronia with the following two misdemeanor offenses:

> Count One: Conspiracy to introduce a misbranded drug into interstate commerce in violation of 21 U.S.C. §§ 331(a) and 333(a)(2); and
>
> Count Two: Introducing a misbranded drug, Xyrem, into interstate commerce, in

violation of 21 U.S.C. §§ 331(a) and 333(a)(2).

(Inf. ¶¶ 12-17).

With respect to Count One, the Information alleged a two-prong conspiracy. The first prong charged that between approximately March 2005 and March 2006, Caronia, "together with others, did knowingly and intentionally conspire to" introduce Xyrem and cause the introduction of Xyrem into interstate commerce when Xyrem was misbranded within the meaning of the FDCA. (Inf. ¶ 13). The second prong alleged that "[i]t was part of the conspiracy that [Caronia], together with others, marketed Xyrem for medical indications that were not approved by [the] FDA when, as [they] . . . well knew and believed, Xyrem's labeling lacked adequate directions for and warnings against such uses, where such uses could be dangerous to the user's health." (Inf. ¶ 14).

The Information alleged, in Count One, that Caronia, "together with others, committed and caused to be committed," the following two overt acts. (Inf. ¶ 15).

> a. On or about October 26th, 2005, . . . Caronia promoted Xyrem to [Charno], a physician, so as to cause [Charno] to prescribe Xyrem for fibromyalgia, excessive daytime sleepiness, muscle disorders, chronic pain and fatigue, which were "off-label" indications.
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> b. On or about November 2, 2005, . . . Caronia introduced [Charno] to [Gleason], a physician, who was paid by Orphan and whom Orphan used to promote Xyrem for "off-label" indications, including fibromyalgia, excessive daytime sleepiness, weight loss and chronic fatigue.

(Inf. ¶¶ 15(a), (b)).

With respect to Count Two, the Information alleged that between approximately March 2005 and March 2006, Caronia "was marketing Xyrem for medical indications that were not approved by [the] FDA when, as the defendant then and there well knew and believed, Xyrem's labeling lacked adequate directions for such uses and adequate warnings against such uses where uses could be dangerous to the user's health." (Inf. ¶ 17).

Additionally, the Information alleged: "A drug that was marketed to the public for an 'off-label' indication or use did not contain 'adequate directions for

use' because such an 'off-label' indication or use and related information were not included in the FDA-approved labeling for the drug." (Inf. ¶ 8). The Information further stated: "Xyrem's labeling lacked adequate directions for such uses and adequate warnings against such uses where such uses could be dangerous to the user's health." (Inf. ¶¶ 14, 17).

Orphan and Gleason were also charged under the misbranding provisions of the FDCA; both pled guilty. *United States v. Caronia*, 576 F. Supp. at 389-90 & n.1.

b. *Caronia's Pre-Trial Motion to Dismiss*

On October 9, 2007, before trial, Caronia moved to dismiss the charges against him. In part, Caronia argued that the application of the FDCA's misbranding provisions to his off-label promotional statements unconstitutionally restricted his right to free speech under the First Amendment and that the provisions were unconstitutionally vague and broad.

On September 11, 2008, the district court denied Caronia's motion, including his First Amendment challenge, which it recognized as raising constitutional issues "very

much unsettled, not only in this circuit but nationwide." *Id.* at 403. Although ruling for the government, the district court rejected the government's argument that Caronia was being prosecuted for the unlawful conduct of misbranding and conspiring to misbrand a drug and not for his promotional speech, the latter of which the government contended only constituted proof of Xyrem's intended use. *See id.* at 394-95. The court observed that "the criminal information . . . allege[d] Caronia's promotion of off-label uses of an FDA-approved drug," and concluded that Caronia stood charged with a crime the *actus reus* of which was First Amendment speech. *Id.* at 395. Nevertheless, the district court held that, to the extent the FDCA criminalizes speech, the law passed constitutional muster under the commercial speech doctrine because the FDCA was not more extensive than necessary to achieve the FDA's objectives. *Id.* at 401-02.

c. *The Trial*

The case was tried before a jury from October 6 to October 16, 2008.

The record makes clear that the government prosecuted Caronia for his off-label promotion, in violation

of the FDCA. The government, in its summation and rebuttal, repeatedly asserted that Caronia was guilty because he, with others, conspired to promote and market Xyrem for off-label use. For example, the government argued:

- "[Caronia is] promoting, he's marketing a dangerous drug for use not approved by the FDA" (*id.* at 825);
- "He knew the rules: you can't promote and market Xyrem for uses that have not been approved by the FDA. He admits it" (*id.* at 839);
- "[Caronia] conspired through some act of misbranding, and that act of misbranding . . . was the promotion on October 26th and November 2nd[,] marketing [a] drug for unapproved uses" (*id.* at 848);
- "That's misbranding. That's promoting and marketing a drug by a pharmaceutical company representative for muscle disorders, chronic pain, daytime fatigue, excessive sleepiness" (*id.* at 870); and
- "[Caronia was] promoting, promoting, selling, selling, trying to get Charno to prescribe Xyrem. He tried on the 26th. He tried with Gleason on the 2nd" (*id.* at 875).[7]

[7] The government's summation and rebuttal include numerous additional examples of the government's assertion that Caronia was guilty because he conspired to promote and market Xyrem for unapproved uses. (*See, e.g.*, Trial Tr. 834 ("On

Thus, the government's theory of prosecution identified Caronia's speech alone as the proscribed conduct.

The district court, in its jury charge, reinforced the idea that Caronia's promotional speech was enough to support a guilty verdict:

> A misbranded drug may be shown by a promotion of the drug by a distributor for an intended use different from the use for which the drug was approved by the [FDA].
>
> . . .
>
> The manufacturer, its agents, representatives and employees, are not permitted to promote uses for a drug that have not been cleared by the United States Food and Drug Administration. These non-cleared uses are commonly

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November 2nd . . . Gleason, comes in to pitch to [Charno] and he right away goes off-label, promotes and markets Xyrem for uses that are not approved by the FDA, clear as a bell."); *id.* ("[Caronia is] misbranding. He's promoting a drug, Xyrem, that's dangerous for unapproved uses."); *id.* at 836 ("[H]e crossed the line and here's the labeling and you can only promote Xyrem for cataplexy associated with narcolepsy and you can't do it for anything else."); *id.* at 847 ("The conspiracy is promoting it and then trying to persuade through off-label communications to get Charno to write prescriptions off-label"); *id.* at 883 ("And the facts are one prong the drug was promoted for unapproved uses in a meeting with Charno on the 26th of October and the 2nd of November with the expectation or with the effort or with the attempt or with the conspiracy that by promoting it for off-label use, Charno would write a prescription and cause the drug to be shipped from St. Louis to some patient out of state."); *see also id.* at 821-22, 827, 829, 840-43, 847-48, 872-74, 878).

> referred to as 'off-label uses' because they are not included in the drug's labeling.

(Trial Tr. 920-21).

Prior to jury deliberation, the district court provided a proposed verdict sheet to the parties. With respect to Count One, the verdict sheet read as follows:

> 1. How do you find defendant, ALFRED CARONIA, on Count One of the Information?
>
> (a) Conspiracy to introduce or deliver for introduction into interstate commerce a drug, Xyrem, that was misbranded?
>
> NOT GUILTY _____ GUILTY _____
>
> (b) Conspiracy to do an act with respect to a drug, Xyrem, when such drug was held for sale after shipment in interstate commerce when such act would result in Xyrem being misbranded?
>
> NOT GUILTY _____ GUILTY _____

(Verdict Sheet, ECF Doc. No. 103, *United States v. Caronia*, No. 06 Cr. 229 (E.D.N.Y. Oct. 23, 2008)). The district court overruled Caronia's objection that the verdict sheet

was erroneous and therefore permitted the jury to reach an inconsistent verdict.

On October 23, 2008, the jury found Caronia guilty as to the first prong of Count One of the Information (Question 1(a)): conspiracy to introduce a misbranded drug into interstate commerce under 18 U.S.C. § 371(a) and 21 U.S.C. § 331(a). As to the second marketing prong of Count One (Question 1(b)), the jury found Caronia not guilty. The jury also found Caronia not guilty of Count Two of the Information.

d. *Caronia's Post-Trial Motion for Acquittal*

After the jury verdict and before judgment was entered, Caronia renewed his Rule 29 motion for acquittal. *See* Fed. R. Crim. P. 29. On December 13, 2008, after briefing, the district court denied the motion.

e. *Caronia's Sentence*

On November 30, 2009, the district court sentenced Caronia to one year of probation, 100 hours of community service, and a $25 special assessment.

This appeal followed.

DISCUSSION

On appeal, Caronia principally argues that the misbranding provisions of the FDCA prohibit off-label promotion, and therefore, unconstitutionally restrict speech.[8] Caronia argues 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 such speech.

We review Caronia's First Amendment challenge to his conspiracy conviction *de novo*. *See Conn. Bar Ass'n v. United States*, 620 F.3d 81, 89 (2d Cir. 2010) ("We review constitutional challenges to a federal statute *de novo*."); *see also United States v. Dhafir*, 461 F.3d 211, 215 (2d Cir. 2006) (same). We agree that Caronia's conviction must be vacated, but for narrower reasons than he urges.

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[8] Caronia also argues that the verdict sheet was improperly phrased and the jury's verdict was inconsistent. In light of our disposition of the First Amendment issue, we need not reach these issues.

While the FDCA makes it a crime to misbrand or conspire to misbrand a drug, the statute and its accompanying regulations do not expressly prohibit or criminalize off-label promotion. *See supra* 7-8, 10. Rather, the FDCA and FDA regulations reference "promotion" only as evidence of a drug's intended use. *See* 21 U.S.C. § 201.128 (discussing how drug's intended use can be demonstrated). Thus, under the principle of constitutional avoidance, explained *infra*, we construe the FDCA as not criminalizing the simple promotion of a drug's off-label use because such a construction would raise First Amendment concerns. Because we conclude from the record in this case that the government prosecuted Caronia for mere off-label promotion and the district court instructed the jury that it could convict on that theory, we vacate the judgment of conviction.

We begin by addressing the government's contention that Caronia's off-label promotion was used only as evidence of intent in this case. Finding the government's argument unpersuasive, we turn to the principal question on appeal: whether the government's prosecution of Caronia under the

FDCA only for promoting an FDA-approved drug for off-label use was constitutionally permissible.

I. ***Speech versus Evidence of Intent***

The government contends -- and the dissent agrees -- that the First Amendment is not implicated in this case. Specifically, the government argues that "[p]romoting an approved drug for off-label uses is not itself a prohibited act under the FDCA" and "the promotion of off-label uses plays an *evidentiary* role in determining whether a drug is misbranded under 21 U.S.C. § 352(f)(1)." (Gov't Br. 51 (citing 21 U.S.C. § 331)). The government contends that Caronia was not prosecuted for his speech, but that Caronia's promotion of Xyrem for off-label use served merely as "evidence of intent," or evidence that the "off-label uses were intended ones[] for which Xyrem's labeling failed to provide any directions." (Gov't Br. 52).

Even assuming the government can offer evidence of a defendant's off-label promotion to prove a drug's intended

use and, thus, mislabeling for that intended use,[9] that is not what happened in this case.

First, the government's contention that it did not prosecute Caronia for promoting the off-label use of an FDA-approved drug is belied by its conduct and arguments at trial. The excerpts quoted above demonstrate that the government repeatedly argued that Caronia engaged in criminal conduct by promoting and marketing the off-label use of Xyrem, an FDA-approved drug. *See supra* 21-22 & n.7. The district court record thus confirms overwhelmingly that Caronia was, in fact, prosecuted and convicted for promoting Xyrem off-label. *See supra* 12-24. Indeed, in the government's summation and rebuttal at trial, Caronia's off-label promotion of Xyrem is highlighted over forty times. (*See* Trial Tr. 819-49, 870-80, 883-85).

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[9] *See Wisconsin v. Mitchell*, 508 U.S. 476, 489 (1993) (concluding First Amendment "does not prohibit the use of speech to establish . . . intent"); *Whitaker v. Thompson*, 353 F.3d 947, 953 (D.C. Cir. 2004) (holding product's labeling may be used to infer its intended use and, thus, whether it is an unapproved drug under FDCA).

Second, the government's assertion now that it used Caronia's efforts to promote Xyrem for off-label use only as evidence of intent is simply not true. Even if the government could have used Caronia's speech as evidence of intent, the district court record clearly shows that the government did not so limit its use of that evidence. *See Mitchell*, 508 U.S. at 489-90 (instructing that, when speech is introduced as evidence of intent, "'[s]uch testimony is to be scrutinized with care to be certain the statements are not expressions of mere lawful and permissible difference of opinion with our own government'" (quoting *Haupt v. United States*, 330 U.S. 631, 642 (1947))). The government never argued in summation or rebuttal that the promotion was evidence of intent. (*See* Trial Tr. 819-49, 870-80, 883-85). The government never suggested that Caronia engaged in any form of misbranding other than the promotion of the off-label use of an FDA-approved drug. The government never suggested, for example, that Caronia conspired to place false or deficient labeling on a drug. *See* 21 U.S.C. §§ 352(a)-(n). Rather, the record makes clear that the

government prosecuted Caronia *for* his promotion and marketing efforts.

Third, the government's summation and the district court's instruction left the jury to understand that Caronia's speech was itself the proscribed conduct. *See supra* 21-23. Indeed, the district court flatly stated to the jury that pharmaceutical representatives are prohibited from engaging in off-label promotion. *See id.* Although the district court explained the remaining elements of misbranding and conspiring to misbrand to the jury, this specific instruction -- together with the government's summation -- would have led the jury to believe that Caronia's promotional speech was, by itself, determinative of his guilt. *See generally United States v. Dyer*, 922 F.2d 105, 107-08 (2d Cir. 1990) (stating specific jury instruction may be reviewed in isolation if "it is so far removed from the standards set by the law that the appellate court is convinced that the jury might have been misled" (internal quotation marks omitted)).

Fourth, the government clearly prosecuted Caronia for his words -- for his speech. A pharmaceutical representative's promotion of an FDA-approved drug's off-label use is speech. As the Supreme Court has held: "Speech in aid of pharmaceutical marketing . . . is a form of expression protected by the Free Speech Clause of the First Amendment." *Sorrell v. IMS Health, Inc.*, 131 S. Ct. 2653, 2659 (2011). Here, the proscribed conduct for which Caronia was prosecuted was precisely his speech in aid of pharmaceutical marketing.

Accordingly, we conclude that the government did prosecute Caronia for his speech, and we turn to whether the prosecution was permissible.

II. ***The Prosecution of Caronia's Speech***

While the government and the FDA have construed the FDCA's misbranding provisions to prohibit off-label promotion by pharmaceutical manufacturers, *see supra* 10; *see* FDA, *Draft Guidance*, *supra*, at 2-3, as we have observed, the FDCA itself does not expressly prohibit or criminalize off-label promotion. *See supra* 7-8, 10. The FDCA defines

misbranding in terms of whether a drug's labeling is adequate for its intended use, and permits the government to prove intended use by reference to promotional statements made by drug manufacturers or their representatives. *See id.* Assuming that this approach to the use of evidence of speech is permissible,[10] it affords little support to the government on this appeal because Caronia was not prosecuted on this basis. Rather, the government's theory of prosecution identified Caronia's speech alone as the proscribed conduct. The district court accepted this theory.

To the extent there is any ambiguity as to whether off-label promotion is tantamount to illegal misbranding, we

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[10] Although we assume, without deciding, that such use of evidence of speech is permissible under Mitchell, 508 U.S. 476, we observe that it still remains unclear how the government would identify criminal misbranding from communications between drug manufacturers and physicians authorized to prescribe drugs for off-label use. For example, would a manufacturer be guilty of misbranding if it ships Xyrem to a doctor who, in placing his order, reveals that he prescribes the drug for off-label use -- on a theory that the manufacturer now knows that the drug is not properly labeled for that use -- but not if the manufacturer ships to a doctor who does not reveal that he prescribes the drug off-label? Because this case does not present us with that circumstance or others that might raise questions about the scope of the misbranding proscription, we need not address them here.

construe the FDCA narrowly to avoid a serious constitutional question. *See Skilling v. United States*, 130 S. Ct. 2896, 2929-30 (2010) (instructing courts to "avoid constitutional difficulties by adopting a limiting interpretation if such a construction is fairly possible" (internal quotation marks and brackets omitted)); *Edward J. DeBartolo Corp. v. Fla. Gulf Coast Bldg. & Constr. Trades Council*, 485 U.S. 568, 575 (1988); *Allstate Ins. Co. v. Serio*, 261 F.3d 143, 150 (2d Cir. 2001) ("Thus, the courts will take pains to give a statute a limiting construction in order to avoid a constitutional difficulty.").

As we now explain, we decline the government's invitation to construe the FDCA's misbranding provisions to criminalize the simple promotion of a drug's off-label use by pharmaceutical manufacturers and their representatives because such a construction -- and a conviction obtained under the government's application of the FDCA -- would run afoul of the First Amendment.

A. ***Applicable First Amendment Doctrine***

The First Amendment protects against government regulation and suppression of speech on account of its

content. *Turner Broad. System, Inc. v. F.C.C.*, 512 U.S. 622, 641-42 (1994); *see Ward v. Rock Against Racism*, 491 U.S. 781, 791 (1989); *R.A.V. v. City of St. Paul*, 505 U.S. 377, 386 (1992). Content-based speech restrictions are subject to "strict scrutiny" -- that is, the government must show that the regulation at issue is narrowly tailored to serve or promote a compelling government interest. *See Brown v. Entm't Merchs. Ass'n*, 131 S. Ct. 2729, 2738 (2011) (citing *R.A.V.*, 505 U.S. at 395). Content-based government regulations are "presumptively invalid." *R.A.V.*, 505 U.S. at 382. Meanwhile, non-content-based regulation and regulation of commercial speech -- expression solely related to the economic interests of the speaker and its audience -- are subject to intermediate scrutiny. *See Turner Broad.*, 512 U.S. at 642; *Cent. Hudson Gas & Elec. Corp. v. Pub. Serv. Comm'n of N.Y.*, 447 U.S. 557, 563-64 (1980). Criminal regulatory schemes, moreover, warrant even more careful scrutiny. *See Holder v. Humanitarian Law Project*, 130 S. Ct. 2705, 2724 (2010) (applying more rigorous scrutiny); *id.* at 2734 (Breyer, *J.*, dissenting) ("It is not surprising that the majority, in determining the constitutionality of

criminally prohibiting the plaintiffs' proposed activities, would apply . . . a more demanding standard. Indeed, where, as here, a statute applies criminal penalties . . . I should think we would scrutinize the statute and justifications strictly." (internal quotation marks and citations omitted) (citing cases))); *see also City of Houston v. Hill*, 482 U.S. 451, 459 (1987) ("Criminal statutes must be scrutinized with particular care." (internal citations omitted)).

In applying these principles, we have a benefit not available to the district court: the Supreme Court's decision in *Sorrell v. IMS Health, Inc.*, 131 S. Ct. 2653 (2011), a case involving speech restrictions on pharmaceutical marketing. In *Sorrell*, the Vermont Prescription Confidentiality Law (the "VPCL") prohibited pharmaceutical companies and similar entities from using prescriber-identifying information for marketing purposes; it was challenged on First Amendment grounds. *Id.* at 2661-62; *see also* Vt. Stat. Ann., Tit. 18 § 4631(e)(4).

The *Sorrell* Court held that "[s]peech in aid of pharmaceutical marketing . . . is a form of expression protected by the . . . First Amendment. . . . [The] creation

and dissemination of information are speech within the meaning of the [Constitution]." *Id.* at 2659, 2667. The Court held that the Vermont statute set forth content- and speaker-based restrictions, and that the statute was therefore subject to heightened scrutiny. *Id.* at 2662-65. Because the VPCL disfavored speech with a particular content (marketing) when expressed by certain disfavored speakers (pharmaceutical manufacturers), the Court held that it unconstitutionally restricted speech. *Id.* at 2662-65, 2672.

In reaching this conclusion, *Sorrell* engaged in a two-step inquiry. First, the Court considered whether the government regulation restricting speech was content- and speaker-based. *See id.* at 2662-64. The Court held that it was; the regulation was therefore subject to heightened scrutiny and was "presumptively invalid." *See id.* Second, the Court considered whether the government had shown that the restriction on speech was consistent with the First Amendment under the applicable level of heightened scrutiny. *Id.* at 2663, 2667-68. The Court did not decide the level of heightened scrutiny to be applied, that is, strict, intermediate, or some other form of heightened scrutiny.

Id. Rather, after observing that "[i]n the ordinary case, it is all but dispositive to conclude that a law is content-based," the Court concluded that the Vermont statute was unconstitutional even under the lesser intermediate standard set forth in *Central Hudson*. *Id.* at 2667; *see Cent. Hudson*, 447 U.S. at 566. The Court further observed that the "outcome is the same whether a special commercial speech inquiry or a stricter form of judicial scrutiny is applied." *Sorrell*, 131 S. Ct. at 2667.

In considering whether the government had shown that the restriction on speech was consistent with the First Amendment, the *Sorrell* Court turned to *Central Hudson*. *See id.* at 2667-68. *Central Hudson* sets forth a four-part test to determine whether commercial speech is protected by the First Amendment. *Cent. Hudson*, 447 U.S. at 566. First, as a threshold matter, to warrant First Amendment protection, the speech in question must not be misleading and must concern lawful activity. *Id*; *see infra* note 11 and accompanying text. Second, to justify regulations restricting speech, the asserted government interest must be substantial. *Id.* Third, the regulation must directly

advance the governmental interest asserted, *id.*, "to a material degree," *44 Liquormart, Inc. v. Rhode Island*, 517 U.S. 484, 505 (1996) (quoting *Edenfield v. Fane*, 507 U.S. 761, 771 (1993)). "[A] commercial speech regulation 'may not be sustained if it provides only ineffective or remote support for the government's purpose.'" *Liquormart*, 517 U.S. at 505 (quoting *Cent.*, 447 U.S. at 564). Fourth, the regulation must be "narrowly drawn," and may not be more extensive than necessary to serve the interest, *Cent. Hudson*, 447 U.S. at 565-56; *see also Sorrell*, 131 S. Ct. at 2667-69 (citing *Bd. of Tr. of State Univ. of N.Y. v. Fox*, 492 U.S. 469, 480-81 (1989)); *Thompson v. W. States Med. Ctr.*, 535 U.S. 357, 374 (2002). The government cannot "completely suppress information when narrower restrictions on expression would serve its interests as well." *Cent. Hudson*, 447 U.S. at 565. "Under the commercial speech inquiry, it is the [government's] burden to justify its content-based law as consistent with the First Amendment." *Sorrell*, 131 S. Ct. at 2667 (citing *Thompson*, 535 U.S. at 373).

B. ***Application***

In prosecuting Caronia, the government construed the FDCA's misbranding provisions to prohibit and criminalize the promotion of off-label drug use. We review the government's theory of prosecution under the *Sorrell* Court's two-step analysis to determine whether it runs afoul of the First Amendment. First, we conclude that the government's construction of the FDCA's misbranding provisions imposes content- and speaker-based restrictions on speech subject to heightened scrutiny. Second, we conclude the government cannot justify a criminal prohibition of off-label promotion even under *Central Hudson*'s less rigorous intermediate test.

1. ***Heightened Scrutiny***

The government's construction of the FDCA's misbranding provisions to prohibit and criminalize the promotion of off-label drug use by pharmaceutical manufacturers is content- and speaker-based, and, therefore, subject to heightened scrutiny. *See id.*

First, the government's interpretation of the FDCA's misbranding provisions to prohibit off-label

promotion is content-based because it distinguishes between "favored speech" and "disfavored speech on the basis of the ideas or views expressed." *See Turner Broad.*, 512 U.S. at 643; *accord Sorrell*, 131 S. Ct. at 2663. Under this construction, speech about the government-approved use of drugs is permitted, while certain speech about the off-label use of drugs -- that is, uses not approved by the government -- is prohibited, even though the off-label use itself is not. *See* 21 U.S.C. §§ 331(a), 333(a)(2). Indeed, the content of the regulated speech drives this construction of the FDCA; as in *Sorrell*, the "express purpose and practical effect" of the government's ban on promotion is to "diminish the effectiveness of [off-label drug] marketing by manufacturers." *See Sorrell*, 131 S. Ct. at 2663.

Second, this construction is speaker-based because it targets one kind of speaker -- pharmaceutical manufacturers -- while allowing others to speak without restriction. *See id.* at 2663. In *Sorrell*, pharmaceutical companies were barred from obtaining and using prescriber-identifying information for marketing purposes, but a wide range of other speakers, including private and academic

researchers, could acquire and use the information. *Id.* Similarly, here, because off-label prescriptions and drug use are legal, the government's application of the FDCA permits physicians and academics, for example, to speak about off-label use without consequence, while the same speech is prohibited when delivered by pharmaceutical manufacturers. *See* 21 U.S.C. §§ 331(a), 333(a). This construction "thus has the effect of preventing [pharmaceutical manufacturers] -- and only [pharmaceutical manufacturers] -- from communicating with physicians in an effective and informative manner." *Sorrell*, 131 S. Ct. at 2663.

Additionally, a claim to First Amendment protection here is more compelling than in *Sorrell* because this case involves a criminal regulatory scheme subject to more careful scrutiny. *See* 21 U.S.C. § 333(a); *Humanitarian Law Project*, 130 S. Ct. at 2724.

Accordingly, the government's construction of the FDCA's misbranding provisions to prohibit and criminalize off-label promotion is content- and speaker-based, and subject to heightened scrutiny under *Sorrell*.

2. ***Central Hudson***

The first two prongs of *Central Hudson* are easily satisfied here. First, promoting off-label drug use concerns lawful activity (off-label drug use), and the promotion of off-label drug use is not in and of itself false or misleading.[11] *See Cent. Hudson*, 447 U.S. at 566. Second, the government's asserted interests in drug safety and public health are substantial. *See id.* Specifically, the government asserts an interest in preserving the

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[11] In *Whitaker*, cited by the dissent (Diss. Op. 14), the D.C. Circuit held that the labeling of a product, which was not approved by the FDA as a drug, constituted speech about unlawful activities and therefore did not enjoy First Amendment protection because it was unlawful to sell an unapproved product pursuant to claims about disease treatment. *See Whitaker*, 353 F.3d at 953.

The government does not contend that off-label promotion is in and of itself false or misleading. Of course, off-label promotion that is false or misleading is not entitled to First Amendment protection. *See Cent. Hudson*, 447 U.S. at 566. Under 21 U.S.C. § 331(a), a defendant may be prosecuted for untruthfully promoting the off-label use of an FDA-approved drug, *e.g.*, making false or misleading statements about a drug.

The government did not argue at trial, nor does it argue on appeal, that the promotion in question was false or misleading. (*See* Trial Tr. 823 (mentioning, in government's summation, that Caronia "did not give accurate and complete information in promoting and marketing Xyrem," but focusing on promotion as misbranding and not pursuing argument that speech was false or misleading); Gov't Br. 58 (considering whether "the commercial speech in question clears [the] hurdle" of *Central Hudson*'s first prong, but not contending that the speech concerns unlawful activity or is false or misleading)).

effectiveness and integrity of the FDCA's drug approval process, and an interest in reducing patient exposure to unsafe and ineffective drugs. *See FDA v. Brown & Williamson Tobacco Corp.*, 529 U.S. 120, 133 (2000) ("[O]ne of the [FDCA's] core objectives is to ensure that any product regulated by the FDA is 'safe' and 'effective' for its intended use.").

The third and fourth prongs of *Central Hudson* require that the regulation directly advance the government's interests and be narrowly drawn. *See Cent. Hudson*, 447 U.S. at 566. We turn to the third and fourth prongs below.

a. *Direct Advancement*

The government's construction of the FDCA as prohibiting off-label promotion does not, by itself, withstand scrutiny under *Central Hudson*'s third prong. First, off-label drug usage is not unlawful, and the FDA's drug approval process generally contemplates that approved drugs will be used in off-label ways. In effect, even if pharmaceutical manufacturers are barred from off-label promotion, physicians can prescribe, and patients can use,

drugs for off-label purposes. *See supra* 4-7. As off-label drug use itself is not prohibited, it does not follow that prohibiting the truthful promotion of off-label drug usage by a particular class of speakers would directly further the government's goals of preserving the efficacy and integrity of the FDA's drug approval process and reducing patient exposure to unsafe and ineffective drugs. *See Sorrell*, 131 S. Ct. at 2668-69 (holding government interest in protecting physician privacy not directly served when law made prescriber-identifying information available to "all but a narrow class of disfavored speakers").

Second, 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. *See Va. Bd. of Pharmacy v. Va. Citizens Consumer Council, Inc.*, 425 U.S. 748, 770 (1976) (discussing "highly paternalistic approach" of government prohibitions on free

flow of information); *see also Sorrell*, 131 S. Ct. at 2670-72 ("[The] fear that [physicians, sophisticated and experienced customers,] would make bad decisions if given truthful information" cannot justify content-based burdens on speech.") (citing sources); *Liquormart*, 517 U.S. at 503 ("[B]ans against truthful, nonmisleading commercial speech . . . usually rest solely on the offensive assumption that the public will respond 'irrationally' to the truth. . . . 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."). In fact, in granting safe harbor to manufacturers by permitting the dissemination of off-label information through scientific journals, the FDA itself "recognizes that public health can be served when health care professionals receive truthful and non-misleading scientific and medical information on unapproved uses" of approved drugs. Dep't of Health and Human Serv., Good Reprint Practices, *supra*, at III, V; *see Wash. Legal Found. v. Henney*, 202 F.3d 331, 335 (D.C. Cir. 2000) (discussing FDA "safe harbor," where certain forums for off-label discussion, such as continuing medical

education programs and scientific publications, would not be used against manufacturers in misbranding enforcement actions).

Here, as the FDA recognizes, it is the physician's role to consider multiple factors, including a drug's FDA-approval status, to determine the best course of action for her patient. *See* FDA Drug Bull., *supra*, at 5; *Buckman*, 531 U.S. at 350*; Weaver*, 886 F.2d at 198-99; 21 U.S.C. § 396; *see also Thompson*, 535 U.S. at 367 (discussing the "general rule" that "the speaker and the audience, not the government, assess the value of the information presented") (quoting *Edenfield*, 507 U.S. at 767); *see also Va. Bd. of Pharmacy*, 425 U.S. at 770 ("[T]he choice . . . is not ours to make or the [legislature's]."). While some off-label information could certainly be misleading or unhelpful, this case does not involve false or misleading promotion. *See supra* note 11. Moreover, in the fields of medicine and public health, "where information can save lives," it only furthers the public interest to ensure that decisions about the use of prescription drugs, including off-label usage, are intelligent and well-informed. *See Sorrell*, 131 S. Ct.

at 2664, 2671; *Thompson*, 535 U.S. at 366 (quoting *Va. Bd. of Pharmacy*, 425 U.S. at 765).

The government's construction of the FDCA essentially legalizes the outcome -- off-label use -- but prohibits the free flow of information that would inform that outcome. If the government's objective is to shepherd physicians to prescribe drugs only on-label, criminalizing manufacturer promotion of off-label use while permitting others to promote such use to physicians is an indirect and questionably effective means to achieve that goal. Thus, the government's construction of the FDCA's misbranding provisions does not directly advance its interest in reducing patient exposure to off-label drugs or in preserving the efficacy of the FDA drug approval process because the off-label use of such drugs continues to be generally lawful. Accordingly, the government's prohibition of off-label promotion by pharmaceutical manufacturers "provides only ineffective or remote support for the government's purpose." *See Liquormart*, 517 U.S. at 504-05 (quoting *Cent. Hudson*, 447 U.S. at 564).

b. *Narrowly Drawn*

The last prong of *Central Hudson* requires the government's regulation to be narrowly drawn to further the interests served. *Cent. Hudson*, 447 U.S. at 566. Here, the government's construction of the FDCA to impose a complete and criminal ban on off-label promotion by pharmaceutical manufacturers is more extensive than necessary to achieve the government's substantial interests. *See id.* Numerous, less speech-restrictive alternatives are available, as are non-criminal penalties. *See Thompson*, 535 U.S. at 372-73.

To advance the integrity of the FDA's drug approval process and increase the safety of off-label drug use, the government could pursue several alternatives without excessive First Amendment restrictions. *See Cent. Hudson*, 447 U.S. at 564. For example, if the government is concerned about the use of drugs off-label, it could more directly address the issue. If the government is concerned that off-label promotion may mislead physicians, it could guide physicians and patients in differentiating between misleading and false promotion, exaggerations and embellishments, and truthful or non-misleading information.

See Osborn, *Can I Tell You The Truth?*, *supra*, at 306-07. The government could develop its warning or disclaimer systems, or develop safety tiers within the off-label market, to distinguish between drugs. *See* Coleen Klasmeier and Martin H. Redish, *Off-Label Prescription Advertising, the FDA and the First Amendment: A Study in the Values of Commercial Speech Protection*, 37 Am. J.L. & Med. 315, 334 (2011). The government could require pharmaceutical manufacturers to list all applicable or intended indications when they first apply for FDA approval, enabling physicians, the government, and patients to track a drug's development. To minimize off-label use, or manufacturer evasion of the approval process for such use, the government could create other limits, including ceilings or caps on off-label prescriptions. The FDA could further remind physicians and manufacturers of, and even perhaps further regulate, the legal liability surrounding off-label promotion and treatment decisions.[12] Finally, where off-label drug use is

[12] Physicians and pharmaceutical manufacturers can be held accountable for off-label drug use through medical malpractice and negligence theories of liability. *See generally Boyle v. Revici*, 961 F.2d 1060 (2d Cir. 1992); *Sita v. Danek Med. Inc.*, 43

exceptionally concerning, the government could prohibit the off-label use altogether. *See, e.g.*, *Bader*, 678 F.3d at 873-75 & n.10 (citing 21 U.S.C. § 333(e) (prohibiting off-label use of human growth hormone)). The possibilities are numerous indeed.

"If the First Amendment means anything, it means that regulating speech must be a last -- not first -- resort." *Thompson*, 535 U.S. at 373. The government has not established a "reasonable fit" among its interests in drug safety and public health, the lawfulness of off-label use, and its construction of the FDCA to prohibit off-label promotion. *See Fox*, 492 U.S. at 480. The government's interests could be served equally well by more limited and targeted restrictions on speech. *See Cent. Hudson*, 447 U.S. at 565. The government contends that these alternative means of reducing patient exposure to unsafe, untested drugs and maintaining the integrity of the FDA-approval process are "indefensible" (Gov't Br. 70), because they are not administrable, feasible, or otherwise effective. In the

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F. Supp. 2d 245 (E.D.N.Y. 1999); *Retkwa v. Orentreich*, 584 N.Y.S.2d 710 (N.Y. Sup. Ct. 1992).

absence of any support, such conclusory assertions are insufficient to sustain the government's burden of demonstrating that the proposed alternatives are less effective than its proposed construction of the FDCA in furthering the government interests identified. *See Ashcroft v. ACLU*, 542 U.S. 656, 665, 669 (2004).

Accordingly, even if speech can be used as evidence of a drug's intended use, we decline to adopt the government's construction of the FDCA's misbranding provisions to prohibit manufacturer promotion alone as it would unconstitutionally restrict free speech. We construe the misbranding provisions of the FDCA as not prohibiting and criminalizing the truthful off-label promotion of FDA-approved prescription drugs. Our conclusion is limited to FDA-approved drugs for which off-label use is not prohibited, and we do not hold, of course, that the FDA cannot regulate the marketing of prescription drugs. We conclude simply that the government cannot prosecute pharmaceutical manufacturers and their representatives under the FDCA for speech promoting the lawful, off-label use of an FDA-approved drug.

CONCLUSION

For the reasons set forth above, we VACATE the judgment of conviction and REMAND the case to the district court.

DEBRA ANN LIVINGSTON, *Circuit Judge*, dissenting:

Alfred Caronia was convicted of conspiring to introduce a prescription drug into interstate commerce with the intent that it be used in ways its labeling neither disclosed nor described. This intent was revealed, *inter alia*, through his speech. Because the First Amendment has never prohibited the government from using speech as evidence of motive or intent, *see Wisconsin v. Mitchell*, 508 U.S. 476, 489 (1993), I would affirm Caronia's conviction. By holding, instead, that Caronia's conviction must be vacated—and on the theory that whatever the elements of the crime for which he was duly tried, he was in fact convicted for promoting a drug for unapproved uses, in supposed violation of the First Amendment—the majority calls into question the very foundations of our century-old system of drug regulation. I do not believe that the Supreme Court's precedents compel such a result. I therefore respectfully dissent.

I. Intended Uses

Alfred Caronia was convicted of conspiring to introduce a "misbranded" drug into interstate commerce. *See* 18 U.S.C. § 371; 21 U.S.C. § 331(a). Under the Federal Food, Drug and Cosmetic Act ("FDCA"), one way in which a drug is misbranded is if its labeling lacks adequate directions for layperson use. *See* 21 U.S.C. § 352(f)(1); 21 C.F.R. § 201.5. Whether a drug's directions are "adequate . . . for use" depends on the drug's intended uses. This is because the

Food and Drug Administration ("FDA") defines "adequate directions for use" as "directions under which the layman can use a drug safely and *for the purposes for which it is intended*." 21 C.F.R. § 201.5 (emphasis added). Directions are adequate only if they include, for example, "[s]tatements of all . . . uses for which such drug is intended," and "usual quantities [of dose] for each of the uses for which it is intended." 21 C.F.R. § 201.5(a), (b). This labeling provision is in part merely a disclosure requirement for the benefit of a drug's lay users. But some uses of drugs are never safe, at least for a layperson; because it is impossible to provide adequate directions for such uses, this provision also effectively prohibits introducing drugs into interstate commerce with the intent that the drugs be used in ways that are unsafe for laypersons.[1]

The labeling on the drug at issue in this case, Xyrem, stated that it was "indicated for the treatment of excessive daytime sleepiness and cataplexy in patients with narcolepsy." At all relevant times, the FDA had not approved Xyrem for any other uses. Xyrem's labeling did not state any other intended

[1] The FDA has exempted certain drugs from the requirement that their labels contain adequate directions for lay use. *See* 21 U.S.C. § 352(f); *see, e.g.*, 21 C.F.R. § 201.100 (exempting certain prescription drugs); *cf. United States v. An Article of Device*, 731 F.2d 1253, 1259 (7th Cir. 1984) ("Obviously there are many medical devices which would be ineffective at best, and dangerous at worst, if left in the hands of a layman, and [FDA regulations] appear[] to deem any such devices 'misbranded' and thus subject to seizure. However, the regulations provide several exemptions from the 'adequate directions for use' requirement."). Caronia does not argue that any such exemption applies here.

uses for the drug, nor provide directions for any other intended uses. Unsurprisingly, then, Caronia did not argue before the jury that Xyrem's labeling included adequate directions for the off-label uses that he was alleged to have promoted. Rather, his trial focused on whether Caronia agreed with his employer, Orphan Medical, Inc. ("Orphan"), and with others associated with Orphan, that Xyrem would be distributed for off-label use.

Determining a product's "intended uses" has long been a central concern of food and drug law. The concept originated in the Pure Food and Drugs Act of 1906, Pub. L. No. 59-384, 34 Stat. 768, which prohibited introducing any adulterated or misbranded drug into interstate commerce, *id.* § 2, 34 Stat. at 768, and which defined "drug" to include "any substance or mixture of substances *intended* to be used for the cure, mitigation, or prevention of disease," *id.* § 5, 34 Stat. at 769 (emphasis added). Courts found violations of that statute where, as in this case, a manufacturer's speech demonstrated an intended use that brought it within the scope of the statute such that its label was required affirmatively to disclose certain information. *See, e.g.*, *United States v. Eleven Cartons of Drug Labeled in Part "Vapex,"* 59 F.2d 446 (D. Md. 1932) (holding that "Vapex" was "intended to be used for the cure, mitigation or prevention of disease," and was thus a "drug," because its label stated that it was "effective to relieve a head cold instantly," *id.* at 447; and further holding that the drug was

misbranded, even "assum[ing] that the inhalation of Vapex is innocuous," because it was "required to contain a declaration on the label of the alcoholic content" yet failed to do so, *id.* at 449).

When Congress expanded the law three decades later in the Food, Drug, and Cosmetic Act of 1938, Pub. L. No. 75-717, 52 Stat. 1040, its revisions remained anchored to the concept of "intended uses." The definition of "drug" was broadened to also include "articles . . . *intended* to affect the structure or any function of the body," *id.* § 201(g)(3), 52 Stat. at 1041 (emphasis added), and the parallel category of "devices" was created and similarly defined in terms of intended uses, *see id.* § 201(h), 52 Stat. at 1041. At the same time, Congress broadened the definition of a "misbranded" drug to include any drug with labeling not bearing "adequate directions for use." *Id.* § 502(f)(1), 52 Stat. at 1051. Under the 1938 Act, courts upheld convictions for introducing drugs into interstate commerce that lacked adequate labeling for their intended uses, and routinely relied on "oral representations made by . . . authorized sales distributors" to determine a product's intended uses. *V.E. Irons, Inc. v. United States*, 244 F.2d 34, 44 (1st Cir. 1957) (upholding a conviction for introducing into interstate commerce "articles of drug [that] were misbranded in that their labeling failed to bear 'adequate directions for use' for the various diseases and conditions for which they were intended," and relying on "both graphic materials

distributed and testimony of oral representations to users and prospective users . . . . show[ing] that the products shipped were to be used as drugs").

The modern FDCA continues to define "drugs" (and "devices") on the basis of an article's intended uses. *See* 21 U.S.C. § 321(g)(1)(B), (C); 21 U.S.C. § 321(h)(2), (3). The concept of "intended uses" therefore largely defines the scope of the FDA's regulatory authority. *See FDA v. Brown & Williamson Tobacco Corp.*, 529 U.S. 120, 126 (2000). To put the matter in practical terms: it is because of the "intended uses" principle that hardware stores are generally free to sell bottles of turpentine, but may not label those bottles, "Hamlin's Wizard Oil: There is no Sore it will Not Heal, No Pain it will not Subdue."[2]

According to regulations that have remained essentially unchanged for sixty years, *see* 17 Fed. Reg. 6818, 6820 (1952) (codified at 21 C.F.R. § 1.106(*o*) (Cm. Supp. 1955)), the FDA defines a drug's "intended uses" on an objective, rather than subjective, basis:

The words intended uses or words of similar import . . . refer to the

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[2] *See* Wikipedia, Hamlin's Wizard Oil, http://en.wikipedia.org/wiki/Hamlin's_Wizard_Oil (last visited May 30, 2012); *cf. United States v. Rutherford*, 442 U.S. 544, 558 (1979) ("Since the turn of the century, resourceful entrepreneurs have advertised a wide variety of purportedly simple and painless cures for cancer, including liniments of turpentine, mustard, oil, eggs, and ammonia; peat moss; arrangements of colored floodlamps; pastes made from glycerin and limburger cheese; mineral tablets; and 'Fountain of Youth' mixtures of spices, oil, and suet. . . . [H]istorical experience does suggest why Congress could reasonably have determined to protect . . . patients[] from the vast range of self-styled panaceas that inventive minds can devise.").

> objective intent of the persons legally responsible for the labeling of drugs. The intent is determined by such persons' expressions or may be shown by the circumstances surrounding the distribution of the article. This objective intent may, for example, be shown by labeling claims, advertising matter, or oral or written statements by such persons or their representatives. It may be shown by the circumstances that the article is, with the knowledge of such persons or their representatives, offered and used for a purpose for which it is neither labeled nor advertised. . . . [I]f a manufacturer knows, or has knowledge of facts that would give him notice, that a drug introduced into interstate commerce by him is to be used for conditions, purposes, or uses other than the ones for which he offers it, he is required to provide adequate labeling for such a drug which accords with such other uses to which the article is to be put.

21 C.F.R. § 201.128. As previously noted, Caronia did not contend at trial that Xyrem's label (which provided dosage and other instructions for Xyrem's use in the treatment of narcolepsy patients who experience cataplexy and excessive daytime sleepiness) provided adequate instructions for any other use. In this case, then, Xyrem was "misbranded"—and Caronia could be guilty of conspiring with others to introduce it into interstate commerce in such a state—if the conduct and statements of the persons legally responsible for labeling the drug (or the conduct and statements of their representatives) demonstrated an objective intent that Xyrem be used for off-label purposes.

II. The First Amendment and Speech as Evidence of Intent

It is well settled that "[t]he First Amendment . . . does not prohibit the evidentiary use of speech to establish the elements of a crime or to prove motive or intent." *Wisconsin v. Mitchell*, 508 U.S. 476, 489 (1993). To demonstrate that

Xyrem was intended for off-label uses (and thus that it was misbranded) the prosecution in this case relied, *inter alia*, upon Caronia's statements that Xyrem could be used to treat "insomnia, [f]ibromyalgia[,] periodic leg movement, restless leg, . . . Parkinson's and . . . MS."[3] Because Caronia's speech was used simply as evidence of Xyrem's intended uses, I agree with the government that Caronia's conviction does not run afoul of the First Amendment.

The majority unsurprisingly agrees that speech may be used as evidence of intent. It even leaves open the possibility that speech may serve as evidence of intent to introduce a misbranded drug into interstate commerce. *See* Maj. Op. at 25. The majority nonetheless concludes that in this particular case "the government clearly prosecuted Caronia for his words—for his speech" and not for conspiring to introduce a misbranded drug into interstate commerce. Maj.

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[3] This was not the only evidence on which the government relied. As the majority acknowledges, Xyrem is a "powerful central nervous system depressant" that the FDA requires to bear a "black box" warning (the most serious warning placed on prescription medicine) in light of its potential side effects, which include seizure, respiratory depression, coma, and death. Maj. Op. at 11. Yet in the tape-recorded meeting of October 26, 2005 between Caronia and Dr. Charno, to which the majority refers, Caronia described Xyrem as "a very safe drug," with no contraindications. At Caronia's second meeting with Dr. Charno on November 2, Dr. Gleason, one of Caronia's co-conspirators, described many potential uses for Xyrem, including in the treatment of obesity and chronic fatigue, and added that "for the problems with insomnia there's no better drug, no safer drug, it's as safe as Ambien and Sonata . . . ." Caronia later admitted that his employer required him to meet an annual sales quota of 520 bottles of Xyrem in 2005, the year these conversations took place, and that he was unable to meet it. In fact, the salaries of Orphan's sales personnel depended to a significant degree on meeting sales targets, and in 2005 Caronia was ranked near the very bottom of Orphan's national sales force.

Op. at 27–28. I disagree that the government prosecuted Caronia for his speech. I also fail to see how the majority's reasoning would ever allow such speech to support a conviction under 21 U.S.C. § 331(a). For this reason, I conclude the majority's opinion is fundamentally at odds both with *Mitchell* and with the underlying premises behind much of the FDCA's regulatory scheme.

I do not agree with the majority that Caronia was "prosecuted and convicted for promoting Xyrem off-label." Maj. Op. at 26. The district court correctly instructed the jury as to all the elements necessary to prove a conspiracy, as well as the additional elements, derived from 21 U.S.C. § 331(a), to prove the conspiracy's unlawful purpose:

> To sustain the charge of conspiracy to introduce into interstate commerce a misbranded drug, the Government must prove the element[s] of conspiracy as I previously described them for you and must also prove the following elements of misbranding through the introduction of a misbranded drug into interstate commerce.
>
> First, the Government must prove that the defendant conspired to introduce or conspired to cause to be introduced a drug into interstate commerce or conspired to deliver a drug for introduction into interstate commerce or conspired to cause a drug to be delivered for introduction into interstate commerce.
>
> Second, the Government must prove that the drug was misbranded, as I've previously defined that term.
>
> If you find that the Government has satisfied its burden with respect to each of these elements, along with satisfying the elements of conspiracy as I have previously explained them to you, then you should find

> the defendant guilty of that prong of the conspiracy count charging him with conspiracy to misbrand in violation of Section 331(a).

The majority makes much of the fact that the district court also instructed the jury that "[a] misbranded drug may be shown by a promotion of the drug by a distributor for an intended use different from the use for which the drug was approved by the Food and Drug Administration." But this wholly appropriate charge was but part of the district court's explanation of the "objective intent" standard with respect to "intended uses":

> The intended use of a drug can be determined from its label, accompanying labels, promotional material, advertising or any other relevant source that reveals the manner in which the drug's distributors expect[ ] the product to be used. A misbranded drug may be shown by a promotion of the drug by a distributor for an intended use different from the use for which the drug was approved by the Food and Drug Administration, the Government agency charged with the responsibility for approving a drug's use. Under 21 Code of Federal Regulations, Section 201.128, intended use or words of a similar import refer to the objective intent of the persons legally responsible for the labeling of drugs. The intent is determined by such persons' expressions or may be shown by the circumstances surrounding the distribution of the drug. This objective intent may, for example, be shown by labeling claims, advertising matter or oral or written statements by such persons or their representatives. It may be shown by the circumstances that the drug is, with the knowledge of such persons or their representatives, offered and used for a purpose for which it is neither labeled, nor advertised.

Granted, in a single sentence at the conclusion of this instruction the district court stated that drug manufacturers "are not permitted to promote uses for a

drug that have not been cleared by the United States Food and Drug Administration." In context, however, the district court was simply instructing the jury that promotion of an off-label use may demonstrate an objective intent that a drug be used for off-label purposes—and thus that it is being placed into interstate commerce without proper labeling. And this, contrary to the majority's suggestion, was not error.[4] *See United States v. Sabhnani*, 599 F.3d 215, 237 (2d Cir. 2010) (admonishing that jury instructions are not to be read in isolation, but in their entirety, to determine whether they communicate the "essential ideas" to the jury); *accord United States v. Tran*, 519 F.3d 98, 105 (2d Cir. 2008); *see also Cupp v. Naughten*, 414 U.S. 141, 146–47 (1973) ("[A] single

[4] Notably, Caronia himself does not argue that the district court's instruction was improper. While I disagree with the majority's conclusion that the jury was improperly instructed, moreover, I note to be clear that an identical instruction *could* be problematic in a different case of alleged misbranding—where a defendant argued, for example, that the drug's labeling included adequate directions for uses that were not FDA-approved. *Cf. United States v. Articles of Drug*, 585 F.2d 575, 585 n.20 (3d Cir. 1978) (instructing the district court, which had "entered no findings of fact as to misbranding" and did not consider the "argument that the drugs were labeled sufficiently for lay use," to "consider these factors" on remand). Provided a drug bears adequate labeling for an unapproved use, a defendant distributing such a drug cannot be convicted under 21 U.S.C. § 331(a) for introducing a misbranded drug into interstate commerce. Labeling a drug with directions for unapproved uses, however, may violate *another* provision of the FDCA. *See, e.g.*, *Wyeth v. Levine*, 555 U.S. 555, 568 (2009) ("The FDA's premarket approval of a new drug application includes the approval of the exact text in the proposed label. *See* 21 U.S.C. § 355; 21 C.F.R. § 314.105(b) (2008). Generally speaking, a manufacturer may only change a drug label after the FDA approves a supplemental application.").

instruction to a jury may not be judged in artificial isolation, but must be viewed in the context of the overall charge.").

The majority also focuses on the prosecution's summations, arguing that the government did not use Caronia's promotion of Xyrem as evidence of misbranding, but rather "prosecuted Caronia *for* his off-label promotion." Maj. Op. at 19 (emphasis added). Suffice it to say, however, that any claim that Caronia was convicted for his speech, as opposed to his conspiracy, is belied by the fact that, as the majority rightly concedes, the district court explained the elements of conspiracy and misbranding to the jury and instructed that each element must be shown beyond a reasonable doubt. We presume that juries follow their instructions. *United States v. Williams*, 690 F.3d 70, 77 (2d Cir. 2012). Caronia, moreover, objected not at all to the prosecution's references to his off-label promotion of Xyrem—and unsurprisingly, since read in context, the government properly referred to this promotion to prove Caronia's participation in a conspiracy to distribute Xyrem for uses that its labeling neither described nor explained.

At bottom, the majority is troubled that "the simple promotion of a drug's off-label use" can lead to criminal liability under the FDCA. Maj. Op. at 30. That is, where all that a drug manufacturer (or its representative) does is sell a prescription drug and promote it for an off-label purpose, the majority

concludes that prosecution raises serious First Amendment concerns—and regardless whether the off-label promotion is presented as mere evidence or as the proscribed conduct itself. The majority's conclusion, clearly stated, is that while speech might serve as evidence of other types of mislabeling, such as false or deficient labeling, *see* Maj. Op. at 26–27, a mislabeling charge simply may not rest on off-label promotion.

This is a departure from precedent. My conclusion here—that promotion of a use may demonstrate an objective intent that the drug be used for that purpose—has long been endorsed by this Circuit. *See United States v. Writers & Research, Inc.*, 113 F.3d 8, 11 (2d Cir. 1997) ("We agree with the district court that, as a matter of law, if 714X was promoted as a treatment or cure for cancer, AIDS, or other diseases, it is subject to the requirements of the FDCA . . . ."); *United States v. An Article . . . Consisting of 216 Individually Cartoned Bottles*, 409 F.2d 734, 739 (2d Cir. 1969) ("It is well settled that the intended use of a product may be determined from its label, accompanying labeling, promotional material, advertising, and any other relevant source. . . . Thus, Congress has made a judgment that a product is subject to regulation as a drug if certain promotional claims are made for it."). Such use of speech, moreover, has never been prohibited by the First Amendment. *See Sorrell v. IMS Health Inc.*, 131 S. Ct. 2653, 2664–65 (2011) ("[T]he First Amendment does not prevent restrictions

directed at commerce or conduct from imposing incidental burdens on speech. That is why a ban on race-based hiring may require employers to remove 'White Applicants Only' signs; why an ordinance against outdoor fires might forbid burning a flag; and why antitrust laws can prohibit agreements in restraint of trade.") (citations and some internal quotation marks omitted).

It is true that the introduction of Xyrem into interstate commerce by Caronia's employer was generally legal so long as the drug was not intended to be used for purposes that lacked adequate directions on its labeling. It is also true that, absent Caronia's speech (and speech by other Orphan representatives), the jury likely would not have found that Xyrem was intended for such off-label uses. Consistent with the First Amendment, however, otherwise permissible conduct may become *impermissible* if undertaken with a prohibited motive, and speech may be used as evidence of such a motive. An employer, for example, is generally free to refuse to promote an employee simply because he does not like the employee's attitude, but he may not refuse to promote the employee because of her sex. *See Wisconsin v. Mitchell*, 508 U.S. at 487 ("In *Hishon*[*v. King & Spalding*, 467 U.S. 69, 78 (1984)], we rejected the argument that Title VII infringed employers' First Amendment rights."). The First Amendment does not bar using the employer's speech to demonstrate his discriminatory motive. *See Wisconsin v. Mitchell*, 508 U.S. at 490 (citing *Price*

Waterhouse v. Hopkins, 490 U.S. 228, 251–52 (1989) (plurality opinion)). Indeed, as the crimes of attempt, conspiracy, and inducement demonstrate, "[w]ords alone may constitute a criminal offense, even if they spring from the anterior motive to effect political or social change." *United States v. Freeman*, 761 F.2d 549, 551 (9th Cir. 1985) (Kennedy, J.). *See generally* Kent Greenawalt, *Speech, Crime, and the Uses of Language* 6–7 (1989) (enumerating twenty-one crimes that "critically involve communication," *id.* at 7). Simply put, that Caronia was otherwise free to introduce Xyrem into interstate commerce does not give him a First Amendment right to introduce it into interstate commerce for any intended purpose he wished.

Caronia attempts to distinguish this line of authority by arguing that he merely discussed "a perfectly lawful practice: the use of a lawful drug, Xyrem, for off-label purposes." Appellant's Reply Br. at 10. But the fact that a physician or a patient could legally use Xyrem for an off-label purpose is not enough to make out Caronia's First Amendment claim. There might be no law forbidding the consumption of arsenic. But this would not endow Abby and Martha with a First Amendment right to offer arsenic-laced wine to lonely old bachelors with the intent that they drink it. *See Arsenic and Old Lace* (Warner Bros. Pictures 1944). And any statements Abby or Martha made suggesting their intent—even if all of the statements were truthful and not misleading—would not be barred

from evidence by the First Amendment simply because arsenic might legally be consumed.[5]

Although Caronia relies heavily on the Supreme Court's decision in *Thompson v. Western States Medical Center*, 535 U.S. 357 (2002), that case did not discuss the use of speech as evidence of intent. The statute at issue in *Western States,* as the government conceded before the Supreme Court, regulated speech directly rather than as evidence of intent. *See id.* at 364–65 ("[T]he pharmacy, licensed pharmacist, or licensed physician compounding the drug may 'not advertise or promote the compounding of any particular drug, class of drug, or type of drug' . . . .") (quoting 21 U.S.C. § 353a(c)); *Western States*, 535 U.S. at 370–71 ("The Government argues that advertising . . . is 'a

[5] Indeed, speech encouraging others to engage in certain legal conduct has long been *directly* regulated or prohibited in a variety of areas. For example, an insider who is privy to an impending corporate merger is prohibited from telling a friend that one of those companies is a good buy—even if that statement is truthful and even if the friend (who does not realize that she has just been made privy to material nonpublic information) may legally buy stock in that company. *See United States v. Gansman*, 657 F.3d 85, 92 (2d Cir. 2011) (elements of tipper liability); *United States v. Falcone*, 257 F.3d 226, 234 (2d Cir. 2001) (elements of tippee liability). Each of two corporations may be free to raise its prices, but the Sherman Act forbids them from discussing such a course of action. *See In re High Fructose Corn Syrup Antitrust Litig.*, 295 F.3d 651, 654 (7th Cir. 2002) (Posner, J.); Louis Kaplow, *On the Meaning of Horizontal Agreements in Competition Law*, 99 Calif. L. Rev. 683 (2011). Likewise, nonlawyers are forbidden from giving legal advice even if the advice is sound, *see, e.g.*, *People v. Alfani*, 125 N.E. 671, 673 (N.Y. 1919), and unlicensed laypersons may not provide medical diagnoses, regardless of their accuracy, *see, e.g.*, *Locke v. Ionia Circuit Judge*, 151 N.W. 623, 625 (Mich. 1915); *Commonwealth v. Jewelle*, 85 N.E. 858, 859 (Mass. 1908).

fair proxy for actual or intended large-scale manufacturing . . . .'") (emphasis added). The statute at issue in *Sorrell v. IMS Health Inc.*, 131 S. Ct. 2653 (2011), also targeted speech directly. *See id.* at 2660 ("Pharmaceutical manufacturers and pharmaceutical marketers shall not use prescriber-identifiable information for marketing or promoting a prescription drug unless the prescriber consents . . . .") (quoting Vt. Stat. Ann., Tit. 18, § 4631(d) (Supp. 2010)). By contrast, Caronia's conviction required a finding that Xyrem was intended by those responsible for its labeling for an off-label use—a finding which "may be shown by the circumstances that the article is, with the knowledge of such persons or their representatives, offered and used for a purpose for which it is neither labeled nor advertised." 21 C.F.R. § 201.128. *See generally* Krista Hessler Carver, *A Global View of the First Amendment Constraints on FDA*, 63 Food & Drug L.J. 151, 187–88 (2008).

Put another way, if the jury had concluded there was a reasonable doubt as to whether Caronia and Orphan actually intended to sell Xyrem to Caronia's customers—to introduce it into interstate commerce—then Caronia could not have been convicted under § 331(a), no matter what he said. By contrast, a pharmacy would violate the statute in *Western States* as soon as it advertised the compounding of particular drugs. *See* 535 U.S. at 364–65 (citing 21 U.S.C. § 353a(c)). Similarly, a Vermont pharmacy would violate the statute in *Sorrell* as

soon as it disseminated prescriber-identifying information for marketing purposes. *See* 131 S. Ct. at 2660. Speech alone was sufficient to trigger punishment under the challenged statutes in those cases. Speech alone is not, however, sufficient to sustain a conviction under 21 U.S.C. § 331(a).

My analysis here is not original. The D.C. Circuit reached the same conclusion in *Whitaker v. Thompson*, 353 F.3d 947, 953 (D.C. Cir. 2004),[6] in which a plaintiff argued that he had a First Amendment right to label his product with a drug claim despite its lack of FDA approval. The *Whitaker* court disagreed, reasoning that:

> Assuming that the government may condition the sale of drugs on passage through the elaborate testing that the statute requires . . . , the key step is the []FDCA principle that classification of a substance as a 'drug' turns on the nature of the claims advanced on its behalf. That principle, in turn, rests on the idea that claims about a product by its manufacturer and vendors, including product labeling, serve as evidence of the sellers' intent that consumers will purchase and use the product for a particular purpose—and, therefore, as evidence whether the product is or is not a drug. The question is whether this use of speech to infer intent, which in turn renders an otherwise permissible act unlawful, is constitutionally valid. In fact, the First Amendment allows 'the evidentiary use of speech to establish the elements of a crime or to prove motive or intent.' Thus it is constitutionally permissible for the FDA to use speech, in the form of labeling, to infer intent for purposes of determining that [the plaintiff's] proposed sale of saw palmetto extract would constitute the forbidden sale of an unapproved drug.

Id. (citations and paragraph breaks omitted). Caronia attempts to distinguish

[6] Then-Judge Roberts was a member of the unanimous panel.

Whitaker by arguing that "the drug itself in *Whitaker* could not be sold lawfully, and so there were no lawful off-label uses to promote." Appellant's Reply Br. at 15 (internal quotation marks and brackets omitted). But the product in *Whitaker*—"'saw palmetto,' an extract from the pulp and seed of the dwarf American palm," *Whitaker*, 353 F.3d at 948—could be sold lawfully so long as it was not a "drug," and whether it was a drug depended entirely upon the plaintiff's speech, as evidence of his intent, when he offered it for sale. That case is therefore indistinguishable from this case; indeed, even if the FDA had not approved Xyrem for any medical uses at all, Caronia could presumably have sold Xyrem as an industrial solvent if it happened to be excellent at removing grease and grime.

Not every prohibition on conduct undertaken with a certain intent is necessarily constitutional: the problem posed by a ban on "sending any leaflet with the intent to influence another's vote" suggests the limits on the analysis here. It remains the case, however, that the simple fact that one is generally allowed to sell something does not imbue one with a constitutional right to sell it for any intended purpose. And the prohibition here on distributing drugs with the intent that they be used for purposes not supported by their labeling is entirely consistent with the broader purposes of the FDCA—namely, minimizing those occasions on which patients use drugs that have not been shown to be safe

and effective.

III. Applying *Central Hudson* and *Sorrell*

Finally, even if using Caronia's speech as evidence of his intent was not *necessarily* constitutionally permissible—in other words, even if the protection afforded to commercial speech requires an analysis of this question where the customers of a product like Xyrem may lawfully use it for purposes not addressed in the label, and where the FDA does not purport to regulate the claims made by unrelated third parties about the efficacy of such uses, *see* George W. Evans & Arnold I. Friede, *The Food and Drug Administration's Regulation of Prescription Drug Manufacturer Speech: A First Amendment Analysis*, 58 Food & Drug L.J. 365, 390 (2003)—I believe the correct application of commercial speech principles requires us to uphold Caronia's conviction. I agree with the majority that our analysis is guided by *Central Hudson Gas & Electric Corp. v. Public Service Commission of New York*, 447 U.S. 557 (1980), and *Sorrell v. IMS Health Inc.*, 131 S. Ct. 2653 (2011). I conclude, however, that the FDCA's misbranding provision survives the scrutiny required by those cases because it directly advances a substantial government interest and is narrowly drawn to further that interest.

"[O]ne of the [FDCA]'s core objectives is to ensure that any product regulated by the FDA is safe and effective for its intended use." *Brown &*

Williamson, 529 U.S. at 133 (2000) (internal quotation marks omitted). The FDCA is meant to achieve this objective through a rigorous premarket approval process. *See* 21 U.S.C. § 355. Under this process, a manufacturer may not sell a drug without first providing proof to the FDA that the drug is "safe for use" and "effective in use." *See id.* § 355(b). There must be "substantial evidence," including evidence from clinical investigations, "that the drug will have the effect it purports or is represented to have." *Id.* § 355(d).

This process is a central, if not *the* central, feature of the FDCA. Prior to the passage of the FDCA, the government could combat misleading drug claims only through post-market enforcement actions. The 1938 Act's "most substantial innovation" was to require approval of a drug's safety before it could enter the market. *Wyeth*, 555 U.S. at 566. This innovation became even more important after Congress amended the FDCA in 1962 to also require premarket approval of a drug's effectiveness for its stated uses. *See* Drug Amendments of 1962, Pub. L. No. 87-781, § 102, 76 Stat. 780, 781. Behind the 1962 amendments were concerns that doctors could not adequately evaluate frequently misleading claims by drug manufacturers without a body of objective, reliable information. *See, e.g.*, Henry A. Waxman, *A History of Adverse Drug Experiences: Congress Had Ample Evidence to Support Restrictions on the Promotion of Prescription Drugs*, 58 Food & Drug L.J. 299, 301–08 (2003); Alan H. Kaplan, *Fifty Years of*

Drug Amendments Revisited, 50 Food & Drug L.J. 179, 184–85 (1995).

The Supreme Court has accordingly stated that "[p]reserving the effectiveness and integrity of the FDCA's new drug approval process is clearly an important governmental interest." *Western States*, 535 U.S. at 369. Given the benefits of premarket approval, "the Government has every reason to want as many drugs as possible to be subject to that approval process." *Id.*

The FDCA's prohibition on off-label marketing directly advances this interest. If 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. *Washington Legal Foundation v. Friedman*, 13 F. Supp. 2d 51, 72 (D.D.C. 1998), *vacated in part*, *Washington Legal Foundation v. Henney*, 202 F.3d 331 (D.C. Cir. 2000). And premarket approval improves drug safety and effectiveness only to the extent that drugs are not sold without such approval.

In concluding that prohibiting off-label promotion does not directly advance the government's interests, the majority places great weight on the fact that "physicians can prescribe, and patients can use, drugs for off-label purposes." Maj. Op. at 39. But this is also true for substances that have not been approved by the FDA for any medical use at all. The law generally permits

a hardware store to sell turpentine, and though such conduct may not be advisable, the law generally permits a consumer to purchase that turpentine and use it as a pain reliever. Under the majority's reasoning, then, any substance that may be legally sold for *some* purpose may be promoted by its manufacturer for *any* purpose—so long as the manufacturer's statements are merely unsubstantiated, rather than demonstrably false or misleading. But this reasoning would invalidate the very definitions of "drug" and "device" that undergird the entire FDCA.

The majority also emphasizes that the prohibition on off-label promotion applies only to a "particular class of speakers"— namely, drug manufacturers. Maj. Op. at 39. But drug manufacturers are the precise group that the government must encourage to participate in the new drug approval process. Indeed, if the prohibition applied to any broader class of speakers, it would likely fail *Central Hudson*'s fourth requirement that a regulation be "narrowly drawn." The Supreme Court's decision in *Sorrell* is thus inapposite in the present circumstances. The statute there did not directly advance Vermont's interest in protecting patient privacy because it applied to only a small subset of those groups that could possibly compromise patient privacy. *See* 131 S. Ct. at 2668. Drug manufacturers, in contrast, form the entirety of those speakers that could possibly undermine the new drug approval process by not participating in it.

Furthermore, allowing drug manufacturers to promote off-label uses would undermine the FDA's approval process for not only new uses of pre-approved drugs, but also for entirely new drugs. As explained above, when determining whether a drug should be approved, the FDCA requires consideration not only of the drug's safety, but also its effectiveness. *See* 21 U.S.C. § 355; *United States v. Rutherford*, 442 U.S. 544, 555 (1979) ("[T]he [FDA] Commissioner generally considers a drug safe when the expected therapeutic gain justifies the risk entailed by its use."). If a drug manufacturer must be allowed to distribute a drug for any use so long as it is approved for one use, the government's balancing of a drug's benefits against its risks becomes very difficult or even impossible. Drugs viewed as safe for certain uses might be considered unsafe overall if the benefits and risks being weighed are not for a specific intended use but rather for any use at all, whether supported by evidence or not.

The prohibition of off-label promotion is thus not simply a "paternalistic" attempt to shield physicians and patients from truthful information. *See* Maj. Op. at 40. Rather, it is a necessary tool for the effective functioning of a regulatory system that the Supreme Court has endorsed as legitimate. The majority implies that prohibiting off-label promotion is unconstitutionally "paternalistic" regardless whether the drug manufacturer's claims are addressed to a physician or to a patient. *See, e.g.*, Maj. Op. at 40 ("[P]rohibiting 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 . . . .") (emphasis added). But if drug manufacturers have a First Amendment right to distribute drugs for any use to physicians or even directly to patients, then the entire FDCA may well be unconstitutional.

Prohibiting off-label promotion by drug manufacturers is also the least restrictive way of advancing the government's interests. Although the majority asserts various alternatives, none would be similarly effective. A disclaimer system or required listing of intended uses would provide manufacturers much less incentive to submit their drugs for FDA approval, and in turn encourage promotion based on data much less reliable than the clinical investigations required under 21 U.S.C. § 355(d).[7] A ceiling on off-label prescriptions would require collecting data from countless numbers of doctors and patients and, given the medical uncertainties involved, could needlessly (and simultaneously) result in the denial of some effective treatments and the overprescription of

[7]Indeed, experts have concluded that most prescriptions for off-label use have little or no scientific support. *See* Randall S. Stafford, *Regulating Off-Label Drug Use: Rethinking the Role of the FDA*, 358 New Eng. J. Med. 1427, 1427 (2008) ("In an examination of off-label prescribing of 160 common drugs, off-label use was . . . found to account for 21% of all prescriptions, and most off-label drug uses (73%) were shown to have little or no scientific support.") (citing David C. Radley, Stan N. Finkelstein & Randall S. Stafford, *Off-Label Prescribing Among Office-Based Physicians*, 166 Archives of Internal Med. 1021 (2006)).

ineffective and even dangerous ones. Finally, a ban on off-label prescriptions would be no better. Indeed, it would constitute an unprecedented intrusion into the practice of medicine, and would result in perhaps an even greater restriction on speech. *See Central Hudson*, 447 U.S. at 563–64 (government free to ban "commercial speech related to illegal activity"). And again, because a product's very definition as a "drug" depends upon its intended use (which is often established by the manufacturer's speech), it is unclear why the majority's less-restrictive-alternatives analysis is not equally applicable to the FDCA's entire scheme of drug regulation.

That the FDCA is both "content- and speaker-based" within the meaning of *Sorrell*, 131 S. Ct. at 2663, does not alter the foregoing analysis. *Every* commercial speech case, by its very nature, involves both content- and speaker-based speech restrictions. *See Va. State Bd. of Pharmacy v. Va. Citizens Consumer Council, Inc.*, 425 U.S. 748, 761 (1976) ("If there is a kind of commercial speech . . . it must be distinguished by its content."). Yet the Supreme Court has long acknowledged—and acknowledged again in *Sorrell*—that "the government's legitimate interest in protecting consumers from commercial harms explains why commercial speech can be subject to greater governmental regulation than noncommercial speech." *Sorrell*, 131 S. Ct. at 2672 (internal quotation marks omitted). Indeed, the Supreme Court struck

down the ban on energy advertising in *Central Hudson* because a *content-based* less-restrictive alternative existed. *See Cent. Hudson*, 447 U.S. at 571 ("[T]he Commission could attempt to restrict the format and content of Central Hudson's advertising. It might, for example, require that the advertisements include information about the relative efficiency and expense of the offered service, both under the current conditions and for the foreseeable future."). *Sorrell* did not purport to overrule the *Central Hudson* test, which has guided First Amendment doctrine in this area for thirty years.

Moreover, in *Sorrell* the Court noted that Vermont did not argue that its challenged statute "will prevent false or misleading speech." 131 S. Ct. at 2672. Rather, Vermont's "interest in burdening the speech of detailers instead turn[ed] on nothing more than a difference of opinion." *Id.* In contrast, Congress intended the FDA approval process to prevent dangerous products with false or misleading labels from entering the market, and also to provide a base of reliable, objective information about prescription drugs that could help physicians and patients identify potentially misleading claims. Clearly this is the type of statute to which *Sorrell* intended that *Central Hudson* would still apply.[8]

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[8]Nor does the fact that 21 U.S.C. § 331(a) applies criminal penalties necessarily mean that it warrants heightened scrutiny. The case that the majority cites for this proposition, *Holder v. Humanitarian Law Project*, did not premise its application of

It is certainly true that "the 'fear that people would make bad decisions if given truthful information' cannot justify content-based burdens on speech." *Sorrell*, 131 S. Ct. at 2670–71 (quoting *Thompson*, 535 U.S. at 374). But this does not mean that conveying non-demonstrably false information to consumers must take precedence over all competing government interests. Our system of drug regulation developed to protect consumers from misleading and unsubstantiated claims about drugs' safety and efficacy, and the prohibition on off-label promotion by drug manufacturers is essential to maintaining the effectiveness of that system. Therefore, even if such a prohibition is considered a direct regulation of speech, it is a regulation that directly advances a substantial government interest in a manner not more extensive than necessary to serve that interest. I would thus find it constitutional under *Central Hudson* and *Sorrell*.

IV. The Verdict Sheet and the Jury's Verdict

Because I believe that the FDCA's misbranding provision may constitutionally be applied to Caronia's conduct, I next address Caronia's

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heightened scrutiny on the statute's criminal penalties. *See* 130 S. Ct. 2705, 2724 (2010). Moreover, the Supreme Court has previously applied *Central Hudson* to statutes that provide for or trigger criminal punishment for speech. *See Greater New Orleans Broad. Ass'n, Inc. v. United States*, 527 U.S. 173, 177 (1999); *44 Liquormart, Inc. v. Rhode Island*, 517 U.S. 484, 490 n.3 (1996); *Bolger v. Youngs Drug Products Corp.*, 463 U.S. 60, 61–62 (1983).

remaining arguments: (1) that the district court erred in breaking down the conspiracy charge on the verdict sheet into two subissues; and (2) that the jury rendered an inconsistent verdict by convicting Caronia of conspiring to introduce or deliver for introduction into interstate commerce a misbranded drug while finding him not guilty of conspiring to do an act to a drug that would result in it being misbranded.

The first count of a two-count information charged Caronia with conspiring both (1) to introduce into interstate commerce a drug that was misbranded and (2) to do an act with respect to a drug that would result in that drug being misbranded.[9] With respect to that count, the district court submitted a two-part verdict sheet to the jury which asked:

> 1. How do you find the defendant, ALFRED CARONIA, on Count One of the Information?
>
> (a) Conspiracy to introduce or deliver for introduction into interstate commerce a drug, Xyrem, that was misbranded?
>
> NOT GUILTY _____ GUILTY _____
>
> (b) Conspiracy to do an act with respect to a drug, Xyrem, when such drug was held for sale after shipment in interstate commerce when such act would result in Xyrem being misbranded?
>
> NOT GUILTY _____ GUILTY _____

The jury concluded that Caronia was guilty with respect to question (a) and not guilty with respect to question (b).

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[9] The second count charged Caronia with doing an act with respect to a drug that resulted in that drug being misbranded.

Caronia argues that the district court erred by subdividing the conspiracy charge on the verdict sheet because, he claims, the district court essentially split the charge into two separate counts. But we have held that a conspiracy charge may allege an agreement to commit more than one offense, *see United States v. Coriaty*, 300 F.3d 244, 250 (2d Cir. 2002) ("We have upheld convictions for multi-object conspiracies charged in the conjunctive even when there was insufficient evidence to support one of the objects of the conspiracy."), and that a district court does not impermissibly constructively amend a charge by subdividing an offense into parts, *see United States v. McCourty*, 562 F.3d 458, 470 (2d Cir. 2009) ("No constructive amendment resulted when the District Court broke the single offense into two parts to be addressed by the jury."). I therefore find no error in the verdict sheet.

Caronia further argues that the jury rendered an inconsistent verdict by finding him not guilty of conspiring to do an act to a drug that would result in it being misbranded while finding him guilty of conspiring to introduce or deliver for introduction into interstate commerce a misbranded drug. But these verdicts were not inconsistent—for example, the jury may have concluded that the drug was not being held for sale after shipment in interstate commerce. And even assuming the verdicts were inconsistent, "the convicted defendant's protection against an irrational verdict is his ability to have the courts review the

sufficiency of the evidence to support his conviction," *United States v. Acosta*, 17 F.3d 538, 545 (2d Cir. 1994). There was ample evidence for a reasonable jury to conclude beyond a reasonable doubt that Caronia conspired to introduce or deliver for introduction into interstate commerce a misbranded drug. Indeed, Caronia was caught on tape with Dr. Gleeson suggesting off-label uses of Xyrem to doctors. I therefore see no error in the verdict sheet and no inconsistency requiring reversal or vacatur in the jury's verdict.

* * *

The majority has chosen to apply heightened scrutiny to this case, though we have not done so in other cases involving the use of speech as evidence of intent—for example, in antidiscrimination actions or prosecutions for criminal inducement, attempt, and conspiracy—cases I cannot meaningfully distinguish from this one. The majority's decision today extends heightened scrutiny further than the Supreme Court ever has, and calls into question a fundamental regime of federal regulation that has existed for more than a century. I respectfully dissent.