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The First Amendment And Off-Label Promotion: Why The Court In *United States V. Caronia* Got It Wrong

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I. INTRODUCTION

The tension between the First Amendment and the United States Food and Drug Administration ("FDA") claims of protecting public safety recently came to a head in Brooklyn, New York when the district court denied a pharmaceutical sales representative's motion to dismiss charges of "off label" promotion.²

In *United States v. Caronia*, the United States charged Alfred Caronia ("Caronia"), a sales representative for a pharmaceutical manufacturer, with violating Sections 331(a) and (k) of the Food, Drug and Cosmetic Act (the "FDCA"). Sections 331(a) and (k) prohibit the introduction or causing the introduction into interstate commerce of any misbranded drug. Judge Vitaliano denied Caronia's argument that Sections 331(a) and (k) of the FDCA violated the First Amendment of the United States Constitution by restricting Caronia's freedom of speech. *Caronia* comes on the heels of the 2007 criminal conviction of two business executives of a medical device manufacturer in Illinois for misbranding. In fact, the past two decades have seen a flurry of enforcement activity surrounding pharmaceutical companies promotion of their drugs for uses other than those approved by the FDA – so called "off label" uses.³

However, the FDA's attempts to regulate manufacturers' speech to promote their products has increasingly been subject to constitutional scrutiny. Over the past decade several courts have been asked to consider whether various FDA statutes and regulations prohibiting off-label promotion violate the Free Speech Clause of the First Amendment.⁴ Of the courts who

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² *United States of America v. Alfred Caronia*, 576 F. Supp.2d 385 (E.D.N.Y. 2008).

³ For example, on January 15, 2009 Eli Lilly and Company agreed to pay a \$800 million civil settlement for its off label promotional activities concerning its drug Zyprexa.

⁴ See e.g. *Washington Legal Foundation v. Friedman*, 13 F. Supp.2d 51 (D.D.C. 1998) (holding that the FDA guidance restricting dissemination of reprints and medical articles discussing off-label uses of drugs violated the First Amendment as unconstitutional restriction on commercial speech); *Thompson v. Western States Medical Center*, 535 U.S. 357 (2002) (holding that it was improper for Congress and the Food and Drug Administration to

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have considered the issue, most have found or implied that Free Speech protections trumped the FDA's interest in protecting its new-drug approval process. In contrast, Judge Vitaliano held in Caronia that the FDA's interest in protecting the public health outweighed Caronia's constitutionally protected right to freedom of speech even though (1) the underlying behavior Caronia sought to promote (i.e. physician prescribing for off-label uses) was not itself illegal and (2) the information he provided was neither false nor misleading.

II. BACKGROUND: THE FDA REGULATORY FRAMEWORK AND ITS UNANTICIPATED PROGENY, THE PHARMACEUTICAL SALES “WEB”

In order to understand the issues presented in the Caronia case, it is important to understand the FDA's regulatory framework. The FDA, after reviewing the clinical data submitted by a pharmaceutical company or drug manufacturer, evaluates whether a “new drug” is safe and effective for its proposed uses. Absent a finding that the “new drug” meets those criteria, the sponsor of the “new drug” cannot market or distribute the drug in the United States.

The process of getting a drug approved by the FDA – the investigational new drug (“IND”) process – is costly and time-consuming. The IND process typically has three separate phases. “Phase I” trials, evaluate the safety of the medication by studying the effect of the drug and are designed to determine the metabolic and pharmacologic actions of the drug in humans, the side effects associated with increasing doses, and, if possible, to gain early evidence on effectiveness. “Phase II” trials are designed to obtain preliminary data on the effectiveness of the drug for a particular indication or indications in patients with the disease or condition. “Phase III” trials, are intended to gather additional information about effectiveness and safety that is needed to evaluate the overall benefit-risk relationship of the drug.⁵ Many drugs, like chemotherapy for an example, have deeply deleterious – sometimes even fatal – side effects, and part of the FDA approval process is weighing the potentiality for those side effects against the disease process the drug is designed to treat. The sponsor's goal at the end of the IND process is an approved New Drug Application (“NDA”).⁶

The FDCA generally prohibits manufacturers of new drugs or new devices from distributing products in interstate commerce for any use not set forth in the approved NDA.⁷ Nevertheless, once an approved NDA exists, a healthcare professional may lawfully use or prescribe that product for any use, within the limits set by professional standards of practice,

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bar the advertising of “compounded” drugs.); and United States v. Caputo, 517 F.3d 935 (7th Cir. 2008)(stating in dicta that some parts of the FDCA relating to off-label promotion may be unconstitutional at least as applied in some circumstances).

⁵ See the CDER Handbook: <http://www.fda.gov/cder/handbook/>.

⁶ Similar procedures and restrictions apply to biologics. See 42 U.S.C. § 262. In the case of biologics, the sponsor must obtain a biologics license or approved BLA. *Id.* However, the same restrictions on off-label promotion apply. *Id.* For purposes of this article, the term “drug” includes an approved biologic.

⁷ 21 U.S.C. §§ 355, 352(o), 351(f)1(B), 331(a) and (d).

including off-label uses not set forth in the approved NDA.⁸ For some conditions, an off-label use of a medication may reflect the standard of care.⁹ Therefore, in many cases health insurers, including the federal government, will pay for off-label treatments.¹⁰ However, under FDA regulations, if the sponsor wants to market or promote the “new drug” for an off-label use, then the FDA requires separate approval by the FDA through the filing, for example, of a NDA deviation.¹¹ Consequently, while physicians may prescribe an approved drug for any purpose, sponsors may only market their drugs for uses set forth in the approved NDA.

In order to ensure that sponsors do not market their drugs for unapproved uses, the FDA controls sponsors’ promotional activities through an intricate series of regulations and statutes. Under the FDCA it is illegal to directly or indirectly distribute a product in interstate commerce that is “adulterated” or “misbranded”.¹² The statute further mandates that an approved drug that is marketed for an unapproved use (whether in labeling or in another manner) is “misbranded” because the labeling of such drug does not include “adequate directions for use”.¹³ A drug is “adulterated” if its labeling includes information regarding a use that the FDA has not approved.¹⁴ Furthermore, the FDA regulations also provide “[a]n advertisement for a prescription drug ... shall not be recommended or suggest any use that is not in the labeling accepted in such approved new-drug application or supplement.”¹⁵ The FDA interprets “advertisement” “to include information other than labeling that originates from the same source as the product and that is intended to supplement or explain the product.”¹⁶ Consequently, in addition to drug labeling, the FDA considers manufacturer speech concerning its products subject to its regulatory prohibitions on off-label promotion.

Pharmaceutical sponsors of approved drugs engage in standard advertising techniques, including mailing sales brochures to physicians and their offices, giving out “free samples” to prescribing physicians and putting advertisements in medical journals.^{17 18} But they also

⁸ *Guidance for Industry on 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; Availability*, 74 F.R. 1694 (January 13, 2009) (the “Good Reprint Practices Guidelines”). The Good Reprint Practices Guidelines are available at <http://www.fda.gov/cder/guidance/> (January 2009). Good Reprint Practices Guidelines at page 2.

⁹ 74 F.R. 2881, 2882 (January 16, 2009).

¹⁰ *Id.*

¹¹ *See generally* 21 C.F.R. Pt. 312.

¹² 21 U.S.C. §§ 351, 352 (2002).

¹³ 21 U.S.C. § 352(f). A drug that is marketed to the public for an off-label indication or use does not contain “adequate directions for use” because such use and related information were not included in the FDA-approved labeling for the drug.

¹⁴ 21 U.S.C. § 351.

¹⁵ 21 C.F.R. § 202.1(e)(i)(a).

¹⁶ Final Guidance on Industry-Supported Scientific and Educational Activities, 62 F.R. 64,074, 64,076 (Dec. 3, 1997).

¹⁷ Much has been made of recent increases in so-called “direct-to-consumer” advertising by pharmaceutical companies and its effect on the “learned intermediary doctrine.” The relationship between that phenomenon and the recent changes in marketing to physicians is not explored in this article.

¹⁸ *See, e.g.,* Kemper and Hood, *Does Pharmaceutical advertising affect journal publication about dietary supplements?*, BMC Complementary and Alternative Medicine, V. 4 (April 9, 2008).

maintain a network of sales representatives that utilize sophisticated technology, including data-mining and personal interviews, to monitor individual physicians' prescribing habits and target those physicians that they believe are under-utilizing their product or utilizing a competitor product instead.¹⁹ A fine line often exists between some pharmaceutical companies' marketing and research activities. Pharmaceutical companies often hire scientists and physicians, sometimes from high-profile academic institutions, to conduct or present the latest research about their products, or lead physician groups dedicated to creating standard uses of medications for particular conditions or diagnoses.²⁰

As applied, then, the already-convoluted FDA regulatory framework is even more byzantine. The FDA regulations do not (and could not, without severely impinging on the basic tenets of academic freedom) prohibit a physician from engaging in research, nor from presenting another's research to a group of physicians. Instead, the FDA's rules require a veritable soft shoe to comply with rules and requirements that require different behavior and limitations depending on who is speaking; to whom one is speaking; whether the speech is accompanied by an article; whether the article provided was published in a peer-reviewed journal; not to mention the regulations that cover the context of the speech and treat it differently depending on whether it is spoken in a waiting room or at a conference table with sandwiches.²¹

III. THE FACTS OF CARONIA'S CASE

Orphan Medical, Inc. ("Orphan"), now known as Jazz Pharmaceuticals, is a specialty pharmaceutical company focused on identifying, developing, and commercializing products to treat pain, sleep disorders and central nervous system disorders.²² One such drug was Xyrem, a sleep inducing depressant, whose principal ingredient was gamma-hydroxybutyrate ("GHB"). Xyrem was first approved by the FDA in July 2002 to treat patients with narcolepsy who experience episodes of cataplexy, a condition associated with weak and paralyzed muscles.²³ In November 2005, the FDA approved Xyrem to treat excessive daytime sleepiness ("EDS") in patients with narcolepsy. Xyrem is not approved for any other medical indications.

Abuse of Xyrem can lead to dependence and withdrawal symptoms as well as medical problems including seizures, coma, and death. Due to the FDA's concerns over Xyrem's potential serious risks, the FDA required, prior to approval, that Xyrem's label include a "black box" warning.²⁴ In addition, distribution of Xyrem was restricted and subject to several

¹⁹ See Carlat, *Dr. Drug Rep*, The New York Times, November 25, 2007; however, the United States Department of Justice and the Office of Inspector General, United States Department of Health and Human Services is taking a close look at these practices. See *Prosecutors Plan Crackdown on Doctors Who Accept Kickbacks*, The New York Times, March 4, 2009.

²⁰ *Id.*

²¹ See generally, the Food and Drug Administration Modernization Act of 1997 and the PhRMA Code of Conduct (January 2009).

²² *United States v. Caronia*, Superseding Indictment (Jul 25, 2007) at ¶1.

²³ *Id.* at ¶2.

²⁴ A black box warning (also sometimes called a black label warning or boxed warning) is a type of warning that appears on the package insert for prescription drugs that may cause serious adverse effects. A black box warning

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conditions. For example, Orphan only distributed it through a single, centralized pharmacy, was required to provide physician and patient education, maintain a physician and patient registry, track prescription usage and detail patient surveillance.

In April 2005 the FDA's Office of Criminal Investigations, Special Prosecutions Staff, opened a criminal investigation of alleged off-label promotion of Xyrem. As part of its investigation, the government used a physician as an undercover cooperating witness to determine if the allegations were true. The government charged that on October 26, 2005, Caronia promoted several off-label uses of Xyrem including fibromyalgia, EDS, muscle disorders, chronic pain and fatigue to its undercover witness.²⁵ The government further alleged that, on November 2, 2005, Caronia introduced to the undercover witness another Orphan-paid physician who also promoted Xyrem for off-label indications, including fibromyalgia, EDS, sleepiness, weight loss and chronic fatigue.²⁶

Pursuant to its misbranding regulations, the U.S. government filed a two-count misdemeanor information against Caronia.²⁷ Count one of alleged that, between March 2005 and March 2006, Caronia knowingly and intentionally conspired with others to misbrand a drug by marketing Xyrem for off-label uses in violation of 21 U.S.C. §§ 331(a), (k), 333(a)(1) and 18 U.S.C. § 371. Count two charged Caronia with a substantive violation of misbranding a drug while it was held for sale after shipment in interstate commerce, violating 21 U.S.C. §§ 331(k) and 333(a)(1).

Caronia moved to dismiss on several bases, including that the misbranding provisions of the FDCA violated the Free Speech Clause of the First Amendment.²⁸ The *Caronia* Court quickly rejected Caronia's first two arguments in support of his motion to dismiss.²⁹ But, the Court spent considerable analysis on Caronia's First Amendment argument as the constitutional

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means that medical studies indicate that the drug carries a significant risk of serious or even life-threatening adverse effects. 21 C.F.R. § 201.57(c)(1).

²⁵ United States v. Caronia, Superseding Indictment at ¶12 and 24(e).

²⁶ *Id.* at ¶24(f)

²⁷ On July 13, 2007, Orphan plead guilty to felony misbranding in connection with the off-label promotion of Xyrem and agreed to pay more than \$20 million in fines.

²⁸ Caronia at 393.

²⁹ First, Caronia argued that the allegations in the indictment actually establish that he did not misbrand Xyrem within the meaning of 21 U.S.C. §331(k) because he administered adequate warnings to the cooperating witness physician. Caronia claims that regardless for what purpose Xyrem is prescribed, it is administered in the same manner and dosage, and therefore the black box warning satisfied the FDCA's branding requirements. The Court rejected this argument as "utterly without merit" based on the FDCA's "intended use" regulations, which prohibit off-label promotion of a drug regardless of what directions the manufacturer or representative provided for that use. The court also rejected Caronia's argument that, even accepting the factual allegations of the information as true, he did not conspire to misbrand Xyrem under either 21 U.S.C. § 331(a) or (k), because the cooperating witness physician never had any intention of prescribing Xyrem for off-label use. The Court rejected this argument because 21 U.S.C. §331(k) only requires the Government to prove that the defendant took some action with respect to the drug that resulted in the drug being misbranded not that the drug was actually used for an off-label purpose. Caronia, 576 F.Supp.2d at 391-93.

issues raised by Caronia were “very much unsettled, not only in this circuit but nationwide.”³⁰ Essentially, Caronia argued that the government cannot restrict truthful, non-misleading promotion by a pharmaceutical representative to a physician of the off-label uses of an FDA-approved drug.³¹ He pointed out the legal inconsistency that prohibits a pharmaceutical manufacturer from promoting off-label uses to physicians and consumers, yet permits physicians to prescribe drugs for an off-label purpose, regardless of whether that purpose has been approved by the FDA.³²

After noting a recent trend among court decisions holding that the FDA’s off-label marketing restrictions were unconstitutional restrictions on commercial speech under the First Amendment, the Court rejected Caronia’s argument, instead finding that, in this case, the FDCA’s prohibition against off label promotion was a reasonable fit for the government’s interest in protecting the public health.³³ A careful analysis of the opinion is warranted.

IV. THE CARONIA COURT’S OPINION

The First Amendment prohibits certain restrictions on freedom of speech. However, not all types of speech are afforded the same level of protection. Thus, the Caronia court first analyzed what category of speech Caronia’s promotional statements fell within.³⁴ Applying the three factor test set forth in Bolger v. Young Drug Products Corp. the Court determined that Caronia’s statements were considered commercial speech because (1) the statements were an advertisement, (2) the statements referred to a specific product (i.e. Xyrem) and (3) Caronia had an economic motive when he made the statements.³⁵ Since the Court determined that Caronia’s statements were commercial speech, it applied the United States Supreme Court’s Central Hudson test to determine if Caronia’s statements were protected by the First Amendment.³⁶

When applying the Central Hudson test, a court must determine as a threshold matter whether the commercial speech concerns unlawful activity or is misleading.³⁷ If the statements in question are found to be unlawful or misleading, then they are not protected by the First Amendment and the inquiry stops.³⁸ Relying on Washington Legal Foundation line of cases, the Caronia court concluded that the promotion of off-label uses of FDA approved drugs is not unlawful or misleading.³⁹ Since physicians may lawfully prescribe drugs for off-label uses, the

³⁰ Caronia, 576 F.Supp.2d at 394.

³¹ *Id.* at 393.

³² *Id.*

³³ *Id.* at 401.

³⁴ *Id.* at 396.

³⁵ Bolger v. Young Drug Products Corp., 463 U.S. 60, 66-68 (1983). It appears from the Opinion that Caronia conceded that his statements were “commercial speech” rather than “pure speech”, which is afforded the highest level of First Amendment protection. However, there is an argument that “off-label speech, which often takes the form of scientific journal articles and academic presentations, should be considered scientific [i.e. pure] speech, even when uttered by manufacturers.” Joseph Leghorn, Elizabeth Brophy, & Peter V. Rother, *The First Amendment and FDA Restrictions On Off-Label Uses: The Call For A New Approach*, 63 Food & Drug L.J. 391, 397-400, (2008).

³⁶ Central Hudson Gas v. Public Service Commission of New York, 447 U.S. 557 (1980).

³⁷ Caronia, 576 F.Supp.2d at 396-397.

³⁸ *Id.*

³⁹ *Id.* at 397, citing Washington Legal Foundation v. Friedman, 13 F. Supp.2d 51 (D.D.C. 1998).

Caronia court found that Caronia’s statements concerning off-label uses of Xyrem were not illegal.⁴⁰ The Court further held that Caronia’s statements were not inherently misleading “simply because the use is off-label.”⁴¹ Rather the test is whether the statements are more likely to deceive the public than to inform it.⁴² The Court noted that Caronia’s statements were made to a physician familiar with the FDA drug-approval process and since the government did not assert that Caronia claimed that the uses he was promoting Zyrem for were FDA approved, Caronia’s statements were not inherently misleading.⁴³

The second prong of the Central Hudson test requires the court to evaluate whether the asserted government interest is substantial.⁴⁴ Consistent with recent case law, the Caronia court quickly concluded that “the government had a substantial interest in promoting the health and safety of its citizens ... and in furtherance of that objective, the government had a substantial interest in compelling manufacturers to get off-label treatments on-label.”⁴⁵ While acknowledging that the Supreme Court held that a “paternalistic assumption that the public will use truthful, non-misleading commercial information unwisely cannot justify a decision to suppress” the information, the Caronia court still found that this did not diminish the government’s substantial interest in subjecting off-label uses of drugs to the FDA evaluation process.⁴⁶

After determining the government had a substantial interest in requiring off-label uses of drugs be submitted to the FDA evaluation process, the court next considered whether restricting manufacturer’s promotion of off-label uses directly advances this interest.⁴⁷ Relying on the Washington Legal Foundation and Caputo court opinions, the court found that “one of the few mechanisms available to the FDA to compel manufacturer behavior is to constrain their marketing options; i.e. control the labeling, advertising, and marketing.”⁴⁸ Accordingly, the court held “that the FDCA’s prohibitions on commercial speech of the kind charged in the information filed against Caronia directly advance the government’s interest in subjecting off-label uses of a drug like Xyrem to the FDA’s evaluation process.”⁴⁹

Finally, the Caronia court considered the fourth prong of the Central Hudson analysis—the “reasonable fit” test; however at this stage of its analysis the Court distinguished the

⁴⁰ *Id.* at 397. As far back as 1972 the FDA conceded that “[o]nce a new drug is in a local pharmacy ... the physician may, as part of the practice of medicine, lawfully ... vary the conditions of use from those approved in the package insert, without informing or obtaining the approval of the Food and Drug Administration.” 37 F.R. 16,503 (August 15 1972). The FDCA also make clear “[n]othing in this chapter shall be construed to limit or interfere with the authority of a healthcare practitioner to prescribe or administer any legally marketed device to a patient for any condition or disease ...” 21 U.S.C. § 396.

⁴¹ *Id.*

⁴² *Id.*

⁴³ *Id.*, quoting United States v. Caputo, 288 F.Supp.2d 912,921 (N.D. Ill. 2003).

⁴⁴ Central Hudson, 447 U.S. 557, 564.

⁴⁵ Caronia 576 F.Supp.2d at 398. See also Washington Legal Foundation, 13 F.Supp.2d at 69-71.

⁴⁶ *Id.*

⁴⁷ *Id.*

⁴⁸ *Id.* citing Washington Legal Foundation, 13 F.Supp.2d at 72.

⁴⁹ *Id.*

Washington Legal Foundation cases it had relied on for much of its analysis.⁵⁰ The Caronia Court also distinguished Thompson v. Western States Medical Center, in which the Supreme Court declared unconstitutional a ban on advertising for compounded drugs because it failed to satisfy the fourth prong of the Central Hudson test.⁵¹ In contrast to Washington Legal Foundation and Western States, the court in Caronia held that the FDA’s restriction on off-label speech were not more extensive than necessary to serve their purpose and therefore satisfied the Central Hudson test.⁵² Distinguishing the Washington Legal Foundation and Caputo opinions, the court reasoned that Caronia’s First Amendment challenge “strikes at the FDA’s ability to proscribe manufacturer promotion of off-label use.”⁵³ Accordingly, the Caronia Court reasoned that the FDCA misbranding provisions were one of the few mechanisms available to the FDA to ensure manufacturers would not seek approval for certain limited uses of drugs and then promote those same drugs for off-label uses.⁵⁴ The Caronia Court noted the fact that the “FDA retained some control over manufacturer marketing of off-label uses through the FDCA’s misbranding provisions ... was crucial to” the court’s determination in Washington Legal Foundation “that the FDA guidances restricting manufacturer sponsorship of seminars and distribution of “enduring materials” was more extensive than necessary.”⁵⁵

Consequently, the Caronia court determined that “[u]ndermin[ing] the delicate balance between ensuring the integrity of the new drug approval process while allowing patients ... to have unfettered access to new and potentially life-saving uses for drugs and devices approved for other purposes” could “very well leave the FDA only with options that would injure that very audience that would purportedly benefit most from the speech at issue.”⁵⁶ Particularly, since the court was “unable to identify non-speech restrictions that would likely constrain in any effective way manufacturers from circumventing the approval process.”⁵⁷ As a result the Caronia court held that the misbranding statute met all the elements of the Central Hudson test and did not unconstitutionally restrict Caronia’s right to truthfully promote Xyrem’s off-label uses.⁵⁸

V. ANALYSIS

The Caronia court purported to address whether to strike as unconstitutional any prohibition of a manufacturer’s truthful promotion of off-label prescription drug usage. However, in its opinion the Court accepted that FDA’s current approach to off-label promotion “appear[s] essential to maintaining the integrity of the FDA’s new drug approval process.”⁵⁹ Furthermore, the Court failed to scrutinize the FDCA’s statutory scheme governing the approval

⁵⁰ *Id.* at 399. In Washington Legal Foundation, the court declared unconstitutional the FDA’s guidance documents on continuing medical education and the dissemination of reprints from peer reviewed journals because the guidance documents were more extensive than necessary to achieve the government’s interests and less burdensome alternatives were available.

⁵¹ *Id.* citing Thompson v. Western States Medical Center, 535 U.S. 357 (2002).

⁵² Caronia, 576 F.Supp.2d at 401.

⁵³ *Id.*

⁵⁴ *Id.*

⁵⁵ *Id.*

⁵⁶ *Id.*

⁵⁷ *Id.*

⁵⁸ *Id.* at 402.

⁵⁹ *Id.* at 401.

of and dissemination of information about approved drugs (including the types of off label information that may be lawfully disseminated under the FDCA.)

A. The FDA’s Misbranding Provisions Violate Constitutional Free Speech Protections Because They Are Paternalistic

A review of the FDCA statutory scheme, the government’s conflicting policies and recent case law related to off-label use of drugs illustrates the flaws in Judge Vitaliano’s analysis. First, Judge Vitaliano failed to even consider whether the FDA’s prohibition of off-label usage is innately paternalistic. The Supreme Court has already reinforced its strong First Amendment protection for commercial speech by striking down a federal law regulating a category of drug advertising. In Western States, a case Judge Vitaliano characterized as analogous to Caronia, the Supreme Court “analyzed pharmaceutical advertising of compounded drugs that were not FDA approved, but could be lawfully sold by pharmacists, as protected commercial speech and stifled FDA efforts to restrict it.”⁶⁰ The Supreme Court specifically rejected the notion that the government has an interest in preventing the dissemination of truthful commercial information in order to prevent members of the public from making unwise decisions based on the information.⁶¹ In its opinion, the Supreme Court stated that “[t]he 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.”⁶² In reviewing the history of the court’s commercial-speech decisions, Justice O’Connor observed that the Supreme Court has recognized that “[i]t is a matter of public interest that [economic] decisions, in the aggregate, be intelligent and well-informed. To this end, the free flow of commercial information is indispensable.”⁶³ Thus, if mistrust of how the public will use the information is the basis of the speech restriction, courts are required to strike it down.⁶⁴

The FDA has consistently argued that its restrictions on off-label promotion of drugs are necessary to ensure that new uses for drugs are evaluated through its drug approval process. The FDA’s reasoning is that without such approval the public may be subject to dangerous or ineffective drugs. Commercial free speech is only protected when it conveys truthful, non-misleading information. Thus, inherent in the FDA’s argument is that it believes that the public may make bad decisions when faced with truthful, non-misleading information concerning off-label uses for drugs. This paternalistic basis is not a constitutionally accepted basis for restricting free speech. This is even more true when the recipient of the information is a sophisticated listener, such as a physician, who is trained in the use of such information and can lawfully prescribe drugs for off-label use. Yet, the Caronia court failed to even consider whether the FDA’s basis for its commercial speech restrictions were paternalistic and instead blithely

⁶⁰ *Id.* at 395, *citing* Western States, 535 U.S. at 366.

⁶¹ Western States, 535 U.S. at 374, *citing* Virginia Bd. of Pharmacy v. Virginia Citizens Consumer Council, Inc., 425 U.S. 748 (1976).

⁶² *Id.* at 375, *citing* Liquormart, Inc. v. Rhode Island, 517 U.S. 484, 503 (1976).

⁶³ *Id.* at 366, *quoting* Virginia Bd. of Pharmacy, 425 U.S. at 765.

⁶⁴ After the Supreme Court’s decision in Western States even the FDA has concerns as to whether its current regime restricting manufacturer’s speech promoting off-label use could withstand a First Amendment challenge. A concern that prompted the FDA to call for public comments on First Amendment issues. 67 F.R. 34942 (May 8, 2002). Over 700 comments were received and while the FDA has posted the comments on its website, it has not formally responded to the comments.

accepted the FDA’s proposition that its restrictions on manufacturer’s off-label promotion was essential to preserve the FDA’s new drug approval process.

B. The FDA’s Misbranding Provisions Violate Constitutional Free Speech Protections Because They Cannot Pass the Central Hudson Test

Even if the FDA’s regulatory scheme is not paternalistic it should have failed constitutional review under the Central Hudson test. The Supreme Court articulated a three part test to determine the validity of restrictions on commercial speech.⁶⁵ The Central Hudson test requires courts to strike laws and any other restrictions on the dissemination of truthful, non-misleading information unless the government can show (i) a substantial interest in restricting the speech; (ii) that the restriction directly advances the interest; and (iii) that the restriction is no more extensive than is necessary to serve that interest. The Supreme Court in Western States found that “preserving the effectiveness and integrity of the FDCA’s new drug approval process is clearly an important government interest, and the government has every reason to want as many drugs as possible to be subject to that approval process” in order to protect the public health.⁶⁶ Thus, subsequent case law addressing FDA restrictions on speech have focused on balancing these interests with free speech concerns.

While historically the FDA has claimed the balance of public policy concerns falls on its side in justifying its misbranding provisions, surely there is also a substantial interest in providing open access to available data about unapproved uses for drugs because it results in more informed and therefore safer medical decision making.⁶⁷ Although the government has only recently begun to study the “effectiveness” of the various healthcare treatments for which it pays,⁶⁸ much of the literature discussing the continuing quest for good quality healthcare has described the benefits of so-called “front-end” or “cutting edge” care that makes use of emerging or aggressive treatments, not all of which have already obtained FDA approval.⁶⁹ In other words, to a certain extent, the provision of “quality” health care depends on physicians’ ability to utilize “off-label” treatments. Therefore, there are compelling reasons to keep physicians apprised of the newest use of drugs even if they are not FDA approved and even if that information is conveyed by a manufacturer.

Furthermore, the “directness” requirement of the Central Hudson test, means that a “regulation may not be sustained if it provides only ineffective or remote support for the government’s purpose.”⁷⁰ The Caronia court held that the FDCA’s commercial speech restrictions directly advances the government’s interest because limiting the manufacturer’s ability to market its drugs for other uses will incentivize the manufacturer to seek FDA approval

⁶⁵ Central Hudson Gas & Electric Corp. v. Public Serv. Comm’n, 447 U.S. 557, 566 (1980).

⁶⁶ Western States, 535 U.S. at 368-369.

⁶⁷ Ralph F. Hall and Elizabeth Sobotka, *Inconsistent Government Policies: Why FDA OFF-Label Regulation Cannot Survive First Amendment Review under Great New Orleans*, 62 Food & Drug L.J. 1, 18-20, (2007).

⁶⁸ For example, the American Recovery and Reinvestment Act of 2009 provides significant funds for “comparative effectiveness” research.

⁶⁹ See generally Gawande, *Better: A Surgeon’s Notes on Performance*, Metropolitan Books (2007).

⁷⁰ Central Hudson, 447 U.S. at 564.

for new uses.⁷¹ But Judge Vitaliano’s analysis ignores the current, completely legal use of off-label drugs, the extensive speech about off-label uses of drugs in non-commercial contexts and the benefits of that information.⁷² In essence, while manufacturers sales representatives cannot discuss off-label uses of their drugs with physicians, it is perfectly legal for anyone else to say whatever her or she wants about off-label uses for drugs.

Consequently, information about off-label uses is in the public domain regardless of the FDA’s off-label prohibitions on manufacturers. Accordingly, it is questionable whether the FDA’s prohibition actually effectively (i.e. “directly”) advances the government’s interest in protecting the public health through its new drug approval process by restricting this particular segment of the population from discussing public information. To the extent that pharmaceutical sales representatives are in the best position to provide timely and important information concerning emerging indications appropriate for its drugs, and existing federal law already permits only truthful and non-misleading “promotion,” Judge Vitaliano’s failure to take into account the real public good provided when physicians are kept up to date on the latest treatments is difficult to understand.

Another flaw in Judge Vitaliano’s analysis is his conclusion that the FDA’s speech restrictions are not “more extensive than is necessary” to achieve the government’s interests. Under Central Hudson, there must be a “reasonable fit” between the means and the ends of the commercial speech restriction. The FDA only characterizes a drug as “misbranded” if the manufacturer promotes it for an off-label (i.e. “new”) use. In fact, a drug can be classified as misbranded even if the drug is never actually prescribed for off-label use.⁷³ As the FDA explains “[a]n approved new drug that is marketed for an unapproved use becomes misbranded and an unapproved new drug with respect to that use.”⁷⁴ Nevertheless, the drug is not considered misbranded if it is routinely prescribed as off-label, so long as the manufacturer did not promote the off-label use. Because drugs may be freely prescribed for off-label use without penalty, “using speech to determine when a regulated product should be subjected to approval requirements for ‘new’ off-label uses is not reasonably related to the FDA’s asserted interest in

⁷¹ Caronia, 576 F.Supp.2d 385, 398, quoting Washington Legal Foundation, 13 F.Supp.2d at 72.

⁷² For example, Judge Vitaliano hypothesized that if the prohibitions did not exist manufacturers may submit a drug for approval for one indication but actually intend to market it for an entirely unapproved use. Therefore, he theorized the FDA’s restrictions are necessary to prevent such a result. This logic ignores the fact that information concerning active clinical trials is publicly available and there is no law preventing the public’s access to the information. Thus, if a patient learns of an active drug clinical trial that relates to his or her medical condition, there is nothing preventing that patient from requesting a physician to prescribe the drug for off label usage. Under those circumstances, the FDA’s restrictions could actually be detrimental to the public because the restrictions deprive the public of information necessary to make informed medical decisions.

⁷³ Caronia attempted to argue that he did not misbrand Xyrem because the undercover witness never intended to prescribe the drug for off-label use. Caronia 576 F.Supp.2 at 392. But, Judge Vitaliano rejected this argument stating that “the plain language of 21 U.S.C. § 331(k) requires only that the government show ‘that the [defendant] undertook some act with respect to the [drug] that [was] held for sale after shipment in interstate commerce, which resulted in the [drug] being adulterated and misbranded.’” *Id.* “It is the mouth of the promoter not the ear or intent of the audience that controls.” *Id.*

⁷⁴ Draft Guidance, *Good Reprint Practices for Medical Journal Articles and Medical or Scientific Reference Publications on Unapproved New Uses of Approved Drugs and Approved or Cleared Medical Devices* (February 2008).

assuring that the new drug approval requirements serve their purpose[.]” especially when the restriction impinges upon an individual’s constitutional right to freedom of speech.⁷⁵

Moreover, Judge Vitaliano’s assertion that he could not identify a single non-speech measure that would effectively prevent manufacturers from circumventing the new drug approval process is unconvincing. In Western States, the Supreme Court mandated that “[i]f the First Amendment means anything, it means that regulating speech must be a last — not first — resort.”⁷⁶ Yet, in this case it seems to have been the only strategy the government thought to try. The FDA could encourage manufacturers to seek FDA approval of new uses for drugs in several ways.⁷⁷ For example, the government could:

1. preempt product liability cases for products that receive FDA approval, but preserve product liability theories against uses which have not received FDA approval;⁷⁸
2. provide several economic incentives to encourage companies to seek FDA approval for new uses such as tax rebates and credits for the cost of FDA new drug submissions, or greater patent protection for on-label products and uses;
3. require companies to seek FDA approval for products that the manufacturer knows are being used in a significant off-label manner;⁷⁹
4. require drugs prescribed for off-label use to be labeled with a warning that the drug had not been approved by the FDA for off-label use and that the risks and benefits of the drug were unknown; or
5. establish a streamlined approval process for an already-approved drugs’ additional widespread uses and/or create a new category of “under consideration” uses and regulate those separately.

Under Central Hudson, the test is not whether the FDA had a “rational basis” for restricting manufacturers from promoting off-label uses of drugs but, rather whether the government had a “substantial interest” to be achieved by the restriction, whether the restriction “directly advances” that interest and is not “more extensive than is necessary” to serve that interest.⁸⁰ In this case, there is considerable debate as to whether the government’s application of its misbranding provisions to manufacturers’ off-label drug promotion directly advances its stated objective of preserving the FDA’s new drug approval process. Even if the FDA’s off-label promotion restrictions did advance its interest, there are obvious non-speech alternatives to encourage manufacturers to submit newly discovered uses for its drugs to the FDA drug approval

⁷⁵ A. Elizabeth Blackwell & James M. Beck, *Drug Manufacturers’ First Amendment Right To Advertise and Promote Their Products For Off-Label Use: Avoiding A Pyrrhic Victory*, 58 Food & Drug L.J. 439, 451 (2003)

⁷⁶ Western States, 535 U.S. at 373.

⁷⁷ Hall & Sobotka, 62 Food & Drug L. J. at 46.

⁷⁸ *Id.* The recent Supreme Court decision in Wyeth v. Levine, slip. Op. No. 00-1249. (Dec. 4, 2009) makes it clear that Congress has the authority to do so

⁷⁹ *Id.*

⁸⁰ Central Hudson, 447 U.S. at 564.

process. Since Judge Vitaliano failed to even identify, much less consider, any alternatives to the FDA's commercial speech restrictions, his analysis is flawed under Central Hudson.

VI. CONCLUSION

Despite the Caronia court's contrary finding, the FDA's restrictions are not constitutionally sound. Moreover, they are bad policies. Particularly since the FDA's prohibitions on off-label promotion do very little to protect its new drug approval process. The FDA does not dispute that information concerning the off-label uses for drugs is already in the public domain through publication of clinical trials, medical articles, and even word of mouth. The FDA also does not dispute that physicians regularly and legally prescribe drugs for off-label uses. Nor does the FDA disagree that the use of off-label drugs may actually be the standard of care in certain cases. Thus, restricting manufacturers from disseminating truthful, non-misleading information concerning off-label uses for its drugs makes no sense in a society where the free flow of truthful information is paramount.

More importantly, holding individuals criminally liable for circulating truthful information concerning off label uses for drugs solely based on their affiliation with a drug manufacturer thwarts the public's ability to accurately assess relevant medical treatment options. Since information on off-label uses for drugs is readily available, the FDA's regulatory enforcement efforts should not be focused on repressing that information but rather ensuring that the information available is complete and accurate. Ultimately, when provided with truthful information the public is in the best position to assess the risks and benefits of a particular treatment option and the FDA should not be allowed to deprive the public of that right by limiting their access to information concerning off-label usage of drugs.