FIRST AMENDMENT CONCERNS IN OFF-LABEL PROMOTION: SCIENCE V. MARKETING

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INTRODUCTION

Off-label marketing has been described as "so common among drug and device makers that it's often dismissed as the equivalent of driving slightly over the speed limit."[i] Studies suggest that more than 20% of prescriptions are written for off-label uses.[ii] Pharmaceutical companies and their supporters emphasize the benefits of off-label prescribing and the need for off-label promotion. Advantages of off-label prescription include delivery of needed new treatments "today," rather than at the end of a lengthy and costly approval process. Supporters also maintain that off-label promotion allows the company that has the most complete information about the product to give accurate, timely information to physicians.[iii] While off-label prescription may be a medically sound option for many physicians, off-label promotion carries substantial risks. The following example illustrates some of those risks.

Assume that a medical "bone cement" was FDA-approved for use in arm and skull surgeries. The product filled fractures and essentially became part of the bone. The manufacturer of the product might logically seek to market it for use in other types of surgeries involving fractures, such as fractures of the spine. Spurred on by the knowledge that Americans suffer some 500,000 spinal fractures a year, as well as surgeons' interest in such a product, the company might begin to test the product in various ways. Assume further, however, that the FDA has concerns about such use of the product because the bone cement could leak into the numerous arteries in the spine causing severe and fatal clotting. Should the manufacturer be allowed to promote its product for the unapproved use in spine surgery?

Norian XR is the product referred to in the hypothetical above.[iv] Norian and its parent company, Synthes, made a calculated decision to pursue the off-label use of its product. At least five people died of pulmonary clots shortly after the bone cement was injected during spine surgery. One physician whose patient died on the operating table stated that the sales representative had pushed the product and that he was not clear about the product's status on the market. [v] His partner, however, believed the product was safe and effective and continued to use it; he subsequently lost a patient during surgery. Ultimately, use of the product was halted. Both Synthes and Norian pled guilty to numerous misdemeanors and paid substantial fines. Four executives from Synthes who were charged with misdemeanors as "responsible corporate officers" served several months in jail.[vi]

The outrageous facts of this case certainly represent the extreme harm that can result from off-label promotion of drugs. But the case illustrates several points that are critical to the debate about off-label promotion. First, the company was willing to overlook serious risks associated with its product in order to reach a large, lucrative market. Second, the company chose to avoid the time-consuming and expensive FDA approval process to get its product to market quickly.[vii] Third, surgeons were led to believe the product was safe and were not fully informed of the risks associated with the product. Fourth, patients were unaware that they were the victims of experimentation.

The Norian case also illustrates some common misconceptions about off-label promotion that have figured prominently in court decisions. First is the perception that because a drug is approved for one use, it must be safe for other uses. As the Norian case illustrates, a product can be safe and effective for some uses, and excessively risky for others. Second, is the perception that doctors, as "learned intermediaries" can successfully safeguard their patients from the aggressive marketing strategies of pharmaceutical companies. The medical literature is replete with information about the impact that pharmaceutical companies have on doctors' decisions and prescribing habits.[viii]

As the government has reached settlements with numerous pharmaceutical companies in cases involving off-label promotion, the industry has complained that such prosecutions are overly aggressive. [ix] It is perhaps more likely that the government has responded appropriately to increasingly aggressive marketing strategies that put patients at risk. The off-label promotion of Neurontin provides an example of the calculated and extensive marketing strategies a company will employ. [x]Approved for use in conjunction with other drugs to treat epilepsy, Parke-Davis marketed the drug for off-label uses including bipolar disorder, pain, and migraines without any proof that the drug was safe or effective for these indications.[xi] Internal company documents revealed that its marketing director referred to Neurontin as the "snakeoil" of the twentieth century. Lifetime sales for Neurontin, if marketed as approved by the FDA, were projected to be approximately $500 million dollars. Following the company's off-label marketing strategy, the drug grossed over two billion dollars.

The FDA discourages off-label promotion because the practice allows manufacturers to evade the kind of testing that allows scientific evaluation of safety and efficacy. Furthermore, the government maintains that a physician's

decision to prescribe a drug for an off-label use should not be influenced by a marketing campaign orchestrated to impact the physician's decision. Following a settlement with Eli Lilly in connection with both criminal and civil charges for off-label promotion of its drug Zyprexa, a U.S. Attorney stated that in ignoring the government's process for drug approval, companies "undermine the integrity of the doctor-patient relationship. . . . People have an absolute right to their doctor's medical expertise, and to know that their health care provider's judgment has not been clouded by misinformation from a company trying to build its bottom line."[xii]

Pharmaceutical companies maintain that most cases involving off-label promotion settle because the risk of being excluded from participation in federal and state healthcare programs is too great.[xiii] In several cases, however, companies and individuals charged with off-label promotion have asserted that such speech is protected by the First Amendment. Two such cases have reached the United States Courts of Appeal. In *United States v. Caronia*, the Court of Appeals for the Second Circuit held in a 2-1 decision that provisions of the Food, Drug and Cosmetic Act (FDCA) cannot be interpreted to prohibit truthful, off-label promotion.[xiv] In *United States v. Harkonen*, the Court of Appeals for the Ninth Circuit, in an unpublished per curiam decision, held that the First Amendment does not protect fraudulent off-label speech.[xv] The cases are not incompatible. The *Harkonen* decision focuses narrowly on the fraudulent nature of the off-label promotion and the defendant's intent to defraud, while the *Caronia* case focuses more broadly on off-label promotion as protected speech.

The pharmaceutical industry's challenges in *Harkonen* and *Caronia* are the latest of several attempts to loosen the FDA's control over various marketing strategies. In previous cases, the industry succeeded in weakening FDA restrictions on dissemination of off-label promotion in printed materials and of material presented at continuing medical education events (CMEs). [xvi] It has increasingly sought First Amendment protection for the speech of pharmaceutical representatives who promote drugs for off-label uses to doctors through detailing. Detailing, promoting drugs and devices to doctors in their offices, is one of the most impactful ways for pharmaceutical companies to reach doctors to influence their prescribing habits. Detailing is especially important to off-label promotion because there is no prohibition against doctors prescribing FDA-approved drugs for off-label uses.

The argument that oral off-label promotion is protected by the First Amendment received a boost from two Supreme Court decisions that addressed advertising and marketing in the pharmaceutical context. In 2002, in *Thompson v. Western States Medical Center*, the Court held that a law that prohibited pharmacies from advertising that they compounded specific drugs violated the First Amendment.[xvii] In 2011, the Court held in *Sorrell v. IMS Health* that a Vermont statute that prohibited pharmaceutical companies from using prescriber-identifying information for marketing purposes violated the First Amendment.[xviii] Language in these decisions provided ammunition for challenging off-label promotion by detailers. This paper questions the reach of the Supreme Court's decisions in *Western States Medical Center* and *Sorrell* and whether the Second Circuit's reliance on these cases in *Caronia* is misplaced.

Part I of this paper explains the laws and regulations that limit off-label promotion as well as exceptions and safe harbors for off-label promotion and dissemination of information. It also summarizes cases that paved the way for the First Amendment challenge in *Caronia*. Part II details the court's reasoning in *Caronia* and its reliance on the Supreme Court's decisions in *Thompson v. Western States Medical Center* and *Sorrell v. IMS Health*. The dissenting opinion, which raises important arguments against the majority's reasoning, is summarized. In Part III, an examination of the relationship between pharmaceutical representatives and physicians reveals that courts should not assume that off-label promotion provides valuable information, nor that doctors are able to distinguish between misleading and non-misleading information. In Part IV, the paper summarizes the Ninth Circuit's decision in Harkonen. The case demonstrates that the government may have more success focusing on the false or misleading nature of off-label promotion rather than the more technical charge of misbranding. The paper concludes that *Caronia* does not signal a significant change in how the government will view off-label promotion. The errors in the prosecution of Caronia can be easily rectified. Furthermore, this paper maintains that regulations prohibiting off-label promotion withstand constitutional scrutiny. The paper also argues off-label promotion is more appropriately characterized as speech that does not deserve First Amendment protection because it is inherently misleading. The paper concludes that courts must be cautious in distinguishing unbiased scientific information from marketing strategies that have the potential to harm the public.

I. THE PARAMETERS OF OFF-LABEL PROMOTION: RULES, REGULATIONS, AND COURT DECISIONS

Regulations related to prohibiting off-label promotion of drugs require a balancing of important goals: ensuring that the medical community has timely and accurate information about new advances in science and protecting the

public health through the FDA's premarket approval process. Rules and regulations, as well as interpretations by courts, should seek to encourage the exchange of scientific information while maintaining a check on information that is merely promotional. The following sections provide background information for understanding the First Amendment challenges to off-label promotion.

A. What is Off-Label Promotion?

Since 1962, the FDCA has required premarket approval of drugs for each indicated use before distribution in interstate commerce.[xix] In seeking approval for a new drug, a manufacturer must specify each intended use. If a company discovers new uses for a drug, new populations to treat, or new dosages, such uses must be approved by the FDA; otherwise, they are considered to be off-label. Because the FDA approval process is time-consuming and expensive drug manufacturers may seek to bypass the approval process by marketing the drug for unapproved or off-label uses. Such promotion may be a tempting option if a company seeks to maximize a drug's potential by reaching a larger, more lucrative market before the patent expires or to avoid the time, costs, and risks associated with the trials required for FDA approval. For example, GlaxoSmithKline settled a lawsuit for the off-label promotion of its antidepressant drug, Paxil, because it allegedly promoted it to a population that was not approved by the FDA. The government alleged that the company prepared and distributed misleading articles about the efficacy of the drug for the under eighteen population and failed to make available data from trials that showed such use was not effective.[xx] The FDA-approved label for Paxil contained a black box warning, stating that antidepressants may increase the risk of suicidal thinking in patients under eighteen. By seeking to introduce a product to an unapproved population and by providing information that was contrary to the FDA-approved label, a company would be guilty of misbranding.

Although neither the FDCA nor FDA regulations specifically prohibit off-label promotion, a combination of provisions and regulations indicates that promoting off-label necessarily leads to illegal activity. The FDCA prohibits misbranding or introducing a drug into commerce without proper labeling about its indicated use.[xxi] Because labeling requirements are construed in a very broad manner, including oral representations made by pharmaceutical representatives, a representative who gives information about off-label use to a doctor, with the intent that the drug be distributed in commerce, is misbranding the drug.

Marketing for pharmaceutical products and devices is often done through oral communication by sales representatives in a doctor's office. Doctors are a critical link in the effort to introduce an off-label use. Because the FDA does not interfere with the practice of medicine, doctors may prescribe FDA-approved drugs for any use.[xxii] Thus, the restrictions that apply to pharmaceutical companies about off-label promotion, do not limit a doctor's ability to prescribe drugs for off-label use. Convincing a doctor to prescribe drugs for off-label uses, then, is an effective route to new markets without FDA approval. One argument that the industry has used in support of off-label promotion is that speech that supports a lawful activity, off-label prescription and use, should not be restricted. The government maintains, however, that allowing companies to promote uses that are not FDA-approved strikes at the very heart of the FDA's premarket approval system and jeopardizes the public health. The following sections summarize the rules and regulations as well as the case law relevant to off-label promotion.

B. Rules, Regulations and Guidance on Information About Off-label Promotion

Under the FDCA, pharmaceutical manufacturers may not introduce a new drug into interstate commerce unless the drug and its label have secured FDA approval.[xxiii] The Act also prohibits the "introduction or delivery for introduction into interstate commerce of any food, drug, device or cosmetic that is adulterated or misbranded."[xxiv] A drug is considered misbranded if its label contains misleading information, lacks information that is sufficient to support its safe use for approved indications, or includes information about unapproved uses.[xxv]

The definitions of "labeling" and "intended use" further explain how misbranding charges are related to off-label promotion. The FDCA and FDA regulations make it clear that labeling includes any conceivable printed or oral statement, including oral statements made by pharmaceutical representatives.[xxvi] Thus, when a pharmaceutical sales representative promotes a drug for off-label use, it is clear that the information he provides is considered "labeling." The "intended use" of a drug is determined by considering the "objective intent of the persons legally responsible for the labeling of the drug" as evidenced by the "labeling claims, advertising matter, or oral or written statements by such persons or their representatives."[xxvii] Thus, when a pharmaceutical representative visits a doctor in his office and provides information about off-label uses, it is logical to conclude that his intent is to introduce a misbranded drug into commerce. The information provided is "labeling" that has not been approved for the "intended" off-label use. Even though the doctor's off-label prescription is legal, the pharmaceutical company and

its representatives may be prosecuted for misbranding.[xxviii] Pharmaceutical manufacturers and their representatives can face misdemeanor charges for misbranding or felony charges for fraudulent misbranding.[xxix]

Although manufacturers are prohibited from introducing misbranded drugs into interstate commerce, the FDA has indicated that responding to unsolicited requests about off-label uses may not indicate intent to misbrand. In draft guidance published in 2011, the FDA issued non-binding recommendations about how companies should respond to both private and public inquiries about off-label uses from health care professionals or consumers.[xxx] The FDA's recommendations respond to the growth of Internet and social media tools that enable interested parties to seek information about emerging medical treatments.[xxxi] When consumers contact a company privately about off-label information, the company should respond privately with "truthful, non-misleading, accurate, and balanced" scientific information.[xxxii] Responses should come from the company's medical affairs office, not its sales force and should be narrowly tailored to the inquiry.[xxxiii] Responses should also include a copy of the FDA-approved labeling with a notice that the off-label use has not been approved by the FDA.[xxxiv] When inquiries are posted on a public forum, the draft guidance recommends that a firm should respond in a non-promotional manner with contact information only about its own product.[xxxv] The FDA states that if firms follow its suggested recommendations, it will not "use such responses as evidence of the firm's intent that the product be used for an unapproved or uncleared use."[xxxvi]

In addition to responding to unsolicited inquiries, the FDA has recognized that pharmaceutical manufacturers may disseminate certain printed material pertaining to off-label drug uses. In 2009 FDA Guidance, the agency issued nonbinding recommendations about the dissemination of off-label information in scientific or medical journals.[xxxvii] The agency states that if the recommendations are followed, it would not consider dissemination of the materials to be evidence of the manufacturer's intent to introduce the product for an unapproved use.[xxxviii] The recommendations emphasize that materials be peer-reviewed, independent of manufacturer funding, and not significantly influenced by a financial relationship with the manufacturer.[xxxix] The information should also be based on "scientifically sound" clinical investigations and not be false or misleading.[xl] Recommendations also include that the materials be unabridged, accompanied by the approved labeling, and not attached to promotional materials.[xli] The recommendations on disseminating printed materials about off-label use are substantially less burdensome than previous regulations. The FDA's revised thinking on this issue is largely due to successful litigation which challenged restrictions on First Amendment grounds.[xlii] This litigation is discussed in the following section.

C. The Road to Caronia

Through persistent efforts, the pharmaceutical industry has loosened FDA restrictions on off-label promotion. Challenges to restrictions on the dissemination of printed material about off-label uses were successful in the *Washington Legal Foundation* litigation. The Supreme Court has not addressed off-label promotion through detailing, but cases decided by the Court expanding protection for commercial speech in general have provided fresh ammunition in the industry's battle for increased First Amendment protection. In response to First Amendment challenges, the government has indicated that it may be more selective in deciding which cases to prosecute. [xliii] The following section summarizes cases that addressed First Amendment challenges to off-label promotion as well as the Supreme Court cases that had a substantial impact on the Second Circuit's holding in *United States v. Caronia*.

1. The *Washington Legal Foundation* Cases: Dissemination of Printed Materials About Off-Label Use is Protected by the First Amendment

In *Washington Legal Foundation v. Friedman*,[xliv] the public interest law and policy center challenged the constitutionality of FDA Guidance that sought to restrict manufacturers' distribution of journal article reprints and textbooks to physicians if they contained information about off-label uses.[xlv] In general, the FDA Guidance stated that manufacturers should distribute materials referencing off-label uses only if the materials were unabridged and were primarily about approved FDA uses.[xlvi] The FDA sought to "strike the proper balance between the need for exchange of reliable scientific data and information within the health care community, and the statutory requirements that prohibit companies from promoting products for unapproved uses."[xlvii] The regulations pertained to so-called "enduring" materials, which include journal articles and medical textbooks and specifically targeted dissemination of such materials by pharmaceutical companies. Among the requirements in the Guidance, the pharmaceutical industry objected most strenuously to the requirement that the primary focus of texts or reprinted articles distributed be about FDA-approved uses.[xlviii]

The court analyzed the speech involved as commercial, finding that it met the criteria articulated by the Supreme Court in *Bolger v. Youngs Drug Products Corporation*:[xlix] the speech is an advertisement; the speech refers to a specific product; and the speaker has an economic motive in disseminating the material.[l] Noting that the purpose of the commercial speech doctrine is to "protect consumers from misleading, deceptive or aggressive sales practices," the court noted that manufacturers have considerable financial resources to influence physicians and that they are more likely to disseminate only materials that favor their own product.[li]

Having concluded that the speech in question was properly classified as commercial, the court applied the test announced by the Supreme Court in *Central Hudson Gas & Electric Corp. v. Public Service Commission of New York*.[lii] *Central Hudson's* four-prong analysis considers: 1. whether the speech is false or misleading; 2. whether the government has a substantial interest in regulating; 3. whether the regulation materially advances the government's interest; and 4. whether the regulation is more extensive than necessary.[liii] The court concluded that the Guidance could not withstand constitutional scrutiny. The court rejected the FDA's argument that off-label promotion is inherently misleading. The court stated that the "FDA exaggerates its overall place in the universe,"[liv] by suggesting that information about uses not approved by the FDA is inherently misleading. In support of this conclusion, the court noted that the FDA did not object to physicians receiving the same information about off-label uses from sources other than the manufacturer.[lv]

The court found that the government had a substantial interest in regulating off-label promotion to protect the public health and in requiring manufacturers to seek approval for new uses. It also found that these interests are materially advanced by the regulations because "one of the few mechanisms available to FDA to compel manufacturer behavior is to constrain their marketing options; i.e. to control the labeling, advertising and marketing."[lvi] Nevertheless, the court found that the Guidance was more restrictive of speech than necessary.[lvii] Full and unambiguous disclosure to physicians that the off-label uses are not FDA-approved would, according to the court, be a less burdensome and more effective manner of advancing the government's interests.[lviii] Because less restrictive means of meeting its interest were available, the court found, the government failed to meet *Central Hudson's* requirements and violated the First Amendment. The court held that the FDA could not prohibit manufacturers from disseminating enduring materials "regardless of whether such [materials] include a significant or exclusive focus on off-label uses" because doing so unduly burdened speech.[lix]

Some language in the decision, however, is critical to later First Amendment challenges to FDA restrictions. The court emphasized that its ruling covered a "*very* narrow form of manufacturer communication" and that the FDA could prohibit many other types of communication to physicians about off-label uses, including "person-to-person contact with a physician."[lx] The court stated that these "incentives . . . to get off-label treatments on-label" were "central" to its decision and that if manufacturers were "permitted to engage in *all* forms of marketing of off-label treatments, a different result might be compelled."[lxi]

Subsequent to the *Friedman* case, Congress passed the Food and Drug Administration and Modernization Act (FDAMA) which contained provisions about the dissemination of material about off-label use by manufacturers.[lxii] These FDAMA provisions were to supersede the previous FDA Guidance that was challenged in the *Friedman* case. Section 401 of FDAMA required manufacturers: to submit a supplemental application to the FDA seeking approval of the off-label use within thirty-six months of dissemination of the material in question; to provide the materials to the FDA sixty days prior to dissemination; to disseminate materials in unabridged form; and to disclose to recipients that the materials pertain to an unapproved use of the drug.[lxiii] In *Washington Legal Foundation v. Henney*,[lxiv] the court held that the provisions of FDAMA, like the FDA Guidance provisions it had previously analyzed, were unconstitutional and infringed on manufacturers' First Amendment rights.[lxv] The court was particularly concerned about the requirements for supplemental applications, stating "the supplemental application requirement of the act amounts to a kind of constitutional blackmail – comply with the statute or sacrifice your First Amendment rights."[lxvi]

On appeal, the FDA maintained that the provisions of Section 401 of FDAMA merely provided a "safe harbor" and that FDAMA did not authorize the FDA to prohibit or sanction speech.[lxvii] The FDA's position led the United States Court of Appeals for the District of Columbia to declare the issue moot and to vacate the injunction of the lower court.[lxviii] The result of the litigation was that manufacturers were free to disseminate reliable scientific information about off-label uses. In 2009, the FDA issued nonbinding recommendations about disseminating printed materials with information about off-label use. The new recommendations are less burdensome to manufacturers.[lxix]

2. *Thompson v. Western States Medical Center*: Dissemination of Information About the Compounding of Specific Drugs is Speech Protected by the First Amendment

First Amendment challenges to the dissemination of information about certain drugs reached the United States Supreme Court in 2002. In *Thompson v. Western States Medical Center*,[lxx] the drug compounding industry complained that certain provisions of FDAMA unconstitutionally burdened protected speech. The Supreme Court's analysis in *Western States* was similar to that in the *Washington Legal Foundation* cases. The Court held that the restrictions on advertising or promoting compounded drugs violated the First Amendment's free speech guarantee.[lxxi] Using the commercial speech analysis from its *Central Hudson* decision, the Court recognized that the restrictions advanced substantial government interests, but found that they were not narrowly tailored, as the test requires.[lxxii]

Drug compounding is a process that is designed to tailor medication to the needs of an individual patient.[lxxiii] Because the FDA approval process would be prohibitively expensive and burdensome for such customized drugs, the FDA has left regulation of compounding primarily to the states and has not required compounders to seek approval for such drugs.[lxxiv] Nevertheless, the FDA became concerned that compounding could provide a loophole for some pharmacists to manufacture and sell drugs "under the guise of compounding."[lxxv] Consequently, Section 503A of FDAMA recognized that compounded drugs are exempt from the FDA drug approval process in general, but required compounders to refrain from certain activities associated with manufacturers such as soliciting business and advertising.[lxxvi] The regulations allowed compounders to advertise their services in general, but prohibited them from advertising the compounding of specific drugs.[lxxvii] Pharmacies that specialized in compounding drugs challenged these provisions.[lxxviii]

In considering whether the provisions prohibiting solicitation and advertising of compounded drugs violates the First Amendment, the Court addressed the speech in question as commercial using the *Central Hudson* test. The government asserted that the FDAMA regulations served three substantial interests: preserving the integrity of the FDA's new drug approval process which protects the public health; allowing compounded drugs to be available to those patients who need them; and balancing these competing interests.[lxxix] The government further asserted that the restrictions on promotion and advertising separate small-scale compounding, which responds to individual patient need, from large-scale drug manufacturing.[lxxx] The Court concluded, however, that even assuming that the restrictions would materially advance the government's interests, the regulations do not satisfy the *Central Hudson* test because they are not narrowly tailored.[lxxxi] The Court suggested several less burdensome alternatives that would be non-speech-related.[lxxxii]

3. *United States v. Caputo*: The First Amendment Does Not Apply if the Use Is Unlawful

The *Washington Legal Foundation* decisions regarding dissemination of printed materials about off-label use and the Supreme Court's expansive protection of advertising in *Western States* encouraged further challenges to restrictions on off-label promotion. In *United States v. Caputo*, the United States Court of Appeals for the Seventh Circuit discussed, but did not decide, whether a seller of drugs or medical devices has a constitutional right to promote off-label uses.[lxxxiii]

In *Caputo*, the defendants were convicted on several charges, including introducing a misbranded device into interstate commerce. The FDA approved a small sterilizer exclusively for use with stainless steel instruments. Recognizing that there was no market for the FDA-approved use, the defendants marketed a larger version of the device for use in sterilizing a variety of surgical instruments.[lxxxiv] The defendants argued that off-label marketing of the larger machine for use with different kinds of instruments was speech protected by the First Amendment.[lxxxv] Because off-label use is legal, the defendants maintained, off-label promotion cannot be restricted.[lxxxvi]

The Seventh Circuit did not have to reach the First Amendment issue because, it concluded, selling the device was not lawful.[lxxxvii] Had the facts raised the issue of a machine lawfully sold, but promoted for an off-label use, however, the court noted that its decision might have been different. The court noted that recent Supreme Court cases addressing commercial speech suggested that the provisions challenged may be unconstitutional in at least some applications.[lxxxviii] The court stated, "if a given use is lawful, and thus can be written about freely in newspapers or blogs, and discussed among hospitals . . . doesn't it make a good deal of sense to allow speech by the manufacturer, which after all will have the best information?"[lxxxix] The court stated that the Supreme Court's analysis in *Western States* indicated that "drugs [and by implication medical devices] are not a special case for first-amendment analysis."[xc]

The Seventh Circuit recognized, however, that there are dangers associated with off-label promotion. Notably, the court stated that the FDA could withhold approval of any use of a drug or device if it anticipated the manufacturer would promote other uses, thereby depriving the public of uses that the FDA excludes.[xci] The court

cautioned that "a court should hesitate before extending an historical reading of the Constitution in a way that injures the very audience that is supposed to benefit from free speech."[xcii] The court stated that it "[f]ortunately" did not have to decide whether manufacturers may promote off-label because there was enough evidence for a jury to conclude that the larger machine was not lawfully sold.[xciii] The machine, it found, was not a mere modification of an approved device, but a new device altogether. Without lawful use, the court held, there is no need for First Amendment analysis.[xciv]

4. Sorrell v. IMS Health, Inc.: The First Amendment Protects Speech in Aid of Pharmaceutical Marketing

In deciding a 2011 case, the United States Supreme Court made a strong statement about protecting the speech of pharmaceutical manufacturers.[xcv] The case involved the Vermont Prescription Confidentiality Law, commonly referred to as Act 80, which prohibited pharmaceutical companies and similar entities from using prescriber-identifying information for marketing purposes. Addressing a First Amendment challenge to the statute, the Court held that "[s]peech in aid of pharmaceutical marketing . . . is a form of expression protected by the Free Speech Clause of the First Amendment."[xcvi] Significantly, the Court found that such speech is subject to "heightened scrutiny" rather than the intermediate scrutiny applied to commercial speech under the *Central Hudson* analysis.[xcvii]

Pharmacies are required by law to collect and maintain detailed files about each prescription filled. [xcviii] The pharmacies can sell these records, containing a doctor's name and address, along with the amount of the drug prescribed, to data miners who, in turn, may lease the information to pharmaceutical companies.[xcix] The information is valuable to companies in effectively targeting doctors who might be inclined to change their prescribing habits. Influencing doctors' prescribing practices is largely achieved through detailing, the practice of pharmaceutical sales representatives visiting doctors in their offices with information about specific products.[c] The Vermont legislature had concluded that the information that pharmaceutical marketers provide to doctors is "incomplete and biased."[ci] Moreover, the legislature found that despite the inadequacy of the information, doctors rely on it because they do not have time to research the constant advances in new drugs.[cii] In addition to protecting medical privacy interests, the state maintained that its law sought to prevent companies from using this information to influence doctors to prescribe the newest, most expensive brand name drugs, thereby driving up health care costs and exposing patients to newer drugs whose side effects may not yet be fully known. [ciii]

The Court's approach to the First Amendment issue was significant, or as the dissenting justices stated, "a remarkable departure from First Amendment analysis of commercial speech."[civ] Rather than using the well-established analysis for commercial speech under *Central Hudson*, the Court found that "heightened scrutiny" was required because the Vermont statute set forth content and speaker based restrictions. The Court found that the Vermont Law disfavored speech with a particular content (marketing) when expressed by certain disfavored speakers (pharmaceutical manufacturers).[cv] The Court also found the law suffered from "viewpoint discrimination" because the Vermont Legislature designed the law to prevent marketers from more effectively selling high-cost brand-name drugs, rather than lower priced generic drugs favored by the state.[cvi] Heightened scrutiny is required, the Court stated, "whenever the government creates 'a regulation of speech because of disagreement with the message it conveys.'"[cvii]

Stating that "content-based" and "viewpoint discriminatory" laws are presumptively invalid; the Court further demonstrated that the law would meet the same fate under the less demanding standard applied to commercial speech.[cviii] Under *Central Hudson*, the state has the burden of proving that it has substantial interests in regulating and that those interests are directly advanced by the law in question.[cix] The Court found that the law does not advance Vermont's purported interests in protecting patient privacy and preventing influence on doctors' prescribing habits in a direct manner, as required.[cx] The confidentiality of prescription decisions is not protected, the Court reasoned, because only marketers are barred from using such information; researchers, journalists and others are not denied access to the information.[cxi] The Court also rejected the state's argument that the law interferes with the doctor-patient relationship by influencing prescribing decisions.[cxii] The Court concluded that the fact that doctors find such speech persuasive does not remove it from First Amendment protection.[cxiii] As in *Western States*, the Court emphasized the fact that the government cannot suppress information out of fear that the public will misuse that information.[cxiv] Furthermore, the Court noted that doctors, as the recipients of information through detailing are "'sophisticated, experienced' consumers."[cxv] The Court noted that a state is free to put forth its own views on topics such as a preference for generic drugs, but that it may not burden the speech of others to promote brand-name drugs.[cxvi]

Before the *Caronia* case was heard in federal district court in 2008, First Amendment challenges to off-label promotion were well-established. The industry had gained a significant victory in changing the FDA thinking on the dissemination of printed materials. Language in Supreme Court decisions such as *Western States* and *Sorrell*

encouraged the industry to expand First Amendment protection for off-label promotion by sales representatives. Neither of the Supreme Court cases, however, specifically addressed issues raised by off-label promotion through detailing. Furthermore, lower courts that considered the implications of off-label promotion through detailing expressed reservations and caution.

II. THE *CARONIA* CASE

The case against Alfred Caronia, a sales representative, arose in the context of a government investigation of Jazz Pharmaceuticals for the unlawful promotion of Xyrem. The investigation was the result of a whistleblower suit brought by a former sales representative. In July 2007, a settlement was reached between the drug manufacturer and the United States Attorney's Office. The manufacturer agreed to pay $20 million in penalties and victim compensation to resolve parallel criminal and civil investigations. The civil settlement included payment to Medicaid participating states to resolve the FCA claims. The plea agreement included a guilty plea to one count of felony misbranding of a drug product for off-label uses under the FDCA.[cxvii] Alfred Caronia, however, chose to fight the charges against him.

A. The District Court Found that Prohibitions on Off-Label Promotion Withstand Constitutional Scrutiny.

Alfred Caronia, a sales representative of the company that manufactures Xyrem, was charged with knowingly and intentionally conspiring with others to misbrand the drug by promoting it for off-label uses. [cxviii] Caronia argued that because doctors can lawfully prescribe FDA-approved drugs for any use, the government cannot restrict truthful, non-misleading promotion by a pharmaceutical manufacturer.

The drug that Caronia allegedly misbranded, Xyrem, is also known as the date rape drug. It is a powerful sleep-inducing depressant that has been approved by the FDA for two indications: cataplexy, a condition associated with narcolepsy, and excessive daytime sleepiness.[cxix] The side effects for the drug are so serious, including seizures, coma, and death, that Xyrem's labeling contains a black box warning, the most serious warning the FDA issues.[cxx] Designated as a Schedule III Controlled Substance for medical use, Xyrem cannot be sold or distributed to anyone other than for a prescribed use.[cxxi]

The government charged Caronia with conspiring to misbrand the drug because he promoted it for unapproved uses such as insomnia, fibromyalgia, muscle disorders, and chronic pain.[cxxii] Despite the serious risks associated with Xyrem, Caronia stated that it was "a very safe drug," with no contraindications.[cxxiii] It is worth noting that Caronia was under substantial pressure to sell the drug for off-label uses: representatives were required to meet an annual sales quota of 520 bottles of Xyrem in 2005, the year of the allegedly illegal off-label promotion; meeting sales targets had a substantial impact on salaries; and Caronia ranked near the bottom of the company's national sales force.[cxxiv]

In analyzing the First Amendment defense to the charge of misbranding, the district court concluded that the speech in question was commercial because it satisfied the test articulated by the Supreme Court in *Bolger v. Young's Drug Products Corp.*,: (1) the expression is an advertisement; (2) it refers to a specific product; and (3) the speaker has an economic motivation for speaking."[cxxv] Having concluded that Caronia's promotion of the drug qualified as commercial speech, the court employed the *Central Hudson* test to assess its constitutionality.[cxxvi] *Central Hudson* requires: (1) that the speech is lawful and not misleading; (2) that the government demonstrate a substantial interest; (3) that the regulation directly advances that interest; and (4) that the restriction is not more extensive than necessary.[cxxvii]

The district court found that the FDCA's restrictions on off-label promotion were constitutional. The court recognized that the government has a substantial interest in the health and safety of its citizens as well as in subjecting drugs to the FDA pre-market approval process.[cxxviii] The court found that restrictions on off-label promotion by manufacturers directly advance the FDA's interest in maintaining its approval process.[cxxix] Citing Friedman and *Caputo*, the court recognized that manufacturers have little incentive to seek FDA approval for off-label uses and that restricting marketing behavior is one of the few methods in which the FDA can encourage manufacturers to seek FDA approval for new uses of a drug that has been approved.[cxxx]

Finally, the court found that the FDA restrictions on off-label promotion are not more restrictive than necessary. Building on the discussion raised in *Friedman* and *Caputo*, the court concluded that the FDA's prohibition on off-label promotion is necessary "to ensure that manufacturers will not seek approval only for certain limited uses of

drugs, then promote that same drug for off-label uses, effectively circumventing the FDA's new drug requirements."[cxxxi]

B. The Second Circuit Held that Restricting Off-Label Promotion by Pharmaceutical Representatives Violates the First Amendment.

The Court of Appeals for the Second Circuit reversed the lower court's ruling, finding that prosecuting a pharmaceutical representative for promoting the lawful, off-label use of an FDA-approved drug violates the First Amendment.[cxxxii] In a 2-1 decision, the court stated that the government improperly construed the misbranding provision of the FDCA to prohibit promotional speech.[cxxxiii]

The court noted that the FDCA criminalizes misbranding or conspiring to misbrand a drug, but the Act does not expressly prohibit the promotion of a drug for off-label use.[cxxxiv] Although the government argued that it emphasized promotion only as evidence of intent to misbrand, the court was not persuaded.[cxxxv] Instead, the court found the trial record showed that the defendant was prosecuted and convicted for his speech.[cxxxvi] Although jury instructions included explanations about the elements of misbranding and conspiring to misbrand, the court found that the government's summation together with the jury instructions gave the impression that the off-label promotion itself was prohibited.[cxxxvii] According to the Second Circuit, construing the FDCA's misbranding provisions to criminalize the simple promotion of a drug's off-label use by pharmaceutical representatives would "run afoul of the First Amendment."[cxxxviii]

When the Second Circuit heard the appeal in *United States v. Caronia*, it had the benefit of the Supreme Court's decision in *Sorrell v. IMS Health*,[cxxxix] which had not been decided when the district court reached its decision. In assessing the constitutionality of Vermont's statute prohibiting pharmaceutical companies from using prescriber-identifying information for marketing purposes, the Court stated that "speech in aid of pharmaceutical marketing . . . is a form of expression protected by the . . . First Amendment."[cxl] In *Caronia*, the Second Circuit followed the approach used by the Court in *Sorrell*, applying both a "heightened scrutiny" standard and the *Central Hudson* test.[cxli]

In *Sorrell*, the Court required heightened scrutiny because the statute imposed both content and speaker based restrictions, restrictions which the Court stated are "presumptively invalid."[cxlii] In *Caronia*, the Second Circuit found that the FDCA's misbranding provisions impose similar restrictions. Off-label promotion is content-based, according to the court, because it distinguishes between favored speech (uses that are FDA-approved) and disfavored speech (uses that are not FDA-approved).[cxliii] Prohibiting off-label promotion is speaker-based, the court reasoned, because it targets one kind of speaker – pharmaceutical manufacturers and their representatives - while allowing others, such as doctors and academics, to speak about off-label use.[cxliv]

Applying the *Central Hudson* analysis to the facts in *Caronia*, the Second Circuit recognized the government's substantial interests in reducing the public's exposure to unsafe and ineffective drugs and in preserving the FDA's drug approval process.[cxlv] The court found, however, that a prohibition on off-label promotion failed to satisfy *Central Hudson*'s requirement that the law directly advance the government's interest because the FDA's approval process anticipates that drugs will be used off-label.[cxlvi] Moreover, drawing on *Sorrell*, the court found that prohibiting off-label promotion "paternalistically" interferes with both doctors' and patients' access to information about off-label use.[cxlvii] The court concluded that 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."[cxlviii] The court also concluded that restrictions on off-label promotion are not narrowly tailored to meet the government's interests and suggested several other ways to regulate for regulating off-label promotion that would intrude less on the First Amendment.[cxlix]

The court noted that the FDCA makes it a crime to misbrand or conspire to misbrand a drug but that the statute and its regulations to do not expressly prohibit or criminalize off-label promotion.[cl] To avoid conflict with the First Amendment, the court concluded that the FDCA should be construed as not criminalizing the simple promotion of a drug's off-label use.[cli]

C. *Judge Livingston's Dissent*

The majority in *Caronia* suggests that a case in which off –label promotion is presented merely as evidence of the intent to misbrand could be successful. At the same time the court's analysis of the First Amendment challenge threatens to eviscerate the prohibition against misbranding – a prohibition which strikes at the very heart of the

FDA's fundamental purpose. In a dissenting opinion, Judge Livingston makes convincing arguments that *Sorrell* and *Western States* do not compel the result reached by the majority and that restrictions on off-label promotion are constitutional.

1. Off-label promotion is evidence of intent to misbrand.

Judge Livingston stated that Caronia's conviction should have been confirmed because his speech was evidence of his intent to misbrand.[clii] Livingston cited the Supreme Court's decision in *Wisconsin v. Mitchell*, in which the Court recognized that the First Amendment "does not prohibit the evidentiary use of speech to establish the elements of a crime or to prove motive or intent."[cliii] She also cited a case decided by the Court of Appeals for the D.C. Circuit which concluded that using speech "in the form of labeling" to infer intent is constitutionally permissible.[cliv] In *Whitaker v. Thompson*, the Court of Appeals for the District of Columbia addressed First Amendment issues similar to those in *Caronia*. A seller marketed saw palmetto extract as a treatment for enlarged prostate symptoms, claiming that the marketing statements he made were truthful and not misleading.[clv] The court found that the statements about the product's intended use were drug claims, subject to the FDA approval process and consequently that the proposed label constituted speech about unlawful activity.[clvi] The court found that "a product's label may often be the only readily available evidence of the product's intended use."[clvii] In *Whitaker*, the court concluded that it is constitutionally permissible for the FDA to use speech, in the form of labeling, to infer intent for purposes of determining whether the seller's proposed sale of the product would be illegal.[clviii]

Judge Livingston expressed concern as to whether the majority's reasoning would ever allow a conviction for misbranding.[clix] The better reasoned analysis, she stated, would be to conclude that Caronia was prosecuted for misbranding and that his speech, the promotion of an off-label use, demonstrated his objective intent to introduce a misbranded drug into commerce.[clx] In other words, "promotion of a use may demonstrate an objective intent that the drug be used for that purpose."[clxi] Even though doctors may legally prescribe for an off-label use, Livingston notes that "otherwise permissible conduct may become *impermissible* if undertaken with a prohibited motive, and speech may be used as evidence of such a motive."[clxii] Livingston provided the following example to illustrate:

> 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. 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 be legally consumed.[clxiii]

2. *Western States* and *Sorrell* Do Not Compel the Result Reached in Caronia.

Judge Livingston was not persuaded that *Western States* and *Sorrell* dictated the outcome in *Caronia.* She found that the cases are distinguishable because in *Western States* and *Sorrell* "[s]peech alone was sufficient to trigger punishment under the challenged statutes."[clxiv] The FDA regulation challenged in *Western States* prohibited pharmacies from advertising or promoting the compounding of a particular drug.[clxv] In *Sorrell*, the statute targeted speech directly because it prohibited pharmaceutical manufacturers from using prescriber identifiable information for marketing or promotion.[clxvi] In contrast, something more than speech is required for conviction under the statute prohibiting misbranding. Without evidence of intent to introduce the drug into commerce for an unapproved use, Caronia could not have been convicted of misbranding "no matter what he said."[clxvii]

The dissent noted that despite its call for heightened scrutiny, *Sorrell* does not overrule *Central Hudson*. Furthermore, according to Judge Livingston, the FDCA's misbranding provisions can be distinguished from the content and speaker based scrutiny required in *Sorrell*. The dissent notes that *Sorrell* reaffirms the principle that restrictions on commercial speech may be constitutionally permissible because of the government's interest in protecting consumers from harm.[clxviii] The dissent points out that the statute challenged in *Sorrell* was not aimed at preventing false or misleading speech; the FDA approval process, by contrast, seeks to prevent dangerous products with false and misleading labels from entering the market.[clxix] The heightened scrutiny for speaker based restrictions used in *Sorrell* is inapplicable to off-label promotion because drug manufacturers are not a targeted group of speakers, as the majority suggests, but rather "form the entirety of those speakers that could possibly undermine the new drug approval process by not participating in it."[clxx]

3. Off-Label Promotion Survives *Central Hudson* Analysis

According to Judge Livingston, the misbranding provisions of the FDCA survive constitutional scrutiny under the *Central Hudson* analysis because the provisions directly advances a substantial government interest and are narrowly drawn to further that interest. Judge Livingston notes that he government's substantial interest in "preserving the effectiveness and integrity" of the FDCA's new drug approval process is not disputed.[clxxi] Moreover, she calls attention to cases in which the Court has recognized that "one of the [FDCA's] core objectives is to ensure that any product regulated by the FDA is safe and effective for its intended use."[clxxii] Given these substantial interests, Judge Livingston finds that allowing pharmaceutical representatives to promote off-label discourages manufacturers from seeking approval for new uses, thereby calling into "question the very foundations of our century-old system of drug regulation."[clxxiii] Unlike the majority, Judge Livingston concludes, as did the courts in *Washington Legal Foundation* and *Caputo*, that prohibiting off-label promotion is " 'one of the few mechanisms available' to encourage participation in the approval process."[clxxiv]

Finally, Judge Livingston concludes that the restrictions on off-label promotion are not more extensive than necessary. She maintains that "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."[clxxv] Judge Livingston refutes each of the alternatives raised by the majority as either ineffective or impractical. Notably, she states that a disclaimer system will still encourage manufacturers to bypass the approval process and a ceiling or prohibition on off-label prescription would require extensive data tracking and could deny some patients the off-label use they need.[clxxvi]

Judge Livingston's dissent more accurately reflects the Supreme Court's concerns about the importance of the FDA approval process than the majority opinion. Moreover, the dissent agrees with lower court decisions that have expressed caution in sweeping too broadly where off-label promotion is concerned because prohibiting such behavior is one of the only mechanisms to incentivize drug manufacturers to seek FDA approval for new uses. In addition to the strong arguments against the majority's decision presented by Judge Livingston, there are other critical factors about off-label promotion and the relationship between physicians and pharmaceutical salespeople that the court has not adequately addressed. In fact, several assumptions about the relationship between physicians and pharmaceutical companies that the Supreme Court relied on in *Western States* and *Sorrell* must be revisited in order to adequately address the dangers of off-label promotion.

III. THE RELATIONSHIP BETWEEN DETAILERS AND PHYSICIANS IN OFF-LABEL PROMOTION

In finding that prohibiting off-label promotion does not directly advance the government's interest in an approval process that insures drugs are safe and effective, the majority in *Caronia* stated that prohibiting such promotion "'paternalistically' interferes with the ability of physicians and patients to receive potentially relevant treatment information."[clxxvii] The court also stated that the public interest is furthered when information that can "save lives" is provided, including information about off-label use.[clxxviii] The court's view of detailing suggests that pharmaceutical representatives are educators who provide truthful, non-misleading information to doctors and that the risks of influencing prescribing habits are few because physicians are a sophisticated group.[clxxix] Yet the medical literature reveals that detailing is not designed to educate physicians but rather is calculated to sell products by influencing doctors' prescribing habits.

A. Off-Label Promotion Through Detailing

The medical literature recognizes that detailing is one of the leading strategies for off-label marketing. Because the conversations between sales representatives and doctors take place largely in private, they are difficult to monitor and thus it is impossible to know the extent to which information is truthful or misleading.[clxxx]Thus, off-label promotion and the strategies that companies have devised come to light almost exclusively through information provided by company insiders or physicians.[clxxxi] This section examines information from doctors and sales representatives about the impact of detailing and off-label promotion on medical decisions.

According to Dr. Jerome P. Kassirer, a Professor at the Tufts University School of Medicine, the idea that sales representatives will present truthful, non-misleading information to physicians is highly problematic. Dr. Kassirer asserts that "the notion that this is all for education is nonsense" and the fact that companies spend so much money on advertising is evidence of their intent to influence physicians.[clxxxii] Several researchers have concluded that the pharmaceutical industry spends more money on marketing than on research and development.[clxxxiii] In 2000,

pharmaceutical firms reportedly spent a total of $8.5 billion on marketing, with most of the money financing physician-industry interactions.[clxxxiv] A 2008 report estimated that companies spend as much as $57.5 billion on advertising, double what they spend on research.[clxxxv] The importance of a manufacturer's detailing sales force is reflected in the fact that it consumes the largest portion of the marketing budget, a budget that exceeds that of any other U.S. industry.[clxxxvi] Since the late 1990s, manufacturers have expanded their sales forces for detailing.[clxxxvii] There is some evidence that marketing to physicians is more profitable than direct-to-consumer advertising because detailing increases sales for the particular brand of drug promoted rather than raising awareness or creating demand across brands as direct-to-consumer advertising tends to do.[clxxxviii]

Detailing plays a critical role in off-label promotion.[clxxxix] Abbot Laboratories' off-label promotion of its drug Depakote provides a good example.[cxc] The company admitted that for eight years it had a sales force dedicated to marketing Depakote for off-label uses. The drug was FDA-approved for use with epileptic seizures, bipolar mania and migraines but was marketed to nursing homes to treat symptoms of dementia in elderly patients. There was no scientific evidence that the drug was effective in controlling dementia. Furthermore, even as Abbott began its off-label campaign, it had halted a trial for treating dementia because of side effects such as dehydration and anorexia. The company pleaded guilty and agreed to pay $1.6 billion for misbranding the drug.

Abbott's use of a sales force dedicated to off-label promotion is not unique. The industry's faith in detailing is evident in the growth of the number of drug representatives in the United States. Between 1995 and 2005, the number of pharmaceutical sales representatives increased from 38,000 to 100,000. Studies suggest that this number would furnish one sales representative for every six physicians, but that the actual ratio is closer to one sales representative per 2.5 doctors because not all physicians practice and physicians who are unlikely to change their prescribing habits are not detailed.[cxci] Researchers have summarized the value of detailers to doctors as follows:

> The concept that reps provide necessary services to physicians and patients is a fiction. Pharmaceutical companies spend billions of dollars annually to ensure that physicians most susceptible to marketing prescribe the most expensive, most promoted drugs to the most people possible. The foundation of this influence is a sales force of 100,000 drug reps that provides rationed doses of samples, gifts, services and flattery to a subset of physicians. If detailing were an educational service, it would be provided to all physicians, not just those who affect market share.[cxcii]

In addition to their role of targeting doctors most susceptible to marketing efforts, detailers are trained to develop a relationship with doctors.[cxciii] To ensure detailers will connect socially with doctors, job qualifications are more likely to include an outgoing personality and keen observation skills than an education or training in science.[cxciv] A former drug representative for Eli Lilly described drug representatives as "young and attractive" and "eloquent and convincing," but lacking in "any significant scientific training."[cxcv] He also stated that representatives usually change jobs relatively quickly as enthusiasm about the product diminishes and that they are "easily replaced by other, younger, less questioning recruits."[cxcvi]

Sales representatives are tasked with developing a social bond with doctors, creating a "quid pro quo" relationship, and constantly reminding the doctor about the company and its generosity. Detailers may bestow free samples, invitations to speak at various events, dinners, and expense-paid trips to doctors who write large numbers of prescriptions.[cxcvii] Even small gifts such as pens bearing the company's logo are effective in developing "reciprocity," the term well-known in psychology and marketing for creating an obligation, conscious or subconscious, to return a favor.[cxcviii]

In assessing the speech related to pharmaceutical speech, the courts have emphasized that information is power and that manufacturers are in the best position to provide relevant information.[cxcix] This argument, however, overstates the scientific expertise of sales representatives and gives insufficient weight to the pressures on sales representatives to sell. The information that sales representatives provide is more likely to be biased than truthful. They are trained to emphasize the benefits of their product, to suppress any negative information about their product, and to highlight negative aspects of a competitor's product.[cc] Thus, while manufacturers are in a unique position to provide information to the medical community, they are more likely to control the information in a manner that best advances sales.[cci] The educational value of information provided by sales representatives is also highly suspect. One doctor explains that an expert in the field would not need the information that a drug representative provides; the doctor who needs information, however, is "hard-pressed to contextualize the information being presented, or even simply to distinguish true from false information."[ccii]

Detailing is widely recognized as having a substantial effect on the prescribing habits of physicians.[cciii] In several cases, courts have insisted that high pressure marketing efforts about off-label uses have little meaningful impact on doctors because they are sophisticated and knowledgeable about the FDA approval process. But the medical literature has emphasized that detailing and salesmanship play dominant roles in physicians' choices about treatment.[cciv] Reports by the American Association of Medical Colleges (AAMC) recognize that pharmaceutical marketing impacts the objective judgment of physicians to act in their patients' best interests.[ccv] Furthermore, studies also conclude that the impact of marketing such as detailing creates a "net harm" to patients.[ccvi] Significantly, studies show that while individual doctors believe they are immune from influence, empirical evidence has shown otherwise. [ccvii] Interestingly, doctors who believe that they are personally immune from commercial messages reportedly believe their colleagues are influenced by commercial channels.

The influence of detailers over physicians may be harmful in several ways: physicians may be influenced to prescribe newer, more expensive drugs when a less expensive drug that may be more efficacious and safer is available; physicians may prescribe a drug when lifestyle changes or other non-drug therapies might be preferable; physicians may prescribe drugs when none are really required; and finally, the public trust may be tested by the perception of collusion between physicians and the pharmaceutical industry.[ccviii] Because data strongly indicates that physicians are unconsciously influenced by detailers, some doctors believe that they should avoid the conflict of interest inherent in drug detailing.[ccix]

B. Doctors Are Not a Sophisticated Audience

Courts have largely assumed that doctors are capable of distinguishing valuable, scientific information from misleading claims about pharmaceutical products.[ccx] Thus, in, *Washington Legal Foundation v. Henney*, the court rejected the argument that the government had in interest in ensuring that physicians receive a balanced flow of information. The court stated, that "[t]he government, however benign its motivations, simply cannot justify a restriction of truthful non-misleading speech on the paternalistic assumption that such restriction is necessary to protect the listener from ignorantly or inadvertently misusing the information," especially when the "recipient of information is a sophisticated listener trained extensively in the use of such information – as are the doctors and other health care providers in this case."[ccxi] Similarly, in *United States v. Caputo*, the district court stated that it could not find off-label promotion to be inherently misleading because physicians are a "sophisticated audience" and are able to "independently evaluate the validity of their claims."[ccxii]

The conclusions that courts have made about doctors' ability to discern valuable from misleading information is hard to understand. When the FDCA was substantially revised in 1962, the amendments addressed "concerns that doctors could not adequately evaluate frequently misleading claims made by drug manufacturers."[ccxiii] This concern should be underscored when off-label promotion is considered, as off-label products have not been proven safe or effective for the intended use, coupled with the fact that physicians are undoubtedly influenced by such promotion.

As early as 1982, the medical literature reported that prescribing practices among physicians are influenced by commercial sources such as advertising and detailing.[ccxiv] One study considered the impact of commercial channels, including advertisements and detailing as well as scientific sources of information, such as published reports of clinical trials and review articles.[ccxv] The study examined doctors' habits and beliefs about the efficacy of drugs in which the message for a particular use was very different in the scientific sources than in the commercial sources.[ccxvi] In fact, the study reported that advertisements for one of the drugs studied was the primary source of "misinformation" about the drugs' efficacy.[ccxvii] The study concluded that physicians were more influenced by commercial than scientific sources but they were either unaware or unwilling to report that they were so influenced.[ccxviii]

One reason that doctors are not the "sophisticated audience" that courts and patients imagine them to be is the unyielding pressure on their time. Practicing physicians rely on information from pharmaceutical representatives because they have little time to assess new products independently.[ccxix] One author states that doctors "can examine only a tiny sliver of the findings and minutiae published in journals concerning just their own specialty, and most read only summaries of most articles that they hear about."[ccxx] Dr. Jerome Groopman, author of *How Doctors Think*, explains that most doctors learn about new products from the pharmaceutical industry and that is rare for doctors to read in depth about new drugs.[ccxxi] Thus, courts should not assume that doctors have the time or the inclination to verify information from pharmaceutical representatives.

With substantial evidence that detailers are trained to sell rather than to educate doctors and that doctors do not have the time to or the ability to distinguish truthful from misleading information provided by pharmaceutical representatives, the potential for harm is evident. The industry targets doctors who are likely to respond to overtures

by changing their prescribing habit and selects the information about the product that is likely to produce a sale. The manufacturer has unique control over the information. The strategies of the pharmaceutical industry are not balanced by the physician's expertise and training. Rather, physicians unwittingly rely on the information provided without the time or resources to verify the information. Thus, the safeguards that the courts have assumed will protect consumers from misleading information do not exist.

In understanding the need to regulate off-label promotion, courts must understand the dangers associated with it as well as the fact that marketing strategies are often devised without scientific or educational goals in mind. In *Washington Legal Foundation*, the court stated that off-label uses are "subject to asymmetrical – if not necessarily inconsistent – regulatory treatment."[ccxxii] Courts have not adequately distinguished the reasons for allowing off-label prescription by doctors and prohibiting off-label promotion by manufactures. [ccxxiii] Doctors should have the option to prescribe off-label when patients need a treatment option that is not yet available or not proven effective.[ccxxiv] A doctor can make decisions about the risks and benefits of an off-label use for a particular patient. [ccxxv] But such decisions should not be influenced by the unreliable and one-sided information that is scripted for pharmaceutical representatives in an effort to reach new lucrative markets, without the time, money and risks involved in the FDA approval process and without reliable scientific knowledge about the safety or efficacy of the product for the use promoted.

In *Caronia*, the defendant maintained that he was prosecuted for truthful, off-label promotion. Given the very nature of off-label promotion – the incentive to sell, the lack of scientific training of sales representatives - and the inability of physicians to ascertain the reliability or the scientific basis for the representatives' claims, it is hard to imagine what value truthful, off-label promotion has. The government chose to prosecute Caronia for the misdemeanor of misbranding and, consequently, the evidence did not focus on whether or not his statements were false or misleading. It appears, however, that had the government chosen another course, Caronia's conviction might have been upheld. Caronia described Xyrem as a very safe drug with no contraindications, stating that "for the problems with insomnia there's no better drug, no safer drug, it's as safe as Ambien and Sonata . . . ."[ccxxvi]

As the government continues to pursue companies and individuals for off-label promotion, it may choose to avoid the First Amendment analysis by emphasizing the fraudulent nature of the speech rather than the more technical aspects of misbranding. The Ninth Circuit's decision in *United States v. Harkonen* provides an example of why this course may be more successful.

IV. *United States v. Harkonen*: THE FIRST AMENDMENT DOES NOT PROTECT FRAUDULENT SPEECH

While the *Caronia* decision purports to protect truthful, off-label speech, the Court of Appeals for the Ninth Circuit, in an unpublished per curiam decision, held that fraudulent off-label promotion is not deserving of First Amendment protection.[ccxxvii] The decisions by the Ninth and Second Circuits do not, however, create a clear circuit split because the *Harkonen* case dealt primarily with a charge of wire fraud and whether the jury could reasonably conclude that the defendant's speech was fraudulent. The fraudulent nature of the speech, according to the Ninth Circuit, removed the case from First Amendment analysis.

The *Harkonen* case illustrates that cases involving off-label promotion are likely to be most successful when the fraudulent nature of a marketing scheme is clear and compelling. The case involved off-label marketing of the drug Actimmune. The drug was FDA approved to treat two rare diseases that afflict approximately 800 Americans. The market for IPF patients was between 50,000 and 75,000 Americans. InterMune's sales tripled after it began marketing Actimmune off-label for idiopathic pulmonary fibrosis (IPF), a lung disease that is fatal unless the patient undergoes a lung transplant.

The off-label promotion for IPF was sparked by a paper published in the *New England Journal of Medicine*. The article indicated that, based on a small trial, Actimmune might be effective in treating IPF. Based on these results, InterMune began marketing the drug off-label. It also organized a larger in-house trial that included 330 patients. This trial showed that the drug was not effective in general. In a subset of patients with milder disease, however, the trial showed a statistically significant result.

Focusing on the results from the subset of patients, Dr. Harkonen, CEO of InterMune, issued a press release with the headline, "InterMune Announces Phase III Data Demonstrating Survival Benefit of Actimmune in IPF," followed by "Reduces Mortality by 70% in Patients with Mild to Moderate Disease."
Beginning with the proposition that the First Amendment does not protect fraudulent speech, the Ninth Circuit focused on whether facts found by the jury established that the Press Release was fraudulent. The court found that the evidence supported the conclusion that the Press Release was misleading, that Harkonen knew it was misleading, and that he had the specific intent to defraud. At trial, witnesses testified that the Press Release misrepresented the results of the company's in-house trial and that Harkonen was "very apologetic" about the Press Release.[ccxxviii]

Furthermore, Harkonen refused to allow colleagues at InterMune to review the Press Release before publication. He also sought to hide the analysis of the trial data from the FDA, stating that he "didn't want to make it look like we were doing repeated analyses looking for a better result."[ccxxix] The court found that Harkonen's statement that he would "cut that data and slice it until [he] got the kind of results [he was] looking for" showed specific intent to defraud.[ccxxx]

Harkonen maintained that his statements were protected by the First Amendment because they involved scientific debate and were beyond the reach of the wire fraud statute.[ccxxxi] This argument rested on a 1902 Supreme Court decision, *American School of Magnetic Healing v. McAnnulty*, which held that "genuine debates over whether a given treatment caused a particular effect are outside the scope of the mail and wire fraud statutes."[ccxxxii] The Ninth Circuit found that *McAnnulty* does not prohibit all prosecutions based on fraudulent statements about the efficacy of a drug. [ccxxxiii] Furthermore, the court cited the Supreme Court's decision in *Seven Cases v. United States* in which the Court found that "false and fraudulent representations may be made with respect to the curative effect of substances."[ccxxxiv]

While other cases alleging false statements in off-label promotion have not reached the courts, companies have admitted to making false statements to doctors pursuant to off-label marketing strategies. Purdue Parma, the manufacturer of the prescription pain medication OxyContin, acknowledged that its sales representatives had made false statements to doctors, claiming that OxyContin was more resistant to abuse and less likely to cause addiction than competing products.[ccxxxv] The company promoted OxyContin for use every eight hours instead of the twelve-hour dosage approved.[ccxxxvi]

CONCLUSION

While the government may face challenges in prosecuting pharmaceutical companies for off-label promotion, it should not be deterred by the Second Circuit's decision in *Caronia*. The government has at least two options in pursuing pharmaceutical companies for off-label promotion. First, emphasizing that a defendant is being prosecuted for his intent to misbrand rather than for promotion itself might be enough to withstand First Amendment scrutiny. Second, prosecutors should focus increasingly on the false or misleading nature of off-label promotion to take it outside of the scope of First Amendment protection. Furthermore, sound arguments distinguish the oral promotional statements by pharmaceutical representatives from the speech the Supreme Court found constitutionally protected in *Western States* and *Sorrell*. Prohibiting off-label promotion directly advances the government's substantial interest in protecting the public health through the FDA's premarket approval process. It does so by preventing physicians from relying on the biased, market-driven information provided by a select sales force.

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[i] Mina Kimes, *Bad to the Bone: A medical horror story*, FORTUNE, http://features.Blogs.fortune.cnn.com/2012/09/18/synthes-norian-criminal

[ii] A 2006 study in the Archives of Internal Medicine examined hundreds of millions of prescriptions and found that more than 20% were written for off-label use. There are reports that as much as 21% of prescriptions are for off-label uses. *See* David C. Radley, et al., *Off-Label Prescribing Among Office-Based Physicians*, 166 ARCH. INTERNAL MED. 1021, 1023 (2006); *see also* Jane Henney, *Safeguarding Patient Welfare: Who's in Charge?* 145 ANNALS INTERNAL MED. 305, 305 (Aug. 15, 2006), available at http://www.annals.org.proxy.bc.edu/cgi/content/full/145/4/305.

[iii] See 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 & ETHICS 299, (2010).

[iv] Kimes, *supra* note 1.

[v] *Id.*

[vi] *Id.*

[vii] FDA approval of medical devices is governed by the Medical Device Amendments (MDA). 21 U.S.C. § § 351-360n(2000). Although some devices require a premarket approval application before they may be marketed to the public, a manufacturer may seek an Investigational Device Exemption (IDE) to conduct tests on human subjects without pre-market approval. *See id.* § 360j(g). The IDE is designed to "encourage . . . the discovery and development of useful devices . . . and maintain optimum freedom for scientific investigators." *Id.* The manufacturer of Norian XR, however, opted not to seek an IDE.

[viii] *See infra* notes and accompanying text.

[ix] *See* Osborn, *supra* note 3, at 301 (describing the American pharmaceutical industry as "under siege"). In May 2009 Attorney General Eric Holder and Kathleen Sebelius, Secretary of the Department of Health and Human Services announced the Health Care Fraud Prevention and Enforcement Action Team (HEAT) initiative. The False Claims Act has been one of the most powerful tools in the effort to reduce and prevent Medicare and Medicaid financial fraud. The Justice Department has recovered more than $10.2 billion since January 2009 in cases involving fraud against federal health care programs.

[x] *See* United States ex rel. Franklin v. Parke-Davis, 147 F. Supp. 2d 39 (D. Mass. 2001). Pfizer acquired the Parke-Davis division when it acquired Warner Lambert.

[xi] *See id.*

[xii] Department of Justice, Press Release, Eli Lily and Company Agrees to Pay $1.415 Billion to Resolve Off-Label Promotion of Zyprexa (Jan. 15, 2009) http://www.justice.gov/opa/pr/2009/January/09-civ-038.html (last visited April 22, 2013). Zyprexa was approved for use with certain psychotic disorders such as Bipolar I Disorder and schizophrenia. Eli Lilly marketed it to primary care physicians in nursing homes and assisted living facilities for treating unapproved uses such as dementia, Alzheimer's dementia, depression, anxiety, sleep problems, as well as behavioral symptoms such as agitation, aggression and hostility. *Id.* The information also alleges that building on its unlawful promotion and success in the long-term care market, Eli Lilly executives decided to market Zyprexa to primary-care physicians. In October 2000, Eli Lilly began this off-label marketing campaign targeting primary care physicians, even though the company knew that there was virtually no approved use for Zyprexa in the primary-care market. Eli Lilly trained its primary-care physician sales representatives to promote Zyprexa by focusing on symptoms, rather than Zyprexa's FDA approved indications. *Id.*

[xiii] See Katherine Helms, at 180.

[xiv] 703 F. 3d 149 (2d Cir. 2012).

[xv] No. 11-10209, No. 11-10242, 2013 U.S. App. LEXIS 4472 (9th Cir. March 4, 2013) (per curiam).

[xvi] *See infra* text accompanying notes .

[xvii] 535 U.S. 357 (2002).

[xviii] 131 S. Ct. 2653 (2011).

[xix] 21 U.S.C. § § 331(d), 355(a).

[xx] Press Release, Department of Justice, GlaxoSmithKline to Plead Guilty and Pay $3 Billion to Resolve Fraud Allegations and Failure to Report Safety Data (July 2, 2012) available at www.justice.gov/printf/PrintOut3.jsp. The company also pleaded guilty to misbranding charges related to its drug Wellbutrin which was approved for Major Depressive Disorder and marketed off-label for weight loss, sexual dysfunction, and Attention Deficit Hyperactivity Disorder. *Id.*

[xxi]

[xxii] 21 U.S.C. § 396 (The FDA does not "limit or interfere with the authority of a health care practitioner to prescribe" approved drugs or devices "for any condition or disease"). The Physicians' Desk Reference states, "Once a product 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." PHYSICIANS DESK REFERENCE 2008, Forward (62nd ed. 2007). The United States Supreme Court has recognized that off-label prescribing "is an accepted and necessary corollary of the FDA's mission to regulate." Buckman Co. v. Plaintiffs' Legal Comm., 531 U.S. 341, 350 (2001).

[xxiii] 21 U.S.C. § 355(a).

[xxiv] 21 U.S.C. § 331(a).

[xxv] 21 U.S.C. § 352(f); 21 C.F.R. § 201.5.

[xxvi] See 21 U.S.C. §321 (k), (m). 21 C.F.R. § 202.1. In *Kordel v. United States*, the Court held that a manufacturer can be found guilty of misbranding even though the product and the labeling information were shipped separately. 335 U.S. 345, 350 (1948).

[xxvii] 21 C.F.R. § 201.128.

[xxviii] *See* Jeffrey N. Wasserstein & Kurt R. Karst, *A Deep Dive into the Second Circuit's Caronia Decision, Potential Next Steps, and Potential Enforcement Fallout*, FDA L. BLOG (Dec. 12, 2012, 1:37 AM); http://www.fdalawblog.net/fda_law_blog-hyman_phelps/2012/12/a-deep-dive-into-the-second-circuits-caronia-decision-potential-next-steps-and-potential-enforcement.html.

[xxix] 21 U.S.C. § 333(a).

[xxx] FDA, Draft Guidance for Industry: Responding to Unsolicited Requests for Off-label Information About Prescription Drugs and Medical Devices (2011).

[xxxi] *Id.*

[xxxii] *Id.*

[xxxiii] *Id.*

[xxxiv] *Id.*

[xxxv] *Id.*

[xxxvi] *Id.*

[xxxvii] FDA, Guidance for Industry: Good Reprint Practices for the Distribution of Medical Journal Articles and Medical or Scientific Reference Publications on Unapproved New Uses of Approved Drugs and Approved or Cleared Medical Devices (2009), http://www.fda.gov/oc/op/goodreprint.html.

[xxxviii] *Id.*

[xxxix] *Id.*

[xl] *Id.*

[xli] *Id.*

[xlii] In *Washington Legal Foundation v. Friedman,* the court held that FDA guidance restricting certain forms of manufacturer promotion of off-label uses were unconstitutional restrictions of commercial speech under the First Amendment. 13 F. Supp. 2d 51, 74-75 (D. D.C. 1998), *order vacated as moot sub nom*, Washington Legal Foundation v. Henney, 202 F.3d 331, 336-37 (D.C. Cir. 2000). *But see* Whitaker v. Thompson, 353 F.3d 947 (D.C. Cir. 2004) (holding that the FDA did not violate the First Amendment's restrictions on commercial speech when it determined that a certain dietary supplement had to be approved as a drug before it could be marketed as effective in the treatment of a disease).

[xliii] See Defendants' Memorandum in Support of Motion to Dismiss, No. 1:11-cv-1820, Par Pharmaceutical, Inc. v. United States, (D.C. Jan. 11, 2012), at 27. ("While manufacturer speech is always a relevant factor in determining intended use, in the absence of other evidence that an unapproved use is intended, a drug manufacturer that engages in truthful and non-misleading speech about an approved use is not placing itself in violation of the FDCA.").

[xliv] 13 F. Supp. 2d 51 (D. C. 1998).

[xlv] *Id. See generally* Elizabeth A. Weeks, *The New Policy on Dissemination of Information on Off-Label Drug Use Under the Food and Drug Administration Modernization Act of 1997*, 54 FOOD & DRUG L.J. 645 (1999). The FDA Guidance also sought to insure that continuing medical education (CME) programs were truly educational rather than mere promotional vehicles for a sponsoring company's product. *Id.* at 649.

[xlvi] *Friedman*, 13 F. Supp. 2d at 58 (D. D.C. 1998) (citing 61 Fed. Reg. 52800 (1996).

[xlvii] *Id.*

[xlviii] *Id.* (citing Guidance to Industry on Dissemination of Reprints of Certain Published, Original Data and Guidance for Industry Funded Dissemination of Reference Texts, 61 Fed. Reg. at 52800 (1996)). Other requirements included that the reprint be from a peer-reviewed journal; prominent notification on the reprint of any differences from the approved labeling; and that the material not be false or misleading. *Id.* The Guidance also required that medical textbooks and compendia provide a balanced presentation and that the text is not substantially prepared or edited by the manufacturer. *Id.*

[xlix] 463 U.S. 60 (1983).

[l] *Friedman*, 13 F. Supp. 2d at 64.

[li] *Id.* at 65 (citing 44 Liquormart, Inc. v. Rhode Island, 517 U.S. 484, 501 (1984); City of Cincinnati v. Discovery Network, Inc., 507 U.S. 410, 426 ((1993)).

[lii] 447 U.S. 557 (1980).

[liii] *Id*. at .

[liv] *Friedman*, 13 F. Supp. 2d at 67.

[lv] *Id.*

[lvi] *Id.* at 72.

[lvii] *Id.* at 73.

[lviii] *Id.*

[lix] *Id.* at 74-75. The court also held that the FDA could not prohibit manufacturers from suggesting content to Continuing Medical Education providers. *Id.*

[lx] *Id.* at 73.

[lxi] *Id.*

[lxii] The Food and Drug Administration Modernization Act of 1997, Pub. L. No. 105-115, 111 Stat. 2296 (1997).

[lxiii] See 21 U.S.C. § 360(a).

[lxiv] 56 F. Supp. 2d 81 (D. D.C. 1999).

[lxv] *Id.* at 87.

[lxvi] *Id.*

[lxvii] Washington Legal Foundation v. Henney, 202 F.3d 331, 335 (D.C. Cir. 2000).

[lxviii] *Id.* at 335.

[lxix] *See supra* text accompanying notes .

[lxx] 535 U.S. 357, 360 (2002).

[lxxi] *Id.* at 377.

[lxxii] *Id.* at 369-73.

[lxxiii] *Western States*, 535 U.S. at 360-61. The Court noted that compounding is a "traditional component of the practice of pharmacy" and "is taught as part of the standard curriculum at most pharmacy schools." *Id.* at 361 (citations omitted).

[lxxiv] *Id.* at 362.

[lxxv] *Id.* The regulations state that pharmacies may "not advertise or promote the compounding of any particular drug, class of drug, or type of drug," but may "advertise and promote the compounding service." 21 U.S.C. § 353a.

[lxxvi] 21 U.S.C. §353a.

[lxxvii] *Id.*

[lxxviii] *Western States*, 535 U.S. at 360.

[lxxix] *Id.* at 368.

[lxxx] *Id.* at 371.

[lxxxi] *Id*. at 371-72.

[lxxxii] *Id.* at 372.

[lxxxiii] 517 F.3d 935, 940 (7th Cir. 2008).

[lxxxiv] *Id.* at 937.

[lxxxv] *Id.*

[lxxxvi] *Id.*

[lxxxvii] *Id.* at 940.

[lxxxviii] *Id.* at 939 (citing Virginia Board of Pharmacy v. Virginia Citizens Consumer Council; Thompson v. Western States Medical Center, 535 U.S. 357 (2002).

[lxxxix] *Id.* at 939.

[xc] *Id.*

[xci] *Id.* at 940.

[xcii] *Id.*

[xciii] *Id.* at 940-41.

[xciv] *Id.* at 941.

[xcv] Sorrell v. IMS Health Inc., 131 S. Ct. 2653 (2011).

[xcvi] *Id*. at 2659.

[xcvii] *Id.*

[xcviii] *Id.* at 2660.

[xcix] *Id.*

[c] I*d*.

[ci] Id. at 2661.

[cii] *Id.*

[ciii] *Id.* at 2659.

[civ] I*d*. at (Breyer, J., dissenting).

[cv] *Id*. at 2663.

[cvi] I*d*. at 2663-64.

[cvii] *Id.* at 2664 (citing Ward v. Rock Against Racism, 491 U.S. 781, 791 (1989)).

[cviii] *Id.* at 2667-72.

[cix] I*d.* at 2667 (citing *Central Hudson*, 447 U.S. 557, 566 (1980)).

[cx] I*d.* at 2670.

[cxi] *Id.* at 2668.

[cxii] *Id*. at 2670.

[cxiii] *Id.*

[cxiv] *Id.* at 267l (citing Western States, 535 U.S. at 374; Virginia Bd. of Pharmacy v. Virginia Citizens Consumer Council, Inc., 425 U.S. 748, 769-770 (1976).

[cxv] *Id.*

[cxvi] *Id.*

[cxvii]

[cxviii] United States v. Caronia, 576 F. Supp. 2d 385, 389 (E.D.N.Y. 2008).

[cxix] *Id.* at 388-89.

[cxx] *Id.* at 389.

[cxxi] *Id.*

[cxxii] *Id.*

[cxxiii] *See* United States v. Caronia, 703 F.3d 149, 172 n.3 (Livingston, J., dissenting).

[cxxiv] *See id.*

[cxxv] *Caronia*, 576 F. Supp. 2d at 396 (citing *Bolger*, 463 U.S. 60, 66-68 (1983)).

[cxxvi] *Id.* at 396-402 (applying the test established in *Central Hudson Gas v. Public Service Commission of New York*, 447 U.S. 557 (1980)).

[cxxvii] *Central Hudson*, 447 U.S. 557 (1980).

[cxxviii] *Caronia*, 576 F. Supp. 2d at 398.

[cxxix] *Id.*

[cxxx] *Id.* (referencing *Friedman*, 13 F. Supp. 2d at 72 and *Caputo*, 288 F. Supp. 2d at 921).

[cxxxi] *Id.* at 401 (citing *Friedman*, 13 F. Supp. 2d at 72).

[cxxxii] *United States v. Caronia*, 703 F.3d 149 (2d Cir. 2012).

[cxxxiii] *Id.* at 168-69.

[cxxxiv] *Id.* at 154.

[cxxxv] *Id.* at 160-62.

[cxxxvi] *Id.* at 161.

[cxxxvii] *Id.*

[cxxxviii] *Id.* at 162.

[cxxxix] 131 S. Ct. 2653 (2011).

[cxl] *Id.* at 2659.

[cxli] *Caronia*, 703 F.3d at 165.

[cxlii] *Sorrell*, 131 S. Ct. at 2662-65.

[cxliii] *Caronia*, 703 F.3d at 165.

[cxliv] *Id.*

[cxlv] *Id.* at 166.

[cxlvi] *Id.*

[cxlvii] *Id.*

[cxlviii] *Id.* at 167.

[cxlix] *Id*. at 167-69. To seek a more limited and targeted approach to off-label promotion, the court suggested the following:

1. More directly address off-label use.
2. Guide physicians and patients to differentiate between misleading and false promotion and truthful or non-misleading promotion.
3. Develop warning or disclaimer systems or safety tiers within the off-label market to distinguish between drugs.
4. 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.
5. Create other limits, including ceilings or caps on off-label prescriptions.
6. Further regulate the legal liability surrounding off-label promotion and treatment decisions (medical malpractice and negligence theories of liability).
7. Prohibit off-label prescription all together where such use is exceptionally concerning, as was done with human growth hormone.

[cl] *Id.* at 160.

[cli] *Id.*

[clii] *Caronia*, 703 F.3d at 169 (Livingston, J., dissenting).

[cliii] *Id.* at 171-72 (citing Wisconsin v. Mitchell, 508 U.S. 476, 489 (1993)).

[cliv] *Id.* at 176 (citing *Whitaker v. Thompson*, 353 F. 3d 947, 953 (D.C. Cir. 2004). The case involved sale of saw palmetto, an extract from a dwarf American palm, and what types of claims the seller could make on its label. The seller proposed a label which read: "Consumption of 320 mg daily of Saw Palmetto extract may improve urine flow, reduce nocturia and reduce voiding urgency associated with mild benign prostatic hyperplasia (BPH)." *Whitaker*, 353 F. 3d at 948.

[clv] 353 F.3d 947, 952 (D.C. Cir. 2004).

[clvi] *Id*. at 953.

[clvii] *Id.* at 952-53.

[clviii] I*d.* at 953.

[clix] *Caronia*, 703 F. 3d at 172. The majority in *Caronia* stated that "[e]ven 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, that is not what happened in this case."). *Id.* at 161.

[clx] I*d.* at 172-73.

[clxi] *Id.* at 174.

[clxii] *Id.* at 175.

[clxiii] *Id.* (referring to *Arsenic and Old Lace* (Warner Bros. Pictures 1944)).

[clxiv] *Caronia*, 703 F. 3d at 176.

[clxv] *Western States*, 535 U.S. at 370-71.

[clxvi] *Sorrell*, 131 S. Ct. at .

[clxvii] *Caronia*, 703 F. 3d at 176.

[clxviii] I*d.* at 180 (citing *Sorrell*, 131 S. Ct. at 2672).

[clxix] *Id*.

[clxx] *Id.* at 179.

[clxxi] *Caronia*, 703 F. 3d at 178 (citing *Western States*, 535 U.S. at 369). In Western States, the Court stated, "preserving the effectiveness and integrity of the FDCA's new drug approval process is clearly an important governmental interest and the Government has every reason to want as many drugs as possible to be subject to that approval process." *Western States*, 535 U.S. at 369.

[clxxii] *Caronia*, 703 F. 3d at 178 (citing FDA v. Brown & Williamson Tobacco Corp., 529 U.S. 120, 133 (2000)).

[clxxiii] *Caronia*, 703 F.3d at 169.

[clxxiv] *Id.* at 178 (citing 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); *see also Caputo*, 517 F. 3d at .940

[clxxv] *Caronia*, 703 F.3d at 179.

[clxxvi] I*d.* at 179-180.

[clxxvii] *Id.* at 166.

[clxxviii] I*d.* at 167.

[clxxix] *Id.* at 166 (citing *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.") (citations omitted).

[clxxx] Michelle M. Mello, David M. Studdert, and Troyen A. Brennan, *Shifting Terrain in the Regulation of Off-Label Promotion of Pharmaceuticals*, N. ENGL. J. MED. 350;15, NEJM.org (April 9, 2009).

[clxxxi] Aaron S. Kesselheim, Michelle M. Mello, David M. Studdert, *Strategies and Practices in Off-label Marketing of Pharmaceuticals: A Retrospective Analysis of Whistleblower Complaints*, PLoS Med 8(4): e1000431. Doi:10.137/journal.pmed.1000431 (2011).

[clxxxii] *See* Marcus Baram, *Ex-Drug Sales Rep Tells All*, ABCNEWS.com, available at http://abcnews.go.com/Health/Story?id=4438095&page=1 (last visited May 31, 2013).

[clxxxiii] *See, e.g.*, Puneet Manchanda & Elisabeth Honka, *The Effects and Role of Direct-to-Physician Marketing in the Pharmaceutical Industry: An Integrative Review*, 5 YALE J. HEALTH POL'Y & ETHICS 785 (2005).

[clxxxiv] *See* Alice LaPlante, *Marketing Directly to Physicians Reaps Higher Returns for Drug Companies*, Stanford Graduate School of Business Marketing Research (Aug. 2006), http://www.gsb.stanford.edu/news/research/mktg narayananpharmaceuticals.shtml.

[clxxxv] Marc-Andre Gagnon & Joel Lexchin, T*he Cost of Pushing Pills: A New Estimate of Pharmaceutical Promotion Expenditures in the United States*, 5 PLOS MED. El (2008).

[clxxxvi] Manchanda & Honka, *supra* note , at 785 (citing Dick R. Wittink, *Analysis of ROI for Pharmaceutical Promotion* (ARPP) (2002)), http://www.rxpromoroi.org/arpp/media/arpp handout 0927.pdf.

[clxxxvii] *See* Lars Noah, *Death of a Salesman: To What Extent Can the FDA Regulate the Promotional Statements of Pharmaceutical Sales Representatives?*, 47 FOOD & DRUG L.J. 309, 309-16 (1992).

[clxxxviii] *See* LaPlante, *supra* note ; *see also* Ashley Wazana, *Physicians and the Pharmaceutical Industry: Is a Gift Ever Just a Gift?* 283 JAMA 373, 373 (2000).

[clxxxix] While detailing may be the most common type of off-label promotion, the practice may be one part of a more extensive off-label marketing strategy. One study showed that companies have used a combination of tactics to promote off-label uses. In combination, these tactics give the appearance to physicians that the off-label use has been accepted or gained traction in the medical community. Creating physician advisory boards, convincing prominent physicians to serve as "thought leaders" to influence colleagues to use a product off-label are tactics that physicians may not recognize as commercially influenced. Drug companies have also hired communication companies that get articles published in medical journals. *See* Sergio Sismondo, *Ghost Management: How Much of the Medical Literature is Shaped Behind the Scenes by the Pharmaceutical Industry?* 4 PLoS MED e286 (2007) (noting that "medical journals have real effects upon physician prescribing behavior, which is why pharmaceutical companies invest so much in their publication"). Even peer-reviewed, double-blind studies published in prestigious medical journals can spread faulty information when drug companies manipulate the results. *See* Richard Smith, *Medical Journals Are an Extension of the Marketing Arm of Pharmaceutical Companies*, 2 PLoS MED. El38 (2005). The former editor of the *New England Journal of Medicine* echoes these sentiments:

[cxc] *See* Department of Justice, Press Release, *Abbott Labs to Pay $1.5 Billion to Resolve Criminal & Civil Investigations of Off-Label Promotion of Depakote* (May 7, 2012), available at www.justice.gov/opa/pr/2012/May/12-civ-585.html.

[cxci] *See* Adriane Fugh-Berman & Shahram Ahari, *Following the Script: How Drug Reps Make Friends and Influence Doctors*, PLoS Medicine 4(4): e150 (2007).

[cxcii] *See id.*

[cxciii] *See id.*

[cxciv] *See id.*

[cxcv] Shahram Ahari, Letter to Congress, Testimony before the Special Senate Committee on Aging (March 2008) available at http://www.aging.senate.gov/events/hr190sa.pdf. Ahari testified that in the training class for the "elite neuroscience division" at Eli Lilly, none of his twenty-one classmates had college level scientific education. *Id.*

[cxcvi] *Id.*

[cxcvii] *Id.*

[cxcviii] *Id.*

[cxcix] *See Caronia*, 703 F. 3d at 166-67.

[cc] *See* Michael A. Steinman & Dean Schillinger, *Drug Detailing in Academic Medical Centers: Regulating for the Right Reasons, with the Right Evidence, at the Right Time*, THE AM. J. OF BIOETHICS,10:1, at 23 (2010); *see also* Ahari s*upra* note (explaining that drug reps were trained to downplay side effects of a drug). *See* Marcus Baram, Ex-Drug Sales Rep Tells All, ABCNEWS.com, available at http://abcnews.go.com/Health/Story?id=4438095&page=1 (last visited).

[cci] A related issue about manufacturer's control of information is raised by Peter Doshi and Tom Jefferson in *Drug Data Shouldn't Be Secret*, NYT (April 10, 2012). The authors criticize Roche for failing to release to the research community most of the clinical trial data that would support claims about the anti-influenza drug Tamiflu. They note that the FDA approved Tamiflu to treat flu symptoms but did not reach conclusions about Tamiflu's ability to reduce hospitalization stays and serious complications. The authors suggest that literature, including peer-reviewed articles, touting the "assumed properties" of the drug, rely solely on information published by Roche. *Id.* Without evidence of the drug's effectiveness, more than $1.5 billion of taxpayer money was devoted to stockpiling the drug. *Id.*

[ccii] *See* Steinman & Schillinger, *supra* note , at 22.

[cciii] *See, e.g.,* Puneet Manchanda & Pradeep K. Chintagunta, *Responsiveness of Physician Prescription Behavior to Salesforce Effort: an Individual Level Analysis*, 15 MARKETING LETTERS 129, 138 (2004) (finding that pharmaceutical detailing impacts prescribing behavior); Natalie Mizik & Robert Jacobson, *Are Physicians "Easy Marks"?: Quantifying the Effects of Detailing and Sampling on New Prescriptions*, 50 MGMT. SCI. 1704, 1714 (2004) (finding that past detailing affects current prescribing habits).

[cciv] *See* Douglas Mossman, MD & Jill L. Steinberg, *Promoting, Prescribing, and Pushing Pills: Understanding the Lessons of Antipsychotic Drug Litigation*, 13 MICH. ST. U. J. MED. & LAW, 263, 268 (2009); *see also* Manchanda & Honka, *supra* note , at 787 ("Detailing affects physician prescription behavior in a positive and significant manner.").

[ccv] Association of American Medical Colleges, *Industry Funding of Medical Education: Report of an AAMC Task Force* (2008), available at http://services.aamc.org/publications/showfile.cfm?file=version114.pdf&prd_id=232 (last visited May 14, 2013).

[ccvi] *See* Steinman & Schillinger, *supra* note , at 21-23.

[ccvii] Association of American Medical Colleges, *The Scientific Basis of Influence and Reciprocity: A Symposium*, Washington, D.C., (2007). The report quoted one doctor as saying,

"You don't really thing that I would let a pizza lunch influence my decision-making process for my patients, do you?"

[ccviii] See Steinman & Schillinger, *supra* note , at 22.

[ccix] *See* Steinman & Schillinger, *supra* note , at 23.

[ccx] *See Caputo*, 288 F. Supp. 2d at 921 ("Defendants' speech was directed at physicians who are familiar with the FDA-approval process and able to independently evaluate the validity of their claims. Given the sophistication of the audience to whom the off-label uses were promoted, this court cannot conclude . . . that Defendants' speech as inherently misleading.").

[ccxi] *Henney*, 56 F. Supp. at 86.

[ccxii] *Caputo*, 288 F. Supp. 2d at 921.

[ccxiii] *Caronia*, 703 F. 3d at 178 (citing 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, 185-86 (1995).

[ccxiv] Jerry Avorn, M.D., Milton Chen, & Robert Hartley, M.D., S*cientific versus Commercial Sources of Influence on the Prescribing Behavior of Physicians*, THE AM. J. OF MED., Vol. 73 (July 1982).

[ccxv] *Id.* at 4.

[ccxvi] I*d.* at 4-6.

[ccxvii] *Id.* at 5.

[ccxviii] *Id.* at 6-7.

[ccxix] *See, e.g.*, Howard Brody, *The Company We Keep: Why Physicians Should Refuse to See Pharmaceutical Representatives*, 3 ANNALS OF FAM. MED. 82, 83 (2005); Melinda L. Randall et al., *Attitudes and Behaviors of Psychiatry Residents toward Pharmaceutical Representatives Before and After an Educational Intervention*, 29 ACAD. PSYCHIATRY 33, 35-36 (2005).

[ccxx] David T. Burke et al., *Reading Habits of Practicing Physiatrists*, 81 AM J. PHYS. MED. & REHABILITATION 779 (2002) ("most physiatrists only scan the table of contents and read the most important abstracts").

[ccxxi] JEROME GROOPMAN, M.D., HOW DOCTORS THINK 221 (2007).

[ccxxii] 202 F. 3d 331, 332 (D.C. Cir. 2000).

[ccxxiii]Even as doctors recognize the benefits of some off-label prescriptions, questions have increasingly arisen regarding the scientific rationale for some off-label uses. *See, e.g.*., Becky A. Briesacher et al., *The Quality of Antipsychotic Drug Prescribing in Nursing Homes*, 165 ARCH. OF INTERNAL MED. 1280 (2005) (more than one fourth of nursing home residents received antipsychotic medications; many prescriptions were off-label and/or exceeded dosage guidelines).

[ccxxiv] *See* Glenn C. Smith, *Avoiding Awkward Alchemy – In the Off-Label Drug Context and Beyond: Fully-Protected Independent Research Should not Transmogrify Into Mere Commercial Speech Just Because Product Manufacturers Distribute It*, 34 WAKE FOREST L. REV. 963, 971 (1999) (explaining that off-label prescribing is particularly important in certain specialties, such as cancer treatment and pediatric medicine).

[ccxxv] *See* GROOPMAN, *supra* note , at 218.

[ccxxvi] *Caronia*, 703 F. 3d at 172 n.3.

[ccxxvii] 2013 U.S. App. LEXIS 4472 at *4.

[ccxxviii] *Id.* at *6.

[ccxxix] *Id.*

[ccxxx] *Id.* at *6-7.

[ccxxxi] Id. at *8.

[ccxxxii] 187 U.S. 94 (1902).

[ccxxxiii] *Id.* at *9.

[ccxxxiv] *Id.* at *8 (citing Seven Cases v. United States, 239 U.S. 510, 517 (1916)).

[ccxxxv] *See* Richard Ausness, *supra* note at 1262-64. The company paid $19.5 million to states to settle a civil suit based on its alleged promotion of off-label use. It paid $470 million in fines and payments to state and federal agencies and $130 million to settle civil lawsuits brought against the company by former patients who claimed to have become addicted to OxyContin. The company paid over $600 million in fines and civil penalties, an amount that was about ninety percent of the profits that it initially made from OxyContin sales. *Id.*

ccxxxvi