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Striking a Balance: Ensuring the Safety and Efficacy of a Drug's Use, While Recognizing the First Amendment Protection of Truthful, Non-Misleading off-Label Drug Communications

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STRIKING A BALANCE: ENSURING THE SAFETY AND EFFICACY OF A DRUG’S USE, WHILE RECOGNIZING THE FIRST AMENDMENT PROTECTION OF TRUTHFUL, NON-MISLEADING OFF-LABEL DRUG COMMUNICATIONS

HANNAH SMOOT COMBS*

“[F]ear that speech might persuade provides no lawful basis for quieting it.”¹

I. INTRODUCTION

Under the Food and Drug Administration’s (“FDA”) broad construction of the Food, Drug, and Cosmetic Act (“FDCA”), current regulations greatly restrict the ability of pharmaceutical firms to engage in communications with physicians concerning a drug’s off-label indications—or uses that have not received FDA approval.² According to FDA regulations, “labeling” includes not only the official label on a drug’s packaging or its accompanying advertisements, but also brochures, detailing pieces, letters, sound recordings, and other “printed, audio, or visual matter descriptive of a drug.”³ Labeling that is false or misleading is considered “misbranded” and therefore subject to prosecution.⁴ Given the FDA’s pervasive regulation of a drug’s off-label indications, the distinction between illegal promotion of off-label uses and legal, off-label communications remains unclear.

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¹ Sorrell v. IMS Health Inc., 131 S. Ct. 2653, 2670 (2011).
As the FDA attempts to further restrict off-label communications, the pharmaceutical industry has raised concerns about the constitutionality of the FDA's actions. Undoubtedly, the FDA has a responsibility to protect patients from the potential harm caused by ingesting medications for uses that are not scientifically supported. This responsibility, however, does not preclude the constitutional guarantee that "Congress shall make no law . . . abridging the freedom of speech," a guarantee courts have interpreted to include the protection of commercial speech.

A Second Circuit holding in favor of pharmaceutical companies' right to engage in truthful, non-misleading off-label promotion has provided the Supreme Court with a blueprint for preserving the First Amendment protection of commercial speech. Given the Second Circuit's position; it may be time for the FDA to consider whether current FDA regulations truly serve the best interests of the public.

This Note examines the Second Circuit's recent expansion of the First Amendment to include the protection of truthful, non-misleading speech promoting off-label uses of FDA approved drugs. Part II provides a brief historical background of the policy reasons behind the FDA's more stringent regulations. Part III discusses the prevalence of current off-label practices within the healthcare industry and the ethical concerns associated with pharmaceutical companies engaging in off-label promotion. Part IV outlines the pertinent commercial speech case law that has shaped the First Amendment discussion surrounding off-label communications, including the Second Circuit decision in United States v. Caronia, which led to the recent district court decision in Amarin Pharma Inc. v. United States FDA. Part V discusses the implications of the Amarin decision, and furthermore questions whether a constitutional analysis is the ap-

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5 U.S. CONST. amend. I.
7 See United States v. Caronia, 703 F.3d 149 (2d Cir. 2012).
8 See id. at 160.
propriate legal method for resolving cases involving FDA regulation of off-label uses. Part VI encourages the FDA to adopt alternative methods of drug regulation that do not violate the First Amendment.

II. THE HISTORICAL BACKDROP

The FDA's overly restrictive methods of drug regulation\(^1\) have evolved in response to growing concern over an unchecked pharmaceutical industry.\(^2\) This concern escalated in 1937 when over one hundred individuals were poisoned by ingesting Elixir Sulfanilamide, a new drug formulation created for the treatment of streptococcal infections.\(^3\) Unbeknownst to prescribing physicians, this new formulation contained Diethylene Glycol, a chemical used in antifreeze.\(^4\) In response to this tragic event, Congress created the FDCA to “protect the health and safety of the public by preventing


\(^{13}\) Id.
deleterious, adulterated, or misbranded articles from entering inter-
state commerce."\textsuperscript{14}

The original purpose of the FDCA was to ensure the safety of a drug's marketed use, but in 1962 Congress enacted the Kefauver-
Harris Amendment, or the "Drug Efficacy Amendments," additionally requiring pharmaceutical companies to prove the efficacy of a drug's intended use.\textsuperscript{15} Thereinafter, once a pharmaceutical company successfully provides the FDA with sufficient evidence of the safety and efficacy of a drug's use, only FDA approved uses may be included in the drug's labeling.\textsuperscript{16} "Labeling" includes not only a drug's packaging, but also the printed, audio, and visual communications utilized by manufacturers when describing a drug's uses.\textsuperscript{17}

To ensure compliance with these labeling requirements, the FDA has promulgated various regulations that affect the ability of pharmaceutical companies to engage in off-label communications.\textsuperscript{18} FDA regulations do not expressly prohibit off-label communications, but manufacturers are prohibited from introducing a drug into interstate commerce without FDA approved labeling.\textsuperscript{19} If a drug's labeling is false or misleading, the manufacturer is guilty of the crime of "misbranding."\textsuperscript{20} In certain circumstances, off-label promotion may even result in civil liability under the False Claims Act ("FCA").\textsuperscript{21}

\textsuperscript{15} 50th Anniversary of the Kefauver-Harris Drug Amendments of 1962 - Interview with FDA Historian John Swann, U.S. FDA (last updated Dec. 3, 2015), http://www.fda.gov/Drugs/NewsEvents/ucm320927.htm. Similar to the circumstances surrounding the adoption of the FDCA, the Kefauver-Harris Amendment was created in response to the unfortunate discovery that Thalidomide, a drug commonly prescribed for morning sickness, caused thousands of birth defects throughout Europe and Africa. Id.; see also 50 Years: The Kefauver-Harris Amendments, U.S. FDA (last updated Feb. 26, 2016), http://www.fda.gov/Drugs/NewsEvents/ucm320924.htm.
\textsuperscript{16} 21 C.F.R. §§ 331(a), 352(a) (2015).
\textsuperscript{21} 31 U.S.C. § 3729 (2013). For the purposes of this Note, discussion will predominantly focus on violations of the FDCA, not the FCA. For more information about the intersection between the FCA and off-label communications, see Joan
overarching threat of a misbranding action or FCA liability makes it difficult for pharmaceutical firms to engage in off-label communications.

In contrast, the FDA recognizes that physicians must be able to use their "best knowledge and judgment" when treating patients. Therefore, the FDA permits physicians to write prescriptions for off-label uses without penalty under the FDCA. This creates a strange paradox where physicians can prescribe medications for off-label uses, but pharmaceutical companies—the companies that make and test these drugs—are not able to provide doctors with information that may be necessary to make the most informed decisions.

III. Off-Label Use and Promotion

A. Off-Label Prescribing by Physicians

To better understand these regulatory inconsistencies, physicians' and pharmaceutical companies' off-label practices must be distinguished. The FDCA mandates FDA approval of a drug's use, but the reality is that more than 20% of prescriptions are written for off-label uses, with this percentage being even higher in specific sub-


23 See id.

populations. Professor Joan Krause notes that this statistic yields varying interpretations. For example, some explain this percentage as evidence that in certain circumstances off-label use is standard practice, while others view this as proof that off-label prescribing practices have reached dangerously high levels. No matter the reader’s interpretation of this statistic, in some situations, off-label use of an approved drug may be a patient’s only option.

The Mayo Clinic outlines several scenarios that require or encourage doctors to prescribe off-label. For example, a physician may prescribe a drug that is FDA approved for one specific group to another non-approved group, such as pediatric or geriatric patients. These non-approved groups tend to be subpopulations that are difficult to conduct FDA testing on, or that have not been studied adequately, including children, cancer patients, psychiatric patients, and the elderly. In fact, one study found that 78.9% of children discharged from pediatric hospitals are prescribed at least one medica-


26 Krause, supra note 4.


29 The Mayo Clinic is a worldwide nonprofit that conducts medical research and provides medical education to the public. For more information, see About Mayo Clinic, MAYO CLINIC, http://www.mayoclinic.org/about-mayo-clinic (last visited March 12, 2016).

30 Wittich et al., supra note 26, at 982.

31 Id.

32 Id.
tion for off-label indications. This includes the well-known drug Morphine, which hospitals commonly prescribe to injured children without specific FDA approval.

In situations involving rare diseases and high-risk illnesses, off-label prescriptions may be a patient’s only treatment option. In fact, approximately 56% of cancer patients are given at least one drug off-label. Even in the absence of a rare disease or high-risk illness, doctors may choose to prescribe a non-FDA approved medication when a drug is in the same class as another FDA approved drug for that indication. Similarly, when the pathologic or physiologic features of two medical conditions are alike, a doctor may prescribe medication (which is approved for only one of the conditions) for the other condition, or both conditions, without FDA approval. As the FDCA explicitly recognizes, some situations require physicians to use their medical knowledge and judgment to prescribe non-FDA approved medications for the sake of their patient’s health.

B. Off-Label Promotion by Pharmaceutical Companies

While physicians are free to prescribe medications for off-label uses, FDA regulations prohibit pharmaceutical companies from

33 Id. at 983 (citing Samir S. Shah et al., Off-Label Drug Use in Hospitalized Children, 161 ARCHIVES PEDIATRIC ADOLESCENT MED. 282-90 (2007)).
34 See Wittich et al., supra note 26, at 984-85 (displaying examples of common off-label uses of drugs in a table).
35 See id. at 983; see also Iraggi, supra note 26, at 1137.
37 Wittich et al., supra note 26, at 982.
38 Id. For example, anxiety and posttraumatic stress disorder are two, similar psychiatric diseases. A doctor may choose to prescribe a medication approved for posttraumatic stress disorder for anxiety, a non-FDA approved use.
39 21 U.S.C. § 396 (2012) ("Nothing in this Act [21 USCS §§ 301 et seq.] shall be construed to limit or interfere with the authority of a health care practitioner to prescribe or administer any legally marketed device to a patient for any condition or disease within a legitimate health care practitioner-patient relationship.").
Ethical concerns arise when pharmaceutical firms use marketing strategies to influence physicians. Such marketing strategies include detailing, giving gifts, supplying medication samples to physicians, and providing grants to health organizations. Although some courts have described doctors as a "sophisticated audience" capable of determining if such information is misleading, it is questionable how truly "sophisticated" physicians can be when faced with pharmaceutical firms that invest billions of dollars in such marketing strategies.

To diminish these ethical concerns, the FDA has extensively fined pharmaceutical companies for the promotion of off-label uses

40 See Greene & Noah, supra note 3, at 250; see also, 21 C.F.R. § 202.1(e)(4)(i)(a) (2015) (advertising may not "recommend or suggest any use that is not in the labeling accepted in such approved new-drug application or supplement").


42 Detailing is when a pharmaceutical company physically visits a physician to conduct a face-to-face pitch. Id.

43 Id.


45 Persuading the Prescribers, supra note 42 ("In 2012, the pharmaceutical industry spent more than $27 billion on drug promotion—more than $24 billion on marketing to physicians and over $3 billion on advertising to consumers.") (internal citations omitted).
in violation of the FDCA's misbranding provisions.\textsuperscript{46} In 2004, for example, Warner-Lambert entered a plea agreement for violating the FDCA's misbranding provisions and agreed to pay $240 million in criminal fines.\textsuperscript{47} Warner-Lambert allegedly promoted Neurontin, an FDA-approved seizure preventative, for unapproved uses such as treating bipolar disorder, attention deficit disorder, and restless leg syndrome.\textsuperscript{48} Additionally, in 2009, Pfizer Inc. and two of its subsidiary companies paid $1.3 billion in criminal fines for the alleged off-label promotion of the anti-inflammatory drug Bextra, which the FDA specifically declined to approve for the treatment of acute pain and surgical pain.\textsuperscript{49}

More recently, in the largest healthcare fraud settlement in U.S. history, GlaxoSmithKline LLC entered into a criminal plea agreement and paid over $750 million in criminal fines for allegedly promoting Paxil and Wellbutrin's off-label uses.\textsuperscript{50} The pharmaceutical firm allegedly promoted Paxil for treating depression in children when the FDA had not approved the drug for pediatric use.\textsuperscript{51} In addition, the firm allegedly promoted Wellbutrin for treating substance addictions, attention deficit hyperactivity disorder, and for other off-label uses when the FDA had only approved Wellbutrin for the

\textsuperscript{46} For the purposes of this Note, discussion is limited to violations under the FDCA. While off-label promotion can lead to violations under the FCA, discussion pertaining to the FCA is beyond the scope of this Note. For further discussion about off-label promotions leading to violations of the FCA, see Krause, supra note 22.


\textsuperscript{48} Id.


\textsuperscript{51} Id.
treatment of major depressive disorder.\textsuperscript{52} Overall, ten of the twenty largest settlements and judgments between 1991 and 2012 related to the unlawful promotion of a prescription medication in violation of the FDCA.\textsuperscript{53}

As staggering as these settlements may seem, pharmaceutical companies continue to engage in off-label promotion,\textsuperscript{54} as the profits generated from promoting off-label uses far exceed the FDA’s penalties.\textsuperscript{55} When pharmaceutical companies promote a drug’s off-label uses, manufacturers can avoid the lengthy\textsuperscript{56} and expensive task of obtaining FDA approval.\textsuperscript{57} Off-label communications between physicians and pharmaceutical representatives may even equip pharmaceutical firms with valuable information concerning the different uses for which physicians are prescribing the firm’s drugs. Considering the informational and economic benefits of engaging in off-label communications, it is not hard to imagine how many pharmaceutical companies could view off-label promotion as a smart business move.

C. The Free Flow of Medical Information

Ethical concerns arise when pharmaceutical companies engage in marketing practices to promote the sale of a drug, prioritizing revenue over science. It is important, however, to balance concerns over pharmaceutical greed and abuse with the reality that off-label prescribing is occurring. To best do so, physicians should have access to information concerning the effects of off-label prescrip-

\textsuperscript{52} Id.


\textsuperscript{54} Marc A. Rodwin, \textit{Do We Need Stronger Sanctions to Ensure Legal Compliance By Pharmaceutical Firms?}, 70 FOOD DRUG L.J. 435 (2015).

\textsuperscript{55} Id. at 436.

\textsuperscript{56} On average, it takes approximately "15 years from the beginning of drug development until a drug can be marketed." Marc A. Rodwin, \textit{Independent Drug Testing to Ensure Drug Safety and Efficacy}, 18 J. HEALTH CARE L. & POL’Y 45, 80 (2015) [hereinafter \textit{Independent Drug Testing}].

tions. By restricting pharmaceutical companies from engaging in off-label promotion, "physicians may find it difficult to establish how others in their fields are using medication outside their FDA approved uses," and, in turn, may not learn about the positive and negative effects of prescribing certain medications for their off-label indications.58

In the alternative, are there other less biased avenues through which physicians can obtain information about a drug's off-label uses? Professor Marc A. Rodwin argues that independent drug testing is needed in order to eliminate the dissemination of biased drug information.59 Since drug firms often bias clinical trials through design, control, and financial influence,60 it is imperative that physicians have access to clinical trials funded by nonproprietary sources, such as the U.S. Department of Health and Human Services' National Institutes of Health ("NIH").61 A recent study, however, suggests that while the number of industry-sponsored trials has increased 43% between 2006 and 2014, the number of NIH-sponsored trials have decreased by 24%.62 Until the requisite reform occurs,63 physicians must continue to prescribe drugs using the available sources of information, keeping the best interests of the patient in mind. The reality is that a vast amount of drug information comes from industry-sponsored clinical trials.64

59 See Independent Drug Testing, supra note 57, at 80.
62 Stephanie Desmon, Industry-Financed Clinical Trials on the Rise as Number of NIH-Funded Trials Falls, HUB (Dec. 15, 2015), http://hub.jhu.edu/2015/12/15/industry-funded-clinical-trials-may-threaten-objectivity ("The number of newly registered industry-sponsored trials increased 43 percent over the time period, from 4,585 in 2006 to 6,550 in 2014. The number of newly registered NIH-funded trials decreased 24 percent over the same period, from 1,376 in 2006 to 1,048 in 2014.").
63 For a potential method of reform, see Independent Drug Testing, supra note 57, at 82–84.
64 See id.
To quote the FDA: “Good medical practice and the best interests of the patient require that physicians use legally available drugs, biologics and devices according to their best knowledge and judgment.” It is curious that the FDA expects physicians to make knowledgeable and informed decisions, yet deprives doctors of a large amount of the medical information necessary to make such decisions. Although the FDA's behavior is not unfounded and physicians do have access to nonproprietary information sources, there must be better alternatives for protecting the public that do not involve the suppression of potentially vital medical information or infringement upon the First Amendment.

IV. The Evolution of Commercial Speech Within the Pharmaceutical Industry

Supreme Court precedent makes clear that truthful, non-misleading commercial speech is protected under the First Amendment. Part IV provides a historical analysis of the landmark cases that led to the recent district court decision in *Amarin Pharma Inc. v. United States FDA* and furthermore suggests that First Amendment protection extends to truthful, non-misleading off-label communications.

A. An Introduction to Commercial Speech

In the 1976 Supreme Court case, *Virginia State Board of Pharmacy v. Virginia Citizens Consumer Council, Inc.*, the Court acknowledged that “society ... may have a strong interest in the free flow of commercial information.” Furthermore:

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68 Id. at 764.
Advertising, however tasteless and excessive it sometimes may seem, is nonetheless dissemination of information as to who is producing and selling what product, for what reason, and at what price. So long as we preserve a predominantly free enterprise economy, the allocation of our resources in large measure will be made through numerous private economic decisions. *It is a matter of public interest that those decisions, in the aggregate, be intelligent and well informed.* To this end, the free flow of commercial information is indispensable.69

Recognizing our democratic interest in preserving the free flow of information, the Court held that commercial speech is constitutionally protected.70 The Court did, however, note limitations to this finding.71 Specifically, regulation of commercial speech is justified when (1) the regulation does not concern content; (2) "the regulation serve[s] a significant government interest"; and (3) there are no alternative channels for communication of the information.72

In the 1980 case, *Central Hudson Gas & Electric Corp. v. Public Service Commission*,73 the Court established a four-part analysis for determining when commercial speech is protected under the First Amendment.74 First, the commercial speech must be lawful and non-misleading.75 Second, the government interest must be substantial.76 Third, the regulation must "directly advance[]" the specific government interest.77 Finally, the regulation cannot be more than necessary to serve the specific interest.78 As the following major off-label decisions evidence, courts continue to apply the *Central Hudson* test

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69 *Id.* at 765 (emphasis added).
70 *Id.* at 770.
71 See *id.* at 771.
72 *Id.*
73 447 U.S. 557 (1980).
74 See *id.* at 566.
75 See *id.*
76 See *id.*
77 *Id.*
78 See *id.*
in determining whether or not the First Amendment protects specific commercial speech.


In its original action, Washington Legal Foundation sought a declaratory judgment finding that FDA policies restricting off-label promotion violated the First Amendment. According to Washington Legal Foundation, these policies were expressed through FDA guidance documents, which attempted to distinguish marketing activities that are subject to regulation under the FDCA's advertising and labeling provisions from activities that serve purely scientific and educational purposes and are therefore exempt from FDA regulation. Before the district court could rule on its final decision, Congress amended the FDCA and enacted the 1997 Food and Drug Administration Modernization Act ("FDAMA"), thus superseding the FDA guidance documents. Most notably, FDAMA § 401 gave manufacturers limited permission to disseminate off-label information. For the reasons discussed below, the court in Washington Legal

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Foundation v. Henney ultimately held that the FDAMA and its implementing regulations perpetuated the policies held unconstitutional in Washington Legal Foundation v. Friedman and unconstitutionally restricted protected commercial speech.

To find that the FDAMA's commercial speech regulations violated the First Amendment, the court in Washington Legal Foundation v. Henney applied the four-prong Central Hudson test. First, the court noted that the speech at issue was neither false nor misleading. Defendants attempted to argue that the pharmaceutical marketer's speech was likely misleading because "manufacturers have an incentive to disseminate information that presents their drugs only in a positive light, omitting negative information." Nonetheless, the court rejected the defendant's arguments for two reasons: (1) the FDA cannot "restrict speech based on its perception that the speech could, may, or might mislead," and (2) the defendants in this case did not express concern over physicians exchanging off-label information, therefore, discriminating among specific speakers.

Second, the court in Washington Legal Foundation recognized that only one of the policies in the FDAMA directly advanced a substantial government interest. The court discussed two government interests at issue in this case, including the concern that doctors receive "accurate and unbiased" information and that manufacturers are encouraged to seek FDA approval. The court quickly rejected the first government interest and stated that it is a violation of the

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85 Wash. Legal Found., 56 F. Supp. 2d at 84-87.
86 Id. at 85 ("The First Amendment is premised upon the idea that people do not need the government's permission to engage in truthful, nonmisleading speech about lawful activity.").
87 Id.
88 Id.
89 Id. at 85-86 (quoting Greater New Orleans Broad. Assoc. v. United States, 527 U.S. 193, 194 (1999) ("Even under the degree of scrutiny that we have applied in commercial speech cases, decisions that select among speakers conveying virtually identical messages are in serious tension with the principles undergirding the First Amendment.")).
90 Id. at 86-87.
91 Id. at 86.
First Amendment to prevent a listener, especially a "sophisticated listener [such as a doctor] trained extensively in the use of such information," from obtaining truthful non-misleading speech for the fear of the listener misusing information.\(^9\) Although the court acknowledged a substantial government interest in encouraging manufacturers to seek FDA approval, it noted that only one of the many policies within the FDAMA directly advanced that interest.\(^93\) Further, that policy was deemed unconstitutional because it substantially burdened speech more than necessary to advance the government's interests.\(^94\)

Washington Legal Foundation set the foundation for the D.C. Circuit to explicitly recognize the First Amendment protection of truthful, non-misleading speech within the pharmaceutical industry. The case, however, was later dismissed at the parties' request when the FDA and Washington Legal Foundation came to an agreement.\(^95\) In this agreement, the FDA stated that §401 of the FDAMA and its corresponding regulations were "safe harbors," wherein "the distribution of certain materials would not be used as evidence of the manufacturer's intent that the product be used in an unapproved manner" so long as the manufacturer met the requirements established in §401 of the FDAMA.\(^96\) The FDA's articulation of these safe harbor provisions suggested that the First Amendment concerns

92 Id. ("The government, however benign its motivations, simply cannot justify a restriction of truthful nonmisleading speech on the paternalistic assumption that such restriction is necessary to protect the listener from ignorantly or inadvertently misusing the information.").

93 Id. at 86–87.

94 Id. at 87 ("The existing factors encouraging supplemental applications, along with the many non-speech-restrictive alternatives available to the government, highlight the degree to which the FDAMA unduly burdens commercial speech. The supplemental application requirement burdens substantially more speech than necessary to advance the government's legitimate interest, and it therefore violates the First Amendment.").


were coming to an end. Unfortunately, Congress allowed the FDAMA provisions to expire in September 2006. The FDA, in turn, issued new guidance documents that have done little to clarify First Amendment concerns. Part V of this Note will return to the discussion of safe harbor provisions as an alternative measure for regulating off-label communications.

C. Thompson v. Western States Medical Center: Drug Advertising and the First Amendment

In the 2002 Supreme Court decision, Thompson v. Western States Medical Center, the Court held that the 1997 FDAMA ban on advertising compounded drugs (drugs mixed together to meet the needs of an individual patient) violated the First Amendment. In applying the Central Hudson test, the Court found that the government failed the fourth prong of the test when it failed to show that the regulations were not more extensive than necessary to serve the government's specific interest. Echoing the sentiments of Washington Legal Foundation, the Court stated, "If the Government could achieve its interests in a manner that does not restrict speech, or that restricts less speech, the Government must do so."

Through dicta, the Court explained its stance on controlling commercial speech that may affect a physician's decisions:


100 Id. at 371.

101 Id.
Even if the Government had argued that the FDAMA's speech-related restrictions were motivated by a fear that advertising compounded drugs would put people who do not need such drugs at risk by causing them to convince their doctors to prescribe the drugs anyway, that fear would fail to justify the restrictions. This concern amounts to a fear that people would make bad decisions if given truthful information about compounded drugs. We have previously rejected the notion that the Government has an interest in preventing the dissemination of truthful commercial information in order to prevent members of the public from making bad decisions with the information. Once again, the Court reiterated that the government's interest in preventing physicians from misusing truthful information does not justify infringing on First Amendment rights. It is clear that courts have taken a position where the concerns for First Amendment protection outweigh the fear or speculation that a healthcare provider may misuse drug information.

**D. Sorrell v. IMS Health Inc.: A New Two-Part Analysis**

In the 2011 Supreme Court case *Sorrell v. IMS Health Inc.*, the Court created a two-step analysis, combining heightened judicial scrutiny with the *Central Hudson* test, to find that a Vermont statute prohibiting pharmaceutical companies from using prescriber-identifying information for marketing purposes violated the First Amendment. The Court applied heightened scrutiny because the speech involved “viewpoint discrimination.” More specifically, the Vermont law placed content- and speaker-based restrictions on speech because the law targeted pharmaceutical manufacturers (a speaker-based restriction) and strictly forbade manufacturers from

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102 *Id.* at 374 (emphasis added).
103 *Id*.
104 131 S. Ct. 2653, 2659 (2011).
105 *Id.* at 2659.
106 *Id.* at 2657.
buying doctors' prescribing history for marketing purposes (a content-based restriction).\(^{107}\)

The *Sorrell* Court noted that under a commercial speech inquiry, the state has to show that "the statute directly advances a substantial government interest and that the measure is drawn to achieve that interest . . . [therefore] ensuring not only that the State's interests are proportional to the resulting burdens placed on speech but also that the law does not seek to suppress a disfavored message."\(^{108}\) In this case, the Court held that the state's justifications—medical privacy and the improvement of public health—did not withstand scrutiny.\(^{109}\) The Court explained that "concern for 'a few' physicians who may have 'felt coerced and harassed' by pharmaceutical marketers" does not justify violating the First Amendment and infringing upon constitutional freedoms.\(^{110}\)

Ultimately, the *Sorrell* Court applied a hybrid analysis of both heightened scrutiny and the *Central Hudson* test,\(^{111}\) holding that the State engaged in content-based discrimination for the sole purpose of "burden[ing] the [disfavored] speech of detailers."\(^{112}\) The Court recognized that the outcome of the case would have been the same regardless of whether it applied heightened judicial scrutiny or the lesser standard set out in *Central Hudson*.\(^{113}\) This decision expanded the First Amendment protection of commercial speech and made clear that protection of the Constitution, specifically the First Amendment, substantially outweighs concerns of healthcare providers potentially misusing information due to ignorance or possible undue influence from pharmaceutical manufacturers seeking sales.\(^{114}\)

E. United States v. Caronia: The *Sorrell* Analysis in Action

\(^{107}\) *Id.* at 2663.

\(^{108}\) *Id.* at 2667-68 (citing Turner Broad. Sys. v. FCC, 512 U.S. 622, 662-63 (1994)).

\(^{109}\) *Id.* at 2668.

\(^{110}\) *Id.* at 2670.

\(^{111}\) *Id.* at 2659, 2667-68.

\(^{112}\) *Id.* at 2672.

\(^{113}\) *Id.* at 2667.

\(^{114}\) *Id.* at 2671.
Under the principle of constitutional avoidance, the 2012 Second Circuit case, United States v. Caronia, held that the FDCA does not prohibit or criminalize off-label promotional speech, standing alone. After an investigation of the off-label promotion of Xyrem—a drug containing gamma-hydroxybutyrate ("GHB") or what is better known as the "date rape drug," and FDA approved for treating narcoleptic patients experiencing cataplexy and for treating narcoleptic patients with excessive daytime sleepiness—the federal government charged a pharmaceutical sales representative from Orphan Medical, Inc. with conspiracy to introduce a misbranded drug into interstate commerce. The government's allegations were based on recorded evidence, which showed Caronia promoting Xyrem for off-label indications, including treatment of fibromyalgia and chronic pain, as well as treatment in "patients as young as fourteen . . . and greater than sixty-five"—even when the drug contained the FDA's highest "black box" warning concerning the safety and efficacy of prescribing Xyrem to children and the elderly. Notably, the court did not find that the case involved false or misleading promotion, nor did the government allege that the promotional speech involved was false or misleading. Caronia, on the other hand, argued that the govern-

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115 703 F.3d 149 (2d Cir. 2012).
116 Id., 703 F.3d at 160 ("While the FDCA makes it a crime to misbrand or conspire to misbrand a drug, the statute and its accompanying regulations do not expressly prohibit or criminalize off-label promotion. Rather, the FDCA and FDA regulations reference "promotion" only as evidence of a drug's intended use. Thus, under the principle of constitutional avoidance . . . we construe the FDCA as not criminalizing the simple promotion of a drug's off-label use because such a construction would raise First Amendment concerns.") (internal citations omitted).
117 Id. at 155–160; see also 21 U.S.C. §§ 331(a) and 333(a)(2) (2012).
119 See Caronia, 703 F.3d at 165–67.
ment convicted him based on his speech, specifically for promoting the off-label use of an FDA approved drug, and therefore the government infringed upon Caronia's First Amendment right to free speech.120

The court in Caronia applied Sorrell's two-step analysis to determine whether the government's interpretation of the FDCA's misbranding provisions violated the First Amendment.121 First, the court found that the speech at issue imposed content- and speaker-based restrictions on speech, thus requiring heightened scrutiny.122 Second, the court noted that even under Central Hudson's intermediate scrutiny standard, the government's regulations did not directly advance the government's goals of safety and efficacy, nor was it necessary to construe the FDCA as criminalizing off-label drug promotion in order to achieve the government's substantial interests.123 Ultimately, it is the role of the speaker and the audience—not the government—to determine whether or not to use off-label information.124

In dicta, the court in Caronia suggested alternative methods for advancing the government's interests in protecting the public and encouraging FDA approval.125 The court's suggestions are helpful in thinking about potential ways to balance protecting the First Amendment and the government's public health concerns. First, the court suggested that the government could create guidelines to assist physicians in differentiating between truthful and misleading in-

120 Id. at 152.
121 Id. at 164.
122 Id.
123 Id.
124 Id. at 167 ("[I]t is the physician's role to consider multiple factors, including a drug's FDA-approval status, to determine the best course of action for her patient...[T]he choice...is not ours to make or the [legislature's]'...Moreover, in the fields of medicine and public health, 'where information can save lives,' it only furthers the public interest to ensure that decisions about the use of prescription drugs, including off-label usage, are intelligent and well-informed.") (internal citations omitted).
125 Id. at 168.
formation. Second, the court noted that the government could require disclaimers warning physicians that the use is not FDA approved. Third, the government could require pharmaceutical companies to list all intended uses when the company first applies for FDA approval. Finally, the government could put a cap on the number of off-label prescriptions or, in specific circumstances, ban off-label use altogether. While the latter options are not without shortcomings, the court's discussion is illustrative of the many available alternatives for regulating pharmaceutical companies that do not impede on the Constitution. Some of these alternatives will be discussed again in further detail in Part V of this Note.

F. Amarin Pharma Inc. v. United States FDA: A New Set of Facts, the Same Finding

The 2015 case, Amarin Pharma Inc. v. United States FDA, is the most recent landmark decision discussing the intersection between the First Amendment and off-label communications. Amarin Pharma Inc. ("Amarin") sought preliminary injunctive relief against the FDA for threatening to pursue a misbranding action if Amarin continued to engage in the truthful, non-misleading promotion of the off-label uses for the FDA approved drug, Vascepa. According to Amarin, the FDA’s threats of a misbranding action were "chilling [Amarin] from engaging in constitutionally protected truthful speech." Guided by the decision in Caronia, the district court granted Amarin relief and held that criminalizing truthful and non-misleading speech that promotes an off-label use violates the First Amendment and "may not form the basis of a prosecution for mis-

126 Id. (citing John E. Osborn, Can I Tell You the Truth? A Comparative Perspective on Regulating Off-Label Scientific and Medical Information, 10 Yale J. Health Pol'y L. & Ethics 299, 305–07 (2013)).
127 Id. (citing Klasmeier & Redish, supra note 66, at 334).
128 Id.
129 Id. (citing United States v. Bader, 678 F.3d 858, 873 (10th Cir. 2012)).
131 Id.
132 Id. at *3.
branding." While some commentators viewed the holding in Caronia as limited to the specific facts of the case, the district court adopted the Second Circuit's holding that the First Amendment protects truthful commercial speech—even when the facts of Amarin were vastly different from those presented in Caronia.

The dispute in Amarin is unique from the facts of Caronia in that Amarin followed the FDA's requirements for approval of the drug Vascepa, but the FDA reneged on its promise. To obtain FDA approval for the use of Vascepa in patients with high triglyceride levels, Amarin followed the FDA's requirements in the "special protocol assessment" ("SPA") and conducted two requisite clinical trials, namely the "ANCHOR study" and the "REDUCE-IT study." In 2012, the FDA approved Vascepa for treating adult patients with triglyceride levels above 500 mg/dL of blood. The FDA did not, however, approve Vascepa for use in statin-treated patients with persistently high triglyceride levels between 200 and 499 mg/dL of blood.

Although the ANCHOR study showed that Vascepa significantly reduced triglyceride levels in patients with persistently high triglycerides, meeting the FDA requirements outlined in the ANCHOR SPA agreement, an FDA Advisory Committee relied on un-

133 Id. at *110.
135 Amarin, 2015 U.S. Dist. LEXIS 103944, at *34.
136 Id. at *34. A special protocol assessment is a written agreement between a manufacturer and the FDA that outlines the specific requirements for drug clinical trials, and the conditions under which the FDA will approve said drug. For more information, see Guidance for Industry: Special Protocol Assessment, U.S. FDA 2 (2002), http://www.fda.gov/downloads/Drugs/.../Guidances/ucm080571.pdf. "The FDA can rescind an SPA agreement only if "a substantial scientific issue essential to determining the safety or effectiveness of the drug has been identified after the testing has begun."" Id.
138 Id. at *31–33 (noting that high triglyceride levels result in an increased risk of pancreatitis and cardiovascular disease in adult patients).
139 Id. at *33.
related clinical trials to find that there was "substantial uncertainty" as to whether a reduction in triglyceride levels would in fact improve cardiovascular health in patients.140 Even though the Advisory Committee did not dispute that Vascepa was safe for use in adult patients with high triglyceride levels,141 the FDA threatened a misbranding action if Amarin marketed Vascepa off-label for that use.142 According to Amarin's Complaint, the FDA's threats inhibited Amarin from promoting the truthful results of the ANCHOR study, which the FDA told the company to conduct,143 thus prohibiting educated healthcare professionals from receiving potentially useful healthcare information.

Amarin advanced two arguments: (1) under Caronia, the FDA was not able to bring a misbranding action based on truthful, non-misleading statements and (2) unlike Caronia's statements, Amarin's proposed statements, specifically those made about the ANCHOR study, were truthful and non-misleading.144 After reviewing both the record of Caronia's trial145 and the Caronia court's First Amendment analysis,146 the Amarin court stated, "Where the speech at issue consists of truthful and non-misleading speech promoting the off-label

140 Id. at *37–39. Furthermore, the FDA Complete Response Letter stated that "[Amarin] will need to provide evidence that Vascepa reduces the risk of major adverse [cardiovascular] events in patients at high risk for cardiovascular disease . . . . We anticipate that the final results from the REDUCE-IT trial [in 2018] could be submitted to satisfy this deficiency." Id. at *40 (citing London Decl., Ex. M.). In other words, even though it is undisputed that Vascepa is safe in patients with high triglyceride levels, the FDA required that Amarin wait three years until 2018 to promote the possible additional benefits of Vascepa to well-educated physicians and healthcare professionals.

141 Id. at *33.
142 Id. at *39–42.
143 Id.
144 Id. at *70.
145 Id. at *74–75 ("To be sure, the Circuit closely reviewed the record of Caronia's trial—in particular, the jury instructions and the government's closing argument. But the Circuit did so to isolate the acts upon which Caronia's conviction had rested—specifically to determine whether Caronia's speech had 'served merely as "evidence of intent"' or whether Caronia had been 'prosecuted for his speech.'").
146 Id. at *76–80.
use of an FDA approved drug, such speech, under Caronia, cannot be the act upon which an action for misbranding is based.\textsuperscript{147}

The FDA argued that the Caronia ruling ran counter to congressional intent, specifically to the 1962 amendments of the FDCA.\textsuperscript{148} The FDA's argument is especially curious when the FDA declined to seek review of Caronia.\textsuperscript{149} Further, the Amarin court noted that the FDA is bound by contemporary First Amendment law, and that "[t]he Supreme Court held in Central Hudson (1980) that the First Amendment gives qualified protection to commercial speech and in Sorrell (2011) that pharmaceutical marketing qualifies as such speech."\textsuperscript{150} Lastly, the decision in Caronia did not interfere with the FDA's ability to pursue a misbranding action for a manufacturer's false or misleading speech or its non-verbal off-label promotional activities.\textsuperscript{151}

The court next directed its attention to Amarin's second argument that the speech at issue was truthful and non-misleading.\textsuperscript{152} Specifically, Amarin sought to disseminate 13 peer-reviewed scientific publications relating to coronary heart disease, a summary of the ANCHOR study, three textual statements, and five disclosures.\textsuperscript{153} After modifying the disclosure statements, including the addition of an explanation for the FDA's decision, the court found that Amarin's speech was truthful and non-misleading.\textsuperscript{154} Even though the FDA expressed concern that the statements relating to Vascepa's effectiveness in treating coronary heart disease could one day be misleading, the court reminded the FDA that:

"[A] governmental body seeking to sustain a restriction on commercial speech must demon-
strate that the harms it recites are real and that its restriction will in fact alleviate them to a material degree”; “[t]his burden is not satisfied by mere speculation or conjecture”. . . . The FDA cannot use the “rote invocation of the words 'potentially misleading' to discharge its burden.”

The court’s position in Amarin is nothing novel, but rather a reverberation of the Supreme Court’s First Amendment decisions discussed above.

V. MOVING FORWARD FROM AMARIN AND CARONIA

Despite First Amendment precedent, it is important to question whether a constitutional finding is an appropriate vehicle for addressing the regulatory actions discussed in this Note. Under the theory of constitutional avoidance articulated in Ashwander v. TVA, if the Supreme Court hears a case that “can be decided on either of two grounds, one involving a constitutional question, the other a question of statutory construction or general law, the Court will decide only the latter.” Justice Brandeis’s concurring opinion in Ashwander suggests that a non-constitutional analysis may be a more apt tool for addressing cases involving the promotion of off-label uses.

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155 Id. at *107 (emphasis added) (internal citations omitted).
156 See supra notes 67–116 and accompanying text.
159 See Ashwander, 297 U.S. at 347 (“The Court will not 'formulate a rule of constitutional law broader than is required by the precise facts to which it is to be applied.' . . . The Court will not pass upon a constitutional question although properly presented by the record, if there is also present some other ground upon which the case may be disposed of. This rule has found most varied application. Thus, if a case can be decided on either of two grounds, one involving a constitutional question, the other a question of statutory construction or general law, the Court will decide only the latter.”) (internal citations omitted).
One alternative to conducting a constitutional analysis may be to address these problems through an administrative law lens. As discussed in Part IV of this Note, since the expiration of the FDAMA provisions in 2006, the FDA has depended on guidance documents in order to control the dissemination of information concerning off-label uses. These procedural shortcuts have allowed the FDA to shape policy without notice-and-comment rulemaking.

Although the Administrative Procedure Act ("APA") does not prohibit the issuance of guidance documents, the FDA's dependence upon them, rather than notice-and-comment rulemaking, has only further complicated the issues surrounding off-label communications.

In addition to the constitutional avoidance doctrine, practical implications suggest that a First Amendment ruling would only exacerbate the tumultuous relationship between the FDA and the pharmaceutical industry. After the decisions in Caronia and Amarin, both the FDA and the pharmaceutical industry have created somewhat of a no-win situation. On one side, the FDA could continue as it is doing and further restrict the pharmaceutical industry's truthful, non-misleading off-label promotion. As the Amarin decision exhibits, however, pharmaceutical firms are ready to fight back. In light of First Amendment precedent, if given the opportunity, it is not unlikely that the Supreme Court would rule in favor of the pharmaceutical industry. The FDA's decision not to appeal in Caronia suggests that this is a path that the FDA is not willing to take.

Alternatively, a First Amendment ruling in favor of the pharmaceutical industry may actually backfire, causing the FDA to control off-label promotion through more restrictive measures.

161 Id. at 1, 3.
163 See Caronia, 703 F.3d at 168 (discussing how the FDA could ban off-label use altogether).
For example, the FDA could make the FDA-approval process even more burdensome by withholding drug approval for longer amounts of time in order to preemptively test for possible off-label uses. Or, as suggested through dicta in Caronia, the FDA could ban off-label use altogether. No matter the outcome, if the FDA and the pharmaceutical industry do not strike some sort of balance, it is difficult to imagine a scenario where either party wins.

Although it may be inappropriate for the Supreme Court to follow the Second Circuit's expansion of protected commercial speech, the Caronia and Amarin decisions serve as a warning to the FDA to adopt alternative measures for regulating the health and safety of patients, without infringing upon First Amendment protections. While not exhaustive, the remainder of this Note will focus on a few of the many viable alternatives for regulating pharmaceutical marketing practices.

A. Defining "False or Misleading"

The inclusion of truthful, non-misleading off-label promotion is a win for First Amendment protection, but as a result of the Second Circuit's decision in Caronia as well as the district court decision in Amarin, the protection of the public health is now an even greater priority. One of the most glaring consequences of these decisions is that prosecution now hinges on whether the off-label communications constitute "false or misleading" information under the FDCA. Markedly, the FDA serves as an arbiter who determines whether a drug's use is approved and whether labeling is considered false or

164 See id. (suggesting that the FDA could require pharmaceutical companies to provide all intended off-label uses in their application for FDA approval).
165 Id.
166 Amarin Pharma, Inc. v. United States, 2015 U.S. Dist. LEXIS 103944, at *85 ("[T]he First Amendment does not protect false or misleading commercial speech. Caronia's construction of the misbranding provisions so to exclude truthful promotion speech affords no protection to a manufacturer that uses false or misleading communications to promote an off-label use.") Although off-label promotion can lead to liability under the False Claims Act ("FCA"), the FCA is beyond the scope of this Note. For a definition of "falsity" under the False Claims Act, see Krause, supra note 22.
misleading. It is therefore imperative that the FDA set a clear threshold for what constitutes false or misleading, in order for courts to determine which cases should move forward with prosecution.

Caronia and Amarin serve as models for what should, and should not, constitute false or misleading information. Notwithstanding the government's failure to recognize Caronia's false and misleading statements,\textsuperscript{167} the facts in Caronia serve as an example of clearly punishable behavior that should meet the threshold requirement. On the other hand, the pharmaceutical firm in Amarin followed the FDA's requirements and conducted the requisite clinical trials.\textsuperscript{168} Amarin serves as an example of a case where the presented facts should not have met the threshold for what constitutes false or misleading communications. If the FDA continues as it did in Amarin, and refuses to be flexible, courts will be forced to articulate a threshold standard. Unless the FDA wants courts to define this standard, it is in the FDA's best interest to institute regulations that clearly define false or misleading information.

B. Disclosure Statements

Physicians, while masters in the field of medicine, are human and therefore susceptible to the influence of pharmaceutical companies. To alert physicians to the potential safety concerns associated with prescribing off-label uses, the FDA should produce guidelines instructing pharmaceutical companies how to create truthful and non-misleading disclosures that provide physicians with the most accurate and truthful information possible. These guidelines, however, should only supplement regulations implemented through notice-and-comment rulemaking, and should not be a replacement for creating clear regulations.

\textsuperscript{167} See United States v. Caronia, 703 F.3d 149, 165–67 (2d Cir. 2012); United States v. Caronia, 576 F. Supp. 2d 385, 389–90 (E.D.N.Y. 2008) (discussing allegations that Caronia promoted Xyrem to a physician for multiple off-label indications, including treatment in children under the age of sixteen and the elderly, despite a “black box” warning about the safety and efficacy concerns associated with prescribing Xyrem to those specific age groups).

\textsuperscript{168} Amarin, 2015 U.S. Dist. LEXIS 103944, at *30–34.
The lengthy discussion in *Amarin* illustrates one method for creating disclosures that provide physicians with truthful and non-misleading information. Specifically, the court focused on the dispute surrounding Disclosure #2:

*Amarin Disclosure #2:* “FDA has not approved Vascepa for the treatment of statin-treated patients with mixed dyslipidemia and high (≥ 200 mg/dL and < 500 mg/dL) triglyceride levels.”

According to the FDA, Disclosure #2 failed to explain to physicians why the FDA had not approved Vascepa for the specific use Amarin sought to promote. After the FDA proposed adding an additional sentence explaining why the FDA did not approve Vascepa for the off-label use, Amarin countered that if the FDA is to require a statement about why a drug is not FDA approved, the disclosure must also explain that the off-label use was not necessarily disproven.

The court in *Amarin* took both parties’ concerns into consideration and ultimately stated that it was necessary to make clear that Vascepa was not yet proven effective, nor ineffective, at reducing cardiovascular events. The court suggested the following modifications:

Vascepa is not FDA approved for the treatment of statin-treated patients with mixed dyslipidemia and high (≥ 200 mg/dL and < 500 mg/dL) triglyceride levels.

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169 Id. at *48–49 (*Amarin Disclosure #1:* “FDA has not approved Vascepa to reduce the risk of coronary heart disease”; *Amarin Disclosure #2:* “FDA has not approved Vascepa for the treatment of statin-treated patients with mixed dyslipidemia and high (≥ 200 mg/dL and < 500 mg/dL) triglyceride levels”; *Amarin Disclosure #3:* “The effect of Vascepa on the risk of cardiovascular mortality and morbidity has not been determined”; *Amarin Disclosure #4:* “A cardiovascular outcomes study of Vascepa designed to evaluate the efficacy of Vascepa in reducing cardiovascular mortality and morbidity in a high risk patient population on statin therapy is currently underway.”; and *Amarin Disclosure #5:* “Vascepa may not be eligible for reimbursement under government healthcare programs, such as Medicare or Medicaid, to reduce the risk of coronary heart disease or for treatment of statin-treated patients with mixed dyslipidemia and high (≥ 200 mg/dL and < 500 mg/dL) triglyceride levels. We encourage you to check that for yourself.”).

170 Id. at *93.

171 Id.

172 Id. at *94–96.

173 Id.
dyslipidemia and high (≥ 200 mg/dL and < 500 mg/dL) triglyceride levels due to current uncertainty regarding the benefit, if any, of drug-induced changes in lipid/lipoprotein parameters beyond statin-lowered low-density lipoprotein cholesterol on cardiovascular risk among statin-treated patients with residually high triglycerides. No prospective study has been conducted to test and support what, if any, benefit exists.\textsuperscript{174}

The alterations made to Disclosure #2 provide guidance to courts trying to discern what constitutes false and misleading disclosures.

This interaction between the FDA and Amarin is a model for future pharmaceutical companies seeking to create truthful and non-misleading disclosures. In summary, when creating disclosure statements for off-label uses, pharmaceutical companies should follow the requirements set forth in Amarin and explain (1) why the FDA did not approve the drug for a specific use, and (2) what studies, if any, have been conducted to test and support what, if any, existing benefits. Providing this guidance would be a positive first step in articulating clear standards to ensure that pharmaceutical firms are not providing false and misleading information to physicians.

C. Monitoring Off-Label Prescribing Practices

As the healthcare industry transitions to electronic medical records, it is imperative that the FDA embrace technological advances as a means to monitor pharmaceutical firms’ off-label communications. Professors Ryan Abbott and Ian Ayres have outlined five methods for increasing the amount of information concerning off-label uses promoted by both physicians and pharmaceutical firms.\textsuperscript{175}

First, the FDA could require manufacturers to report off-label uses to the FDA on an annual basis.\textsuperscript{176} This requirement would not

\textsuperscript{174} Id. at *97–98 (emphasis added).

\textsuperscript{175} Ryan Abbott & Ian Ayres, Evidence and Extrapolation: Mechanisms for Regulating Off-Label Uses of Drugs and Devices, 64 DUKE L.J. 377, 399 (2014).

\textsuperscript{176} Id. at 399.
be overly burdensome given that most manufacturers already acquire this data for marketing purposes such as detailing.177 This method would allow the FDA to identify the off-label uses of FDA-approved drugs, while also promoting transparency within the pharmaceutical industry.178

Second, since physicians ultimately bear the burden of deciding whether or not to prescribe off-label, the FDA must monitor physician prescribing practices. Because many doctors already report adverse events to the FDA, Abbott and Ayres's second recommendation is to give physicians the option to include diagnostic codes in reports to the FDA Adverse Event Reporting System ("FAERS").179 The data obtained from these reports could then be used to group or identify adverse effects of drugs used for off-label indications.180

Third, Abbott and Ayres contend that the Center for Medicare and Medicaid Services (CMS) could make all Medicare/Medicaid reimbursement requests contingent upon the inclusion of diagnostic codes.181 Because CMS covers over 100 million people, requiring diagnostic codes in all requests would provide the FDA with a wealth of data concerning off-label prescriptions.182 Professor Jennifer Herbst aptly cautions, however, that diagnostic coding requirements should be implemented incrementally and that "prescribers and pharmacists...need to [first] understand diagnostic coding as a part of effective, coordinated patient care as opposed to a mere administrative requirement for payment."

177 Id. at 400.
178 Id. at 400–02.
179 Id. at 403–05; see also Questions and Answers on FDA's Adverse Event Reporting System (FAERS), U.S. FDA (last updated Feb. 19, 2016), http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/.
180 Abbott & Ayres, supra note 176, at 403–04.
181 Id. at 405–07; see also Jennifer L. Herbst, How Medicare Part D, Medicaid, Electronic Prescribing, and ICD10 Could Improve Public Health (But Only If CMS Lets Them), 24 HEALTH MATRIX 209, 217 (2014) ("[T]here is no single database within the federal health care system in which a patient's outpatient prescription drug use can be cross-referenced with his medical diagnoses.").
183 Herbst, supra note 182, at 213.
Fourth, Abbott and Ayres argue that the FDA should have the ability to impose stricter requirements on certain drugs that have had a higher number of adverse events. Stricter requirements for "FDA-designated" drugs could include requiring a diagnostic code at the prescription stage. Abbott and Ayres state that stricter requirements for "FDA-designated" drugs would allow the FDA to "pick and choose" their battles. If this strategy were implemented, there would need to be a clear standard for what constitutes a high number of adverse events, so as to ensure that the FDA does not use this as a loophole for targeting specific pharmaceutical firms or drugs, without scientific evidence for doing so.

Finally, the FDA should publish the de-identified data to the public in order to encourage "crowd sourcing" of important medical data. Abbott and Ayres point out that this data would be beneficial to an array of stakeholders, including government agencies and non-profit organizations studying off-label use, insurers making coverage determinations, academics conducting research, and pharmaceutical firms developing new drugs. Further, the availability of this valuable medical data would ultimately help the greatest stakeholder of all, patients.

D. Greater Sanctions

Stronger sanctions are needed to make the economic loss from unlawful promotion outweigh the economic gains of off-label promotion. The Public Citizen Health Research Group tracked pharmaceutical firm settlements between 1991 and 2012, and found that most penalties paid were for off-label promotion totaling

\[184\] Abbott & Ayres, supra note 176, at 407–08.
\[185\] Id. at 408.
\[186\] Id.
\[187\] Id. at 409.
\[188\] Id.
Additionally, only six pharmaceutical companies were responsible for 60.5% of the total penalties. Clearly, the penalties imposed on these large pharmaceutical companies are not enough to deter them from engaging in off-label promotion.

Given the recidivism of pharmaceutical firms, it might not be the amount of the financial penalties that matters, but rather the persons to whom these penalties are inflicted. An alternative option may be to penalize individuals, rather than corporations. As noted in a recent Department of Justice memorandum, prosecuting individuals "deters future illegal activity, [] incentivizes changes in corporate behavior, [] ensures that the proper parties are held responsible for their actions, and [] promotes the public’s confidence in our justice system."


Finally, while this is not a recommendation for the FDA per se, it is time for Congress to reinstate the FDAMA’s safe harbors or

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191 Do We Need Stronger Sanctions?, supra note 191, at 436.

192 For a more in depth discussion about sanctions and the reasons they are not already utilized, see id.

193 Almashat & Wolfe, supra note 191, at 42 (Table 5). The settlements listed between 1991 and 2012 are not specific to violations under the FDCA, but rather include an array of violations such as overcharging government health programs and unlawful promotion. Id. at 14.

comparable provisions.¹⁹⁵ FDAMA § 401 and the FDA’s implementing regulations, collectively the “safe harbor provisions,” outlined certain conditions under which a pharmaceutical firm could discuss the off-label uses of an FDA approved drug.¹⁹⁶ If the pharmaceutical firm met the specified conditions, the manufacturer’s off-label communications—specifically its distributed journal articles and reference publications—would not serve as evidence of the “manufacturer’s intent that the product be used for unapproved uses.”¹⁹⁷

Without a safe harbor provision, the First Amendment challenges will only continue to escalate. Although guidance documents can be beneficial, such documents cannot serve as a replacement for clear laws and implementing regulations. As illustrated by the decisions in Caronia and Amarin, without clear and binding guidance for the pharmaceutical industry, courts will be forced to address these conflicts through First Amendment challenges, an outcome that may not be favorable to either the FDA or the pharmaceutical industry.

VI. CONCLUSION

Caronia and Amarin reflect the Supreme Court’s opinion over the past three decades, stemming from the decision in Virginia State Board of Pharmacy to the more recent decision in Sorrell.¹⁹⁸ During this time, the Court has consistently opined that the constitutional protection of the First Amendment outweighs any concern or speculation about well-educated physicians potentially making the wrong decision.¹⁹⁹ Therefore, in striking a balance between preserving the First Amendment right to commercial speech and protecting the public health, the FDA must look towards alternative methods for regulating the health and safety of patients.

¹⁹⁶ See Food and Drug Administration Modernization Act of 1997 § 401; Good Reprint Practices, supra note 99.
¹⁹⁷ Good Reprint Practices, supra note 99.
¹⁹⁸ See supra notes 67–115 and accompanying text.
¹⁹⁹ See id.
As briefly discussed in this Note, alternative methods include clearly defining false or misleading information, creating updated guidelines for pharmaceutical companies structuring disclosure statements, monitoring off-label prescription practices, increasing sanctions on pharmaceutical companies and individuals, and considering the return of the FDAMA’s safe harbor provisions. While these suggestions are not exhaustive, they serve to highlight that alternative methods for regulating illegal off-label promotion do exist. The government has a constitutional duty to implement measures that do not restrict truthful, non-misleading commercial speech.

200 See supra notes 158–198 and accompanying text.