

**FDA AND THE PRACTICE OF MEDICINE:
LOOKING AT OFF-LABEL DRUGS**

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I. INTRODUCTION

The Food and Drug Administration (“FDA”) has always taken a deferential stance with regard to the practice of medicine, and maintains that it will not interfere with the physicians’ autonomy in this regard.

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This is otherwise known as the “practice of medicine exception.” However, the reality is that it is often difficult to draw a clear line between the role of FDA in safeguarding the public from unsafe drugs and the autonomy that physicians have in prescribing off-label medication in the practice of medicine.

This article first will first define what constitutes the “practice of medicine” and outline the deferential stance position that the FDA has adopted towards this practice. This is supported by a discussion of the legal basis for this deferential stance, a position that Congress has also reiterated over the years. The article then explores the prevailing attitudes of physicians and patients toward off-label drugs, current regulations pertaining to the prescription and advertising of off-label drugs, and recent cases that look into restriction of advertising and promoting of off-label uses of drugs. Next, the article dives into a balanced and in-depth discussion as to whether the FDA should regulate the use of off-label drugs, even if it means potentially encroaching and infringing the boundaries of the practice of medicine exception. Lastly, the article sets out brief recommendations that may help address the dilemma.

II. FDA AND THE PRACTICE OF MEDICINE

A. *Defining the “Practice of Medicine”*

Before plunging into a meaningful discussion of the interaction between the FDA and the practice of medicine, it is first appropriate to define what the “practice of medicine” encompasses.

What exactly is the “practice of medicine?” Is the “practice of medicine” whatever that the physicians say it is, or is it a question of how to properly treat patients? If it is the former, then the “practice of medicine” clearly lies within the prerogative of physicians and is a field in which regulatory bodies have no role intruding upon. If it is the latter, then in the name of safeguarding the public health, perhaps there is some foundation for the government to intervene and impose regulations.

It naturally follows that the definition of “practice of medicine” that this paper chooses to adopt will influence all of the arguments subsequently raised. However, there is no clear uniform answer: the definitions of “practice of medicine” have fluctuated over time, states and jurisdictions. For instance, an article in the *Journal of American Medical Association* in 1908 defined the practice of medicine simply as the “art of healing,” while at the same time, states like New York and Ohio only considered that an individual practiced medicine if he administered drugs

or performed surgery.¹

Modern legal definitions do not provide much clarity, with different states reaching different conclusions on whether the same activity involves the practice of medicine. For example, the District of Columbia Court of Appeals considers a physician's testimony as a non-treating expert witness to fall under the umbrella of the practice of medicine.² The Missouri Court of Appeals however, takes the opposite stance.³ Therefore, it is difficult to reach a uniform position on certain activities, and states and courts have also grappled with defining and delineating the boundaries of the practice of medicine. For instance, it is unclear if physicians can rightfully claim to engage in the practice of medicine when they review insurance coverage decisions or when non-physicians, whose duties overlap with actual physicians, can be said to cross the line into practicing medicine.⁴

Generally, most state statutes and courts broadly define the practice of medicine as involving at least two activities: (1) diagnosing a disease, condition or injury; and (2) prescribing, administering or providing a treatment for that disease, condition or injury.⁵

B. Legal Basis for the Non-Interference with the Practice of Medicine

The FDA has always been clear on its stance: it does not regulate the practice of medicine between physicians and patients.⁶ Although there are no existing statutes that specifically outline or guide this prohibition, the FDA's deference to physicians is borne from Congressional intent.

The Federal Food, Drug, and Cosmetic Act of 1938 ("FFDCA") provides the primary source of FDA's regulatory power over drugs. Although the FFDCA, in effect, expanded the federal regulatory

¹ *What Constitutes the Practice of Medicine*, 299 JAMA 463, 463 (2008); *Smith v. Lane*, 31 N.Y. Sup. Ct. (24 Hun 632) 634-35 (1881); *see also* *Nelson v. State Bd. of Health*, 57 S.W. 501, 505 (Ky. 1900) (holding that an osteopath is not required to be licensed because he does not "prescribe or administer medicine or perform surgery"); *State v. Liffing*, 55 N.E. 168, 168-69 (Ohio 1899) (concluding that a treatment is not medical practice unless it includes the administration of drugs).

² *See Joseph v. D.C. Bd. of Med.*, 587 A.2d 1085, 1091 (D.C. 1991).

³ *See Missouri Bd. of Registration for the Healing Arts v. Levine*, 808 S.W.2d 440, 443 (Mo. Ct. App. 1991).

⁴ Lars Noah, *Ambivalent Commitments to Federalism in Controlling the Practice of Medicine*, 53 KAN. L. REV. 149, 162-64 (2004).

⁵ Noah, *supra* note 4, at 162; Cynthia Marietta & Amy L. McGuire, *Direct-to-Consumer Genetic Testing: Is It the Practice of Medicine?*, 37 J. L. MED. AND ETHICS, 369, 371 (2009).

⁶ Carol Berry, *The Dividing Line Between the Role of the FDA and the Practice of Medicine: A Historical Review and Current Analysis*, HARV. UNIV. LIBRARY (1997).

authority, the legislative debates preceding the enactment of the FFDCa demonstrated that Congress had never intended for FDA to regulate the practice of medicine.⁷

During the course of amending the FFDCa in passing the Drug Amendments of 1962, Congress once again repeated their stance of FDA's non-interference with the practice of medicine.⁸ In subsequent amendments, provisions were included to reinforce this stance. Section 214 of the Food and Drug Administration Modernization Act of 1997 states that "nothing in [the FFDCa] shall be construed to limit or interfere with the authority of a healthcare practitioner to prescribe or administer any legally marketed device to a patient for any condition or disease within a legitimate health care practitioner-patient relationship."⁹ Furthermore, the Food and Drug Administration Amendments Act of 2007 explicates that "nothing in this section shall be construed to. . . limit the practice of medicine."¹⁰ Evidently, this doctrine has been reiterated throughout the years, and it is important to note that Congress has adopted a similarly deferential stance in protecting professional autonomy in other federal healthcare legislation, such as the Medicare statute, Fertility Success Rate and Certification Act of 1992 and the Drug Addiction Treatment Act of 2000.¹¹

⁷ See ROBERT P. BRADY, FUNDAMENTALS OF LAW & REGULATION: AN IN-DEPTH LOOK AT FOOD & DRUG ADMINISTRATION MODERNIZATION ACT 423-424 (David G. Adams & Richard M. Cooper eds., 1st ed. 1997); see also *Buckman Co. v. Plaintiffs' Legal Comm.*, 531 U.S. 341, 350 (2001) ("[T]he FDA's mission [is to] . . . regulate . . . without directly interfering with the practice of medicine"); James M. Beck & Elizabeth D. Azari, *FDA, Off-Label Use, and Informed Consent: Debunking Myths and Misconceptions*, 53 FOOD & DRUG L.J. 71, 76 (1998) ("[The] FDA never has had authority to regulate the practice of medicine; physicians may use legally marketed drugs or devices in any way that they believe, in their professional judgment, will best serve their patients").

⁸ Pub. L. No. 87-781, 76 Stat. 780 (codified in scattered sections of 21 U.S.C.). See S. Rep. No. 87-1552, at 1998 (1962) ("[T]he . . . [Act] should not interfere with the professional function of the physician. FDA clearance would assure physicians that a drug effectively produces certain physiological actions, but the physician, not the FDA, would determine whether these specific physiological effects would be useful or beneficial with respect to particular patients.").

⁹ Pub. L. No. 105-115, § 214, 111 Stat. 2296, 2348 (codified at 21 U.S.C. § 396).

¹⁰ Food and Drug Administration Amendments Act of 2007, Pub. L. No. 110-85, § 1111(d), 121 Stat. 823, 976 (codified at 42 U.S.C. § 247d-5a(d)).

¹¹ Health Insurance for the Aged Act, Pub. L. No. 89-97, § 102(a), 79 Stat. 290, 291 (1965) (codified at 42 U.S.C. § 1395) ("Nothing in [the Medicare statute] shall be construed to authorize any Federal officer or employee to exercise any supervision or control over the practice of medicine."); Pub. L. No. 102-493, § 3(i)(1), 106 Stat. 3146, 3149 (codified at 42 U.S.C. § 263a-2(i)(1)) ("In developing the [federal embryo laboratory] certification program, the [Department of Health and Human Services] may not establish any regulation, standard, or requirement which has the effect of exercising supervision or control over the practice of medicine in assisted reproductive technology programs."); Pub. L. No. 106-310, § 3502, 114 Stat. 1222, 1226 (codified at 21 U.S.C. § 823(g)(2)(H)(i)) ("Nothing in such regulations or

C. The Dilemma that the FDA Faces

Not surprisingly, there exists an apparent tension between respecting physicians' autonomy in caring for individuals in their practice of medicine and the need for the government to regulate such practices and safeguard public health. A common viewpoint amongst physicians is that flexibility is crucial for them to judge what is best for each individual patient and to provide effective medical care of the highest quality.¹² The focus of ethical medical teaching has always been to do what is in the best interest of the individual patient and to respect each patient's autonomy. In contrast, the focus with the study of medicine in public health lies on the well-being of the entire population at large.¹³ As Jeffrey Drazen—a physician and editor-in-chief of the *New England Journal of Medicine*—pointed out, the practice of medicine is done “on an individual basis, with the best interests of the patient foremost in the practitioner's mind.”¹⁴

The tension between the FDA and physicians over the scope of practice of medicine has led to various clashes in the field, such as the use of pre-approved medical devices or autologous stem cell therapies. In the latter, the FDA determined in 2008 that the autologous stem cell therapies performed by Regenerative Sciences (a Colorado-based medical practice and its physician owners) constituted a “drug” under section 201(g) of the Federal Food, Drug, and Cosmetic Act (“FFDCA”) and a “biological product” under section 351(i) of the Public Health Service Act (“PHSA”).¹⁵ This move expanded the scope of FDA's regulatory authority over physicians working on stem cell research and treatment.

This paper will focus closely and solely on the tension and controversy generated by the use of off-label drugs by physicians.

practice guidelines may authorize any Federal official or employee to exercise supervision or control over the practice of medicine or the manner in which medical services are provided.”).

¹² Solomon J, Raynor DK, Knapp P, Atkin K, *The Compatibility of Prescribing Guidelines and The Doctor-Patient Relationship: A Primary Care Mixed-Methods Study*, 62 *BR J GEN PRACT.* 275, 275 (2012).

¹³ BERNARD LO, *RESOLVING ETHICAL DILEMMAS: A GUIDE FOR CLINICIANS* 12–14 (5th ed. 2013); *see also* LAWRENCE O. GOSTIN, *PUBLIC HEALTH LAW: POWER, DUTY, RESTRAINT* (2nd ed. 2008).

¹⁴ Jeffrey M. Drazen, *Government in Medicine*, 356 *NEW ENG. J. MED.* 2195, 2195 (2007).

¹⁵ Letter from Mary A. Malarkey, Dir. of Compliance and Biologics Quality, U.S. Food & Drug Admin., to Christopher J. Centeno, M.D., Med. Dir., Regenerative Sci., Inc. (July 25, 2008), *available at* <http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ComplianceActivities/Enforcement/UntitledLetters/ucm091991.htm>.

III. OFF-LABEL DRUGS

With respect to the use of off-label drugs, it is crucial to note that this tug-of-war over the scope of practice of medicine goes beyond the FDA and physicians; there are other important stakeholders deeply involved with vested and personal interests. Third party payers increasingly question their duty to expend payments for drugs that have not been proven reliably effective, even if these drugs may be the only viable treatment option available.¹⁶ Pharmaceutical companies are interested in expanding their markets and increasing profits by bypassing expensive by bypassing expensive clinical trials needed for FDA approval.¹⁷ The consumers, i.e., the public at large, wants to know that drugs that are available in the market are supported by clinical evidence and are sold at affordable prices.¹⁸ The FDA, being responsible for matters that affect the nation's health and welfare, has an obligation to try and balance these seemingly incompatible goals. In view of these conflicting and contradictory interests, where should the line be drawn?

Before examining the interests of these parties and the weight of the arguments for and against regulation of the use of off-label drugs, it makes sense to first gain a better understanding of the current state of affairs by looking at the current regulations and recent legal cases about the use of such drugs.

A. *What Does "Off-Label" Mean?*

The FDA acts on behalf of the federal government and is responsible for regulating the entry, sale, promotions, and marketing of drugs in United States. The relevant statute that guides this process is the Federal Food, Drug, and Cosmetic Act, which was first enacted in 1938 and underwent a series of amendments in 1962. The FFDCA stipulates a "preclearance" regulatory system, which states that "[n]o person shall introduce or deliver for introduction into interstate commerce any new drug, unless an approval of an application . . . is effective with respect to such drug."¹⁹ The approval process for a new drug is long, arduous, and highly expensive, involving numerous phases of testing on animals and humans.

The FDA only allows new drugs to enter the marketplace for the

¹⁶ Randall Stafford, *Regulating Off-Label Drug Use – Rethinking The Role of The FDA*, 358 NEW ENG. J. OF MED. 1427, 1428 (2008).

¹⁷ *Id.*

¹⁸ *Id.*

¹⁹ 21 U.S.C. § 355(a) (2012). *See also* Federal Food, Drug, and Cosmetic Act, Pub. L. No. 75-717, 52 Stat. 1040, 1043 (1938), *amended by* Drug Amendments of 1962, Pub. L. No. 87-781, 76 Stat. 780 (1962) (current version at 21 U.S.C. §§ 301-399f).

uses that the pharmaceutical company has applied and managed to get approval for.²⁰ Moreover, given that the FDA is also responsible for regulating the advertising of such drugs by pharmaceutical companies, it requires that all of the approved uses be indicated on a drug's label.²¹ "Off-label" uses of a drug refer to the use or prescription of the drug in a manner that has not been authorized by the FDA through its approval process for new drugs.

B. Use of Off-Label Prescription Drugs

Off-label use can arise in different ways, but it mainly refers to the use of drugs in ways that have not been approved by the FDA. Drugs can be used for an unapproved indication. For example, the antipsychotic agent, quetiapine, is approved for treating psychosis, but can also be prescribed for different medical conditions like depression. They can also be used in unapproved populations, like paroxetine, that is approved for treating depression in adults, but is also used to treat depression in children.²² Other ways of using drugs in an off-label manner is to prescribe them in a non-approved dosage form or dose regimen.²³ Physicians use drugs for indications outside of the approved uses when they extend the use of approved drugs to milder forms of an approved indication, or a closely related condition (e.g., the use of anti-asthmatic montelukast (commonly known as Singulair) for chronic obstructive pulmonary disease), or other conditions which have similar physiological pathways (e.g., the use of the antidiabetic drug metformin to treat polycystic ovarian syndrome) or to conditions that have similar and overlapping symptoms.²⁴

Off-label prescribing is legal and is so common that it can be found in almost every field of modern medicine. In a recent study done in 2006, off-label use was shown to account for approximately twenty-one percent of all prescriptions of 160 common drugs.²⁵

The most common medical fields in which off-label drugs are being prescribed are oncology, rare diseases, AIDS treatment, and pediatrics; while the highest rates of off-label use were for anticonvulsants (seventy-four percent), antipsychotics (sixty percent), and antibiotics (forty

²⁰ Rodney Smolla, *Off-Label Drug Advertising and The First Amendment*, 50 WAKE FOREST L. REV. 81 (2015).

²¹ 21 U.S.C. § 321(p)(1) (2016).

²² Stafford, *supra* note 16, at 1427.

²³ Stafford, *supra* note 16, at 1427.

²⁴ Stafford, *supra* note 16, at 1427.

²⁵ David C. Radley, Stan N. Finkelstein & Randall Stafford, *Off-Label Prescribing Among Office-Based Physicians*, 166(9) ARCHIVES OF INT'L MED 1021 (2006).

percent).²⁶ In 1911, the General Accounting Office found that twenty-five percent of all anticancer drugs were prescribed off-label and fifty-six percent of cancer patients were on at least one drug that was being prescribed off-label.²⁷ In the field of pediatric medicine, it has been estimated that sixty-two percent of drugs prescribed for children are for off-label uses.²⁸

The use of off-label drugs is so ubiquitous that, not only are they being used in most medical specialties, they can be part of guideline-recommended practices, including in the use of aspirin in diabetes for prophylaxis against cardiovascular disease, and can even be a first-line therapy in some cases, such as the use of gabapentin for painful diabetic neuropathy, in addition to its approved use in the treatment of herpes zoster. Some drugs that pose a high risk of side effects, even for their approved uses, are also being used off-label as a last resort, e.g., the use of tacrolimus for autoimmune disease, in addition to its approved use in transplantation.²⁹

C. Current Regulations Pertaining to Off-Label Drugs

Broadly speaking, off-label activities can take three basic forms: off-label use by consumers at large who purchase these drugs over the counter, off-label prescription of drugs by physicians and providers, and off-label marketing and promotion by pharmaceutical companies.³⁰ In general, off-label prescribing largely influences off-label use by consumers, which is in turn influenced greatly by off-label advertising and promotion to physicians. The FDA has sought to regulate and restrict the extent of off-label use, mainly by restricting the pharmaceutical industry's marketing practices and, to a much smaller extent, prescribing by physicians.³¹ This unique behavior is presumably driven by the FDA's deferential stance toward the practice of medicine exception, although it is debatable whether interfering with the industry's attempts to promote off-label uses to physicians is in effect an indirect interference with the practice of medicine.

²⁶ Stafford, *supra* note 16, at 1427; James O'Reilly and Amy Dalal, *Off-Label or Out of Bounds? Prescriber and Marketer Liability for Unapproved Uses of FDA-Approved Drugs*, 12 ANNALS OF HEALTH L. 295, 298 (2003).

²⁷ U.S. GENERAL ACCOUNTING OFFICE, GAO/PEMD-91-14, OFF-LABEL DRUGS: REIMBURSEMENT POLICIES CONSTRAIN PHYSICIANS IN THEIR CHOICE OF CANCER THERAPIES (1991).

²⁸ Alicia T.F. Bazzano et al., *Off-Label Prescribing to Children in the United States Outpatient Setting*, 9 ACAD. PEDIATRICS 81, 83 (2009).

²⁹ Stafford, *supra* note 16, at 1427.

³⁰ O'Reilly and Amy Dalal, *supra* note 26.

³¹ Stafford, *supra* note 16, at 1428.

With regard to prescribing off-label uses, the FDA uses changes in drug labeling such as black box warnings to alert physicians that special caution is required, and imposes specific restrictions on drug availability to curb off-label uses to limited settings.³² The FDA imposes much stricter rules on the industry's marketing practices. Prior to its 1997 amendments, the FDCA expressly forbade the sale of a drug that has unapproved uses written on its label or was advertised for unapproved uses.³³ In other words, pharmaceutical companies were only allowed to promote or advertise prescription drugs for uses that were approved by the FDA or uses that were "on" the new drug's label.

Following major lobbying from pharmaceutical companies, the FDCA underwent a series of amendments in 1997. Section 401 of the FDA's Modernization Act allows drug manufacturers to distribute information regarding the off-label use, on the condition that the manufacturer satisfies a list of requirements.³⁴ These requirements include only disseminating information that is not abridged, false, misleading, or posing a significant health risk to the public; the manufacturer has to conduct all clinical research found in the disseminated materials, and include in all disseminated materials prominent disclaimers clarifying that the information disclosed concerns a drug that has not been approved by the FDA for that particular use.³⁵

The medical industry has always welcomed the exchange of scientific information with the drug industry and preferred the open dissemination of truthful, non-misleading information relating to all beneficial uses for approved products.³⁶ In fact, both the pharmaceutical industry and the medical professions believe that the FDA's regulations encroach upon their freedom of speech and freedom to practice medicine respectively, and hinder them from keeping up with medical breakthroughs and scientific discoveries.³⁷

D. *Off-Label Drugs and the First Amendment*

Given that the full exchange of drug-related information between pharmaceutical companies and physicians influences the latter's medical knowledge, it follows that pharmaceutical companies' freedom of speech

³² Stafford, *supra* note 16, at 1428.

³³ See 21 U.S.C. §§ 355(a), 331(d), 321(p) (2000).

³⁴ Pub. L. No. 105-115, § 401, 111 Stat. at 2356-57 (codified at 21 U.S.C. § 360a).

³⁵ *Id.*

³⁶ Katherine Helm, *Protecting Public Health from Outside the Physician's Office: A Century of FDA Regulation From Drug Safety Labeling to Off-Label Drug Promotion*, 18 FORDHAM INTELL. PROP., MEDIA AND ENT. L. J. 1177, 153-55 (2007).

³⁷ *Id.* at 153-54.

is intimately linked to physicians' freedom to practice medicine. Hence, in examining the FDA's possible interference with the practice of medicine, we also need to look at how it might do so indirectly by restricting the freedom of speech.

First Amendment challenges to the FDA's ban on off-label promotion have been raised on the grounds that it restricts the freedom of speech. There are two recent cases that directly impacted the constitutionality of the FDA's authority. In *Sorell v. IMS Health*, the U.S. Supreme Court held that a Vermont law that restricted the "sale, disclosure, and use of pharmacy records falsereveal[ing] the prescribing practices of individual doctors" violated First Amendment free speech protections.³⁸ To reduce state healthcare costs, Vermont intended to hinder drug manufacturers' ability to use the information gained from the prescribing practices of doctors to influence them to prescribe brand-name drugs instead of generic equivalents.³⁹ The Supreme Court explicitly stated that "[s]peech in aid of pharmaceutical marketing. . . is a form of expression protected by the Free Speech Clause of the First Amendment" and that Vermont sought "to achieve its policy objectives through the indirect means of restraining certain speech by certain speakers – that is, by diminishing detailers' ability to influence prescription decisions."⁴⁰ The court in *Sorell* stated, "the 'fear that people would make bad decisions if given truthful information' cannot justify content-based burdens on speech."⁴¹ The court noted that the First Amendment's hostility to paternalistic regulations is applied with "full force, when the audience, in this case prescribing physicians, consists of 'sophisticated and experienced' consumers," which is the same audience of the off-label promotions that the FDA is attempting to restrict.⁴²

Although the *Sorell* holding examined pharmaceutical marketing and not specifically at the FDA regulatory authority to regulate off-label promotion, it predicted how courts would decide the FDA's ability to restrict manufacturers from providing truthful information to physicians about off-label uses of approved drugs.⁴³

This prediction came to fruition in the Second Circuit decision, *United States v. Caronia*, where a pharmaceutical company, and its

³⁸ *Sorell v. IMS Health Inc.*, 564 U.S. 552, 557 (2011).

³⁹ *Id.* at 560-61.

⁴⁰ *Id.* at 557, 577.

⁴¹ *Id.* at 577.

⁴² *Id.*

⁴³ Ashley Zborowsky, *Rethinking Off-Label Regulation in The Wake of Sorrell v. IMS Health: Can State Involvement Compensate for Waning State Authority to Curb Commercial Free Speech?*, 13 MINN. J. L. SCI. & TECH. 925, 934 (2012).

marketing agents, were caught promoting statements based on their personal experiences on the off-label uses of the prescription drug Xyrem.⁴⁴ Given that the statements made by the defendants were truthful and not false or misleading, the issue in *Caronia* revolves purely around the legality of the FDA's restrictions on the act of off-label marketing itself.⁴⁵ At the time *Caronia* was decided, the key case on commercial speech protections was *Central Hudson Gas and Electric Corp. v Public Service Commission*, where the Supreme Court created a four-part test: (1) whether the expression is protected by the First Amendment and for commercial speech to fall under this category it must concern lawful activity and not be misleading; (2) whether the asserted governmental interest is substantial; (3) whether the regulation directly advances the governmental interest asserted; and (4) whether it is not more extensive than is necessary to serve that interest.⁴⁶

Accordingly, in *Caronia* the Second Circuit applied the four-pronged commercial speech test set out in *Central Hudson*.⁴⁷ Consequently, the court found that the speech concerned lawful activity and was not misleading under the first prong and that the FDA's interest in safeguarding public safety and health was "substantial" under the second prong, but the FDA's regulatory regime failed to advance the governmental interest in a direct and material way under the third prong.⁴⁸ Further, the court found that the regulation is broader than necessary to serve the interest under the fourth prong.⁴⁹ The Court pointed out that, "prohibiting off-label promotion . . . while simultaneously allowing off-label use 'paternistically' interferes with the ability of physicians and patients to receive potentially relevant treatment information . . . [which] could inhibit, to the public's detriment, informed and intelligent treatment decisions."⁵⁰

In holding that the restricting commercial speech should be a last resort under the First Amendment, the court in *Caronia* dealt a blow to the FDA's authority to restrict off-label marketing, thereby compromising the FDA's authority to use commercial speech as a proxy to regulate undesirable off-label prescriptions.⁵¹ The Court's decision in

⁴⁴ Unites States v. Caronia, 703 F.3d 149, 156-57 (2d Cir. 2012).

⁴⁵ *Id.* at 165.

⁴⁶ *Central Hudson, Gas & Elec. Corp. v. Pub. Serv. Comm'n of N.Y.*, 447 U.S. 557, 566 (1980).

⁴⁷ Unites States v. Caronia, 703 F.3d 149, 164-66 (2d Cir. 2012).

⁴⁸ *Id.* at 166.

⁴⁹ *Id.* at 165-67.

⁵⁰ *Id.* at 166.

⁵¹ Zborowsky, *supra* note 43, at 937; Rodney Smolla, *Off-Label Drug Advertising and The First Amendment*, 50 WAKE FOREST L. REV. 81, 110 (2015).

Caronia brings the FDA closer to confronting its dilemma: how can it balance its role in safeguarding public health without interfering with physicians' autonomy to freely practice medicine?

IV. SHOULD THE FDA REGULATE THE USE OF OFF-LABEL DRUGS?

Should the FDA regulate the use of off-label drugs in the name of public safety, but at the risk of interfering with the practice of medicine, which may in turn also endanger public health? As Helm points out, the "double-edged sword of drug regulation can cut deeply both ways."⁵²

A. Arguments for Regulations

There are various reasons for which the FDA should take on a more active role in regulating off-label uses. For starters, in view of the conflicting interests of different stakeholders, one can argue that it is the role of the FDA as a federal regulatory body to step in to balance these interests.⁵³ Interests such as increasing access and availability can be at odds with ensuring safety and efficacy.⁵⁴

There is also a highly worrying possibility that pharmaceutical companies may shun the expensive and complicated approval process by "gaming the system."⁵⁵ Equipped with the knowledge that they can sell their products for a wide range of uses once a singular use has been approved, drug companies will choose to seek approval for narrow indications. The relevant clinical trials for narrow indications are less expensive and tedious, and they do so with the hope that they can gain approval faster and market the product for both its approved and unapproved uses.⁵⁶ In the short term, patients will be placed at risk of being harmed by drugs that are being used for purposes that have not been proven to be safe and effective.⁵⁷ In the long run, the underhanded shortcuts adopted by pharmaceutical companies to bypass the FDA's strict review and approval process severely undermines the drug efficacy requirements, which may end up chipping away at the foundation of evidence-based medicine.⁵⁸

Save for regulations imposed by the FDA on off-label prescription and promotion, drug companies also have minimal incentives to expend time, money, and resources to prove the safety and efficacy of the

⁵² Helm, *supra* note 36, at 167.

⁵³ Stafford, *supra* note 16, at 1427.

⁵⁴ Helm, *supra* note 36, at 163-64.

⁵⁵ Stafford, *supra* note 16, at 1427-28.

⁵⁶ Helm, *supra* note 36, at 164.

⁵⁷ O' Reilly and Dalal, *supra* note 26, at 307.

⁵⁸ Stafford, *supra* note 16, at 1427.

unindicated uses.⁵⁹ Generic drugs are often produced by smaller pharmaceutical firms that do not have the capital or financial backing to pay for the expenses that are required to push a drug through the new drug application process. Brand-name drugs that are already widely used off-label are rarely put through the process by pharmaceutical companies that can afford the trials, simply because carrying out such expensive trials could potentially end up producing clinical evidence that does not support the unapproved use and thus subjects the companies to suffering from loss of profits.⁶⁰ Competing drug manufacturers are also less inclined to carry out research about the safety of their own drugs when they see other manufacturers making sales from similar drugs sold for the same unindicated use, especially since doing research will only lead to lost sales from creating delays.⁶¹ Thus, there is an obvious need for the FDA to step in to impose regulatory control, as market forces provide insufficient incentives for drug companies to protect their consumers.⁶²

Another potential concern is that it would be wholly irresponsible to leave it to the pharmaceutical industry and physicians to dictate the use of drugs, when pharmaceutical companies have minimal incentives to monitor the safety and efficacy of the drugs and individual physicians do not have the resources to carry out the extensive and expensive trials needed to reliably and accurately prove its efficacy. In fact, the trials reported in the materials that pharmaceutical companies distribute to physicians to convince them of the efficacy of off-label uses are often of poor quality, industry-sponsored, and are compared to placebos rather than existing approved therapies.⁶³ With minimal incentives to drive the pursuit of reliable, controlled data on the efficacy of drugs for new indications, physicians run the risk of making treatment choices that are unsafe.⁶⁴

This is especially important as the average consumer expects the FDA to have thoroughly screened and evaluated every drug that is available in the market for drug safety and efficacy, which is in line with the common expectation that FDA is irrefutably responsible for safeguarding public health and safety. By permitting off-label uses to occur without subjecting the drugs to rigorous safety checks, the FDA is undermining the expectations of the average consumer.⁶⁵ As Public

⁵⁹ Stafford, *supra* note 16, at 1427.

⁶⁰ Stafford, *supra* note 16, at 1427.

⁶¹ O'Reilly and Dalal, *supra* note 26, at 307.

⁶² O'Reilly and Dalal, *supra* note 26, at 309.

⁶³ Stafford, *supra* note 16, at 1428.

⁶⁴ Helm, *supra* note 36, at 167.

⁶⁵ Stafford, *supra* note 16, at 1428.

Citizen, a consumer watchdog group, asserted in a congressional submission, deregulating the drug companies will “place the economic well-being of multinational pharmaceutical manufacturers above the health and safety of the American public and. . .weaken [the] law meant to protect the public from needless drug – induced injury.”⁶⁶ Besides, if serious safety concerns about approved uses for drugs already on the market are constantly being raised, surely that equates to even more cause for concern when it comes to off-label uses that have not gone through the rigorous testing process.

In 2006, a study revealed that 73 percent of off-label prescriptions lacked any “firm scientific evidence.”⁶⁷ This may be driven in part by the fact that physicians may hold wrong or inaccurate beliefs of the level of evidence supporting a drug’s indications. A survey done by the University of Chicago Medical Centre revealed that physicians were more likely to (incorrectly) believe that a specific use of a drug was FDA-approved if they themselves prescribed it for that indication.⁶⁸ This underscores the potential risk of off-label uses, even if that risk is unintentional, and emphasizes the need for the FDA to step in and oversee drug prescribing practices.⁶⁹

Proponents for imposing regulation go even further and claim that the untested use of drugs is unethical and potentially unsafe.⁷⁰ After all, isolated case reports published in peer-reviewed journals telling the successes of unapproved uses cannot compare to controlled and rigorous clinical trials and strict FDA scrutiny of the drug’s safety profile.⁷¹

A case in point is the increased risk of heart attack and stroke that were brought about from Merck’s promotion of the off-label use of rofecoxib (Vioxx) in treating rheumatoid arthritis, outside of its FDA-approved use for relieving pain.⁷² What makes the situation more aggravating is that these risks were only discovered after widespread use

⁶⁶ O’ Reilly and Dalal, *supra* note 26, at 305-06.

⁶⁷ Radley et. al, *supra* note 25, at 1023.

⁶⁸ Rick Nauert, *Off-Label Use May Be Off-Track*, PSYCH CENTRAL, (Aug. 24, 2009), <http://psychcentral.com/news/2009/08/24/off-label-use-may-be-off-track/7926.html>.

⁶⁹ Amy E. Todd, *No Need for More Regulation: Payors and Their Role in Balancing the Cost and Safety Considerations of Off-Label Prescriptions*, 37 AM. J.L. & MED. 422, 426 (2011) (“[W]hile off-label prescribing can be very beneficial to some patients, this common practice can also be unnecessary and, in some cases, very risky.”).

⁷⁰ Steven R. Salbu, *Off-Label Use, Prescription, and Marketing of FDA-Approved Drugs: An Assessment of Legislative and Regulatory Policy*, 51 FLA. L. REV. 181, 202 (1999).

⁷¹ See Charles Marwick, *Implementing the FDA Modernization Act*, 279 JAMA 815 (1998).

⁷² Stafford, *supra* note 16, at 1429; John Cairns, *The Coxibs and Traditional Nonsteroidal Anti-Inflammatory Drugs: A Current Perspective on Cardiovascular Risks*, 23(2) CAN. J. CARDIO, 125 (2007).

of the drug among patients who didn't stand to benefit much from choosing rofecoxib over the existing treatment of choice.⁷³

There are other notorious examples where the use of off-label medications have gone awry and caused more harm than good. The E1 prostaglandin analogue, Misoprostol, was approved in 1988 for the prevention and treatment of gastric ulcers, but was later prescribed off-label to induce labor for elective abortions.⁷⁴ Unfortunately, it was later found to cause uterine rupture in pregnant women.⁷⁵ Thalidomide is another tragic example; it was initially used as a sedative and was later approved to treat leprosy, but it was also prescribed for off-label purposes such as cancer and AIDS.⁷⁶ It was found that when pregnant women consumed the drug, their babies were born with severe and permanent limb deformities.⁷⁷ These examples serve to highlight the dangers of permitting un-indicated uses of drugs that have not been approved by the FDA.

B. Arguments Against Regulations

There is some force in the argument that science should dictate the practice of medicine, not law. As Beck and Azari say, “[f]or a product to have the most effective potential benefits, law and regulation. . . must follow, not precede science.”⁷⁸ It often takes a prolonged period of time for regulations to be put in place because the FDA approval process is notorious for being time-consuming, arduous and expensive.⁷⁹ The process for approval in 2000 was estimated to take between seven to ten years.⁸⁰ In practical terms, this means that medical discoveries in the field of practice often happen at a faster pace than the FDA approval process.⁸¹ For instance, the approved use for aspirin was for pain relief as an anti-

⁷³ Carolanne Dai, Randall Stafford, Caleb Alexander, *National Trends in Cyclooxygenase-2 Inhibitor Use Since Market Release: Non-Selective Diffusion of a Selectively Cost-Effective Innovation*, 165 ARCHIVES OF INT'L MED. 171 (2005).

⁷⁴ Dov Fox, *Safety, Efficacy and Authenticity: The Gap Between Ethics and Law in FDA Decisionmaking*, 2005 MICH. S. L. REV. 1135, 1168 (2005).

⁷⁵ *Id.*

⁷⁶ Shuang Zhou, Fengfei Wang, Tze-Chen Hsieh, Joseph Wu, Erxi Wu, *Thalidomide – A Notorious Sedative to a Wonder Anticancer Drug*, 20 CURR MED CHEM 4102 (2014).

⁷⁷ Fox, *supra* note 74, at 1168; see also Joseph G. Contrera, *The Food and Drug Administration and the International Conference on Harmonization: How Harmonious will International Pharmaceutical Regulations Become?*, 8 ADMIN. L.J. AM. U. 927, 935 n.33 (1995).

⁷⁸ James M. Beck & Elizabeth Azari, *FDA, Off-Label Use, and Informed Consent: Debunking Myths and Misconceptions*, 53 FOOD & DRUG L.J. 71, 79 (1998).

⁷⁹ O' Reilly and Dalal, *supra* note 26, at 304.

⁸⁰ O' Reilly and Dalal, *supra* note 26, at 304.

⁸¹ Fox, *supra* note 74, at 1165.

inflammatory drug but it was prescribed by physicians off-label for many years to reduce the risk of heart attacks and it wasn't until 1998 that the FDA finally approved such use.⁸²

Furthermore, while new additions may eventually be included on the list of approved uses following a supplemental new drug application, this is more of an exception than the norm. The FDA approval process is immensely expensive and a recent study done by Tufts Centre for the Study of Drug Development pegs the cost of developing a new drug that ultimately gains market approval at \$2.6 billion.⁸³ As mentioned earlier, drug companies either do not have the financial backing to do so and even if they do, they have no incentives to carry out expensive trials that could produce undesirable outcomes for their drugs and thus reduce profits.⁸⁴ Given that there are minimal incentives for pharmaceutical companies to push for FDA approval for off-label uses of drugs, it is not surprising that the unapproved additions may never be added onto the label.

In treating patients, there are often many variations in clinical histories and the best form of treatment for one patient with a condition may not necessarily be the most ideal treatment of choice for a different patient with the exact same condition. For physicians to act in the best interest of the individual patient, the physician needs to have the freedom to prescribe the most appropriate medication for that particular patient, even if it is for a use that has not been approved. In fact, an off-label drug is sometimes the first-line of therapy or the recommended drug in clinical guidelines. In 1994, George Lundberg of the American Medical Association said when he testified before Congress and stated, "prescribing FDA-approved drugs for off-label uses often is necessary for optimal patient care."⁸⁵ For a physician to be so restricted as to be unable to prescribe what is appropriate or even necessary to treat the patient would entail a regrettable step backwards and a clear, unwanted intrusion into the practice of medicine.

Although, approved drugs for treating a medical condition may exist, the current treatments available may be unsatisfactory.⁸⁶ There are still many medical conditions for which there is no cure, and these conditions range from infectious diseases such as AIDS to hereditary

⁸² Peter J. Gross & Linda S. Svitak, *Drug and Device Litigation in the 21st Century*, 27 WM. MITCHELL L. REV. 271, 286 (2000).

⁸³ *Cost to Develop and Win Marketing Approval for a New Drug Is \$2.6 Billion*, TUFTS CENTRE FOR THE STUDY OF DRUG DEVELOPMENT, available at http://csdd.tufts.edu/news/complete_story/pr_tufts_csdd_2014_cost_study (last visited Apr. 19, 2016).

⁸⁴ Stafford, *supra* note 16, at 1427-28.

⁸⁵ Beck & Azari, *supra* note 78, at 79.

⁸⁶ Fox, *supra* note 74, at 1165.

conditions such as cystic fibrosis and even cancer.⁸⁷ As a result, a practitioner's freedom to prescribe an off-label drug that is not approved by the FDA has advantages: it drives innovation in clinical practice and enables physicians to adopt new practices based on emerging clinical or research evidence that may be insufficient for FDA approval or have yet to be presented to FDA for approval. In doing so, physicians offer much-needed hope to patients who have run out of viable approved options amongst approved drugs.

A perfect example of an area of medicine in which patients and physicians often must rely on innovative uses of off-label drugs is the area of oncology. A drug may be approved to treat Cancer A but has not been approved to treat Cancer B. If the principle of pathophysiology behind both cancers is the same, as is the case with most cancers, it is likely that the drug will also be of benefit to a patient afflicted with Cancer B. Therefore, it is medically appropriate for physicians, in the absence of other safe or effective options, to resort to a last ditch attempt in prescribing these drugs for unapproved ways.⁸⁸ In fact, the use of off-label drugs in the field of oncology is so extensive that the American Society of Oncology wrote a letter to the FDA in 1998 stating that "the labeling of anticancer products frequently presents an incomplete or even inaccurate picture of the current state of medical knowledge. . .for virtually every cancer drug, appropriate medical usage differs from the terms of the product labeling."⁸⁹

Another group of patients for whom off-label drugs may be life savings are patients who suffer from "orphan" conditions.⁹⁰ Federal Law defines "orphan" diseases as those diseases that affect fewer than 200,000 Americans, including debilitating conditions such as Lou Gehrig's disease and cystic fibrosis.⁹¹ The expected profits to be gained from such a small group of consumers is dwarfed by the anticipated costs of conducting research and carrying out expensive clinical trials for "orphan" conditions, which accounts for the reluctance of drug

⁸⁷ Fox, *supra* note 74, at 1165.

⁸⁸ Fox, *supra* note 74, at 1166.

⁸⁹ Letter from John R. Durant, Executive Vice President, Am. Soc'y of Clinical Oncology, to Michael A. Friedman, Acting Comm'r, FDA (July 21, 1998), *available at* <https://www.fda.gov/ohrms/DOCKETS/dockets/98n0222/c000039.pdf>.

⁹⁰ See O'Reilly and Dalal, *supra* note 26, at 305 (citing Karen Bradshaw, *The Food and Drug Administration Modernization and Accountability Act of 1997: Is It the Answer to the Off-Label Advertising Debate?*, 12 ANNALS OF HEALTH L. 295 (1998)).

⁹¹ See, e.g., I. Scott Bass et al., *Off-Label Promotion: Is FDA's Final Guidance on Industry-Supported Scientific and Educational Programs Enforceable?*, 53 FOOD & DRUG L.J. 193 (1998).

companies to invest in making drugs to treat these diseases.⁹² Hence, it is hardly surprising that patients afflicted with orphan conditions rely heavily on the use of off-label drugs, so much so that the Abbey Meyers, President of the National Organization for Rare Diseases reports that “90% of [such patients] must rely on ‘off-label uses to have any treatment at all.’”⁹³

It is understandably misleading to think that patient populations who rely heavily on off-label drugs are restricted only to small, isolated groups. Large patient populations such as pregnant women and children are also immensely reliant on off-label use of drugs too. It is much more tricky, problematic and expensive to conduct controlled clinical human trials on children and pregnant women, and drug companies lack the financial motivation to pursue such research.⁹⁴ The American Academy of Pediatrics estimates that 80% of drugs prescribed for children are being prescribed for off-label uses.⁹⁵ Without off-label drugs, these significantly large patient populations will be left out in the cold without any treatment at all.⁹⁶

In light of these arguments, it becomes clear that the unethical human experimentation objection to off-label drug use is severely undermined, especially when one draws a distinction between medical research and medical practice. Medical practice refers to the diagnosis and treatment of the individual patient while medical research refers to the general development of scientific knowledge of the human body, for which tests must be carried out under strict controls and with patient’s informed consent.⁹⁷ Since off-label use often arises with the primary goal of benefitting the individual patient, rather than the desire to advance the general progress of scientific knowledge, it falls squarely into the field of medical practice, not medical research.⁹⁸ Bearing this in mind, the objection to “unethical human experimentation” is less persuasive and may even be misplaced.

There are also benefits that can be derived from lifting restrictions

⁹² O’ Reilly and Dalal, *supra* note 26, at 304.

⁹³ *Off-Label Drug Use and FDA Review of Supplemental Drug Applications, Hearing Before the Subcomm. on Human Resources and Intergovernmental Relations of the H. Comm. on Government Reform and Oversight*, 104th Cong. 1 (1996) (statement of Abbey S. Meyers, President, Nat’l Org. of Rare Disorders).

⁹⁴ Fox, *supra* note 74, at 1165.

⁹⁵ Robert Levine, *ETHICS AND REGULATION OF CLINICAL* 241 (Yale U. Press, 2nd ed. 1986).

⁹⁶ William L. Christopher, *Off-Label Drug Prescription: Filling the Regulatory Vacuum*, 48 *FOOD AND DRUG L.J.* 247, 248 (1993).

⁹⁷ George J. Annas, *Questing for Holy Grails: Duplicity, Betrayal and Self-Deception in Postmodern Medical Research*, 12 *J. CONTEMP. HEALTH L. & POL’Y* 297, 323 (1996).

⁹⁸ Fox, *supra* note 74, at 1169.

on data sharing between drug companies and physicians. Precisely because the use of off-label drugs is so widespread, the dissemination of accurate information by drug companies can increase physicians' access to the most updated literature on these drugs, which in turn allows them to provide the optimal care for their patients.⁹⁹ Given advances in information technology made in the last decade, physicians are finding it increasingly difficult to keep abreast of the deluge of information that is available in every medical journal regarding the efficacy of off-label uses in treating a variety of conditions and there is the risk of physicians missing out on a key study or crucial piece of research that may influence his treatment choices.¹⁰⁰ Having drug companies present physicians with information on how and when to use a drug for un-indicated uses in a concise and truthful manner may be beneficial for both patients and physicians.¹⁰¹ The fear that pharmaceutical companies will insidiously sway the minds of unknowing physicians with misleading information can also be allayed. Physicians themselves believe that off-label promotion to physicians should be without restrictions, in view of the physicians' general familiarity with the FDA-approval process and their capability to independently assess the legitimacy of a drug manufacturer's claims.¹⁰² The Second Circuit in *Caronia* astutely observed that "as off-label drug use itself is not prohibited, it does not follow that prohibiting the truthful promotion of off-label drug usage would. . . reduc[e] patient exposure to unsafe and ineffective drugs."¹⁰³

An explicit argument must be made for the autonomy of physicians and for their freedom to practice medicine without undue interference from the FDA. All the aforementioned arguments support this point directly or indirectly, e.g. off-label drugs benefit patients' and physicians' act in the best interests of patients in their practice of medicine. As Beck and Azari puts it succinctly, "if the physician's considered professional judgment is that a particular use of a particular product is the best treatment for a particular patient, professional responsibility demands that this course of treatment be followed."¹⁰⁴ In fact, physicians may be guilty of malpractice if they fail to act according to the off-label standard

⁹⁹ Gregory Conko, *Hidden Truth: The Perils and Protections of Off-Label Drug and Medical Device Promotion*, 21 HEALTH MATRIX 149, 165 (2011).

¹⁰⁰ *Id.* at 150 ("[Physicians not paid by a drug or device manufacturer] are free to tout to benefits of off-label uses in any way to any listener.").

¹⁰¹ Richard C. Ascroft, *The Impact of the Washington Legal Foundation Cases on Pharmaceutical Manufacturer Practices in the United States*, 34 IND. L. REV. 95, 99 (2000).

¹⁰² Helm, *supra* note 36, at 153-154.

¹⁰³ *Caronia*, 703 F.3d at 166.

¹⁰⁴ Beck & Azari, *supra* note 78, at 100.

of care.¹⁰⁵ In 2007, the American Medical Association (“AMA”) passed Resolution 918 that not only permits physicians to use off-label drugs, but also encourages it when clinical evidence, expert consensus opinion, or accepted standards of care support such uses.¹⁰⁶ Furthermore, the resolution calls for support for “the autonomous clinical decision making authority of a physician.”¹⁰⁷ Many in the medical community also adopt this stance, and feel that the government should not hinder a physician’s freedom to practice medicine when using an off-label drug is optimal for patient care.¹⁰⁸

V. POSSIBLE SOLUTIONS

Given the FDA’s dilemma in choosing to safeguard public safety versus overstepping its boundaries and intervening with the practice of medicine, there is merit in briefly exploring a few solutions that could possibly address both of these concerns.

A. State Regulations

Unlike the FDA, states have traditionally been recognized to have broad authority to regulate the practice of medicine in order to protect the safety, health, and welfare of the people within the state.¹⁰⁹ In contrast to the skepticism that FDA faces for intervening with the practice of medicine, states have always been able to exercise this authority in a variety of ways; including adopting vaccination and quarantine laws, as well as establishing modern licensing requirements for medical practitioners.¹¹⁰ Courts have also upheld a broad range of state laws that regulate the practice of medicine—making it clear that the states have the authority to do so.¹¹¹ Since regulating the practice of medicine is a space that has always been reserved for states, states should be involved in examining off-label prescribing practices.¹¹² There is a caveat, however, that different states must cooperate to ensure successful regulation of off-label activity, or else state residents can choose to travel to other states

¹⁰⁵ Margaret Z. Johns, *Informed Consent: Requiring Doctors to Disclose Off-Label Prescriptions and Conflicts of Interest*, 58 HASTINGS L.J. 967, 969 (2007).

¹⁰⁶ Zborowsky, *supra* note 43, at 939.

¹⁰⁷ Zborowsky, *supra* note 43, at 939.

¹⁰⁸ Zborowsky, *supra* note 43, at 939.

¹⁰⁹ Patricia J. Zettler, *Toward Coherent Federal Oversight of Medicine*, 51 SAN DIEGO L. REV. 427, 446 (2015).

¹¹⁰ Noah, *supra* note 3, at 159.

¹¹¹ Noah, *supra* note 3, at 159.

¹¹² Amy E. Todd, *No Need for More Regulation: Payors and Their Role in Balancing the Cost and Safety Considerations of Off-Label Prescriptions*, 37 AM. J.L. & MED. 422, 429 (2011).

with fewer restrictions; hence, defeating the goal of implementing state-based restrictions.¹¹³

B. Drugs Not Approved in United States

Another option that can be explored but has not yet gained much traction is for the FDA to speed up approval of new indications of drugs that have already been approved in other countries.

The European equivalent of the FDA is the European Medicines Agency, and pharmaceutical companies have to satisfy both the different approval processes set out by both the EMA and the FDA in order for new drugs to be marketed in the European Union and the United States respectively.¹¹⁴ This can be costly, duplicative, and time consuming. There has been academic debate calling for the cooperation of both the FDA and EMA to streamline and align the approval processes, which will facilitate drug development and allow for quicker (and less expensive) access without necessarily compromising the safety and efficacy of drugs.¹¹⁵

Even if the approval processes in both agencies were to remain different, there is value in permitting the use of drugs that have been approved by either agency (*i.e.* reciprocity), consequently reducing delay or the waste of duplicated resources.¹¹⁶ A case of meningitis outbreak in Princeton in 2013 highlights the feasibility of reciprocity: seven cases of the type B strain were diagnosed in Princeton, and while there exists a vaccine (Bexsero) for treatment of the outbreak the FDA has yet to approve its use.¹¹⁷ This same vaccine has been approved by EMA since January 2013 and is available in Europe and Australia, and after lobbying by the Centers for Disease Control and Prevention, the FDA gave special permission to import and use the vaccine.¹¹⁸ In fact, reciprocity is the major premise behind a bill introduced by Senator Ted Cruz and Mike Lee, “Reciprocity Ensures Streamlined Use of Lifesaving Treatments Act

¹¹³ Zborowsky, *supra* note 43, at 94.

¹¹⁴ *The FDA and Slower Cures*, W.S.J. (Feb. 28, 2011), <http://www.wsj.com/articles/SB10001424052748703766704576009512990553104>.

¹¹⁵ Lynn Howie et al, *A Comparison of FDA and EMA Approval: Implications for Drug Development and Cost of Care*, 27 *ONCOLOGY* 1195, 1195 (2013).

¹¹⁶ *Reform Options*, FDAREVIEW.ORG, http://www.fdareview.org/09_reform.php#3 (last visited Apr. 20, 2016).

¹¹⁷ Paul Howard and Yevgeniy Feyman, *If a Drug Is Good Enough for Europeans, It's Good Enough for Us*, HEALTH AFFAIRS BLOG (Feb. 14, 2014), <http://healthaffairs.org/blog/2014/02/14/if-a-drug-is-good-enough-for-europeans-its-good-enough-for-us/>.

¹¹⁸ Conor Friedersdorf, *Ted Cruz's Best Idea for Overhauling The FDA*, THE ATLANTIC (Dec. 18, 2015), <http://www.theatlantic.com/politics/archive/2015/12/ted-cruzs-best-idea-for-overhauling-the-fda/421158/>.

of 2015.” The proposed bill will allow for “reciprocal marketing approval of [drugs]. . . that are authorized to be lawfully marketed abroad” in a list of selected countries.¹¹⁹ There have also been previous bills, such as Speeding Access to Already Approved Pharmaceutical Act, that attempt to tackle this “drug lag”.¹²⁰

Legislation which aim to push for approval or the speeding up of approval of new indications of drugs already approved in other countries, such as the bill discussed above, is a feasible measure that warrants more attention.

C. FDA to Explore Other Options

Instead of viewing the FDA as an opposing regulatory body whose sole aim is to set up indiscriminate barriers for the use of off-label drugs at every turn, it is worthwhile looking to the FDA to adopt a role where it works alongside physicians and pharmaceutical companies to ensure that consumers derive the maximum benefit from off-label uses. For instance, the FDA may consider taking it upon itself to collect post-marketing data from users in a methodical manner to assess and balance harms and benefits of off-label uses. Alternatively, the FDA can collate and analyze existing evidence from any reliable non-randomized controlled clinical trial before distributing its findings to practitioners.¹²¹

As the Second Circuit in *Caronia* suggested, there are many regulatory mechanisms other than restricting speech that FDA could impose to advance its interests—*e.g.* providing guidance to doctors and patients to help differentiate misleading and inaccurate promotion from truthful information; developing disclaimer systems to warn consumers and providers; developing “safety tiers within the off-label market. . . to distinguish between drugs”; or making it mandatory for drug manufacturers to list all anticipated indications when they first submit a new drug for the approval process—which could “enabl[e] physicians, the government and patients to track a drug’s development.”¹²² The last suggestion has also been echoed by critics like Stafford, in the hope that this will preempt any attempt on the part of pharmaceutical companies to circumvent the rigorous testing process for what is most likely the

¹¹⁹ BILL FOR RECIPROCITY ENSURES STREAMLINED USE OF LIFESAVING TREATMENT ACTS OF 2015, http://www.cruz.senate.gov/files/documents/Bills/20151211_FDA.pdf.

¹²⁰ Alexander Gaffney, *Bill Wants Drugs Approved in Europe to be Available More Quickly to US Patients*, REGULATOR AFFAIRS PROFESSIONAL SOCIETY (Mar. 20, 2015), <http://www.raps.org/Regulatory-Focus/News/2015/03/20/21778/Bill-Wants-Drugs-Approved-in-Europe-to-be-Available-More-Quickly-to-US-Patients/>.

¹²¹ Stafford, *supra* note 16, at 1429.

¹²² *Caronia*, 703 F.3d 149, at 167-68.

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primary use.¹²³

VI. CONCLUSION

There is no easy solution to the existing dilemma of how FDA can strike a balance between safeguarding public safety and respecting physicians' autonomy to practice medicine freely without any intervention. This article has highlighted the numerous arguments supporting, as well as resisting the implementation of regulations by the FDA. Fortunately, there exist a few solutions that we can explore in isolation or combination to help address this dilemma; such as looking into allowing EMA-approved indications to be applied here in the U.S. or speeding up the FDA approval process. It remains to be seen if the aforementioned suggestions will ever gain sufficient traction to achieve tangible outcomes, but it is important nonetheless to encourage intellectual discourse in this area, with the hope that patients can benefit from the even the smallest steps taken in the right direction.

¹²³ Stafford, *supra* note 16, at 1429.