# Restoring Free Speech in Medicine

## How state lawmakers can overcome FDA regulations that keep doctors and payers in the dark

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Naomi Lopez Bauman,
Director of Healthcare Policy, Goldwater Institute
and Christina Sandefur,
Executive Vice President, Goldwater Institute

# Executive Summary

Better-informed physicians and payers, such as health insurance carriers, other third-party payers, and plan sponsors, can help patients gain access to a wider array of potentially effective treatment options. But federal regulations restrict physician and payer access to the most current medical information.

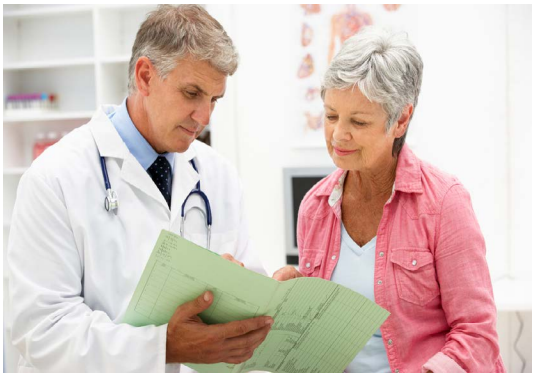
These regulations are related to the way the U.S. Food and Drug Administration, or FDA, restricts the labeling and marketing of prescription drugs, biologics, and medical devices. These rules prohibit the sharing of knowledge that could help doctors discover optimal medical treatments, and patients obtain them.

Commonly known as "off-label use," about one-fifth of prescriptions written annually are legally prescribed for purposes, patient populations, or dosages different from what the FDA originally approved. For example, aspirin is FDA approved for a variety of ailments, including pain, fever, and cardiovascular disease, but is also a commonly used prophylaxis for coronary disease in diabetic and other high-risk patients, a use for which it is not FDA-approved, making it "off label." The FDA limits how and what information drug, biologic, and medical device companies can share with healthcare providers and payers about the already-legal use of their products.

These speech restrictions have serious implications for patients. According to a recent survey of specialists and primary care physicians, roughly one-quarter indicated that FDA approvals for narrow indications had a high impact on treatment decisions.[1]

Companies are at constant risk of prosecution and criminal penalties for "misbranding," or communicating off-label uses for a product outside of a narrow and often murky set of federal requirements. But the sharing of truthful, scientific information about off-label uses need not conflict with patients' interests and well-being.

The benefits of off-label prescribing include expanding physicians' and other providers' arsenals of treatments and bringing potential treatments to patients sooner. Restrictions barring the truthful, scientific sharing of information about an FDA-approved device or treatment are not only increasingly inconsistent with the rapid availability of healthcare information in the 21st century, but they are also at odds with constitutionally protected speech. Indeed, the U.S. Constitution provides a floor of protection for individual rights, not a ceiling, leaving states free to enact laws that protect those rights more broadly than the federal Constitution does.



Just as informed patients are empowered to engage in a more productive conversation with their physicians, physicians who are up to speed on the latest medical and pharmaceutical advances are best equipped to provide optimal treatment for their patients. That is why state lawmakers can and should take steps to pursue reforms to ensure access to information for physicians and payers.

These reforms should:

- Allow for truthful and nonmisleading information to be shared between manufacturers and healthcare providers, whether solicited or not,
- Provide that shared information be truthful and nonmisleading, and
- Allow for manufacturers to communicate with payers.

# I. Introduction

## FDA regulations hinder healthcare providers' and payers' access to truthful information

When we think of advances in medicine, many of us might think about the Human Genome Project, HIV cocktails, advances in the treatment of cancer, or bionic limbs. But one of the most revolutionary impacts to medicine may be the easy availability of healthcare information—and the growing patient demand for it. The availability of healthcare information, as well as access to patient groups on the Internet, is giving rise to patient empowerment.


According to data from the Pew Research Center, two-thirds (67 percent) of U.S. adults have home broadband, and another 13 percent who lack home broadband have a smartphone.[2] What that means is that four of every five adults in the U.S. have a tool that allows them to connect to social networks, access entertainment online, conduct around-the-clock financial transactions, and access information.

When they do seek online information, more than half (55 percent) of all adult internet users look for information on a specific disease or medical problem, 43 percent for a certain medical treatment or procedure, and 16 percent for drug safety or recalls. But despite this active engagement with online healthcare information, 70 percent still reported getting information, care or support from a doctor or other healthcare provider.[3]

A strong interest in seeking out information on one's own is complementing traditional medical care—not replacing it. Informed patients can learn about their conditions and engage in a more productive conversation with their physicians.

Unfortunately, physicians and other healthcare providers often lack the most up-to-date information on potential treatments for their patients. That is because current FDA rules and regulations have essentially criminalized the sharing of truthful and nonmisleading information between manufacturers and healthcare providers and payers.

The rapid expansion of online healthcare information is occurring at a time when access to data has never been greater, yet communication about truthful and nonmisleading information about off-label uses is stalled.

**Laura's story**

The rules that limit the sharing of truthful, nonmisleading information have direct consequences for patients. Take for example the case of Laura.

Laura has colorectal cancer, and her previous treatment has failed. But it turns out there is an FDA-approved treatment for a different type of cancer that her doctors believe might save her life. In fact, staff who developed the treatment at one of the nation's premier academic research facilities agree it can help her.

Laura had genomic testing that found the same two genetic mutations the researchers identified in patients with various forms of cancer. Their treatment targets these two specific gene mutations, and the results seem to be working.

Unfortunately, Laura's insurance carrier has denied coverage for the treatment because it has not yet been approved for colorectal cancer or generally for those two genetic mutations. But the insurer might have granted approval had the manufacturer been allowed to explain why these experts believe this treatment might work for Laura.

But the manufacturer can't do that. It is illegal. In fact, sharing this information would subject the manufacturer to criminal penalties.

The treatment is FDA approved but not specifically for Laura's condition. For Laura, the treatment would be considered "off-label," which simply means that the prescription is for a condition, dose, or population other than that which was specifically tested for FDA approval. And prescribing off-label treatments to patients like Laura is perfectly legal.

But while the drug is legal, and prescribing it for off-label use is also legal, it is not legal for the manufacturer to share information with the insurer about how the researchers are effectively using this treatment for patients like Laura.

Dr. Edith Perez, a former oncologist and professor of medicine at the Mayo Clinic, now at Genentech, summarized the problem succinctly in recent testimony before the FDA: "Without the benefit of advanced knowledge of new drugs or new uses of drugs, an insurer may be unable to plan appropriately for annual budgets, and may also be limited in their ability to recognize the medically appropriate use of a medicine without FDA approval. This may negatively limit patient access to a medicine, even if prescribed by a physician."[4]

# II. Off-label use

## What is it?

The FDA evaluates and approves prescription drugs, biologics, and devices for specific medical indications. When an approved treatment or device is used for another medical condition (progression of the illness or different illness) or patient type (gender or age), or is prescribed in a manner or dose different than the approval, the treatment or device is "off-label."[5]


Approximately four billion prescriptions are dispensed annually in the United States.[6] About one in five prescriptions are "off-label."[7] Researchers who studied more than nine million clinical notes of more than one million patients found that:

"Based on the strength of associations and by compensating for frequent co-morbidities, we have identified 44,925 putative off-label uses worth further investigation. For example, in our preliminary results, we found that bevacizumab (a cancer drug) appears to be used to treat macular degeneration and retinal vascular occlusion, and modafinil (a sleep disorder drug) appears to be used as a treatment for Parkinson's disease. This work documents off-label uses occurring in practice, and, more importantly, enables us to address patient safety by prioritizing our search for the adverse event profiles of prevalent drugs having limited supporting evidence."[8]

Discoveries of new applications are frequent in clinical practice. According to one study, more than half (57 percent) of drug therapy innovations were discovered by practicing clinicians through field discovery—and not by the manufacturers.[9]

New and innovative applications of approved drugs are occurring rapidly. The medicine is FDA-approved, and doctors may legally prescribe off-label, but federal law strictly limits pharmaceutical companies from sharing information about off-label uses, so doctors and patients are often unaware of these effective alternate uses. This same law is doubtless stifling manufacturers from sharing important safety information about off-label uses as well.

Off-label prescribing errors are not infrequent and may involve the majority of medication errors.[10] Some providers may be failing to prescribe off-label when it is the most effective patient treatment or, perhaps of even more concern, incorrectly prescribing off-label due to a lack of the most up-to-date medical information.

Why in the midst of the internet age does the government restrict the flow of truthful medical information to physicians? Highly trained and educated medical professionals, who have the capacity to understand complex medical issues, often have access only to the same information available to the general public—and it is the direct result of federal rules.

**Rationale for off-label use**

The FDA approves the commercial availability of medications but not the practice of medicine, which falls within the domain of state authority. Except for some controlled substances such as opioids, it is legal in the United States for authorized providers to prescribe drugs off-label.

The cost and time required for approval of additional indications can be prohibitive. The Tufts Center for the Study of Drug Development estimates the average cost of drug development at almost $2.9 billion.[11] In order to obtain approval for an additional indication, a supplemental drug application must be submitted to the FDA. Even if approval for an additional indication is approved, the pharmaceutical company may not be able to recoup the expense involved,[12] and the approval times for new indications are not shorter than for the original FDA approval of that drug.[13]

Off-label use is not only common, it is also an important treatment option used by physicians in providing the best possible care to their patients. The exclusion of certain patient groups—such as children, the elderly, and pregnant women—from some clinical trials, often results in a higher rate of off-label prescriptions for these groups.

In the case of a seriously or terminally ill patient, providers may be more willing to use a treatment off-label. For example, off-label treatments for cancer might be more common in instances where a drug approved for a particular cancer disease is logically and potentially effective in treating a similar type of cancer.[14]

In a study of 10 leading chemotherapies in 2010, researchers found that off-label use accounted for about 30 percent of the treatments. Of those, roughly half were treatments supported by Compendium[15] and, as a result, could have been included in off-label communications. But it would have been unlawful for the manufacturers to share

truthful and nonmisleading information for the other half of the off-label treatments if those off-label treatments were not yet included in select journals at that time.[16]

**Examples of off-label use**

A common example of off-label prescribing is the antibiotic amoxicillin which is used to treat ear infections in children.[17] A drug approved for treating depression, citalopram, is prescribed off-label to treat a wide array of ailments that include hot flashes, irritable bowel syndrome, and stuttering.[18] Magnesium sulfate is approved to prevent seizures for women in preeclampsia and to control seizures in eclampsia. Off-label, it is commonly used to stop preterm labor in pregnant women.[19]

A precursor to what we now refer to as aspirin is found in writings dating back to 400 B.C. It was first marketed as a medical product in the late 1800s.[20] Today, aspirin is FDA approved for a variety of ailments, such as pain, fever, and cardiovascular disease, but is a commonly used prophylaxis for coronary disease in diabetic and other high-risk patients, a use that is not FDA approved, making it "off label."[21] See Table 1.

Among commonly prescribed drugs, 21 percent have been found to be off-label.[22] That proportion is much higher in some medical specialty areas. For example, a 2007 analysis of 31 tertiary care pediatric hospitals in the U.S. found that: "At least 1 drug was used off-label in 297,592 (78.7%) of 355,409 patients discharged during the study. Off-label use accounted for $270,275,849 (40.5%) of the total dollars spent on these medications."[23] The study authors also found a wide variation in off-label use within drug categories and across clinical diagnoses.[24]

A 2008 survey of oncology practices found that off-label use is somewhat important to their practice (87 percent), and half reported it to be extremely important. Of those practices using off-label treatments, the vast majority revealed that off-label treatments offered a superior treatment option or were needed because other treatments were unavailable, ineffective, or nonexistent.[25] See Figure 1.

An overwhelming number of providers - 95 percent - report that off-label coverage and reimbursement policies for anticancer drugs have changed their clinical decisions. This is another area where allowing for the truthful and nonmisleading sharing of off-label information could expand patient access to promising treatments.[26] Furthermore, one study of older patients with breast cancer predicts that off-label use will only increase as more drugs are proven useful in treating cancers in multiple sites of the body.[27]


When there is a sudden medical need but no approved treatment, off-label prescriptions may be a patient's best (or only) hope. This is the situation we face with the Zika outbreak.

The current Zika crisis has spurred a search for potential off-label treatments. The Zika virus (ZIKV) can cause microcephaly in fetuses, which sometimes results in severe congenital disabilities. Researchers from Florida State University, Johns Hopkins University, and the National Institutes of Health found that a drug already on the market as a treatment for tapeworm may be an effective treatment against Zika. Niclosamide may inhibit ZIKV replication.[28]

Despite substantial resources directed toward this global health emergency, it will likely take years to develop, test, and produce a new treatment. In this case, off-label use may provide an important—and more immediate—treatment for those infected. But for all the potential benefits off-label use might deliver, it also comes with risks.

**Table 1. Common off-label drug uses by specialty**

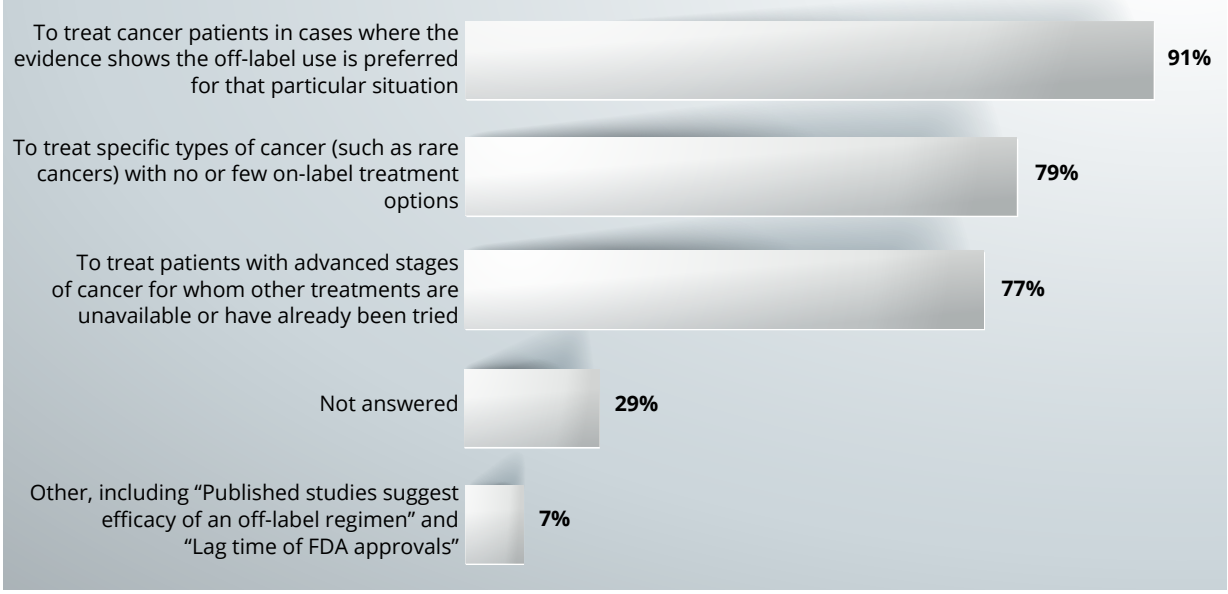
| Category and Drug | Off-label use(s) |
|---|---|
| *Allergy* | |
| Diphenhydramine | Chemotherapy-related emesis, insomnia |
| Anesthesiology | |
| Propofol | Intracranial hypertension |
| Dexamethasone, propofol | Postoperative nausea |
| Meperidine | Postanesthetic shivering |
| *Cardiology* | |
| Amiodarone | Supraventricular tachycardia |
| Aspirin | Antithrombosis in atrial fibrillation, Kawasaki disease |
| Atorvastatin, Simvastatin | Extended-interval dosing for hyperlipidemia |
| Indomethacin | Pharmacologic closure of patent ductus arteriosus |
| *Dermatology* | |
| Azathioprine | Atopic dermatitis, pemphigus; psoriasis |
| Biologic agents (e.g., etanercept, infliximab, intravenous immunoglobulin, rituximab) | Alopecia areata, atopic dermatitis, Behçet disease, dermatomyositis, hidradenitis suppurativa, pemphigoid, pityriasis, vasculitis |
| Gastroenterology | |
| Erythromycin | Gastroparesis |
| Omeprazole | Reflux-related laryngitis |

| | |
|---|---|
| *Hematology/Oncology* | |
| Alendronate | Hypercalcemia of malignancy |
| Dabigatran | Venous thromboembolism prophylaxis in orthopedic surgery |
| Doxorubicin | Refractory multiple myelomas |
| Furosemide (nebulized) | Dyspnea |
| Rituximab | Idiopathic thrombocytopenic purpura, Waldenström macroglobulinemia |
| *Infectious disease* | |
| Linezolid | Infective endocarditis |
| Sulfamethoxazole-trimethoprim | Sinusitis |
| *Nephrology* | |
| Acetylcysteine | Prevention of contrast nephrotoxicity |
| Albuterol | Hyperkalemia |
| Erythropoietin | Anemia of chronic disease |
| *Neurology* | |
| Atenolol, metoprolol, propranolol | Migraine prophylaxis |
| Isoflurane | Seizure, status epilepticus |
| Donepezil | Frontotemporal dementia |
| Gabapentin | Bipolar disorder, diabetes, fibromyalgia, neuropathic pain symptoms, headache, hiccups, hot flashes, restless leg syndrome |
| Lidocaine | Postherpetic neuralgia |
| Tricyclic antidepressants | Bulimia, insomnia, irritable bowel syndrome, neuropathic pain symptoms |
| *Obstetrics* | |
| Magnesium sulfate | Premature labor |
| Volatile anesthetics (e.g., enflurane, isoflurane, halothane) | Intraoperative uterine contraction |
| *Pediatrics* | |
| Amoxicillin (high dose) | Otitis media in children |
| Atenolol | Hypertension in children |
| Intranasal desmopressin | Nocturnal enuresis |
| Morphine | Pain in children |
| Sildenafil | Pulmonary hypertension in children |
| *Pulmonary* | |
| Volatile anesthetics (e.g., enflurane, isoflurane, halothane) | Status asthmaticus |
| *Psychiatry* | |
| Atypical antipsychotics (e.g., risperidone, olanzapine, quetiapine) | Anxiety, dementia, eating disorders, obsessive-compulsive disorder, personality disorders, posttraumatic stress disorder, substance abuse |
| β-Blockers | Social phobia, public speaking |

| | |
|---|---|
| Citalopram | Alcoholism, fibromyalgia, irritable bowel syndrome, obsessive-compulsive disorder, pathologic gambling, stuttering |
| Fluoxetine | Borderline personality disorder, diabetic neuropathy, fibromyalgia, hot flashes, premature ejaculation |
| Trazodone | Insomnia in elderly patients |
| *Urology* | |
| Sildenafil | Sexual dysfunction symptoms in women |

Note: This list is provided for general purposes only and does not constitute professional medical advice or treatment recommendations.
Source: Christopher M. Wittich, Christopher M. Burkle, and William L. Lanier, "Ten Common Questions (and Their Answers) about Off-Label Drug Use," *Mayo Clinic Proceedings* 87, no. 10 (October 2012): 982-90, and WebMD.com.

**Figure 1. Most frequently cited reasons in response to question: Why is off-label use of anticancer therapies important to the treatment of practices' cancer patients?**




Source: Covance Market Access Services Inc. for the Association of Community Cancer Centers (ACCC), "Impact of Payer Coverage and Reimbursement Policies on Off-Label Use of Anticancer Therapies," Final Report, September 24, 2008, based on a survey of 3,500 office-based oncology practices. Survey respondents included physicians, practice managers, and administrators of mixed practice sizes and in geographically diverse areas and settings. In the overall survey, N=165. For this question, N=129.

## Risks of off-label

When off-label prescribing is used, it is done without equivalent evidence of an FDA-approved treatment. There is often less evidence, and in some cases no evidence, that the drug is likely to be effective in that particular case, and often there is no information about potentially dangerous side effects of using the treatment off-label.

Legal scholars Ryan Abbott and Ian Ayres succinctly described the situation: "The central problem with off-label use is that there is an information deficit. Whereas on-label use is based on scientifically valid and statistically significant evidence indicating the potential risks, off-label use lacks that information."[29]

In fact, off-label use often involves scant scientific evidence. See Table 2.

**Table 2. Distribution of off-label use by AHFS therapeutic class and the level of scientific support**

| Drug Class | # Prescriptions | Off-Label Use No. | Percentage of Off-Label Use | Percentage with Strong Evidence | Percentage without Stong Evidence |
|---|---|---|---|---|---|
| Central nervous system | 58,914 | 15,491 | 26.3 | 18.2 | 81.8 |
| ENT | 10,622 | 1,613 | 15.2 | 1.6 | 98.4 |
| Gastro-intestinal | 14,237 | 1,770 | 12.4 | 15.1 | 84.9 |
| Hormone and synthetics | 34,868 | 1,366 | 3.9 | 34.5 | 65.5 |
| Skin and mucous membrane | 15,815 | 760 | 4.8 | 65.9 | 34.1 |
| Formulary restricted | 11,174 | 327 | 2.9 | 48.6 | 51.4 |
| Antihistamine | 348 | 21 | 6.0 | 19.0 | 81.0 |
| Anti-infective | 21,000 | 3,599 | 17.1 | 4.6 | 95.4 |
| Antineoplastic | 234 | 28 | 12.0 | 0 | 100.0 |
| Autonomic | 13,854 | 540 | 3.9 | 12.2 | 87.8 |
| Blood and coagulation | 1,328 | 23 | 1.7 | 0 | 100.0 |
| Cardiovascular | 70,953 | 2,313 | 3.3 | 58.8 | 41.2 |
| **Total** | **253,347** | **27,851** | **11.0** | **21.0** | **79.0** |

Source: Tewodros Eguale, MD, MSc, et al. "Drug, Patient, and Physician Characteristics Associated With Off-Label Prescribing in Primary Care," *Archives of Internal Medicine* 172, no. 10, (May 28, 2012): 781-788.

An additional concern is that physicians are often unaware of whether a drug is approved for a specific indication. In a national survey of primary care physicians and psychiatrists, physicians correctly identified the approval status of drugs for the given indication in only about half of the instances.[30] See Table 3.

**Table 3. Physician awareness of FDA approval status**

| Drug | Off-Label Indication | Evidence Level | Percentage Rx for Indication | Percentage Rx Thinking Drug is FDA Approved for Indication |
|---|---|---|---|---|
| Trazodone | Insomnia | Inconclusive | 79 | 11 |
| Bupropiron | Adult ADHD | Inconclusive | 61 | 15 |
| Venlafaxine | Adjustment disorder | Not in DrugDEX | 25 | 17 |
| Quetiapine | Dementia with agitation | Not in DrugDEX | 42 | 19 |
| Lorazepam | Chronic anxiety | Not in DrugDEX | 72 | 33 |
| Budesonide | Chronic obstructive pulmonary disease | Ineffective | 42 | 51 |
| Paroxetine | Bipolar disorder - depression | Ineffective | 38 | 25 |

Source: Donna T. Chen, MD, MPH, et al. "U.S. Physician Knowledge of the FDA-Approved Indications and Evidence Base for Commonly Prescribed Drugs: Results of a National Survey," *Pharmacoepidemiology and Drug Safety* 18, issue 10 (November 2009): 1094-1100, http://onlinelibrary.wiley.com/doi/10.1002/pds.1825/abstract.

This lack of awareness further demonstrates why it important to remove the barriers that prevent physicians and other providers from having the best available timely and accurate information about off-label uses. Some of the biggest potential benefits will come from better treatment decisions for individual patients. In an FDA hearing on off-label communications, a representative from the Biotechnology Innovation Organization explained that:

"The ability to responsibly communicate this type of information including information about indications and other conditions of use will help advance healthcare decisions by focusing more precisely on the individual patient. The ability to responsibly communicate in this manner in a scientifically substantiated way is key to realizing the benefits of personalized medicine and will provide significant benefits not only for patients and families, but for our healthcare system overall."[31]

## How off-label is currently regulated

The Food, Drug, and Cosmetic Act of 1938 imposed the requirement that a new medication be safe. It wasn't until 1962 that the Kefauver-Harris Amendment mandated that FDA-approved new drugs also demonstrate efficacy.[32]

The mandate has essentially created a two-tier drug approval system. The FDA requires treatments to pass its standards for both safety and efficacy in order to receive the Agency's stamp of approval for the treatment's "FDA-approved indication." Off-label uses must meet only the safety requirement. A de facto two-tiered approval now operates, each with its own set of rules for the sharing of information.

The FDA requires the approval of all medication labeling before distribution into interstate commerce. This includes the package insert, print and broadcast advertisements, brochures, and patient education materials. The FDA also prohibits "misbranding" of medications, such as labeling a medication with misleading information. The FDA considers including an off-label use to be "misbranding."[33]

**How off-label regulations limit free speech**

While pharmaceutical manufacturers can't promote off-label uses, they may respond to unsolicited questions from healthcare professionals about off-label use. Those responses must be completed by the manufacturer's medical affairs office, and all interactions with the provider must be documented. Pharmaceutical manufacturers are also permitted to distribute select journal articles and textbook chapters that examine and discuss off-label use if the off-label information is accurate, the relationship between the distribution of information and the sponsoring drug manufacturer is disclosed, and the published material is not edited or presented in an abridged form.[34]

But these limitations are insufficient. As explained by Dr. Samuel Nussbaum, former chief medical officer at Anthem Inc. and now senior fellow at the USC Schaeffer Center for Health Policy & Economics:

"So in the current framework, even if a healthcare decision maker asks all of the right questions, they may still not be able to access the necessary information they need because manufacturers are hesitant to provide some information due to uncertainties in the laws and regulations that govern what they can and cannot share.

So this is why healthcare decision makers need access to better and timelier information from manufacturers, so they can have access to all of the puzzle pieces and put together a complete picture to best care for the patients they serve."[35]

Given the constraints on the sharing of information, it is important to explore what information manufacturers have and with whom it should be shared.

**What changes are needed?**

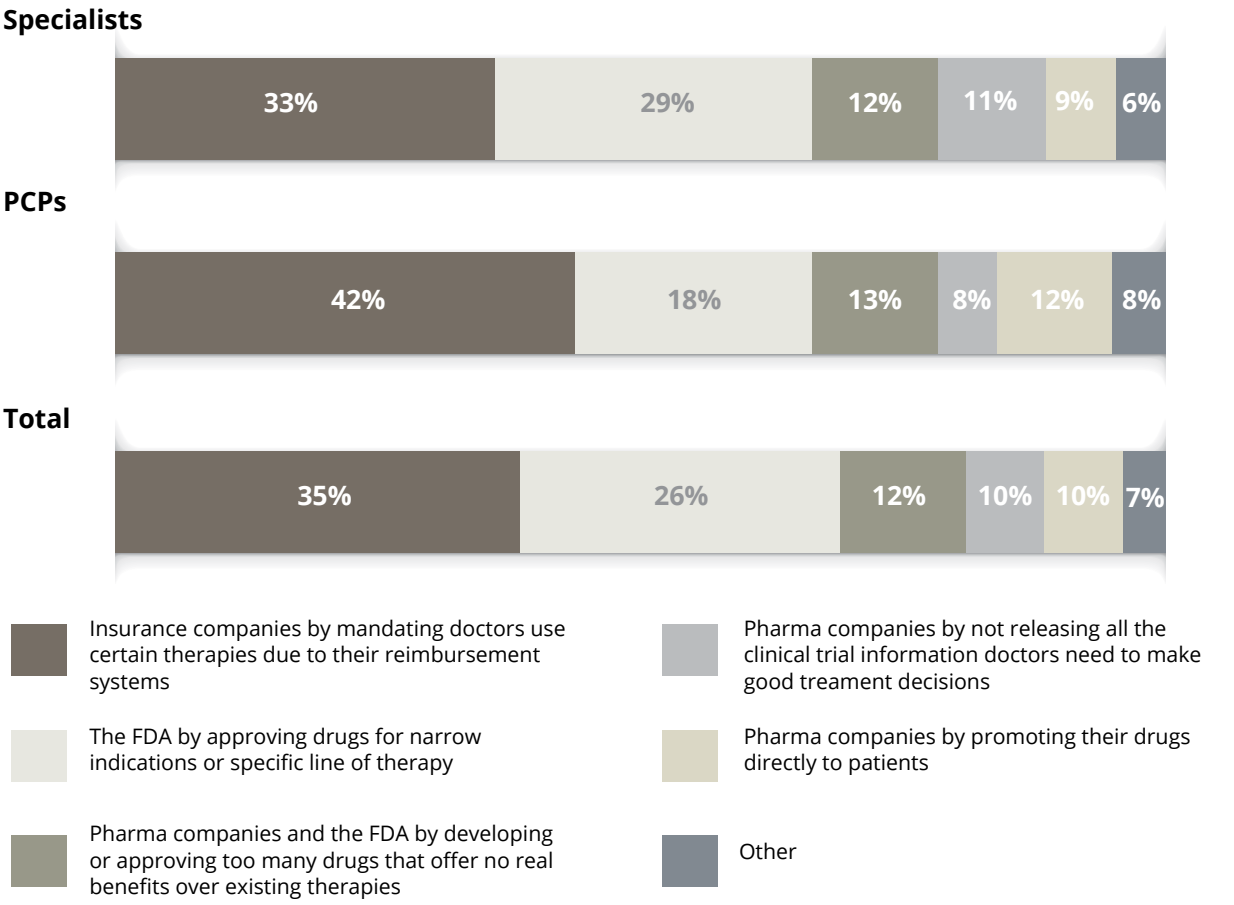
In the Food and Drug Law Journal, representatives of the pharmaceutical industry wrote: "While all other individuals and entities may freely discuss and exchange

information about both approved uses and alternative uses of FDA-approved medicines, the Agency—through its current interpretation of the Federal Food, Drug, and Cosmetic Act (FDCA)—significantly limits biopharmaceutical companies' ability to communicate proactively about the medicines they research, develop, and bring to patients."[36]

The limitations placed on physicians do, indeed, have important implications for patients. According to a recent survey of specialists and primary care physicians, roughly one-quarter indicated that FDA approvals for narrow indications had a high impact on treatment decisions.[37]

The same survey also revealed that reimbursements also influenced treatment decisions. Allowing manufacturers to share information with health systems, pharmacy benefit managers, and formulary committees could open additional treatment options for providers and their patients.

**Figure 2. What has the highest impact on treatment decisions?**




Source: "Infographic: What Information Doctors Need from Pharma," *Medical Marketing and Media*, November 8, 2016, http://www.mmm-online.com/commercial/infographic-what-information-doctors-need-from-pharma/article/571593/2/.

# III. Constitutional precedent

**The right to communicate truthful information about legal treatments**

The right to speak and share information freely is protected by the federal Constitution and each of the state constitutions. While federal law allows for off-label treatments, the government routinely censors the communication of valuable and truthful information that could help medical professionals and patients make informed decisions, take full advantage of such treatments, and even save lives. Federal law strictly limits how pharmaceutical companies—those with the most knowledge about drugs and their possible uses and side effects—can share information about the legal use of their products. In this area, as Wayne State University Professor Peter Henning puts it, "Speaking the truth can violate the law."[38]

The FDA subjects companies and their representatives who promote or advertise a drug's off-label use to prosecution for the crime of "misbranding."[39] In other words, while the drug is legal, and prescribing it for off-label use is legal, it is not legal to share information about prescribing the drug for off-label use. As a result, doctors and patients may never learn of effective alternate uses for legally approved medications. And pharmaceutical companies wanting to promote their products by sharing truthful scientific information about off-label uses face harsh criminal penalties.

The First Amendment protects the freedom of speech and makes no distinction between different kinds of speech.[40] Oddly, the Supreme Court has held that the Constitution does not protect commercial speech—speech that advertises a product or service—as much as it protects other types of speech. Under the Central Hudson Test, government may even censor lawful, nonmisleading commercial speech if the regulation directly serves a substantial government interest and the regulations are not more extensive than necessary.[41]

**Legal precedent**

Nevertheless, in 2011, the Supreme Court confirmed that the First Amendment protects a pharmaceutical company engaging in speech for a commercial motive. It struck down a Vermont law that prohibited the transmission of information relating to doctors' prescribing practices for commercial use.[42] The court held that targeting specific types of companies and activities for censorship was unconstitutional.

More recently, the Supreme Court struck down an Arizona ordinance that imposed different restrictions on speech based on whether the speech was political, commercial, or religious. Any limit on freedom of expression that is based on the content of the message expressed, the court said, was a content-based restriction subject to the most stringent constitutional limits.[43] It seems clearer than ever that federal rules that make it illegal for pharmaceutical companies to tell doctors true information about the legal use of federally approved medicines violate the First Amendment.

Few courts have directly addressed whether or to what degree the Constitution protects a company's right to share information about off-label uses. In 2000, the D.C. Circuit Court of Appeals struck down FDA guidelines that regulated the information drug companies could provide for use in textbooks, and limited the ability of companies to sponsor continuing medical education programs.[44] But the FDA later capitulated, declaring that the regulations did not actually prohibit off-label promotion under those circumstances. That rendered the case moot, so the Supreme Court never heard the case.

Over a decade later, in United States v. Caronia, the Second Circuit Court of Appeals overturned the conviction of a pharmaceutical sales representative who was punished for promoting off-label use of the drug Xyrem. The court held that "the government cannot prosecute pharmaceutical manufacturers and their representatives . . . for speech promoting the lawful, off-label use of an FDA-approved drug."[45] In other words, because the conduct the representative was promoting was lawful, truthful speech about the conduct was constitutionally protected.

Despite the apparent breadth of that decision, the FDA announced the ruling would not significantly affect its enforcement practices. Instead of prosecuting off-label advertising, which would be a direct prosecution of speech, the agency would simply use off-label speech as evidence of conduct: the crime of misbranding.[46] But rather than clarifying the FDA's approach or reconciling it with the Constitution, this announcement further complicated the matter. Indeed, what is "branding" if not speech?

The agency's narrow interpretation of the Caronia decision was put to the test in Amarin v. FDA. In that case, a New York federal judge issued a preliminary injunction

against the FDA, permitting Amarin to share information about the off-label use of its fish-oil drug, Vascepa.[47] Vascepa was FDA approved to treat adults with severe triglyceride levels, and Amarin was in the process of seeking approval for use in adults with slightly lower triglyceride levels. While that approval was pending, Amarin wanted to share its research regarding that larger population but feared the FDA would prosecute. Amarin's initial victory established that First Amendment protections extend to all truthful and nonmisleading promotional speech, even speech used as evidence to prosecute conduct.

The Amarin case seemed on-track to establish some much-needed precedent to guide the pharmaceutical industry and settle the off-label speech question. Then less than a year later, the FDA once again thwarted efforts to establish clear guidelines by entering into a settlement agreement with Amarin that allows the company to market Vascepa as it desired. The FDA also agreed to review up to two proposed off-label communications from Amarin per year under an arbitration process.[48]

Some see the Amarin settlement as a deliberate move by the FDA to avoid establishing legal precedent regarding when and how drug companies can share information. As Coleen Klasmeier of Sidley Austin LLP noted, "Most legal issues presented by the cases never get ventilated in court or any open legal forum" and settlements "behind closed doors" undermine "nuanced interpretation."[49] Indeed, the FDA made clear that its settlement "does not signify [any] position on the First Amendment and commercial speech."[50]

The lack of certainty about the law and hefty punishments wielded against the provision of truthful information continues today. Only a few months ago, the FDA attempted yet again to punish a company for sharing information about its products' off-label use, this time threatening pharmaceutical representatives for Vascular Solutions for telling doctors that one of their company's medical devices could treat different kinds of varicose veins. According to CEO Howard Root, the FDA treated this communication as "a felony even though our device was FDA-cleared for treating all varicose veins, over two-thirds of our salespeople never sold even one unit of it, sales constituted only 0.1 percent of our total sales and not a single patient was harmed."[51] Although Root's company, which develops lifesaving medical devices, was finally vindicated, the five-year, $25 million legal battle took a toll.

Manufacturers, doctors, and patients will suffer from the lack of clear standards regarding what information can be shared about treatment options so long as Congress and the courts continue to allow the FDA to censor speech by medical experts about the legal use of legal medicines. It is time for the states to take action to protect patients, medical professionals, and healthcare freedom.

**U.S. and state constitutions set precedent for state control over free speech in healthcare**

The U.S. Constitution provides a floor of protection for individual rights, not a ceiling, leaving states free to enact laws that protect those rights more broadly than the federal Constitution does.[52] America's founders envisioned the federalist system providing a "double security . . . to the rights of the people"[53] by enabling each state to "exercise its police power or its sovereign right to adopt in its own Constitution individual liberties more expansive than those conferred by the Federal Constitution."[54] As Justice William Brennan wrote nearly 40 years ago, "State constitutions, too, are a font of individual liberties, their protections often extending beyond those required by the Supreme Court's interpretation of federal law."[55] This system enables states to "respond, through the enactment of positive law," to protect the rights of citizens "without having to rely solely upon the political processes that control a remote central power."[56]

State constitutions already provide broader protections for free speech,[57] property rights,[58] and the right to privacy[59] than their federal counterpart. And the Supreme Court has recognized that "regulation of health and safety is 'primarily, and historically, a matter of local concern,'" and while federal officials can sometimes override state choices, states have "great latitude . . . to legislate as to the protection of the lives, limbs, health, comfort, and quiet of all persons."[60]


Thus, states can protect the rights of doctors, patients, and medical professionals to share truthful information about legal medical treatments.

As the Supreme Court put it 40 years ago, "Information is not in itself harmful . . . people will perceive their own best interests if only they are well enough informed, and . . . the best means to that end is to open the channels of communication rather than to close them."[61] This is especially true in cases where the underlying behavior being communicated—here, prescribing off-label treatments—is itself perfectly lawful. Or, expressed another way by a Vermont doctor, "We have a saying in medicine, information is power. And the more you know, or anyone knows, the better decisions can be made."[62]

# IV. State-based solution

**The path forward for states to empower doctors and payers with the best healthcare information possible**

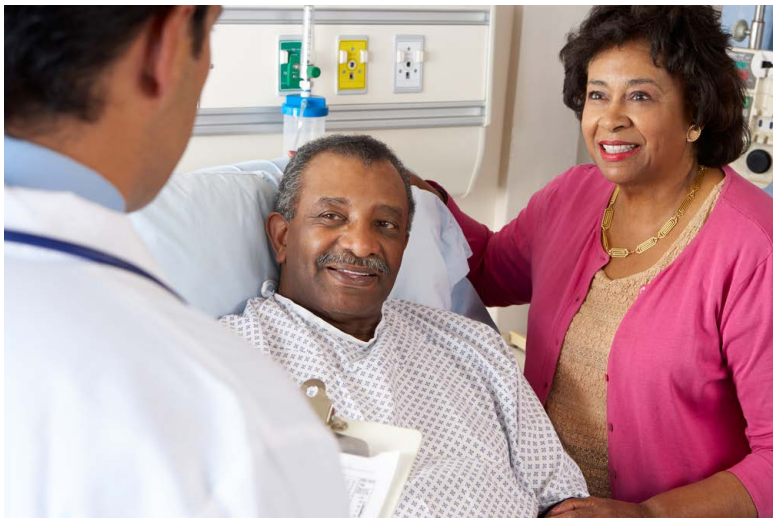
Economist Alexander Tabarrok explained the FDA-approval anomaly as follows: "Every drug available for prescription in the United States must have gone through at least phase I clinical trials. Phase I trials examine a drug for toxicity in healthy volunteers and establish that the drug meets a minimum level of safety. Drugs used in FDA-approved ways have also been through phase II and phase III 'efficacy' trials. Drugs prescribed off-label, however, have not been through this process; hence, off-label drugs are regulated essentially according to the FDA's pre-1962 rules whereas drugs prescribed for labeled uses are regulated according to the post-1962 rules."

He further contends that off-label prescribing "speeds medical innovations to patients, increases the number of drugs available to doctors, and lowers the costs of medical innovation. Because of these benefits, off-label prescribing is common in the United States today."[63]

But states can—and should—go a step further. By protecting free speech, as guaranteed in state constitutions across the country, lawmakers can safeguard an important freedom while giving healthcare providers more tools and options to treat their patients. These reforms should:

- Allow for truthful and nonmisleading information to be shared between manufacturers and healthcare providers, whether solicited or not,
- Provide that shared information be truthful and nonmisleading, and
- Allow for manufacturers to communicate with payers.

Access to healthcare information has never been greater. Shouldn't we allow healthcare providers and payers to obtain truthful and nonmisleading information so that they can make treatment and coverage decisions using the most up-to-date, accurate information?



Arizona lawmakers thought so. In March 2017, Governor Doug Ducey signed HB 2382, Arizona's Free Speech in Medicine Act, which safeguards the free speech rights of those in the medical field to share truthful research and information about off-label uses for FDA-approved medicines. That bill passed the Arizona State House and Senate with unanimous, bipartisan support. Arizona is the first state in the country to enact this protection, which will expand the number of treatment options in doctors' toolkits, enhance patients' medical autonomy, and increase access to healthcare.

Lawmakers in other states can—and should—follow Arizona's example, restoring the right to freely exchange truthful information about legal treatments, and providing healthcare providers and payers with the tools they need to make informed healthcare decisions for patients.

## APPENDIX: PROPOSED LEGISLATION

Sec. 1.

As used in this act, and unless the context otherwise requires:

A. "Off-label" means the use of an United States Food and Drug Administration-approved drug, biological product, or device other than the use(s) approved by the FDA.

B. "Misbranding" shall refer to either the federal definition under 21 U.S.C. § 352 or the state definition under [STATE LAW].

Sec. 2

A. A pharmaceutical manufacturer or its representatives may engage in truthful promotion of off-label uses.

B. This article does not require a health insurance carrier, other third-party payer, or other health plan sponsor to provide coverage for the cost of any off-label treatment. A health insurance carrier, other third-party payer or other health plan sponsor may provide coverage for an off-label treatment.

Sec. 3.

A. Notwithstanding any other law, no official, employee or agent of this state shall enforce or apply [STATE LAW] against or otherwise prosecute a pharmaceutical manufacturer or its representatives for engaging in truthful promotion of off-label uses.

B. Notwithstanding any other law, no state regulatory board may revoke, fail to renew or take any other action against a pharmaceutical manufacturer's or representative's, health care institution's, or physician's license solely for engaging in truthful promotion of off-label uses.

Sec. 4.

This state and all political subdivisions of this state are prohibited from using any personnel or financial resources to enforce or cooperate with federal attempts to enforce or apply 21 U.S.C. §§ 331 or 352 against or otherwise prosecute a pharmaceutical manufacturer or its representatives solely for engaging in truthful promotion of off-label uses.

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