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Truth or Consequences

The Benefits of Off-Label Drug and Device Promotion

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Over the past half-century, the U.S. Food and Drug Administration (FDA) has made it increasingly harder for Americans to get access to innovative new drugs and medical devices. By raising the hurdles medical products manufacturers must clear before they get approval, the agency has increased the cost of new treatments and delayed their availability.

Fortunately, physicians and patients often have access to drugs and devices that can treat certain illnesses, but which have been approved by the FDA for *other* uses. This practice, called "off-label" prescribing, provides greater choice in treatment options for millions of Americans, but the FDA and many congressional critics have tried to stymie its use for decades. At Congress's urging, the FDA has long forbidden drug and device makers from disseminating information about off-label uses, which makes it difficult for doctors and their patients to learn about important therapeutic options. This may change, however, if a pending lawsuit against the FDA is successful.

In October 2009, the California-based drug manufacturer Allergan filed a lawsuit against the FDA seeking a declaratory judgment that distributing truthful and relevant information about the safe and effective off-label use of drugs and devices violates no federal statute and that the agency's regulatory ban on off-label promotion is an unconstitutional restriction of free speech. A hearing on procedural motions is scheduled for April 26, 2010, though it could be years before the case is finally resolved. Nevertheless, an eventual victory for Allergan would also be a victory for the millions of American patients who rely on off-label uses.

What Is Off-Label Prescribing? Every new drug, and most medical devices, must be certified by the FDA as both safe and effective for a specified use before they can be sold in the United States. This specific use approval is known as the product's "label

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indication" or "on-label" use. But FDA's regulatory authority does not extend to the *practice* of medicine. So, once a drug or device is on the market, physicians may legally prescribe it for any safe and effective "off-label" use, governed only by professional medical standards and the licensing authorities of each state.

For example, an oncology drug called Platinol has been approved for the treatment of bladder, testicular, and ovarian cancer. But, because its mechanism of action makes it useful in combating many different kinds of cancerous tumors, Platinol is also frequently prescribed to treat thyroid and lung cancers.[1]

Similarly, the drug Rituxan was approved in 1997 to treat certain forms of Non-Hodgkins Lymphoma. It proved to be so beneficial, the drug was soon being used off-label to treat various other cancers and several conditions affecting the immune system, including lupus, multiple sclerosis, and arthritis. These off-label uses developed by practicing physicians led the manufacturer to conduct clinical trials, eventually resulting in additional FDA approvals for Chronic Lymphocytic Leukemia and rheumatoid arthritis.[2]

The practice of off-label prescribing is widespread, and is common in every field of medicine. By some estimates, at least 20 percent of all prescriptions written are for off-label uses,[3] and most hospital patients receive at least one drug off-label.[4] Indeed, off-label uses are frequently considered to be state of the art treatment, and often constitute the medically recognized standard of care.[5]

The federal Food, Drug and Cosmetics Act and the FDA itself expressly recognize that health care professionals may legally prescribe approved drugs for off-label uses.[6] And practice guidelines and similar materials disseminated by various agencies within the U.S. Department of Health and Human Services (the FDA's parent body), such as the National Cancer Institute and the National Cholesterol Education Program, specifically recommend certain off-label uses.[7]

The American Medical Association (AMA) has repeatedly studied the practice and concluded that "physicians have the training and experience to determine what is the best or preferred method of treatment for their patients."[8] Accordingly, the AMA has said that off-label prescribing should often be considered "reasonable and necessary medical care, irrespective of labeling." Consequently, physicians may even be subject to malpractice liability if they do not use drugs and devices for off-label indications when doing so constitutes the medically recognized standard of care.

Although it is used in every field of medicine, off-label prescribing is particularly important in psychiatry, oncology (cancer treatment), cardiology, and pediatrics.[9] A 1991 study by the U.S. General Accounting Office (now the Government Accountability Office) found that, in any given year, one-third of all drugs prescribed for the treatment of cancer were for off-label uses, and that more than half of all cancer patients received at least one drug for an off-label indication.[10] According to another study, off-label uses accounted for nearly 50 percent of cardiac medications and anticonvulsant drugs prescribed in 2001.[11]

Similarly, patients with rare, so-called "orphan" diseases—who constitute as much as 10 percent of the population—are especially dependent on off-label uses for their treatment because the number of patients with each orphan disease is often too low to justify the tremendous expense of seeking FDA's approval for those indications.[12] Clinical testing and the supplemental application process generally take five to 10 years and cost hundreds of millions of dollars,[13] so getting on-label approval for an orphan disease could put the price of many treatment options out of reach for the most vulnerable patients.

How Are Off-Label Uses Discovered? Many off-label uses are discovered by drug and device manufacturers or academic researchers who conduct clinical trials with the hope of generating data to support an FDA approval for new label indications. But practicing physicians often discover new and important off-label uses on their own—by, for example, observing the beneficial side effects of certain medicines or by applying their knowledge of chemistry and physiology to use remedies approved for one illness to treat other illnesses with similar underlying causes. In one study, 59 percent of drug therapy innovations were discovered by practicing physicians in the field, independent of pharmaceutical company or university research.[14]

Once they are developed, physicians learn about beneficial off-label uses of drugs and devices through medical and science journals, medical specialty association newsletters, conferences, seminars, Internet sources, and from their colleagues. Naturally, medical products companies are another important source for this information.

Physicians try to keep abreast of new research findings, but they cannot read every issue of the hundreds of medical journals published in the U.S. So, drug and device makers have long distributed journal reprints and excerpts from medical reference works in an effort to promote their products. Manufacturers also present research information in speeches to physician groups or at scientific and medical conferences. They also occasionally have sales representatives tell physicians directly about off-label uses—though many of these activities are heavily restricted, and the dissemination of off-label information by sales representatives can subject manufacturers and the representatives as individuals to criminal and civil sanctions.[15]

Regulators and drug industry critics regard these promotional practices as grubby commercial marketing, but the distribution of scientific information they entail allows physicians to become better informed about new developments and enables them to make better treatment recommendations for their patients. That, however, has not stopped the FDA and other federal agencies from trying to restrict the distribution of even peer-reviewed medical journal articles, along with other kinds of off-label promotion. The agency argues that most off-label uses have not been proven safe and effective in double-blinded, case-controlled clinical trials, and that an ability to promote off-label uses eliminates the incentive for manufacturers to seek formal approval for off-label uses.[16]

The federal and state governments have aggressively prosecuted many drug and device manufacturers for providing unapproved information about off-label uses. From 2003 to

2007, the FDA issued 42 notices of violation demanding that drug companies cease disseminating information describing off-label uses. And, during that period, the Department of Justice settled at least 11 civil and criminal cases involving off-label promotion.[17] In 2009, the drug manufacturer Pfizer pled guilty to criminal charges and paid a record $2.3 billion to settle allegations of promoting 14 of its products for off-label uses. The same year, Eli Lilly was forced to pay $1.4 billion for promoting its schizophrenia drug Zyprexa for off-label uses.[18]

The ban on off-label promotion applies not just to pharmaceutical and medical device companies, but also to financially-interested third parties, such as physicians who participate in clinical trials on the manufacturer's behalf. In the words of one observer, "[T]he same speech, delivered to the same audience by doctors with the same qualifications, [is] treated differently if one of those speakers has been funded by a pharmaceutical company."[19] The FDA recently sent a warning letter to a Florida dermatologist and medical researcher for illegally mentioning in interviews with *Elle* magazine and NBC's "Today" show that an anti-wrinkle drug on which she was conducting clinical trials had shown positive results and was better than a competitor's product.[20]

Physicians themselves, however, value the distribution of information regarding off-label uses. A series of national surveys has shown that a large majority of physician specialists—including oncologists, cardiologists, emergency room physicians, orthopedic surgeons, and neurologists—believe the FDA has made it more difficult for them to learn about new uses for drugs and devices, and that the agency should not restrict information about off-label use.[21]

Regulation of Off-Label Uses. The FDA first proposed regulating off-label drug use in 1972, but gave this up after strenuous objection from the medical community. However, with the Drug Amendments Act of 1962, Congress gave the FDA authority to regulate drug and device labeling and promotion, and the agency has tried to prevent manufacturers from discussing or disseminating most information about unapproved uses ever since.[22] The Food and Drug Administration Modernization Act of 1997 (FDAMA) eased the agency's restrictions somewhat by permitting medical products manufacturers to distribute peer-reviewed medical journal articles, but only if the manufacturer first filed a supplemental application with the FDA seeking approval for those uses.[23]

The non-profit Washington Legal Foundation (WLF) mounted a court challenge to the FDAMA off-label provisions, arguing that the restriction of truthful and non-misleading information was an unconstitutional restriction of commercial speech.[24] The court sided with WLF on its constitutional challenge. The FDA avoided having its regulations fully overturned, however, when the agency's lawyers insisted that the rules merely established a "safe harbor" under which drug and device manufacturers would be automatically deemed in compliance with the law, but that the regulations did not establish any new authority for FDA to prevent off-label promotion.[25]

As a result of this case and other litigation, federal courts have explained that the FDA may not ban all off-label promotion, such as distribution of journal article reprints to physicians, though the agency may regulate and monitor the practice to ensure the information is not biased or misleading. In *United States v. Caputo*, for example, the federal Seventh Circuit Court of Appeals upheld the conviction of a medical products manufacturer for selling a medical device that was not approved for any use. In dicta, though, the court indicated that at least some prohibitions on off-label promotion were likely to be unconstitutional. [26] And, in *Thompson v. Western States Medical Center*, the U.S. Supreme Court concluded that the FDA may not forbid the advertising by pharmacists of compounded drugs, which are mixtures of two or more approved drugs in a manner not approved by the FDA.[27]

Nevertheless, the limits on the dissemination of information regarding off-label uses remained unclear, and the FDAMA off-label provisions expired in 2006. So, in October 2007, the agency attempted to clarify the rights of drug and device firms by circulating a draft guidance document describing how manufacturers could distribute such information to physicians without running afoul of the law.[28] The draft guidance explained that drug and device manufacturers are permitted to distribute peer-reviewed journal articles and reference documents containing studies of off-label uses as educational materials, but it also carefully circumscribed the kinds of literature that may be distributed, to whom, and in what form.

Given existing court precedent, the guidance document provided only the bare minimum of flexibility required by constitutional free speech protections. Nevertheless, Rep. Henry Waxman (D-Calif.), then-chairman of the House Oversight and Government Reform Committee, immediately criticized and mischaracterized the draft guidance. He claimed that it would promote "potentially dangerous uses" of drugs and that it appeared to be "an effort by FDA to displace Congress and establish by administrative fiat a new system for use of journal articles that lacks the safeguards set by Congress."[29]

Rep. Waxman even attacked the integrity of the peer review process and of the medical journals themselves, claiming that drug and device firms manipulate peer review and that "peer-reviewed articles could not be relied on as a substitute for FDA review."[30] He further insisted that only FDA's medical reviewers should have the ability and authority to judge the quality of the scientific literature.

Fortunately, FDA disregarded these claims and issued a final version of the guidance document in January 2009.[31] That is important, because physicians—not members of Congress or FDA bureaucrats—are best trained and qualified to decide the proper treatment for their patients. Regardless of what information has or has not been vetted by the FDA, or what is printed on a drug or device's label about its approved uses, physicians are tasked with assessing what they know about the propriety of various treatment options and providing their patients with the very best possible care. Having access to better information about off-label uses will promote, not hinder, patient care.

However, despite the guidance document's availability, there remains considerable uncertainty regarding other off-label promotional practices that are—or appear to be—legal under the Food, Drug and Cosmetics Act, and which are likely to be protected under the First Amendment.

Furthermore, congressional critics, including Rep. Waxman, remain opposed to even the narrow safe harbor created for the distribution of peer reviewed, scientific research findings. "This fundamentally undermines the requirement that companies prove to FDA that each new use is safe and effective," said Waxman upon release of the final guidance in January 2009. He encouraged the Obama administration FDA to withdraw the guidance document, telling a Reuters reporter, "I hope this policy will be carefully re-examined by the new administration."[32] Waxman is now chairman of the House Committee on Energy and Commerce, where he has direct oversight authority over the FDA, so the agency is likely to take his concerns very seriously.

The Allergan Lawsuit. Ironically, one recent FDA action may actually *require* the drug manufacturer Allergan to disseminate information about off-label uses of its product, Botox. Botox has been approved for the treatment of certain types of muscle spasm in the neck and eyes, as well as for its more popular cosmetic purposes, but it is also widely used off-label for the treatment of various other muscle spasticity conditions.[33] In September 2009, the FDA instructed Allergan to send detailed safety updates to physicians who prescribe Botox for both on-label and off-label indications. But the company argues that fully complying with this order could violate FDA's policy regarding the dissemination of off-label use information.[34]

Caught in a Catch-22, in which complying with either of FDA's requirements could lead to a prosecutable violation of the other, Allergan decided to challenge the agency's blanket prohibition on off-label promotion in court. The company argues that, although FDA "may regulate speech that is actually or inherently false or misleading consistent with the First Amendment," the agency's regulatory scheme restricting all off-label promotion "reach[es] protected speech that is neither actually nor inherently false or misleading."[35]

Federal courts generally permit vigorous regulation of commercial speech, such as the promotion of medical drugs or devices, but such speech may not be banned altogether unless it is false or misleading or concerns an unlawful activity. Under the U.S. Supreme Court's *Central Hudson Gas & Electric Corp. v. Public Service Commission* test:

1. Any restriction on commercial speech must be premised on a substantial governmental interest;
2. The regulation must directly advance that interest; and
3. It must be no more extensive than necessary to advance that interest.[36]

In earlier cases, federal courts have agreed that the government has a substantial interest in ensuring that promotional activities are truthful and "provid[ing] an incentive for manufacturers to go through the strict FDA preclinical and clinical trial process to get off-label uses on-label," and that the agency's regulations did advance those interests.[37]

However, in the *Washington Legal Foundation* litigation, the federal District Court for the District of Columbia concluded that the governmental interest could be advanced just as well by less burdensome alternatives to an outright restriction on free speech. Among these alternatives is a "full, complete, and unambiguous disclosure by the manufacturer that the use has not been approved by the FDA."[38] And in the pharmacy compounding case, *Thompson v. Western States Medical Center*, the Supreme Court concluded that the "First Amendment directs us to be especially skeptical of regulations that seek to keep people in the dark for what the government perceives to be their own good."[39]

This skepticism is especially warranted when the recipients of information regarding off-label uses are trained physicians, capable of analyzing the value of one additional piece of information in the context of everything else they know about the safety and efficacy of various treatment options and the individual physiology and preferences of each of their patients. As Seventh Circuit Judge Frank Easterbrook explained in his unanimous *U.S. v. Caputo* opinion, "The manufacturer has an incentive to slant the speech in its favor and may withhold bad news, but many listeners (especially professionals such as physicians) understand this and can discount appropriately."[40]

Indeed, one can argue that the federal government has an interest not only in promoting the FDA approval process, but also in ensuring that doctors and their patients receive truthful and non-misleading information about all available treatment options. This seems particularly relevant in light of the situation now confronting Allergan.

The federal District Court for the District of Columbia will take up the case this spring, as a hearing on procedural motions is scheduled for April 26. A positive resolution of the case would reaffirm the Constitution's protection of truthful and non-misleading speech and strike down the most aggressive of FDA's restrictions on off-label promotion.

Conclusion. Every day, many thousands of treatment choices are made by patients and doctors. Physicians take into account individual patient trade-offs and preferences, drug interactions, and biological variations such as efficacy and side effects. The FDA's medical reviewers and advertising enforcers do not have access to this dispersed knowledge or interest, so the agency's crude, centralized, one-size-fits-all decisions actually harm many more people than they help.

The proponents of central control over truthful information seek to impose more government regulations and destroy the individual choices of patients and physicians. They do this by ignoring the basic principles of economics and marketing, downplaying the exorbitant costs of FDA approval, exaggerating both the incentive of manufacturers to use biased information and the effects such bias has on physicians' behavior, and ignoring the significant benefits that off-label prescribing brings to patient care.

Off-label prescribing is not just useful, but essential to the proper provision of necessary medical care. Doctors and their patients both reap tremendous benefits from the distribution of truthful and non-misleading information about off-label uses. It is long

past time for Congress and the FDA to loosen their restriction on the dissemination of such information by the very firms that have the resources and interest to do so.

Notes

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