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Off-Label Prescribing: A Call for Heightened Professional and Government Oversight

Rebecca Dresser and
is the Daniel Noyes Kirby Professor of Law and Professor of Ethics in Medicine at Washington University in St. Louis. She earned her J.D. from Harvard Law School

Joel Frader
is a Professor of Pediatrics and Professor of Medical Humanities and Bioethics at North-western University. He earned his M.D. from Tufts University School of Medicine

Off-label prescribing is an integral part of contemporary medicine. Many patients benefit when they receive drugs or devices under circumstances not specified on the label approved by the Food and Drug Administration (FDA). An off-label use may provide the best available intervention for a patient, as well as the standard of care for a particular health problem. In oncology, pediatrics, geriatrics, obstetrics, and other practice areas, patient care could not proceed without off-label prescribing.[1] When scientific and medical evidence justify off-label uses, physicians promote patients' interests by prescribing products off label.

Off-label prescribing can also harm patients, however. The potential for harm is greatest when an off-label use lacks a solid evidentiary basis. A 2006 study examining prescribing practices for 169 commonly prescribed drugs found high rates of off-label use with little or no scientific support.[2] Researchers examining off-label use in U.S. children's hospitals concluded, "[W]e still have incomplete knowledge about the safety and efficacy of many medications commonly used to treat children across a range of drug classes and clinical diagnoses."[3] More than half the respondents in a survey of academic medical centers reported that innovative off-label prescribing raised concerns in their institutions, such as lack of data, costs, and unfavorable risk-benefit ratios.4 When substantial uncertainty exists about off-label applications, patients are at risk of receiving harmful or ineffective treatments.

Legal authorities recognize physicians' discretion to prescribe products off label.[5] In the existing regulatory framework, once the FDA approves a product for marketing, physicians may prescribe it for indications or patient populations not included on the label. They may also prescribe drugs at dosages or using methods of administration not specified on the label.[6] Omission from the approved label does not mean that the FDA disapproves of an off-label use, it simply indicates that the agency has not reviewed that use. Of course, like other parts of medical practice, off-label prescribing can lead to malpractice liability if it fails to conform to accepted standards of care.[7]

In a perfect world, all uses of drugs and devices would be supported by solid research. The existing regulatory system fails to impose this high standard, however, and the private sector often lacks incentives to conduct rigorous evaluations of off-label uses. In the current situation, the medical community has primary responsibility for determining when off-label prescribing is appropriate for patients. But appropriate off-label prescribing can be challenging for physicians today, because of time pressures, information overload, and the involvement of industry in research and education about off-label uses.

Responsible off-label prescribing requires physicians to: (1) evaluate whether there is sufficient evidence to justify an off-label use; (2) press for additional information and research when

adequate evidence is lacking; and (3) inform patients about the uncertainties and potential costs associated with off-label prescribing. Policy efforts are also needed to improve the quality of off-label prescribing. Federal authorities should systematically monitor patient responses to off-label uses, regularly collect and publicize information about off-label uses, and consider proposals to regulate certain off-label uses, as well as other proposed policy measures that could decrease risky and ineffective off-label prescribing. In the remainder of this article, we examine the current federal policies governing off-label prescribing, ethical standards governing off-label prescribing, and policy reforms to promote patient and public interests in evidence-based off-label prescribing.

The Existing Regulatory Structure

The Initial Approval Process

The Food, Drug, and Cosmetic Act (FDCA) governs interstate distribution of medical products.[8] Manufacturers may distribute drugs and certain devices for commercial use only after the FDA has approved the products as safe and effective for their intended use. As part of the product approval process, sponsors submit detailed information about trials done for specific indications in specific populations. The process "can involve dozens of FDA scientists poring over extensive databases of studies in animals, toxicologic evaluations, and clinical trials."9 With the help of outside advisers, FDA officials evaluate safety and effectiveness and determine whether the probability and magnitude of potential benefits are sufficient to justify a product's risks.

Although the FDA review process is far from perfect and could be improved,[10] it generally produces highquality information that enhances clinical practice. In most cases, the FDA review process gives physicians a reasonable evidentiary basis for on-label prescribing. But the initial FDA review fails to answer whether a product should be used off label. A product may be safe and effective for one indication, but could present a different risk-benefit ratio for another indication. Products found safe and effective for adult trial participants may not work safely and effectively in children or elderly people. Drugs can have different effects at different dosages or with different methods of administration.

When FDA officials approve a product, they approve a specific label for that product, too. The label includes information about the approved indications for product use, as well as the approved dosage, method of administration, and patient population. Federal law permits the use of marketed products in wider circumstances, however. Physicians may prescribe drugs and devices in situations not covered by the approved label. The FDCA authorizes the FDA to regulate manufacturers' activities in interstate commerce, including advertising, but does not authorize the agency to regulate physicians' behavior.[11]

Federal officials, medical organizations, and others defend the current approach by citing benefits to patients. They say that patients' access to potentially helpful treatments should not be delayed until an off-label use receives formal FDA approval.[12] Consistent with this view, Medicare, Medicaid, and private insurers reimburse for off-label uses when there is some evidence to support such uses.[13]

Off-Label Promotion

Although physicians are free to prescribe off-label, the federal regulatory system imposes constraints that affect off-label use. Consistent with its jurisdictional authority, the FDA controls manufacturers' product marketing. To promote the use of a product according to its label, manufacturers may advertise, distribute other forms of promotional material, and solicit business through their sales representatives. In contrast, the FDA restricts manufacturers' freedom to promote off-label uses. The FDCA and FDA regulations prohibit manufacturers

from distributing in interstate commerce products intended for off-label uses. According to the FDA, approved drugs that are promoted for an unapproved use are misbranded, and devices promoted for unapproved uses are adulterated and misbranded.[14]

During the 1990s, Congress amended the FDCA to permit a limited form of off-label promotion. The amendments allowed manufacturers to distribute to physicians reprints of so-called "enduring materials," defined as articles from peer-reviewed journals and reference books, that discussed off-label uses.15 A separate FDA guidance allowed manufacturers to provide financial support to educational programs at which speakers discussed off-label uses, as long as the programs were organized by independent entities.[16] At the same time, however, the amendments and guidance imposed a number of conditions on these activities. For example, the FDCA amendments required manufacturers distributing enduring materials to certify that they would seek FDA approval for the relevant off-label use or obtain an agency exemption from the requirement (because, for example, the required studies would be too burdensome for an off-label use serving a very small patient population). They also had to submit the enduring materials for FDA review at least 60 days before distributing them to physicians.

Manufacturers' statements about their products qualify as commercial speech, and the First Amendment to the U.S. Constitution has been interpreted to require giving them some freedom to communicate about off-label uses. In the late 1990s, a federal court found that the above statutory and FDA provisions on off-label promotion were more restrictive than necessary to advance the government's interest in maintaining incentives for manufacturers to obtain FDA approval for off-label uses.[17] According to the court, some of the limitations on promotion unnecessarily abridged protected speech rights. The judge said the government could require manufacturers to disclose their financial interests and the fact that the product uses discussed in the materials and educational sessions were not FDA approved. The agency could not enforce several other restrictions, however, such as the requirements to seek FDA approval for the off-label uses and FDA review of the materials on off-label uses.

The government appealed this decision, but in the appellate argument portrayed the contested limitations on promotion as merely a "safe harbor" for manufacturers' conduct, rather than as requirements the agency intended to enforce.[18] As a result, the case was dismissed without establishing clear constitutional boundaries for government restrictions on commercial speech about off-label uses.[19]

In early 2009, the FDA issued a new guidance on distribution of enduring materials addressing off-label uses,[20] but its constitutionality and policy impact remain uncertain. In a later part of the essay, we discuss the current debate over federal efforts to limit off-label promotion and question whether such efforts are the best way to promote public health interests in appropriate off-label prescribing.

Supplemental Approval and Industry

Decision-Making—Although the specifics remain unclear, courts are likely to uphold the government's authority to impose some restrictions on off-label promotion, such as disclosure requirements and prohibitions on consumer advertising. If this prediction is accurate, medical product manufacturers seeking to engage in the full range of promotional activities will have to secure from the FDA supplemental approval to add new uses to the approved label.[21] Some information needed to evaluate a supplemental application may come from the initial product approval studies, but manufacturers must also submit additional data demonstrating the product's effectiveness for the new use.

Drug and device companies determine what uses to emphasize in the initial product review process and make choices shaped by market forces, such as the size of the potential patient

population.22 Market forces also influence companies' decisions after their products gain initial FDA approval. In some cases, profits from off-label uses may be sufficient to deter manufacturers from seeking supplemental approval of a new product use.[23] Company officials may prefer to invest their resources in developing new drugs rather than sponsoring costly trials that might (or might not) demonstrate the safety and effectiveness of new uses for already-approved products.

Federal legislation has altered this situation by extending market exclusivity periods for manufacturers evaluating products in certain populations commonly treated off label, such as children[24] and patients with rare diseases,[25] but there are still many situations in which companies lack financial incentives to pursue supplemental approval for new uses. Products may be beneficial when used in ways that deviate from the label, but because neither the FDA nor the private sector evaluates off-label uses in a systematic and transparent way,[26] this determination is often left to the medical community.

Ethical Standards

The ethical justification for off-label prescribing is that it can provide the best available therapy for a particular patient. This contrasts with the ethical justification for conducting clinical trials, which is to develop new therapies or clarify the best use of existing treatments for future patients.[27] Investigators often test off-label uses in formal research and, as we discuss below, there are often ethical reasons to conduct such tests. But clinical off-label prescribing has a therapeutic purpose and individual patient interests should guide such use.

In an effort to guide professional practice, a few medical organizations have issued policies on off-label prescribing. The American Medical Association supports off-label use "when such use is based on sound scientific evidence and sound medical opinion."[28] Similarly, the American Academy of Pediatrics (AAP) Committee on Drugs endorses off-label prescribing "based on sound scientific evidence, expert medical judgment, or published literature" and "done … in the best interest of the patient."[29] The AAP Committee on Drugs also recognizes an obligation to promote knowledge about off-label uses: "Physicians who choose to prescribe a medication with limited pediatric data have a public and professional responsibility to assist in the systematic development of the information about that drug for the benefit of other patients."30

Implicit in these advisory statements are two ethical considerations relevant to off-label prescribing: (1) evaluating the existing evidence for off-label prescribing; and (2) collecting information and conducting research when there is inadequate evidence about an off-label use. A third consideration addresses disclosure to patients: what should physicians tell patients about off-label interventions? In this section, we examine these considerations and apply them to different categories of off-label prescribing, with the goal of helping physicians exercise appropriate ethical judgment about off-label prescribing.

Evaluating the Evidence for Off-Label Uses

Off-label uses can be supported by different levels of evidence. Authorities recognize a hierarchy of scientific and clinical evidence that can justify medical interventions. Typically at the top are large randomized controlled trials (RCTs), followed by smaller RCTs, cohort studies, case-control studies, poorly controlled or uncontrolled studies, case reports, and expert opinion.[31] Off-label prescribing can also be a logical extension of an approved use, as when a drug approved for one condition is prescribed for another condition that has genetic or physiologic similarities to the first.32 Physicians may prescribe a drug approved for one indication to patients with less or more serious forms of the condition or for conditions causing similar symptoms.33 Off-label applications may emerge through an organized research process

or through "field discovery," in which clinicians identify new applications as they care for patients.34

Compendia, such as the American Hospital Formulary Service Drug Information[35] and DrugDex,[36] evaluate and rate the evidence supporting specific off-label uses. The Agency for Healthcare Research and Quality offers up-to-date summaries of the scientific evidence on some off-label applications.[37] At least one independent, not-for-profit professional organization provides assessments of off-label uses.[38] Peer-reviewed medical journals also supply credible support for off-label uses.[39] These resources can be useful, but offer clear guidance only after high-quality research has evaluated a particular off-label use.[40] Moreover, the evaluations are not as rigorous as FDA review, for they typically involve fewer people and a less comprehensive data analysis than the FDA requires.[41] A recent review of Medicare-approved compendia governing reimbursement for off-label anticancer chemotherapies found the compendia lacking in consistency, quality, transparency, and timeliness.[42]

The medical product industry's influence on research and education about off-label applications can complicate physicians' assessment of the evidence supporting off-label prescribing. As noted earlier, the law permits manufacturers to engage in limited promotion of products for off-label uses and, as discussed below, some form of promotion is likely to be permitted in the future. Allowing manufacturers to distribute peer-reviewed materials and to sponsor educational programs can help physicians learn about potentially beneficial off-label uses. Yet manufacturers at times violate the letter or spirit of the rules requiring independent and high-quality information, often with the assistance of physicians whose judgment may be clouded by the compensation they receive for favorable presentations about off-label uses.[43] A well-known example is the case involving off-label promotion of gabapentin, in which company representatives subverted the rules by providing financial benefits to researchers and physicians willing to convey positive views of off-label applications.[44] Product manufacturers may also exercise undue control over studies of off-label uses, through influencing study design, data analysis, and publication content.[45] Manufacturers may fail to publicize studies with unfavorable findings, as well.[46] For these reasons, physicians must closely scrutinize the quality of industry-funded studies and presentations supporting off-label uses.

Although industry-sponsored research and education may encourage questionable off-label prescribing, industry is not solely responsible for such prescribing. Studies suggest that many physicians rely on experience, anecdotal reports, and opinion leaders to guide their treatment decisions, often failing to demand solid evidence for their prescribing choices.[47] This approach to clinical knowledge can encourage inappropriate off-label prescribing even in the absence of industry encouragement for it.[48]

The justification for off-label prescribing is strongest when rigorous research supports it. Support that rests on other forms of evidence may also be sufficient, depending on the circumstances. Below we discuss different off-label uses that can be justified by unconventional evidence. In most cases, however, physicians should seek to develop a solid research basis for off-label prescribing.

Collecting Information and Conducting Research

When an off-label use lacks an adequate evidentiary basis, the medical community should work to rectify the situation. High-quality evidence about off-label applications not only protects patients from harmful and ineffective interventions, it increases their access to beneficial treatments. Public and private insurers are more likely to cover off-label uses that are supported by solid evidence.[49] Indeed, Medicare and other drug plans may deny payment when off-label uses are not included in one of the major drug compendia.[50] High-quality research indicating that off-label uses are safe and effective can also encourage manufacturers to obtain FDA

approval for new uses, which in turn produces a more informative label and increases patient access to the product.[51]

Professional organizations and the academic community should actively identify emerging off-label uses and gather information about such uses. As physicians learn about patient responses to off-label uses, they should share information about side effects and outcomes with colleagues through publications, presentations, and other methods of communication.[52] They should also alert manufacturers and the FDA to any adverse events associated with an off-label use.[53] Medical journals and websites should promote communication by setting aside space for reports about emerging off-label applications.[54] Health care institutions should develop policies on off-label prescribing and exchange information about positive and negative experiences with off-label applications.[55]

The medical community should also promote necessary research about off-label uses. If innovative use of a drug or device suggests that an off-label use has benefits, formal study should commence.[56] As the AAP Committee on Drugs observes, "Although [important] uses are often discovered through off-label therapeutic use, confirmation of efficacy and safety in formal studies is usually required."[57] If members of the profession think that an off-label use is developing without adequate evidentiary support or examination of potential harms, they should urge manufacturers to sponsor the needed research,58 or seek government or other independent support for it.59

Informing Patients

There is debate over whether physicians should tell patients when a drug or device is prescribed for an off-label use. A 2006 poll suggests that much of the U.S. public is confused and ambivalent about off-label prescribing, with about half the respondents believing that physicians are permitted to prescribe drugs only for on-label indications and about half believing that physicians should be prohibited from prescribing drugs for off-label indications.[60] These findings suggest that explaining off-label regulatory status and its significance in particular situations could be a complicated task.

Some commentators argue that information about off-label status is less important than information about the evidence that supports a product's use in an individual patient's case.[61] The few courts that have considered the question have concluded that a product's regulatory status is not part of the medical information that physicians must disclose about a proposed off-label treatment (unless it is administered in the context of research).[62]

At the same time, professional groups support disclosure in some situations. The AAP Committee on Drugs advises physicians to use professional judgment in deciding when to discuss with patients and parents a drug's off-label status and its acceptance in the medical community.[63] Three European regulatory officials call on prescribers to discuss potential benefits and harms of off-label applications with patients.[64] An Australian group suggests informing patients when a proposed off-label use is unusual or offered as a "last resort."[65] And several legal commentators support a general legal requirement to disclose whether drugs are FDA approved for a specific patient's condition.[66]

Disclosure duties are designed to ensure that patients have sufficient information to evaluate their treatment options. We think that reasonable patients would want to know when an off-label application lacks strong support in the scientific or medical literature,[67] when experience suggests the use involves substantial risk, or when there is a possibility that insurers will refuse to cover a costly off-label application. In clinical trials evaluating investigational products, researchers are required to disclose the uncertainties and possible costs associated with trial

participation.[68] Similarly, patients should be given an opportunity to choose whether to accept the uncertainties and possible costs associated with some off-label uses.

Ethical Considerations in Specific

Off-Label Situations—Off-label prescribing occurs in different situations that raise different ethical issues. The appropriate approach to off-label prescribing can depend on whether the use is new or old. Appropriate off-label prescribing can also depend on the urgency of the patient's situation and the availability of alternative treatment approaches. Off-label prescribing in specific patient populations raises distinct ethical issues, as well.

Substantial uncertainty usually accompanies the off-label use of newly approved products. Drugs and devices may be approved based on studies of relatively small groups followed for a relatively short time. Even when physicians prescribe products according to the label, previously undiscovered risks can emerge once products enter the clinical arena.[69] The possibility of undiscovered risks also exists when recently approved products are prescribed off label.[70]

Novel off-label uses of both newly approved and older products typically present substantial uncertainty about effectiveness, as well. As the American College of Physicians Ethics Manual advises, physicians considering an unprecedented off-label indication or dosage "should consult with peers, an institutional review board, or other expert group to assess the risks, potential adverse outcomes, potential consequences of foregoing a standard therapy, and whether the innovation is in the patient's best interest."[71] Physicians prescribing products for innovative off-label uses should tell patients about the unknowns, monitor them closely, and begin collecting formal study data as soon as possible. An example of this approach is the ongoing study of thalidomide, approved in 1998 for treating complications of leprosy, as an anti-tumor agent.[72]

Some older products have been routinely prescribed off label for many years. Much off-label prescribing in this category may benefit patients, but some of it may not.[73] History demonstrates that "without a formal method of evaluation, some widely adopted applications of technologies can be nonbeneficial or even harmful to patients."[74] For example, the recent increase in studies of off-label medication uses in children has produced label revisions that change previously accepted prescribing practices.[75]

Even established off-label prescribing needs a solid evidentiary foundation. One problem in this area is that product manufacturers often lack financial incentives to sponsor research on older products, because the products are no longer protected by patent or are widely prescribed without formal supplemental approval.[76] As a result, it may be necessary to seek government or other noncommercial support for research on off-label uses of older products. Another option is for government agencies and professional organizations to conduct systematic reviews of the existing evidence about off-label uses of older products.[77]

Off-label prescribing can also have different objectives. An off-label use may be the only treatment option for seriously ill patients. In these circumstances, off-label prescribing can be ethically justified on the basis of evidence that would be considered inadequate in other contexts. For less seriously ill patients, off-label prescribing should have a stronger evidentiary basis.[78] And prescribing products off-label to improve patients' appearance or lifestyle is ethically justifiable only when very strong evidence demonstrates product safety. The goal should be to avoid repeating incidents like the one involving dexfenfluramine, in which a drug approved for obese patients whose weight put them at high risk of other illnesses was rapidly prescribed for a broader range of patients who wanted to lose weight. Soon it became clear that the drug could cause pulmonary hypertension and cardiac valve disease, and it was withdrawn

from the market.[79] But by that time, some patients taking the drug for cosmetic reasons had suffered serious harm.[80]

Most off-label prescribing has clear therapeutic goals, and in certain practice areas, off-label prescribing is both extremely common and necessary. For example, physicians treating patients with rare ("orphan") diseases rely heavily on off-label prescribing. Commercial sponsors lack financial incentives to develop products for small populations and the small number of people with these diseases makes it impossible to evaluate products according to ordinary clinical trial criteria.[81] During the 1980s, Congress passed legislation creating incentives for manufacturers to develop products aimed at orphan diseases,82 but there are still many rare diseases lacking effective approved therapies.83

Off-label use can be justified in these cases, but evidence about safety and effectiveness is just as important for this patient population as it is for others. Data-gathering methods must be flexible, but systematic study is often possible. Indeed, in approving products aimed at treating orphan diseases, the FDA has accepted the results of trials involving as few as eight people as adequate evidence of safety and effectiveness.[84]

Off-label prescribing is also common in pediatric, obstetric, and geriatric practice. Relatively few prescription drugs on the market include labeling information about appropriate use in these groups.[85] This problem can be traced to sponsors' and researchers' reluctance (often based on liability fears) to enroll minors, pregnant women, and elderly people in drug trials, a reluctance that persists despite policy actions to promote research in underrepresented populations.[86]

The failure to study these populations exposes patients to risks from drugs and dosages presenting distinct risks to certain groups. For example, there is growing recognition that off-label use of selective serotonin reuptake inhibitors for psychiatric disorders in young people may increase the risks of suicidal thinking and depression.[87] The failure to include children, pregnant women, and older people in studies can also deprive patients of possibly beneficial therapies, because physicians may hesitate to prescribe off label in light of the uncertain effects in these populations. Children, elderly people, and pregnant women should have access to treatments grounded in evidence-based data. The medical community should continue to advocate for high-quality research evaluating product safety and effectiveness in these major patient populations.

Policy Reforms

A former FDA official has criticized the agency for taking a "hear-no-evil, see-no-evil approach to the off-label use of drugs."[88] Recent congressional action could improve this situation. The FDA Amendments Act of 2007[89] made three changes to the FDCA that are relevant to off-label prescribing.[90]

First and most significantly, the Act strengthened the postmarketing surveillance system governing approved products. Congress increased funding for the FDA division charged with monitoring the safety of approved drugs. Lawmakers also increased funding for the adverse event reporting system, with the aim of creating an active monitoring system to replace the current dependence on product manufacturers, physicians, and patients to report problems. Other revisions in federal law will enable the agency to use information from large clinical databases to evaluate product safety, including off-label uses.[91] And the 2007 Act gives the agency clear authority to order manufacturers to undertake post-approval studies so that risks can be identified earlier than in the past. All of these measures could generate more information about patients receiving products off label, thus improving the evidence base for off-label prescribing.

Second, the 2007 Act requires public registration of many industry-sponsored studies, which could increase professional and public access to study information about off-label uses. The revision will make it harder for manufacturers to conceal unfavorable results of such studies, as some have done in the past.[92] A third set of revisions increases the agency's authority to intervene when marketed products appear harmful to patients. The 2007 law empowers FDA to mandate label changes to reflect newly discovered risks. It also authorizes FDA to restrict the use of drugs known to be risky through limiting drug distribution to physicians with specialized training.[93]

In 2009, the FDA adopted another new policy relevant to off-label prescribing. The agency published a (nonbinding) guidance with FDA recommendations for "Good Reprint Practices."[94] The guidance replaces the previous statutory provisions permitting manufacturers to distribute enduring materials about off-label uses, which expired in 2006. It recommends that manufacturers distribute articles published in peer-reviewed journals with independent editorial boards and policies requiring full disclosure of "any conflict of interest or biases."95 It advises against distributing articles in manufacturer-funded special supplements or publications. The guidance contains other provisions designed to ensure that distributed materials contain high-quality information about off-label uses.96 But the guidance fails to recommend or require that manufacturers work toward FDA approval of the uses discussed in the enduring materials. It also omits the previous requirement for manufacturers to give the FDA an opportunity to review the materials before they are given to physicians.

In issuing nonbinding recommendations and omitting the supplemental approval and prior review requirements, the FDA was probably attempting to avoid First Amendment challenges to the policy. Indeed, after the litigation challenging the previous law governing off-label promotion, the FDA reportedly stopped enforcing those requirements.[97] Nevertheless, leading medical journals have published commentaries criticizing the FDA's guidance.

Critics of the guidance say that selective publication of studies, manipulation of the literature, and an inadequate knowledge base keep the published peer-reviewed literature from supplying adequate information on the safety and effectiveness of off-label uses. Because of these problems, they argue, manufacturers should be prohibited from distributing peer-reviewed materials to physicians.[98] The critics, however, underestimate the First Amendment problems with imposing severe restrictions on distribution of scientific and medical publications about off-label uses. They also assume that physicians will make better prescribing decisions if manufacturers are prohibited from distributing enduring materials about off-label uses. Such a ban might reduce the incidence of off-label prescribing, for it could reduce the number of physicians aware of potential off-label applications. Off-label prescribing would still occur, however, and physicians would rely on the peer-reviewed literature, as well as less rigorous information sources, such as expert opinion and anecdotal evidence, to guide that prescribing.[99]

The real value of government limits on off-label promotional activities is that they give manufacturers an incentive to sponsor the research needed to determine whether off-label uses are safe and effective. A more direct approach to promoting patients' interests would be to require manufacturers to submit more off-label uses for FDA review. Consistent with this view, several commentators discuss the possibility of new statutory provisions authorizing the FDA to mandate safety and effectiveness data for off-label uses that are widespread or based on questionable evidence.[100] Because this approach would regulate conduct, rather than speech, it would avoid First Amendment challenges. Congress and the FDA would have to develop a plan for implementing such a review requirement, but it could be a more effective way to protect patients than measures that attempt to curb distribution of enduring materials on off-label uses.

Physicians and policymakers concerned about inappropriate off-label prescribing offer other ideas for government actions that could improve the current situation. The FDA could simplify the requirements for adding new uses to the approved product label or allow labels to include more information about off-label uses.[101] The agency could also analyze and distribute reports about the evidence on selected off-label uses and require manufacturers seeking initial product approval to present information about potential off-label uses.[102] Congress could create financial incentives, such as an additional period of market exclusivity, for manufacturers sponsoring research on widespread or promising off-label uses.[103] Federal officials could adopt more rigorous policies on reimbursement for off-label uses, limiting Medicare and Medicaid payments to off-label uses that are either supported by solid evidence or administered in the context of clinical trials evaluating their safety and effectiveness.[104]

Conclusion

Without solid evidence, off-label prescribing can expose patients to harm. In the current debate, the medical community often holds the FDA responsible for the problems with off-label prescribing, while FDA officials expect the medical profession to ensure appropriate off-label prescribing. But improving the quality of off-label prescribing will require action from both groups.

Members of medical profession will likely remain essential gatekeepers to off-label prescribing. As long as the regulatory system gives physicians the freedom to prescribe off label, patients will depend on the medical profession to exercise this freedom responsibly. The medical community should more actively promote efforts to identify appropriate and inappropriate off-label prescribing and professional societies should urge members to limit off-label prescribing to situations in which it is ethically justified.[105] At the same time, members of Congress and FDA officials should recognize a more affirmative role for government oversight in this area. FDA officials should use their new legal powers to detect and publicize problems with off-label use more effectively than they have in the past. Congress should consider whether additional measures are needed to deter inappropriate off-label prescribing.

Patients need access to beneficial off-label treatments, but they also need protection from risky and ineffective interventions. With a robust approach to professional oversight and policy efforts to better evaluate the benefits and harms of specific off-label applications, physicians and officials can fine tune off-label prescribing and promote the best interests of patients.

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