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## Perspective

# Regulating Off-Label Drug Use — Rethinking the Role of the FDA

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The Food and Drug Administration (FDA) provides a barrier to market entry and use of unproven and unsafe products. For prescription drugs, the FDA approval process requires substantial evidence of efficacy and safety for specific clinical situations. Although approval is indication-specific, the FDA has a limited role once a drug is on the market. Recent draft guidelines covering manufacturers' promotion of drugs through the distribution of journal articles suggest that the FDA is moving toward an even more minimal role.<sup>1</sup>

Although off-label prescribing — the prescription of a medication in a manner different from that approved by the FDA — is legal and common, it is often done in the absence of adequate supporting data. Off-label uses have not been formally evaluated, and evidence provided for one clinical situation may not apply to others. As an area of controversy, off-label use is subject to the contradictory expectations of various stakeholders, including health care payers, the pharmaceutical industry, physicians, and consumers. The FDA has a role in balancing these expectations, but it currently does so primarily through regulating corporate marketing. Although there is a strong rationale for greater FDA involvement in off-label use, it is moving toward relinquishing control in its new draft guidelines.

Off-label use arises through many pathways but usually entails the use of drugs for unapproved clinical indications (e.g., the antipsychotic agent quetiapine [Seroquel] prescribed for depression) or in unapproved subpopulations (e.g., paroxetine [Paxil] for depression in children). Off-label use may originate from a presumed drug class effect, extension to milder forms of an approved indication, extension to related conditions (the use of the antiasthmatic montelukast [Singulair] for chronic obstructive pulmonary disease), expansion to distinct conditions sharing a physiological link (the use of the antidiabetic drug metformin to treat polycystic ovarian syndrome), or extension to conditions whose symptoms overlap with those of an approved indication.

The spectrum of off-label use includes guideline-recommended practice (aspirin in diabetes for prophylaxis against cardiovascular disease), last-resort therapy (tacrolimus [Prograf] for autoimmune diseases, in addition to transplantation), and first-line therapy (gabapentin [Neurontin] for painful diabetic neuropathy, in addition to its use in herpes zoster). Though new indications may be added to a drug's label through a supplemental new drug application, this occurs infrequently: generic drugs lack a corporate sponsor to bear the required expenses, and for brand-name drugs

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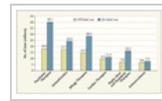
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that are already widely used off-label, conducting costly clinical trials that could produce nonsupportive evidence is a potentially risky business decision.

Evaluations have shown that off-label use is common (see [graph](#)) but often not supported by strong evidence.<sup>2</sup> A 2003 report showed that for the 3 leading drugs in each of the 15 leading drug classes, off-label use accounted for approximately 21% of prescriptions.<sup>3</sup> The highest rates of off-label use were for anticonvulsants (74%), antipsychotics (60%), and antibiotics (41%). In an examination of off-label prescribing of 160 common drugs, off-label use was also found to account for 21% of all prescriptions, and most off-label drug uses (73%) were shown to have little or no scientific support.<sup>2</sup> Atypical antipsychotics and antidepressants were particularly likely to be used off-label without strong evidence.<sup>2</sup> Off-label use is also common for many biologics (such as epoetin alfa [Procrit] and bevacizumab [Avastin]).



Estimated Numbers of Prescriptions for On-Label and Off-Label Uses of Medications in Various Functional Classes, 2001.

Physicians' freedom to prescribe drugs off-label carries important advantages. It permits innovation in clinical practice, particularly when approved treatments have failed. It offers patients and physicians earlier access to potentially valuable medications and allows physicians to adopt new practices based on emerging evidence. And it can provide the only available treatments for "orphan" conditions. At the same time, off-label use has potentially negative consequences. It undercuts expectations that drug safety and efficacy have been fully evaluated. When newer, more expensive drugs are used off-label, it increases health care costs. It undermines the incentives for manufacturers to perform rigorous studies — and instead subtly encourages them to game the system by seeking approval for secondary indications for which clinical trials are less complicated and less expensive. And off-label use may discourage evidence-based practice.

During the past decade, there have been numerous conflicts about off-label use. Payers increasingly question the need to pay for products that are not proven. Physicians desire the autonomy to prescribe drugs that match individual patient needs regardless of label, but they face difficulties staying abreast of rapidly evolving evidence. The pharmaceutical industry seeks to enlarge its markets to ensure future profits and sustain drug development. The public wants drugs that are safe, evidence-based, and affordable; although consumers want the newest therapies, they may also want the level of supporting evidence to be disclosed. Recent indications suggest that the FDA is unlikely to strengthen its role in balancing these disparate expectations. I believe that the agency is making a mistake, particularly given the faith that physicians and consumers place in it.

The FDA influences the prescribing of all available drugs in several limited ways. Initial and subsequent changes in drug labeling, including black-box warnings, can alert physicians that special caution is required. Specific restrictions on drug availability constrain use to specific settings. Most important, the FDA regulates the industry's marketing practices. Current FDA policy on marketing for off-label uses follows the FDA Modernization Act of 1997 (even though these regulations formally expired in 2006). This legislation greatly eased restrictions on drug promotions. FDA policy currently prohibits the direct promotion of products for unapproved uses.

The drug industry, however, may facilitate off-label use by exploiting areas of ambiguity where policy is permissive, undefined, or not enforced. Besides sponsorship of continuing medical education programs, a key promotional strategy is providing physicians with journal articles about off-label uses. This practice does educate physicians, but it is problematic because the trials reported are too often of limited quality, industry-sponsored, and placebo-controlled (rather than comparisons with approved therapies). Although it has not been well enforced, FDA policy also limits such promotion to drugs and indications for which a supplemental new drug application is under way and requires advance FDA review of any articles to be used in this fashion. But more and more frequently, it is not FDA action but litigation that raises important questions about off-label drug prescribing, as in the examples of the

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off-label promotion of gabapentin for chronic pain and olanzapine (Zyprexa) for dementia.

The FDA's recently published draft guidelines address the distribution of journal articles by pharmaceutical sales representatives.<sup>1</sup> Although the guidelines nearly nullify themselves by emphasizing their nonbinding nature, they also suggest a more permissive attitude toward the promotion of off-label uses of drugs. Though they carry forward many provisions of the FDA Modernization Act, there are two glaring omissions. First, manufacturers need no longer limit their promotion of off-label uses to drugs and indications for which they are working toward FDA evaluation; and second, there is no requirement for advance FDA review of the journal articles to be distributed.

Although such a relaxation of oversight may merely formalize the FDA's de facto policies, some observers had been expecting the agency to seek a greater role in moderating off-label use. This backward shift seems oddly incongruous with current pressures aimed at improving postmarketing drug evaluation. If there are substantial safety concerns about approved indications, there is even greater uncertainty with regard to off-label uses. The harms associated with rofecoxib (Vioxx) that were recognized only after the drug's widespread use among patients who were unlikely to receive incremental benefits<sup>4</sup> represent but one of many cautionary examples.

There are several reasons why the FDA may be reluctant to take a more active role in diminishing non-evidence-based off-label use. Historically, restrictions on marketing that is not misleading have been successfully challenged as infringements of commercial free speech. The FDA may be conceding to drug manufacturers the responsibility for regulating their own off-label marketing practices. The agency may also believe that its limited resources can be put to better or more effective use in confronting other ongoing challenges. Nevertheless, I believe that the FDA must take an active role in fostering evidence-based practice, eliminating subversion of the approval process, and requiring a balanced and fair presentation of scientific evidence.

The FDA might consider undertaking a range of new activities in regulating off-label use, including systematically collecting postmarketing data to quantify the harms and benefits of common off-label uses; synthesizing evidence regarding off-label uses and disseminating its reports; scrutinizing marketing efforts to restrict materials on off-label uses that don't have strong support; increasing the use of active drugs as comparators in postmarketing clinical trials; and requiring information about anticipated off-label uses to be presented at the time of a drug's review for initial approval.

The FDA is accepting comments on its draft guidelines through April 21, 2008. Comments may be submitted through [Regulations.gov](http://www.regulations.gov), under Docket No. FDA-2008-D-0053, using the "send a comment" option.

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#### SOURCE INFORMATION

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