The FDA's New Guidance for Off-Label Promotion Is Only a Start

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INTRODUCTION

As has been reported widely in the press and in the February 2008 issue of *P&T*, the Food and Drug Administration (FDA) has proposed new rules to guide the pharmaceutical industry in promoting off-label uses of drugs.[1] Known as "Good Reprint Practices," the document lists conditions under which sales representatives may distribute reprints of journal articles describing drug indications that the agency has not approved.[2] The draft was issued on February 15, 2008, and a 60-day period was allowed for comments before its formal adoption.

This is a highly contentious area, and the arguments on both sides have already started to fly from the public, the press, and members of Congress. A tremendous amount is at stake, both financially and clinically, because more than 20% of overall prescription drugs in the U.S. and close to 50% of products in some specialties are used in an off-label manner.[3]

The debates over restrictions on off-label promotion of products may seem arcane to those outside of the pharmaceutical industry, but these discussions get to the heart of pharmaceutical marketing practices and the role of FDA oversight. For this reason, it is important to understand both points of view. The ultimate resolution will determine much more than the kinds of paper that can fill a physician's inbox.

LEGAL STATUS OF OFF-LABEL PROMOTION

Off-label prescribing resides in a regulatory "no-man's land." The FDA's approval of drugs is specific to the diagnosis or treatment of delineated symptoms, conditions, and diseases for which a drug is indicated. Although marketing materials are not permitted to promote additional uses, physicians are free to prescribe any approved drug for any purpose, even a use that the FDA has not approved. With a sizable share of the potential market at stake, the incentive for manufacturers to promote unapproved indications is substantial.

In 1997, Congress included standards for off-label promotion in the Food and Drug Administration Modernization Act (FDAMA). This act allowed manufacturers to distribute copies of peer-reviewed articles and book chapters and to sponsor independent continuing medical education programs describing uses of products beyond the approved indications.[4]

There were two important conditions: (1) the materials had to be provided to the FDA, and (2) the manufacturer had to verify its plans to seek approval for the new indications. In 1998, however, the federal district court for the District of Columbia prohibited the FDA from enforcing the additional conditions in the case of *Washington Legal Foundation* v. *Friedman* on the grounds that they infringed on free speech rights.[5]

In response to the court ruling, the FDA issued regulations adopting the FDAMA standards as a "safe harbor" against prosecution.[6] Under this approach, failure to comply is not necessarily a violation, but strict compliance guarantees immunity from prosecution for engaging in false or misleading advertising. Since then, numerous enforcement actions have been brought against drug companies for overstepping the bounds of legitimate off-label promotion, including one action that led to a $30 million fine against Pfizer over its marketing of gabapentin (Neurontin).[7] In 2006, a psychiatrist was arrested and charged with accepting more than $100,000 from Jazz Pharmaceuticals for promoting off-label uses of gamma hydroxybutyrate (Xyrem), a product that had been approved to treat narcolepsy.[8]

FDAMA's limitations on off-label promotion expired on September 30, 2006, and Congress has yet to reauthorize them. The FDA's draft guidance is an attempt to fill the void. The agency continues to require that materials be reprinted from *bona fide* independent peer-reviewed sources, but it omits mandates for prior agency approval and for manufacturers to verify their intent to conduct clinical trials of unapproved uses. However, it adds two important stipulations: (1) the lack of approval of the indications in question must be clearly disclosed, and (2) if any published findings in the peer-reviewed literature contradict the efficacy of a drug's off-label use, an article reflecting that conclusion must be distributed as well.

ARGUMENTS FOR STRICT LIMITS ON PROMOTION

If legitimate scientific findings suggest that a drug can help a broader pool of patients, why would the government want to limit its dissemination?

The answer is that a long history of aggressive drug marketing has, at times, resulted in the promotion of questionable uses, as the level of enforcement activity to date indicates. Critics also point to financial ties to the industry among many researchers who have produced favorable findings of off-label uses. Without adequate safeguards, there would be no oversight of the integrity of the information that is generated and patients could be subjected to drugs that might be ineffective or even harmful for their conditions.

Given this risk, the FDA is the only impartial external arbiter of scientific data on drug safety and efficacy that has the resources and independence to evaluate claims in a thorough manner. Even if physicians receive articles presenting both sides of a drug's profile, they might not have the time or expertise to assess

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them. Without sufficient oversight, the opportunities for abuse are too great.

ARGUMENTS AGAINST STRICT LIMITS ON PROMOTION

Unfortunately, the FDA's approval process for new indications is very slow and expensive. The clinical trials that are needed can take several years and can cost hundreds of millions of dollars. After the FDA receives the data, it can take many months or even years for a decision. All the while, the patent on the drug is nearing expiration, at which point the manufacturer realizes greatly diminished financial rewards for its efforts.

The cumbersome nature of FDA approvals is an important reason that such a large percentage of prescription drugs are presently used for off-label indications, many with life-saving effects. For example, many oncology drugs that are approved to treat one kind of cancer have been used for another type, and many drugs approved for use only in adults are also used in children. In some medical specialties, therapeutic options would be severely limited without off-label prescribing.

ISSUES FOR POLICY FOCUS

Ultimately, the focus for public policy should center on ways to encourage companies to submit new indications for FDA review. Even the court in the *Washington Legal Foundation* case, with its skeptical attitude toward regulation of commercial speech, recognized this as a legitimate government interest. If logistical impediments to approval can be controlled, this would be the best way to differentiate effective new uses for drugs from unsubstantiated claims.

It is in regard to promoting FDA review that resolution of this issue will affect broader pharmaceutical policy concerns. To facilitate the approval process, three key elements must be considered.

First, the lengthy period for reviewing additional indications should be shortened to reduce the current disincentive to filing. To accomplish this, the level of FDA resources to conduct such oversight must be increased. Even though there are many competing demands for FDA funds, faster reviews are not feasible without them. Finally, rules on patents must recognize the time pressures involved in filing for approval of new indications during the term of the drug's patent protection.

Each of these elements raises significant issues, but without reforms of a fundamental nature, the incentives that drive the current dynamics of off-label marketing are unlikely to change.

CONCLUSION

Drug companies will always seek to extend the markets for their products, and regulators will always be concerned that the promotion of these products be truthful. The challenge is to strike a balance that best protects patients. To this end, marketing of off-label uses should not be considered in isolation or simply as a matter of which journal reprints can be sent to whom. It is part of the broader life cycle of drugs, and policies regarding off-label uses should consider that larger process.

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