

Reforming Off-Label Promotion to Enhance Orphan Disease Treatment

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Once the U.S. Food and Drug Administration (FDA) approves uses for new drugs, physicians are free to prescribe them for any clinical condition they see fit (1). Promotion (by manufacturers) and patient use (guided by clinicians) for any indication, population, dosage, administration, or treatment duration other than that approved by a country's regulatory authority is deemed "off-label" (2). Such use is highly prevalent; 21% of all prescription drug use, and up to 83% for certain diseases and drugs, are off-label (3).

Off-label prescribing allows physicians to innovate with treatments based on emerging clinical data (4). They can monitor individual patients to assess what newer, unapproved treatments are beneficial (5). But many physicians lack knowledge about rare diseases, leaving patients without a definitive diagnosis or treatment (6). This occurs despite efforts to disseminate rare disease information, including accurate diagnosis and treatments (7, 8). In addition, the ad hoc nature of off-label regulation, knowledge, and drug use may constitute human experimentation without informed consent. Off-label promotion can present clear patient safety risks, such as efforts to market Zyprexa (olanzapine) for dementia treatment in the elderly (9). But carboplatin, FDA-approved for adult cancer treatment, is appropriately used (under evidence-based medical assessments) off-label for children (10).

Drug manufacturers have little incentive to seek FDA approval for orphan diseases (defined in the United States as affecting <200,000 patients) because of the generally low return on investment, despite some well-known treatments such as epoetin. So off-label drug use may be the only means to provide effective treatment. Indeed, up to 90% of drug use for rare conditions is off-label (11). Yet off-label access to drugs by orphan disease patients is inconsistent (12–14). Although

FDA may provide exceptions regarding access, stakeholders have indicated a need for reform (12–15). A systemic approach is essential to better serve these patients. Permitting appropriate off-label drug promotion for orphan disease treatment can accomplish this goal.

Orphan Drug Act

Under the 1983 Orphan Drug Act (ODA) (Public Law 97-414), FDA reviews and approves manufacturer applications for orphan designations (16). Other countries have similar laws (17). If approved, companies are eligible for incentives, including 7-year market exclusivity (i.e., no drug sales by a competitor); tax credits for clinical trial costs; federal grants to support clinical testing of rare disease treatments; exemption from FDA user fees; and expedited review of orphan drugs treating life-threatening diseases (16).

Although ODA has arguably provided treatment for some rare disease patients, concerns remain. Market exclusivity and high prices limit access to orphan drugs (18). ODA's effectiveness in encouraging orphan disease drug development has also been questioned (18). Only 300 approvals for orphan disease indications have been made since ODA enactment, out of an identified 6800 rare diseases (14) (table S1). Up to 20 million U.S. orphan disease patients do not have access to treatments because of limited physician knowledge and/or drug manufacturer investment (14).

Regulatory Confusion and Evolution

The Food, Drug, and Cosmetic Act [21 U.S. Code (U.S.C.) Ch. 9] (which authorizes FDA to oversee drug safety) prohibits drug manufacturers from promoting, marketing, or labeling for off-label uses. However, these prohibitions do not extend to medical practice (19), which results in confusion about off-label regulation. In the

Allowing off-label promotion by drug companies may improve access to key treatments for orphan disease patients.

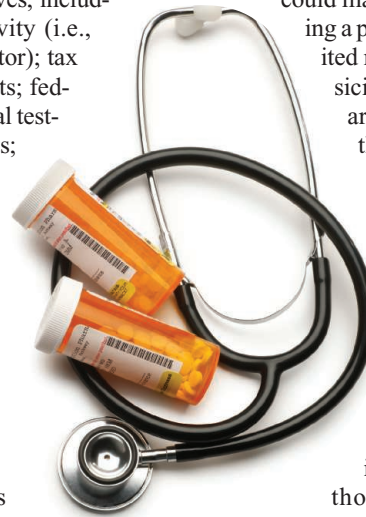
1990s, drug companies attempted indirect means to promote off-label use by distributing scientific literature and funding continuing medical education (19). FDA issued guidance documents attempting to regulate these activities (20, 21), but a court ruled these violated commercial free speech protections (19).

Shortly thereafter, the 1997 FDA Modernization Act (Public Law 105-115) permitted, for the first time, some off-label activities (5). It required manufacturers to apply for approval of off-label uses through a supplemental new drug application (sNDA); they could market off-label while indicating a pending sNDA review. It limited materials to be given to physicians (i.e., only peer-reviewed articles submitted to support the sNDA application) and disclosure that they were not FDA "approved or cleared" (5).

Recent FDA guidance is more permissive (22). The policy no longer limits manufacturers to disseminating only those materials filed with the sNDA, nor does it require that FDA review those materials (23). However, concerns regarding selective publication, data manipulation and omission, and ghostwriting have raised concerns regarding whether this new policy will protect public health (22).

Physicians must be able to extend use of approved drugs to orphan conditions and patients, particularly where no other alternative is approved. This requires greater education of providers and patients, improved patient access and consent, and, critically, a policy infrastructure that yields information on drug effects and provides for risk management and pharmacovigilance for patient safety. To reach these goals, we suggest the following.

Manufacturer application. Manufacturers would apply for authorization to promote off-label uses directly to physicians through an application similar to an ODA request for orphan designation. This application would



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include rare disease treated, disease prevalence, biological rationale for the drug's use, drug regulatory and marketing status and history, drug safety or efficacy data for the orphan disease, promotional materials for FDA review and approval, risk-management and pharmacovigilance plan for monitoring and reporting off-label use effects, and attestation that promotion would not be false or misleading and that all materials would be peer-reviewed and FDA-approved before use. An application could be rejected or additional information required if FDA determined the risk versus benefit unacceptable or supporting evidence insufficient. This application would be updated when additional clinical information became available. Fraudulent materials would subject the applicant to federal fraud claims and patient tort suits if they are injured.

Patient base. Authorized off-label promotion would be limited to a fraction of the rare disease population, such as 4000 patients often required for standard FDA drug approval. If off-label prescribing exceeded this threshold, the manufacturer would be required to file a sNDA to continue any off-label promotion. Patients could still gain access through other, albeit cumbersome, FDA programs such as compassionate use, or existing low-cost or no-cost drug programs (24).

Drug monitoring. Similar to FDA-restricted distribution programs for high-risk drugs such as Tysabri (natalizumab) in Crohn's disease, FDA would establish efficacy parameters, and all patients and physicians participating in the off-label program would enroll in risk-assessment programs and would agree to extensive education and monitoring guidelines (25). A mandated efficacy assessment (after a defined time, based on the specific drug) would be established to collect data on clinical effectiveness and adverse events using enhanced data detection techniques as employed in the European Union (EU) for biosimilars (24). Updated off-label program data would be listed on a public Web site similar to clinicaltrials.gov (e.g., offlabeldrugs.gov).

The manufacturer would be responsible for an approved risk-management and pharmacovigilance plan to detect and report adverse events associated with off-label use. This approach is consistent with extensive monitoring guidelines that have been successful in other, similar contexts (24).

Funding. Given the financial benefits they would likely realize from off-label promotion, manufacturers would support this program by paying user fees for FDA review (but discounted compared with fees required for full New Drug Application review).

Program Benefits

The enrollment, risk-management, and pharmacovigilance mandates will ensure proper drug study and monitoring. Provider knowledge and patient informed consent are better addressed than in the current haphazard system, which may rely on limited physician knowledge and disparate sources of information (14). Indeed, under the program, physicians, professional societies, patients, and advocacy groups would have access to organized data and drug information. Generated data could be a basis for FDA assessment of warnings and use limits of these drugs, as well as more efficient identification of drugs that need further testing. Grant funding for clinical research would promote development of a knowledge base of off-label uses in orphan disease populations, again to the benefit of provider knowledge and patient informed consent. This program will also provide an expanded opportunity to study these drugs and orphan diseases, a particularly challenging area for physician-scientists (14). Organized manufacturer monitoring and adverse-event reporting would allow FDA to more proactively to enact drug-safety measures if needed.

Appropriate off-label promotion and information-sharing for orphan diseases, by promoting and expanding the systematic collection of and access to data, could also increase the potential that reimbursement for off-label use would be approved by public programs. This could lead to lower patient costs and increased access, as has occurred in the Medicare program for cancer drugs (26).

Drug manufacturers would also benefit, including small companies that have developed many of these drugs but face substantial financial issues. They would be able, legally, to increase awareness of and access to these drugs. This would remove large barriers to investing in orphan drugs, both by reducing costs of entry due to discounted fees and increasing manufacturer revenues from drug sales. It could also lead to competition and to lower patient costs by facilitating market entry of additional manufacturers, since exclusivity incentives (as in the ODA) would not apply. Manufacturers whose unapproved, off-label drug use in the program that proved successful could subsequently also access ODA incentives and full market approval to maximize returns for these drugs, or clinical trials-oriented accelerated approval (15).

The themes of this proposal can serve as an approach for developed countries to address the problem of uneven access and regulation of off-label drug use in orphan disease populations while improving efforts to

monitor drug safety. For example, EU regulators can adapt the Committee for Orphan Medicinal Products (COMP) to serve as the prime off-label program authority. COMP would then coordinate drug review, monitoring, and oversight, by using established drug surveillance systems (24).

Manufacturers' obligations and marketing content must be monitored to ensure program integrity. The policy and included drugs must be revisited so that stakeholders have up-to-date information. Through this system, better access, knowledge, and benefits of off-label drug use can inure to orphan disease populations.

References and Notes

- 21 U.S.C. § 396 (2000).
- B. M. Psaty, W. Ray, *JAMA* **299**, 1949 (2008).
- D. C. Radley, S. N. Finkelstein, R. S. Stafford, *Arch. Intern. Med.* **166**, 1021 (2006).
- R. S. Stafford, *N. Engl. J. Med.* **358**, 1427 (2008).
- S. Salbu, *Fla. Law Rev.* **51**, 181 (1999).
- M. G. Kramer, *National Organization for Rare Disorders and the Experiences of the Rare Disorders Community* (National Organization for Rare Disorders, Washington, DC, 2003).
- National Institutes of Health (NIH), NIH launches undiagnosed diseases program, *NIH News* (NIH, Bethesda, MD, 2008); www.nih.gov/news/health/may2008/nhgri-19.htm.
- In Need of Diagnostics, Inc., <http://inod.org/default.aspx>.
- A. Berenson, *New York Times*, 18 December 2006, p. A1.
- J. Boos, *Ann. Oncol.* **14**, 1 (2003).
- T. Hampton, *JAMA* **297**, 683 (2007).
- Rarer Cancers Forum, *Off Limits: An Investigation into How NHS Organisations Determine Requests for the Use of Off-Label Treatments for Cancer Patients* (Rarer Cancers Forum, Canterbury, UK, 2009); www.rarercancers.org.uk/news/current/off_limits__new_rarer_cancers_forum_report/.
- M. Schlander, M. Beck, *Curr. Med. Res. Opin.* **25**, 1285 (2009).
- G. J. Brewer, *Transl. Res.* **154**, 314 (2009).
- E. A. Richey et al., *J. Clin. Oncol.* **27**, 4398 (2009).
- Department of Human and Health Services (DHHS), *The Orphan Drug Act: Implementation and Impact* (OEI-09-00-00380, DHHS, Washington, DC, 2001).
- Canadian Organization for Rare Disorders, *Canada's Orphan Drug Policy: Learning from the Best* (Canadian Organization for Rare Disorders, Toronto, 2005).
- A. Pollack, *New York Times*, 30 April 1990, p. D1.
- Wash. Legal Found. v. Friedman*, 13 F. Supp. 2d 51, 55 (D.D.C. 1998).
- FDA, *Fed. Regist.* **61**, 52800 (1996).
- FDA, *Fed. Regist.* **62**, 64073 (1997).
- M. M. Mello, D. M. Studdert, T. A. Brennan, *N. Engl. J. Med.* **360**, 1557 (2009).
- FDA, *Good Reprint Practices for the Distribution of Medical Journal Articles and Medical or Scientific Reference Publications on Unapproved New Uses of Approved Drugs and Approved or Cleared Medical Devices* (FDA, Silver Spring, MD, 2009).
- B. A. Liang, *Harvard J. Legis.* **44**, 363 (2007).
- FDA, *FDA Approves Tysabri to Treat Moderate-to-Severe Crohn's Disease* (FDA news release, FDA, Silver Spring, MD, 2008); www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2008/ucm116835.htm.
- R. Abelson, A. Pollack, *New York Times*, 27 January 2009, p. A22.

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