

HEALTH LAW, ETHICS, AND HUMAN RIGHTS

Shifting Terrain in the Regulation of Off-Label Promotion of Pharmaceuticals

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In regulating the promotion of unapproved, or off-label, uses of approved drugs, the Food and Drug Administration (FDA) has sought to strike a balance between supporting the ability of physicians to prescribe according to their best clinical judgment and preventing drug manufacturers from inappropriately driving prescribing practices. The agency has long maintained the general position that although physicians may freely prescribe drugs for off-label uses, drug manufacturers may not promote such uses. However, the FDA's specific regulatory strategy has varied over time, particularly regarding the extent to which manufacturers may disseminate information about off-label uses. In January, the FDA issued a new guidance document that again changes the regulatory regime by explicitly allowing drug and device manufacturers to distribute reprints of articles from medical journals that describe unapproved uses of their products.^{1,2}

In this article, we discuss the legal and policy issues arising in this area. The prevalence and cost of off-label prescribing and the potential patient-safety risks associated with it make it imperative to get the regulatory balance right.^{3,4} Yet the legal history of off-label promotion reveals considerable uncertainty about what the optimal regime entails.

The effectiveness of the successive regimes in achieving the balance sought by the FDA has not been established, and the likely impact of the latest move is similarly unclear. On the one hand, loosening restrictions on the distribution of journal reprints may reduce the motivation of companies to engage in other, less easily monitored forms of promotion. On the other hand, it could dampen incentives to conduct clinical trials and present challenges for medical journals, as companies seek to ensure that their products are described favorably in articles.

We begin by reviewing the history of FDA regulation of off-label promotion and then describe the major litigation. We conclude with some reflections on the new guidance and the future course and effect of regulation in this area.

MECHANISMS OF OFF-LABEL PROMOTION AND ITS DETECTION

The visibility of off-label promotion to an external regulator like the FDA varies considerably across a range of promotion activities (Fig. 1). The agency's attention has focused on relatively visible ones. That focus is partly a matter of capability; tracking behavior that is squarely in the public domain is easier and less expensive than monitoring less visible activities. However, the FDA's concern for its reputation as an oversight agency has probably also influenced its regulatory strategy: activities that are visible to a regulator are generally also visible to others, such as members of watchdog groups, who may publicly

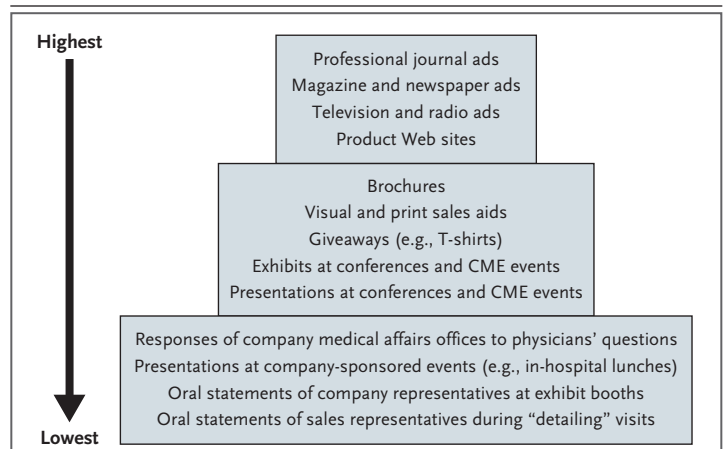


Figure 1. Detectability of Types of Off-Label Promotion of Pharmaceuticals. CME denotes continuing medical education.

criticize the regulator's competence if flagrant abuses go unchecked.

Journal reprints are among the most visible forms of promotion. The FDA has required companies to submit reprints and advertisements for review, although a recent report by the Government Accountability Office raised serious questions about the effectiveness of this review process.⁵ Brochures, posters, and other visual and documentary sales aids have somewhat less visibility, as do giveaway items and presentations made at conferences and continuing medical education (CME) events. These promotional materials also must be submitted to the FDA at the time of dissemination, but they are not in the public domain. Moreover, although the FDA attends some CME events to monitor compliance with marketing rules, it cannot attend all.^{5,6}

In the lowest tier of visibility are oral statements made by company representatives, as well as statements by physician "peers" or "key opinion leaders" who are paid by drug manufacturers to educate their colleagues about the manufacturer's products. The lack of documentation of these communications, combined with their delivery in private or semiprivate settings, makes them notoriously difficult to track. Communications from the medical affairs offices of companies in response to unsolicited requests for information by physicians are also hard to monitor, although their content is likely to be vigorously policed by company compliance officers. In general, the ability of regulators to detect and respond to inappropriate oral communications relies heavily on reports from insiders — physicians and other persons who receive the communications and company whistle-blowers who generate or learn of them.

FDA REGULATION — PAST
AND PRESENT

HISTORICAL EVOLUTION

Under the federal Food, Drug, and Cosmetic Act (FDCA) of 1938, the FDA has authority to regulate the promotional materials of pharmaceutical companies, including print, broadcast, and Internet advertisements, materials produced for dissemination to health care professionals (such as visual aids and handouts used by sales representatives for in-office visits), and materials produced for dissemination to patients (such as bro-

chures, letters, and flyers).⁷ FDA regulation is intended to ensure that promotional communications are truthful, balanced, not misleading in their representations or omissions, and supported by substantial evidence from clinical trials or clinical experience. The FDA exercises these regulatory powers by reviewing promotional materials and issuing warning letters, injunctions, and referrals for criminal investigation.⁷

The FDCA does not directly prohibit promotion of off-label uses, but two related provisions operate to that effect.⁸ One provision bars pharmaceutical manufacturers from introducing a new drug into interstate commerce unless the drug and its label have secured FDA approval⁹; marketing drugs in a way that departs from their approved uses violates this provision.^{10,11} A second provision prohibits manufacturers from introducing "misbranded" drugs into interstate commerce.¹² A drug is considered misbranded if its label contains misleading information, lacks information that is sufficient to support its safe use for approved indications, or includes information about unapproved uses.^{12,13} Printed and visual materials are considered part of a drug's labeling if they are distributed by the manufacturer for the purpose of explaining the uses of the drug, even if they are not packaged with the drug.^{14,15} Notwithstanding these provisions, companies are permitted to respond to unsolicited questions from health care professionals and other persons about unapproved uses.¹⁶ Inquiries must be handled by the company's medical affairs office, not its sales staff, and responses must be narrowly tailored to the question, balanced, and carefully documented by the company.¹⁷

The FDA has long reviewed promotional materials for compliance with these rules. However, the agency's stance concerning two particular mechanisms for off-label promotion — proactive dissemination of reprints of scientific articles and sponsorship of CME programs — has varied over time.¹⁸ Before the 1980s, the FDA imposed relatively few restrictions on the use of these methods by companies for conveying information about off-label uses. However, during the 1980s, public and congressional concern about these practices grew, prompting congressional hearings in 1990.

The FDA published regulatory guidance in 1992 establishing instances in which CME programs would be viewed as inappropriately pro-

moting off-label uses.¹⁹ At the same time, it began issuing warning letters to manufacturers regarding their dissemination of article reprints. Its evolving policy that these activities could constitute illegal off-label promotion under certain conditions was set forth in final guidance documents issued in 1996 and 1997.^{20,21} These rules permitted manufacturers to send out reprints of scientific articles and textbooks describing off-label uses if the “principal subject” of the article or book section was an approved use and the manufacturer included a prominent disclosure regarding the unapproved nature of other uses mentioned.

The FDA Modernization Act of 1997 (FDAMA) ushered in a change of policy. The FDAMA allowed manufacturers of drugs (as well as biologic agents and medical devices) to disseminate peer-reviewed articles from scientific journals if the off-label use described therein was included in a filed or soon-to-be-filed supplemental new drug application.^{22,23} The company was also required to provide the FDA with advance copies of any materials it intended to disseminate and to comply with certain other conditions (Table 1). If these conditions were met, dissemination of information regarding off-label uses would not be viewed as evidence that the manufacturer intended to promote the product for an unapproved use.¹

CHALLENGES TO FDA AUTHORITY

A series of important legal cases have defined the constitutional boundaries of government regulation of activities involving drug promotion.²⁴ Although the FDA receives its regulatory powers from acts of Congress, Congress may not delegate authority in ways that violate constitutional rights, including the First Amendment right of drug and device manufacturers to engage in commercial speech.²⁵ Recent litigation has suggested that pharmaceutical companies may enjoy greater latitude to communicate information about off-label uses than FDA policy historically has permitted.^{8,24}

The case of *Washington Legal Foundation v. Friedman*²⁶ involved a challenge to the 1996 and 1997 FDA guidance documents restricting reprint distribution and CME sponsorship. The challenge was later broadened to include the reprint provisions in the FDAMA.¹⁸ A federal district court held that the policies were unduly restrictive be-

cause their objective — to motivate companies to seek FDA approval for new uses of products — could be achieved by simply requiring manufacturers to make clear disclosures that the uses described lacked FDA approval.²⁶

When the case was appealed, the FDA unexpectedly backed away from the position that the FDAMA created new authority for the agency to regulate off-label promotion. The appellate court indicated that it agreed with the lower court's reasoning. However, it held that given the FDA's concession, there was no longer a live constitutional issue to resolve; therefore, it vacated the lower court's decisions.¹³ This decision left the key question — whether restrictions on truthful communications about off-label uses were permissible — in limbo. Two subsequent judicial rulings further muddied the waters. A decision by a federal district court granted a wider berth for the FDA regulation of speech promoting off-label uses,²⁷ and a Supreme Court decision affirmed that drug advertising is entitled to First Amendment protection as commercial speech.²⁵

Behavior on the ground gives the best indication of perceptions of the state of the law. In the aftermath of *Washington Legal Foundation*, it became common for pharmaceutical companies to send out journal reprints describing the off-label use of drugs, accompanied by the suggested disclosure. The FDA did not attempt to stop them.⁸

Congress allowed the FDAMA provisions to expire in September 2006, perhaps because of the murkiness surrounding their force and constitutionality. This expiration left something of a regulatory vacuum. Technically, it restored a general ban on distribution of journal reprints describing off-label uses, but the legitimacy of such a policy was cast into doubt by the constitutional litigation.

THE 2009 GUIDANCE

In January, after a period of public comment on an earlier draft, the FDA issued a finalized guidance document that again changes the regulatory regime.² Companies are allowed to distribute peer-reviewed scientific articles and texts describing off-label uses, subject to several conditions (Table 1).

The FDA characterizes this guidance as a clarification of existing policy rather than a change in it,²⁸ but it is more permissive than both the previous regime and the old FDAMA rule (Table 1).

Table 1. Conditions under Which Information about the Uses of Off-Label Drugs May Be Disseminated.*

Condition	FDAMA Section 401†	2009 Guidance‡
Drug approval	Information must concern a drug or device that has received FDA approval for some use	Drug-approval status not mentioned
Commitment to file a supplemental new drug application	Manufacturer must have submitted a supplemental new drug application for proposed new use or completed required studies and certified that this application will be submitted within 6 months after initial dissemination (or within 36 months if supporting studies not yet completed); may request exemption from this requirement if studies are prohibitively expensive or unethical	Not mentioned; companies encouraged to seek approval for new uses of a drug
Advance provision to the FDA	Manufacturer must submit copy of article and other safety and efficacy information concerning unapproved use 60 days before dissemination	Not mentioned
Source of underlying clinical data	Information must not be derived from another manufacturer's clinical research (unless other manufacturer gives permission) and must be from "scientifically sound" clinical investigation	Information should be based on adequate and well-controlled clinical investigations
Accuracy	Information must not be false or misleading, must not involve inappropriate conclusions, and must not pose significant risk to public health if relied on; company may need to include other safety and efficacy information to ensure objectivity and balance	Information should be truthful and not misleading and should not pose a significant public health risk if relied on
Provision of countervailing scientific findings	Information must be disseminated along with approved labeling and comprehensive bibliography of publications related to off-label use (including unfavorable studies) and other available information about risks of this use	Information should be disseminated with approved labeling and comprehensive bibliography of publications related to off-label use, plus representative publications (if any) reaching conclusions regarding this use that are contrary or different
Required disclosures	Must include prominent disclosure stating that use is not FDA-approved and identifying other products (if any) approved for that use	Should include prominent disclosure statement regarding unapproved use that identifies study sponsors, discloses relevant financial interests, and mentions any known significant risks not discussed in publication
Presentation of journal article	Must provide entire, unabridged article or section of reference publication; no promotional materials may physically accompany it, and company representative may not verbally promote the new use	Should provide entire, unabridged article or reference; it should not be marked, highlighted, summarized, or characterized in any way
Journal requirements	Information must be published in peer-reviewed scientific or medical journal (listed in <i>Index Medicus</i>) and must not have appeared in industry-funded special supplement or publication; unabridged reference texts may also be distributed (including non-peer-reviewed texts if specific unapproved use not highlighted)	Information should be published by an organization with editorial board that involves experts with demonstrated expertise in subject of article and objectively reviews proposed articles, adhering to standard peer-review procedures; organization should adhere to published conflict-of-interest policy; information should not have appeared in an industry-funded special supplement or publication
Distribution	Distribution must be limited to health care practitioners, pharmacy-benefits managers, issuers of health insurance, group health plans, and federal and state agencies (no distribution to consumers)	Information should be provided separately from promotional information; distribution should be limited to health care practitioners and entities such as pharmacy-benefits managers, health insurers, and government agencies (no distribution to consumers)
Other avenues of dissemination	Manufacturers may still disseminate information about off-label uses in response to unsolicited requests from health care practitioners	Manufacturers may still disseminate information about off-label uses in response to unsolicited requests from health care practitioners

* FDA denotes Food and Drug Administration, and FDAMA FDA Modernization Act.

† Data are from the FDA²² and the Code of Federal Regulations.²³

‡ Data are from the FDA.²

In contrast to the previous regime, some dissemination of journal articles is explicitly permitted. Unlike the old FDAMA rule, companies are not restricted in their dissemination activities to off-label uses for which they have filed or will file a supplemental new drug application, and they are not required to submit the disseminated materials to the FDA in advance.²⁹

Political forces have massed for and against the new policy. A coalition of 10 large pharmaceutical companies has joined patient advocacy groups to express support, and a group of consumer organizations and health insurers, including Public Citizen and the Blue Cross and Blue Shield Association, are voicing objections.^{28,30} Opposition has been fueled by revelations of ghostwriting of journal articles reporting on the safety and efficacy of rofecoxib (Vioxx)³⁰⁻³² and of the practice by manufacturers of initiating and publishing "seeding trials" for marketing, rather than scientific, purposes.^{32,33} Critics of the guidance point to these problems, among others, as evidence that peer review is insufficient protection against corporate influence over the content of publications.³⁴

LITIGATION CONCERNING OFF-LABEL PROMOTION

The regulatory environment for off-label promotion also has been shaped by enforcement actions brought by federal and state prosecutors and private persons (Table 2). Most such suits are initiated after reports from whistle-blowers, who are often former sales representatives of the manufacturer. By illuminating a set of practices that historically have been difficult for the FDA to detect, such as the conversations between sales representatives and prescribers, this litigation has added a potent new dimension to the regulation of off-label promotion.

Enforcement actions may be brought under the FDCA, the federal antikickback act, the federal False Claims Act,⁴⁶ and state fraud statutes. Many such actions have led to major financial hits for pharmaceutical manufacturers, with settlements typically ranging from tens of millions to hundreds of millions of dollars. At the federal level, the Department of Justice leads these prosecutions, although the FDA may play a supportive role, providing legal and technical assistance.⁵

A trend toward bringing criminal as well as

civil charges has been notable in recent years.⁴⁷ Some prosecutions have resulted in jail time for company executives, in addition to heavy criminal fines for the company. For example, in 2004, a former director of sales at Cell Therapeutics pleaded guilty to mail fraud and served a 2-month jail sentence in connection with off-label marketing of the leukemia drug Trisenox.⁴⁸

Another dramatic development in prosecutorial strategy occurred in 2006, when federal agents arrested a psychiatrist in private practice, Peter Gleason, at a Long Island train station on criminal misbranding, fraud, and conspiracy charges for his role in promoting the narcolepsy drug Xyrem for off-label uses, including the treatment of depression and fibromyalgia.⁴⁹ A sales representative at Xyrem's manufacturer, Orphan Medical, had noticed Gleason's high prescription rate for Xyrem in 2003 and hired him to give speeches and visit other physicians to discuss off-label uses of the drug. This work ultimately became Gleason's primary source of income. Jazz Pharmaceuticals, which acquired Orphan Medical in 2005, settled its own civil and criminal charges related to Xyrem for \$20 million in 2007. Gleason pleaded guilty to misdemeanor misbranding in August 2008; he currently awaits sentencing.

Another noteworthy case involved the promotion of the antiepileptic drug Neurontin, which culminated in \$430 million in civil and criminal fines in 2004. The Neurontin litigation had considerable legal significance because it established that the federal False Claims Act⁴⁶ could be used by private persons and the federal government to enforce prohibition of off-label promotion in circumstances in which the company's representations prompted health care professionals to submit false claims for payment to government health care programs. These actions are available even if the company conveyed no false or misleading information: the court indicated that "truthful off-label marketing . . . and financial incentives like kickbacks would suffice."⁵⁰

This ruling is important in practical terms because of the availability of "qui tam," or whistleblower actions under the False Claims Act. Company insiders and others with special knowledge of practices that may violate the act may initiate legal actions, which the government may join or take over, and they may keep a sizable portion of any resulting settlement or award. This bounty system has proved to be a powerful incentive in

Table 2. Examples of Federal and State Enforcement Actions Concerning Off-Label Promotion, 2004–2009.*

Company	Product	Approved Indication	Alleged Off-Label Promotion	Alleged Promotional Methods	Settlement	Year
Bristol-Myers Squibb and Otsuka American Pharmaceutical	Abilify	Adult-onset schizophrenia and bipolar disorder	Pediatric use and dementia-related psychosis	Made direct calls to child psychiatrists and other pediatric specialists; created marketing strategy focused on nursing homes	\$515 million for Bristol-Myers Squibb, \$4.0 million for Otsuka American Pharmaceutical	2007, 2008
Cell Therapeutics	Trisenox	Acute promyelocytic leukemia	Other types of cancer	Marketed as FDA-approved and medically accepted for types of cancer for which the drug was not approved; paid doctors to attend marketing sessions on unapproved uses; provided illegal kickbacks to induce prescriptions	\$11 million	2007
Eli Lilly	Zyprexa	Schizophrenia and bipolar disorder	In elderly patients with dementia and Alzheimer's disease and in children with attention deficit-hyperactivity disorder	Encouraged primary care physicians to prescribe the drug; downplayed seriousness of side effects	\$62 million for state consumer protection claims; \$1.4 billion for federal and additional state claims	2008, 2009
GlaxoSmithKline	Paxil	Depression and other conditions in adults	Pediatric use	Suppressed negative results from studies of off-label uses	\$2 million	2004
InterMune	Actimmune	Osteopetrosis and chronic granulomatous disease	Idiopathic pulmonary fibrosis	Issued misleading press release detailing results of clinical study about drug's effectiveness in treating idiopathic pulmonary fibrosis	\$37 million	2006
Jazz Pharmaceuticals	Xyrem	Cataplexy and narcolepsy	Fatigue, insomnia, chronic pain, weight loss, depression, and bipolar disorder	Made sales calls to physicians who did not specialize in narcolepsy; distributed written materials concerning off-label uses which did not adhere to FDA guidelines; paid psychiatrist to give professional talks encouraging off-label use	\$20 million	2007
Pfizer	Neurontin	Epilepsy and post-herpetic neuralgia	Bipolar disorder, various pain disorders, amyotrophic lateral sclerosis, attention deficit-hyperactivity disorder, and migraines	Encouraged sales representatives to discuss off-label uses without previous inquiries from doctors, making exaggerated claims of safety and efficacy; encouraged medical liaisons to misrepresent their scientific credentials; paid doctors to attend presentations on off-label use and planted people in audience to ask questions highlighting benefits of drug; paid doctors to allow sales representative to accompany them in patient treatment	\$430 million	2004
Purdue Pharma	OxyContin	Management of specific types of moderate-to-severe pain	Wider pool of patients and conditions	Gave doctors sham payments, ostensibly for clinical trials and consulting, and gifts for a high volume of prescriptions; wrote misleading article in medical journal for use in marketing	\$634 million	2007

Schering-Plough	Temodar	Glioblastoma multiforme and refractory anaplastic astrocytoma	Other kinds of brain cancers	Developed national marketing plan for both drugs that included off-label promotion; paid doctors to allow sales representatives to accompany them in patient treatment; placed doctors on medical advisory boards that existed solely to provide emoluments; awarded clinical studies to doctors based on how many off-label prescriptions they wrote; paid doctors consulting fees and for attendance at company-sponsored events	\$435 million	2006
	Intron A	Chronic hepatitis B and C virus infection, condylomata acuminata, Kaposi's sarcoma, hairy-cell leukemia, melanoma, and follicular lymphoma	Superficial bladder cancer			
Serono	Serostim	AIDS wasting syndrome	Lipodystrophy and new definition of AIDS wasting syndrome based on loss of body cell mass	Conspired with medical-device manufacturer to market software for analysis of bioelectrical impedance for use in calculating body cell mass, even though device unapproved for that use; with the use of this device, redefined AIDS wasting syndrome on the basis of loss of body cell mass in order to increase demand for the drug; offered doctors all-expense-paid trip to medical conference in France in return for writing prescriptions; paid doctors to enroll patients in clinical trials	\$704 million	2005

* Data are from LexisNexis,³⁵ the Department of Justice,^{36,45} and the Government Accountability Office.⁵ Dollar amounts have been rounded to the nearest million. FDA denotes Food and Drug Administration.

a variety of health settings and has led to a well-spring of litigation under the False Claims Act.⁵¹ Since the Neurontin litigation, such claims have become a common feature of prosecutions for off-label promotion.⁵²

These developments have clearly worried pharmaceutical manufacturers, in part because of the potential financial exposure and negative publicity and in part because companies perceive the boundary between legal and illegal promotional activities to be unclear. Indeed, the concern among companies that dissemination of journal articles might lead to criminal charges reportedly contributed to the FDA's decision to issue the proposed guidance in 2008.⁵³

WHAT DOES THE FUTURE HOLD?

In the short term, debate over the appropriate regulatory strategy for off-label promotion will center on the policy regarding reprint distribution. It is quite possible that the new guidance, which was issued in the final days of the Bush administration, will be revisited as FDA leadership turns over in the Obama administration.

Although drug companies have welcomed the new policy, objections have been raised by a number of commentators.^{24,31,54-56} Concerns include the publication bias in the scientific literature toward positive studies, strategic decisions by pharmaceutical sponsors to seek publication of only positive trial results, misleading presentations or interpretations of study data in journal articles, the dissemination of low-quality studies, the suppression of data on safety risks, the ghostwriting of journal articles by pharmaceutical sponsors, and the limited ability of medical journals and the FDA to detect these problems.⁵⁷ Experts are also concerned that the rule change will enervate companies' incentives to conduct the clinical trials necessary to win FDA approval for new uses,^{54,56} undermining the regulatory framework that Congress and the FDA have erected to monitor drug risks and minimize the effects of unsafe drugs on public health.²⁴ The FDA itself previously took this position, opposing reprint dissemination out of concern that it would create incentives for companies to seek approval of very narrow uses and then use journal articles to promote other, more lucrative uses.⁵⁶

However, pharmaceutical companies weigh other factors in making decisions about whether

or not to file supplemental new drug applications. They may elect to conduct trials to obtain the FDA's imprimatur with respect to the safety of their product for a particular use. FDA approval for a new use also clears the way for a full range of marketing strategies to be deployed in relation to that use.

Two further criticisms warrant mention. First, lawyers have highlighted several areas of legal ambiguity in the guidance.²⁹ Greater clarity is needed regarding the meaning of key terms like "significant" safety concerns "known to the manufacturer" and "inconsistent with the weight of credible evidence." It is also unclear what criteria the agency will use to determine that an article has undergone sufficient peer review and expert editorial oversight, and how the FDA will monitor whether or not companies are providing reprints with all of the balancing information that the guidance requires.⁵⁶ Second, the recent report by the Government Accountability Office flags dangers associated with eliminating the requirement that reprints be submitted for FDA review before dissemination. Despite well-documented problems in the review process, both the FDA and the Government Accountability Office have acknowledged that this step is crucial to the agency's ability to prevent or minimize dissemination of inappropriate materials.⁵

Although the reprint rule has attracted the most attention, it is only one move among many in a wider regulatory landscape. Even while regulation becomes more permissive in this area, federal enforcement of other promotional practices will probably remain very vigorous, especially if more states or the Congress adopt "sunshine laws" requiring disclosure of prescribers' financial relationships with manufacturers. Such disclosures may alert state and federal prosecutors to companies and prescribers who could become targets of enforcement actions.

Highly publicized settlements in these cases, in turn, fuel public demands for additional oversight of pharmaceutical promotional practices through legislation. The amount of state legislative activity in this area in the past 3 years has been extraordinary. For example, a number of states have adopted or considered legislation requiring sales representatives to provide only evidence-based information in conversations with prescribers, to adhere to a code of conduct, or to be licensed by the state. Other states (and federal

bills) have sought to restrict or ban gifts from manufacturers to prescribers. Thus, the regulatory environment for off-label promotion and other controversial marketing practices features a growing number of players and tactics.

Future lawmaking in this area will be shaped by constitutional limitations on the government's ability to restrict commercial speech.²⁴ In particular, restrictions may need to be narrowly tailored to the prevention of misleading communications about pharmaceutical products. For example, some commentators have called for the reinstatement of FDAMA's requirement that companies commit to submitting a supplemental new drug application in order to disseminate information about off-label uses, along with a requirement that companies conduct clinical trials for any off-label uses that have become widespread in physician prescribing.^{24,54} It is unclear whether the courts would deem such conditions on commercial speech constitutional.

Private actors will continue to play a key role in the regulation of off-label promotion. First, qui tam litigation will probably continue to increase. The financial incentives for whistle-blowing are becoming better known, and the risk for drug companies can only increase as they shed large segments of their sales forces in response to financial pressures, creating a flock of potentially disgruntled ex-employees with knowledge of the companies' promotional practices. Second, under the new reprint policy, medical journals will have an increasing responsibility to act as gatekeepers of findings from clinical trials as today's scientific articles become tomorrow's promotional mailings. Finally, personal-injury lawsuits filed by patients injured by drugs prescribed for off-label uses will function as a backup regulatory mechanism in cases in which off-label prescriptions result in concrete harms.

In sum, the regulatory terrain for off-label promotion will continue to be uneven and shifting. The guidance on reprint distribution brings the issue of off-label promotion to the fore, but it should not obscure the potential influence of a range of more covert and troublesome promotional practices. The FDA is not well positioned to police them with its current practices and resources. Prosecutions and enforcement actions, though they are highly selective interventions, will help fill the regulatory gap, as will legislative initiatives aimed more generally at aggressive

marketing practices. All of these regulatory forces coalesce around the goal of forcing off-label promotional practices to the surface, where they can be subjected to public scrutiny and action through legislative and judicial, as well as FDA, processes.

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