An Examination of Off-Label Marketing and Promotion: Settlements, Issues, and Trends

Efforts to Prevent Off-label Marketing and Promotion Should Include Novel Approaches to the Problem

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It is shaping up to be another banner year of settlements for Big Pharma. Kicking off the year was an announcement on January 17 by the United Kingdom's largest drugmaker, GlaxoSmithKline PLC, that it expected "to record a legal charge" of $3.4 billion for the fourth quarter of 2010 — an amount set aside for the probable settlement of an investigation by the U.S. Attorney's Office for the District of Colorado into the company's U.S. sales and promotional practices and for product liability cases regarding its diabetes drug, Avandia®.[1] Reportedly, the company is under federal investigation for allegedly promoting nine of its products "off-label" from 1997 to 2004.[2]

Next came a guilty plea on February 28 by Elan Pharmaceuticals, Inc., a U.S. subsidiary of Irish drugmaker Elan Corporation, PLC, finalizing a $203.5 million settlement agreement that was reached in December 2010[3] — in connection with the marketing of its epilepsy drug, Zonegran®.[4] Then, on March 10, in a settlement that did not include an admission of guilt by the company, AstraZeneca PLC agreed to pay a civil settlement of $68.5 million to 37 states and the District of Columbia to resolve allegations that it promoted off-label prescribing of its schizophrenia drug, Seroquel®.[5] This — the largest multi-state, consumer protection-based pharmaceutical settlement on record — was separate from the $520 million federal settlement over similar allegations announced last year.[6]

On May 13, the Wall Street Journal reported that according to unnamed sources, federal prosecutors are seeking approximately $1 billion to settle a six-year investigation into whether Janssen Pharmaceutical Inc., a Johnson & Johnson (J&J) company, promoted the off-label use of

its antipsychotic drug, Risperdal®.[7] According to one of the sources, prosecutors are using the 2009 Eli Lilly settlement (which involved a $1.4 billion payment relating to the marketing of the antipsychotic, Zyprexa®) as a benchmark to resolve the Janssen matter. In its April 3 Securities and Exchange Commission (SEC) filing, the J&J subsidiary "recorded a reserve for a potential settlement of the penalties under the Food Drug and Cosmetic Act."[8] The attorneys general of over 40 states have either already filed — or intend to file — actions against Janssen seeking repayment of Medicaid funds, civil penalties, and other compensation for Risperdal® prescriptions written for off-label use.

The month of June certainly did not disappoint industry onlookers. The Justice Department announced on June 9 that UCB Inc., the U.S. subsidiary of Belgian pharmaceutical company UCB SA., pleaded guilty and will pay more than $34 million for promoting the off-label use of its epilepsy drug Keppra®.[9] And, just one day later, the Justice Department announced that the U.S. subsidiary of Danish pharmaceutical company Novo Nordisk Inc. agreed to pay $25 million to settle allegations of off-label promotion of NovoSeven®, its hemostasis management drug.

With settlements like these announced almost every month, many in the industry are wondering how and why off-label marketing and promotion of approved drugs has become such a chronic problem and whether there is more that could be done to protect the public. It is unclear with the mounting expense of these settlements whether the government is discouraging fraud and abuse or merely siphoning funds allocable to post-marketing pharmacovigilance efforts. Let's examine the issues.

Drug Development in the United States

The U.S. Food and Drug Administration (FDA, or "agency") regulations that govern the development of new drugs are intentionally strict. Manufacturers are required to conduct several time-consuming and costly studies (including pre-clinical or nonclinical laboratory and animal testing, as well as multiple phases of research on human subjects — *i.e.,* clinical trials) to demonstrate proof of safety and efficacy of their drug.[10] Prior to granting market approval, the FDA requires manufacturers to file a new drug application (NDA), which provides FDA reviewers with all of the necessary study data to determine whether the drug is safe and effective for its proposed use(s) and whether the benefits of the drug outweigh its risks.

As part of this review, the FDA scrutinizes known adverse drug reactions or events that were identified during clinical trials, as well as any potential side effects of the drug. Reviewers rely on this data to critically evaluate whether the proposed labeling language is appropriate for the new drug and, if not, what the labeling should include. Most importantly, the FDA reviews this information to ensure that all of the claims that will be printed on the label for the drug are supported by — and consistent with — the evidence from clinical trials.

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What Does "Off-label Use" Mean?

The term "off-label use" means the use of a drug for indications beyond those formerly evaluated by the manufacturer and approved by the FDA. Before a manufacturer is authorized to market a new drug, the FDA must approve the drug's label. The label explicitly states the "intended uses"[11] or use of the drug (*e.g.*, for treating particular diseases and in specific patient groups), the recommended dosage, the route of administration, possible side effects, warnings and other important information. By definition, a drug's "labeling" or label includes any "written, printed, or graphic matter" affixed-to or "accompanying" the product (*e.g.*, a package insert).[12] The law also notes that intended use(s) or labeling claims can be presented in advertising and promotional materials or in oral or written statements by companies or their representatives.

Why Is Off-label Marketing Illegal?

Marketing or promoting a drug "off-label" is illegal because it constitutes "misbranding," which is prohibited by the FDA.[13] As the agen-

cy explains, "[a]n approved new drug that is marketed for an unapproved use is an unapproved new drug with respect to that use."[14,15] For this reason, the FDA refers to "off-label use" as a "new use" or "unapproved use."

When a drug is misbranded, the labeling is considered "false and misleading" or not providing "adequate directions for use."[16] It is also illegal for a drug company to introduce misbranded drugs into interstate commerce.[17] In other words, companies are not allowed to distribute for sale nationwide drugs that are being marketed for use off-label. The government has the authority to criminally prosecute and/or file civil suit against anyone who markets misbranded drugs.[18]

Legal and Regulatory History

The legal and regulatory issues that form the basis for the high dollar settlements that we are seeing in the media have a long and deep-rooted history that dates back to the early years of the regulation of medicine in the United States. From the late 1800s to the early 1900s, the practice of medicine in the United States underwent historic changes — states began licensing physicians, physicians formed medical associations, and formal medical education gained legitimacy. In this climate, government-formed public health agencies interjected themselves into the medical profession and began to regulate activities believed by physicians to be rightfully their own.[19]

With the enactment of the Federal Food, Drug and Cosmetic Act of 1938 (FD&C Act, or "Act"),[20] the FDA was entrusted with the responsibility to ensure, among other things, that pharmaceuticals, biologics, and medical devices intended for human use are both safe and effective. Though the Act (and its subsequent amendments) charged the FDA with overseeing the research, development, and marketing of new drugs, they have never regulated physicians' prescribing practices. This is because throughout the FDA's long and complicated legislative history, the agency has maintained the "Practice of Medicine Exception" — in other words, the role of the FDA is not to regulate the practice of medicine.[21]

While this exception has never been clearly stated in the legislation that gives the FDA regulatory authority over drugs, it is believed that the original intent of Congress, in enacting and amending the FD&C Act, was not for the FDA to interject itself into — or interfere with — the doctor-patient relationship. It is partly for this reason that physicians are (in most cases) allowed to prescribe medications "off-label."

How Did Off-label Marketing Become a Problem?

Physicians have for many years been prescribing FDA-approved drugs for unapproved uses, and the practice has become relatively routine in certain clinical settings.[22] Beginning roughly around the early 1990s, manufacturers started to realize that they were making considerable profits from selling drugs that were being prescribed off-label. Regulators recognized that this was happening and expressed apprehension over the potential for serious financial conflicts of interest between health care professionals and these drug makers. More importantly, the FDA was concerned with the enormous unknown risks that widespread off-label prescribing posed to the health and safety of the American public.

The agency realized that it lacked the technological and regulatory capability to oversee the practice of off-label use and marketing. Because the FDA exercises the "Practice of Medicine Exception," regulating off-label prescribing practices was not an option for it in regulating off-label use to protect the public. Instead, it focused on regulating the dissemination of materials provided by manufacturers to physicians on off-label use of approved drugs.

Sailing into "Safe Harbor"

In two guidance documents published in 1996 — Guidance to Industry on Dissemination of Reprints of Certain Published, Original Data and Guidance for Industry Funded Dissemination of Reference Texts — the FDA

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outlined its stance on the appropriate dissemination of information on unapproved uses of approved drugs.[23] These documents, which were later incorporated into Section 401 of the Food and Drug Administration Modernization Act (FDAMA) of 1997, met fierce opposition by the pharmaceutical industry, who by law would soon be required to drastically change their practices for sharing drug information and also be required to submit a supplemental new drug application (with supporting study data) to the FDA.[24]

Prior to enactment of FDAMA in 1998, however, Washington Legal Foundation (WLF), a pro business, conservative-leaning advocacy group, filed suit against the FDA claiming its guidance documents (and later, its regulations) were unconstitutional on the grounds of violating the First Amendment to the U.S. Constitution.[25,26,27] The U.S. District Court for the District of Columbia sided with WLF and ordered a permanent injunction that reversed the law and rendered the FDA's regulations invalid. Subsequent to this ruling, the FDA issued a notice clarifying its stance, indicating that a "safe harbor" would be provided to manufacturers who complied with the FDAMA provisions in Section 401 and that distribution of peer-reviewed medical and scientific journal articles discussing unapproved uses of their drugs would not be held against them as a violation of misbranding law.[28]

Then in an interesting turn of events, ruling on an appeal by the FDA, the U.S. District Court of Appeals dismissed both the FDA's appeal and vacated the District Court's decisions and injunctions, but only to the extent that they declare the FDAMA and the continuing medical education (CME) guidance unconstitutional.[29] This divided ruling resulted in the FDA retaining its right to use arguably promotional material (*i.e.*, reprints and references that are disseminated outside of the FDA's "safe harbor") as evidence in a misbranding or "intended use" enforcement action. At the same time, manufacturers retain their rights to use the First Amendment to challenge the government in the event that such cases are brought against them.

Today, FDAMA Section 401 and the accompanying FDA's regulations[30] are no longer in effect. The FDA relies on its existing statutory authority[31] and accompanying guidance as its primary enforcement tool to prosecute companies who misbrand or market their approved drugs "off-label." Where does this leave us in terms of policing the practice of off-label marketing?

Current State of Affairs

With off-label marketing settlements getting a lot of attention in the media lately, it appears as though the practice is continuing and widespread. The general perception among the public, including many prominent government officials, is that not much has changed in the industry. If anything, the evidence indicates that we are seeing an increase in both violations and financial penalties related to illegal off-label marketing and promotional activities.[32]

Companies are being prosecuted multiple times for the same or related offenses despite enforcement efforts.[33] The Department of Justice has tried to make an example of some companies accused of wrongdoing, most notably the 2009 Eli Lilly and Pfizer settlements.[34] But experts argue that this has been largely ineffective at curbing the practice of off-label marketing because the fines and associated legal costs pale in comparison to the profits made by companies convicted of the crime; moreover, while stock prices inevitably dip after announcements like these, they don't take long to climb back up to where they were.[35,36] At least one federal prosecutor noted — in discussing with a reporter what he thinks of Pfizer's takeaway from the 2009 Bextra® settlement — "that dealing with the Department of Justice may be 'just a cost of doing business.'"[37]

Despite the fact that the government has recovered nearly $4 billion since 2006 for off-label marketing violations alone, federal prosecutors are worried that their efforts might not be having much of an effect on this practice. In light of this, the government has stepped up the pressure by holding individu-

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als (chief executive officers (CEOs) and other executives) personally accountable for the illegal activity, going so far as to exercise the Inspector General's "exclusion" authority.

In a recent landmark case, the former chairman of the board of K-V Pharmaceutical Co., Marc Hermelin, was excluded from participating in federal health care programs (effective November 18, 2010) after Ethex Corp., a wholly owned subsidiary of K-V, pled guilty to two felony counts for allegedly misbranding and adulterating drugs. This marked the first case in which a pharmaceutical company executive was officially excluded without being convicted of a crime.

In the company's press release, they noted that he voluntarily resigned from the company "in an effort to avoid adverse consequences to the company, including a discretionary exclusion of the company..." — a penalty that would have effectively rendered the company insolvent.[38] Citing a more recent case, Forrest Labs CEO was threatened with exclusion from federal health care programs after the company pleaded guilty last year for illegally promoting its antidepressant Celexa off-label to children and adolescents suffering from depression.[39]

Excluding an executive (and/or the company), however, may have unwanted consequences that could disrupt the flow of life-saving drugs to patients, thus threatening public health. Such an outcome would prove utterly counterproductive to the government's original intentions. It is for this reason that some people believe that exercising exclusion authority amounts to an empty threat; unless the government also divests the businesses and forces the offending company to continue operating and manufacturing their medicines, when executives do not resign and the company is effectively excluded from doing business with the government, the possible detriment to the supply of drugs and patients who take them is something the government will not be able to accept. As one reporter described it, like the investment giants on Wall Street, pharmaceutical companies are "too big to nail."

Still, there may be evidence that the settlements and actions taken to date on this issue may be having some effect. Last year, federal prosecutors reported that we are witnessing the start to a slowdown in new "whistleblower" suits, and, of the complaints that have recently been filed, the alleged misconduct is generally less flagrant;[40] however, prosecutors also acknowledge that these cases are becoming harder to prosecute. Even so, we may not know for some time whether settlement actions like the ones we are seeing are changing the behavior of drug companies, or if companies are just coming up with more clever marketing schemes that do not — or do not appear to — violate the law.

Discussion

If the billion dollar settlement announcements and career-ending exclusions are not enough to convince the leadership of drug companies to stop the practice of marketing drugs off-label, what will work? Considering the fact that settlements are having no material adverse effects on companies' financial positions, at least the larger pharmaceutical giants have greater financial incentive to continue the practice than they do to end it. And with the way the laws are currently written, we may be coming to an impasse. Corporate integrity agreements (CIAs) that require strict compliance standards and continuing oversight by the federal government serve an important purpose. But are they working? Repeat offenses by drug companies do not support such a conclusion. Fines and penalties are simply not enough of a deterrent for pharmaceutical companies from continuing the practice.[41]

Another reason why off-label marketing is so difficult to control is because the legal and regulatory policies that we rely upon to oversee the research, development, approval, marketing, and use of drugs are not aligned well with the primary aim of our public health agencies — to protect and promote public health; however, the country is not ready to make the necessary concessions to make public health a priority over the health of our businesses. Chang-

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ing our health priorities would require a massive legislative effort to overhaul the way we regulate the pharmaceutical industry — something on par with the Affordable Care Act of 2010.

Considering the social complexity of the American health care system and the divided views over the role of government in the practice of medicine and business, it is highly unlikely that we will see substantial changes to the way we regulate drugs in the near future. The off-label promotion quandary we see today is the result of more than 100 contentious years of history between the federal government, the medical profession, and pharmaceutical manufacturers. While both the federal government and pharmaceutical manufacturers each have a stake in improving the current state of affairs, no regulation or enforcement measure will be effective in thwarting off-label marketing and promotion without the physicians themselves leading the campaign.

Placing the responsibility to solve this problem squarely on the shoulders of physicians is, in fact, a point of view shared by some people in the medical community.[42] But should physicians be expected to play the added role of whistleblower? If history is any indication, it will take their commitment, if not their leadership, to solve this problem. Just what role they will play, however, remains to be seen.

With the dominant mood on Capitol Hill being one for cutting government spending, perhaps now is a good time for Congress to examine the true cost that off-label prescription drug use and promotion have on our health care system. At least one study has shown that most (73 percent) off-label prescription drug use is not supported by scientific evidence of therapeutic efficacy.[43] This amounts to millions (if not billions) of dollars of wasteful spending on prescription drugs by government and private payers. The authors of this particular study — a team of researchers from Dartmouth, MIT/Harvard, and Stanford — suggest that policymakers consider mandatory post-marketing surveillance (or pharmacovigilance) of drugs that are used off-label.

The millions of dollars that companies spend promoting drugs off-label, plus the added expense from subsequently litigating and settling off-label cases, might well cover the cost of post-marketing pharmacovigilance efforts, and if more investment is needed, perhaps some of the money that government health care programs end up saving — by eliminating wasteful spending on off-label prescription drugs that do not work or, worse yet, cause harm and require additional health care expenditures — could be used to partially subsidize or off-set some of the costs of implementing and maintaining a mandatory pharmacovigilance system for off-label prescription drugs. This idea may sound extreme, but if coupled with a novel regulatory pathway that makes expanding approved drug labels more cost-effective for manufacturers, everyone could stand to benefit — especially the patients.

Note: Since the time of writing this article in July, news of an important legal action has kept off-label promotion fresh in the minds of industry observers. The U.S. Department of Health and Human Services had a change of heart when, in a letter to Forest Labs on August 5, it notified the company that it was abandoning its effort to bar the 83-year old CEO from participating in federal health care programs.[44] This could be a sign that the Office of Inspector General (OIG) is realizing that excluding CEOs from dealing with the government is unlikely to have its desired effect.

Endnotes:

1. www.gsk.com/media/pressreleases/2011/2011_pressrelease_10014.htm.
2. www.bbc.co.uk/news/business-12207300.
3. www.justice.gov/usao/ma/news/2010/December/2010-12-15—Elan-Civil-Settlement%20Agreement-F-W-ALL-SGNTRS.pdf.
4. www.fbi.gov/boston/press-releases/2011/bs022811a.htm.
5. www.nj.gov/oag/newsreleases11/pr20110310a.html.
6. www.justice.gov/opa/pr/2010/April/10-civ-487.html.
7. online.wsj.com/article/SB10001424052748704681904576319283821943622.html.
8. www.investor.jnj.com/secfiling.cfm?filingID=950123-11-48125.
9. www.justice.gov/opa/pr/2011/June/11-civ-751.html.
10. 21 U.S.C. § 355(d).
11. 21 C.F.R. § 201.128.

12. 21 U.S.C. § 321(m).
13. FD&C Act, Sec. 301(b); 21 U.S.C. 331(b).
14. Guidance for Industry - 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. Department of Health and Human Services, Food and Drug Administration; January 2009.
15. FD&C Act § 505(a); 21 U.S.C. § 355(a).
16. FD&C Act §§ 502(a) and (f); 21 U.S.C. §§ 352(a) and (f); 21 C.F.R. § 201.100(c)(1).
17. FD&C Act, § 301(a); 21 U.S.C. § 331(a).
18. 21 U.S.C. § 333.
19. Paul Starr."The Social Transformation of American Medicine: The rise of a sovereign profession and the making of a vast industry" (1982) ISBN: 0-465-07935.
20. 21 U.S.C. §§ 301 et seq.
21. Carol R. Berry. The Dividing Line Between the Role of the FDA and the Practice of Medicine: A Historical Review and Current Analysis. Harvard Law School (1997).
22. National Cancer Institute Web site Understanding the Approval Process for New Cancer Treatments - Off-label Drugs
23. 61 FR 196 [52800–52801] (October 8, 1996).
24. Public Law 105-115 [Page 111 STAT. 2296]; FDAMA § 401; FD&C Act §§ 551-557 (21 U.S.C. §§ 360aaa–360aaa-6); 21 C.F.R. §§ 99.1 et seq.
25. Washington Legal Foundation v. Friedman, 13 F .Supp.2d 51, 62-65 (D.D.C. 1998) (WLF I).
26. Washington Legal Foundation v. Friedman, 36 F.Supp.2d 16, 18 (D.D.C. 1999) (WLF II).
27. Washington Legal Foundation v. Henney, 56 F.Supp.2d 81 (D.D.C. 1999) (WLF III).
28. (65 FR 14286, March 16, 2000).
29. Washington Legal Foundation v. Henney, 202 F.3d (D.C. Cir. 2000).
30. 21 C.F.R. §§ 99.1 et seq.
31. FD&C Act § 502; 21 U.S.C. § 352.
32. Sammy Almashat, M.D., M.P.H, Charles Preston, M.D., M.P.H, Timothy Waterman, B.S., Sidney Wolfe, M.D. Rapidly Increasing Criminal and Civil Monetary Penalties Against the Pharmaceutical Industry: 1991 to 2010. Public Citizen's Health Research Group; (December 16, 2010).
33. US Department of Justice Press Releases: Warner-Lambert to Pay #430 Million to Resolve Criminal & Civil Health Care Liability Relating to Off-label Promotion (May 13, 2004) and Justice Department Announces Largest Health Care Fraud Settlement in Its History (September 2, 2009). Note: Having already incurred a $430 million fine and a 5-year CIA for its subsidiary's off-label marketing and promotion of Neurontin in 2004, Pfizer agreed to pay another $2.3 billion to settle with the Department of Justice for its alleged off-label marketing of the now-withdrawn painkiller Bextra®.
34. U.S. Department of Justice Press Release: Eli Lilly and Company Agrees to Pay $1.415 Billion to Resolve Allegations of Off-label Promotion of Zyprexa (January 15, 2009).
35. www.bnet.com/blog/drug-business/pfizer-stock-shrugs-off-23b-bextra-fine-can-anything-deter-off-label-promotion/2818.
36. www.thestreet.com/story/10595021/record-fine-unlikely-to-end-bogus-drug-marketing.html.
37. articles.cnn.com/2010-04-02/health/pfizer.bextra_1_bextra-pfizer-and-pharmacia-generic-drugs/3?_s=PM:HEALTH.
38. www.kvpharmaceutical.com/news_center_article.aspx?articleid=329.
39. www.justice.gov/opa/pr/2010/September/10-civ-1028.html.
40. Federal prosecutors report slowdown in the filing of new fraud claims, say less egregious violations cited: Qui tam attorneys say evidence of off-label promotion is becoming harder to establish. Rx Compliance Report, 9(9); 2010.
41. www.cchrint.org/2011/05/31/in-shift-feds-target-top-execs-for-health-fraud.
42. Kesselheim AS, Mello MM, Studdert DM (2011) Strategies and Practices in Off-Label Marketing of Pharmaceuticals: A Retrospective Analysis of Whistleblower Complaints. PLoS Med 8(4).
43. David C. Radley, MPH; Stan N. Finkelstein, MD; Randall S. Stafford, MD, PhD. Off-label Prescribing Among Office-Based Physicians, *Archives of Internal Medicine,* 2006;166:1021-102.
44. www.bloomberg.com/news/2011-08-05/forest-labs-says-regulators-considered-u-s-business-ban-on-8-executives.html.

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