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Shifting Focus toward a New Strategy against Off-Label Marketing

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Is REMS the Solution?

In November 2011, GlaxoSmithKline PLC announced its willingness to pay $3 billion[1] in order to settle with the U.S. government civil and criminal investigations into its sales and marketing practices for nine of its drugs (including Avandia® a type-2 diabetes drug that was allegedly being promoted off-label and was significantly restricted last year after it was linked to cardiovascular risks).[2] Expected to be finalized in 2012, the total settlement would be the largest False Claims Act penalty imposed on a pharmaceutical company in history, exceeding the previous record of $2.3 billion paid by Pfizer Inc. in 2009.[3]

For several years, the U.S. Department of Justice (DOJ) has settled federal fraud investigations with pharmaceutical companies accused of illegally marketing drugs off-label, recovering tens of billions of dollars for Medicaid and Medicare. Off-label marketing is the promotion of a drug for indications beyond those formerly evaluated by the manufacturer and approved by the Food and Drug Administration (FDA).[4] Although physicians are (in most cases) legally allowed to prescribe medications off-label, the FDA prohibits drug companies from promoting a drug off-label because it constitutes "misbranding" — a violation of the Federal Food, Drug and Cosmetic (FD&C) Act, Sec. 301(b).[5]

The False Claims Act (FCA) is the federal government's primary means for publicizing and holding accountable the pharmaceutical industry for its illegal, off-label marketing activities. The FCA imposes a civil penalty of not less than $5,000 and not more than $10,000, plus treble damages which the government sustains because of the act of that person, on any person who knowingly presents or causes to be presented a false or fraudulent claim for payment or approval by the govern-

ment.[6] Additionally, any person who knowingly makes, uses, or causes to be made or used a false record or statement material to a false or fraudulent claim is also liable to the government for this amount.[7]

False claims investigations into off-label marketing activities are intended to discipline companies for their illegal behavior and deter ongoing (or future) fraudulent promotional activities, and result in the government's recovery of improper payments.[8] In fiscal year 2011, the DOJ recovered more than $3 billion in settlements and judgments in civil cases involving the FCA, with enforcement actions totaling $2.2 billion in civil claims against the pharmaceutical industry alone — the largest source of recoveries for the year.[9]

With the creation in 2009 of the Health Care Fraud Prevention and Enforcement Action Team (HEAT) — a U.S. Department of Health and Human Services (HHS)/DOJ interagency task force — and the numerous provisions in the Affordable Care Act of 2010 aimed at fighting health care fraud and abuse, including an additional $350 million for Health Care Fraud and Abuse Control Program (HCFAC) activities, it is clear that fighting health care fraud has been a top priority for the Obama Administration.[10] What is not as clear is how well FCA prosecutions work in deterring pharmaceutical companies from continuing to market drugs off-label.

Examining the Evidence

My article published in the September/October 2011 issue of the *Journal of Health Care Compliance* examined off-label marketing settlements, issues and trends from the first half of 2011, and postulated that fines and penalties were doing little to curb this lucrative yet illegal practice.[11] Later that year, researchers at Harvard published an analysis of the relationship between off-label prescribing and a major federal fraud prosecution targeting illegal off-label promotion: the Neurontin® case against Warner-Lambert (a Pfizer Inc. subsidiary).[12] They conducted a study "to identify whether any of the milestones in the case's timeline — the initiation of the FCA investigation, public announcement of the investigation, and settlement of the case — affected trends in off-label prescribing or spending for this drug."[13]

Contrary to their initial hypothesis — that the prosecution would be associated with a slower rise in off-label prescribing as the manufacturer changed its marketing practices and as physicians and payers became aware of the company's dubious behavior — they found that the sales of Neurontin® generally remained strong throughout the duration of the case and afterward. While the authors noted important limitations to their analysis, including the slow pace of its enforcement actions, their study "raises fundamental questions about the deterrent role of the False Claims Act."[14] The authors further suggest that FCA settlements may not deter fraudulent promotional activities because "the size of these settlements are dwarfed by the potential financial gains from thwarting the law."[15] Indeed, this is the sentiment echoed by many industry observers.[16, 17, 18]

One might argue that larger fines would have a greater impact on changing the unlawful behavior of the pharmaceutical industry; however, the evidence suggests that relying on negative publicity generated by heavy punishments is ineffective in preventing companies from offending. Punitive action is an appropriate consequence of defrauding the government and should be calculated in proportion to the severity of the crime committed. And if the goals of enforcement in these cases were to recover taxpayer money and fair punishment for crimes committed, settlement agreements like those meted out with increasing frequency, by their very nature, would seem to achieve this goal.

At least in the case of off-label promotion, however, deterrence, as a strategy for altering the marketplace behavior of pharmaceutical companies, simply does not work.

In fact, if the trend of high-profile, high-award settlements continues, pharmaceutical companies may simply conclude such prosecution is an unfortunate but inevitable consequence of doing business. This suggests the need to reconsider the goals of enforcement and to realize other means and incentives for achieving compliance.[19]

Shifting Focus

Reconsidering the goals of enforcement requires an understanding of the role of the FDA in regulating drugs and an awareness of the inherent risks of off-label use. Among other roles, the U.S. FDA is the agency responsible for protecting the public health by assuring the safety and efficacy of drugs.[20] Central to its mission is identifying and responding to risks from marketed drugs and ensuring that the benefits of a drug outweigh its risks to patients for whom the drug is indicated.[21]

There is no way to know all of the risks associated with a drug at the time of approval; however, the drug's labeling is required to contain warnings or restrictions for those risks that are known prior to marketing (based on clinical trials data). When a drug is used off-label, the risks and benefits are largely unknown. That is why the FDA's stance on off-label marketing is so simple: "[a]n approved new drug that is marketed for an unapproved use is an unapproved new drug with respect to that use."[22] When a drug is marketed for purposes or populations beyond those for which it is approved, the labeling is considered "false and misleading" or not providing "adequate directions for use."[23]

As noted earlier, misbranding a drug is illegal.[24] The goal of the FDA in investigating and prosecuting pharmaceutical companies for misbranding is to protect the American people from potentially dangerous drugs that don't work and/or threaten the public health. Their intent in enforcing the law is consistent with their mission: to assure the safety and efficacy of marketed drugs.

Because deterrence is ineffective in regulating off-label marketing, and the FDA's primary goal is to protect the American public from unsafe and ineffective drugs, it is time for the FDA to refocus its efforts on achieving its goal using other means. Certainly, companies who break the law should be prosecuted, but prosecution is not making off-label use any safer or more effective. Considering the current political appetite for increasing the FDA's regulatory authority, the agency must rely on its existing legal jurisdiction to achieve its goal.

A New Strategy

The Food and Drug Administration Amendments Act of 2007 (FDAAA; P.L. 110-85) provided the FDA with the authority to require, under specific conditions, a Risk Evaluation and Mitigation Strategy (REMS) from manufacturers to ensure that the benefits of a drug outweigh the risks of the drug. A REMS is "a strategy to manage a known or potential serious risk associated with a drug or biological product."[25] Arguably, off-label use of prescription drugs inherently carries with it the potential for serious risk because the safety for such use has not been formally evaluated and approved by the FDA. The challenge in using REMS as a means to ensure safe off-label use is that the law narrowly defines the circumstances in which the FDA may require a manufacturer to submit a REMS for a drug that is already approved without a REMS at the time of approval.

Requiring a manufacturer to submit a REMS for a drug that is already on the market simply because the drug is being used (even widely used) off-label is, in and of itself, not justified under the law. In the post-marketing approval environment, the FDA is only authorized to require manufacturers of drugs (or biologics) approved without a REMS at the time of approval to submit a proposed REMS if the FDA becomes aware of "new safety information" and determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks of the drug.[26]

The term "new safety information," however, is statutorily defined as "a serious risk or an unexpected serious risk" of a "serious adverse drug experience."[27] There are a number of limitations in this approach.

One limitation is that serious adverse drug experiences — including death, immediate risk of death, hospitalization, incapacity or substantial disruption to conduct normal life functions, birth defect, or based on medical judgment would result in one or more of these experiences — sometimes take years to surface before the FDA becomes aware of them. The stringency and severity of these health conditions coupled with the delayed notice of such complications does impair the agency's ability to intervene.

Another limitation is that the elements of a REMS that would be most likely to assure safer off-label use of a drug — such as limiting prescribing to only physicians with specialized training and/or certification, limiting dispensing to certified pharmacies, and limiting use to patients who meet clinical criteria and who are enrolled in a patient registry[28] — may only be included in the REMS if known serious risks are already listed in the drug's labeling. In order for the FDA to require a manufacturer of an approved drug that does not already have a REMS to implement one, the FDA would first have to require the manufacturer to change the labeling for the drug to include such known serious risks.

However, if the FDA were to require a REMS for a drug that is being used off-label, and the REMS included "elements to assure safe use"[29] of the drug with known serious risks, it is entirely possible for the FDA to restrict the use of the drug to include only patients for whom the drug is indicated in its approved labeling. This would not only assure safer use of the drug, but it also would discourage manufacturers from actively promoting the drug off-label.

Requiring a REMS for a drug that is being prescribed off-label also may encourage manufacturers to conduct post-market studies and clinical trials (if they are not already required by the FDA to do so due to the identification of new safety information[30]). Post-market studies and clinical trials serve several important purposes. Manufacturers may propose a modification to a drug's REMS requirements based on post-market studies and/or clinical trials data.[31] Additionally, safety and efficacy data from post-market studies and clinical trials can be used in a supplemental application for a new indication for use.[32] This data is, in fact, required in a REMS assessment when submitting a supplemental new drug application.[33] The FDA has for many years indicated that it wanted manufacturers to submit supplemental new drug applications for drugs that are used off-label,[34] and increasing the use of REMS also may lead to a greater number of applications.

Conclusion

Undoubtedly, if the FDA stepped up its use of REMS to assure the safety of drugs being used off-label, it would face heavy criticism from industry. Manufacturers would dispute such an effort by the FDA as merely an attempt to restrict sales of their drugs. Physicians would charge that the FDA is interfering with the practice of medicine. As it stands now, however, the FDA is having little success in fulfilling its mission when so many drugs on the market are being used without having established safety and efficacy for the purposes or populations for which they're being prescribed.

While pharmaceutical companies that are punished for promoting drugs off-label repay the government for the cost of the drug to federal health care programs, they do not end up subsidizing the additional health care costs attributed to treating serious adverse drug experiences caused by off-label use of their drugs. Increasing the fines and even holding officers of such offending companies responsible likely is not going to change the behavior of the industry. It is also quite possible that introducing and requiring REMS more aggressively will not change manufacturers' marketing practices. But what it would accomplish is far more important; it would improve the

federal government's ability to protect the health of the American public.

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