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Compliance Counsel and 'Off-Label' Issues

Increased governmental inquiries elevates attorneys' importance to pharmaceutical companies

Compliance counsel for pharmaceutical companies are becoming more involved in "off-label" promotion and marketing issues than in the past. Compliance counsel — both inside the corporation and in their outside law firms — are in great demand as a result of increased governmental informal inquiries, informational subpoenas and formal investigations. Both corporate law departments and outside law firms are adding to their compliance departments to service the needs of their clients on an expanding basis.

The Department of Justice and U.S. Attorneys offices throughout the country are increasingly targeting the sales and marketing practices of pharmaceutical companies and, in particular, such companies' off-label marketing. Federal prosecutors have benefited from increases in funding, personnel and other resources at various federal agencies seeking to investigate and deter health-care fraud, including the Department of Health and Human Services and the Food and Drug Agency's Office of Criminal Investigations. Congress has participated, as well, by allocating substantial funds to help identify and prosecute health-care fraud. The prosecution of pharmaceutical companies allegedly engaged in off-label promotion practices has resulted in criminal convictions and individual fines reaching hundreds of millions of dollars which, in turn, have prompted pharmaceutical companies to re-examine their sales and marketing practices to make sure they comply with the law and would withstand federal scrutiny, if necessary.

"Off-label" is a short-hand term for a drug (or medical procedure) that is prescribed for a use other than the use approved by the FDA, the federally sanctioned agency charged with ensuring that all drugs are safe and effective for their intended uses. Off-label (or unapproved) treatment includes the following:

- Promoting the drug for a new or different disease or condition that is not stated on the drug's label or label insert (e.g., not FDA-approved);
- Changing the dosage;
- Combining the drug with any other treatment; and
- Using the drug in a new population (e.g., suggesting that a drug approved for treatment of an adult could be used to treat a child).

The promotion of drugs for off-label uses is a controversial subject among manufacturers, regulatory agencies, physicians, third-party buyers and insurers, and has generated vigorous debate over the right to convey truthful and non-misleading information regarding off-label uses. It is important to understand that, for purposes of off-label promotion, pharmaceutical manufacturers and physicians are treated very differently. It is illegal for pharmaceutical companies to promote off-label uses of prescription drugs, except under certain, limited exceptions, such as those involving peer-reviewed medical journals. By contrast, doctors are legally permitted to prescribe medications off-label.

Many in the pharmaceutical industry argue that if pharmaceutical companies were permitted to promote off-label uses, these companies would develop new medical findings that doctors could immediately implement into their patients' active drug treatments without the usual regulatory costs and delays. The FDA strongly disagrees and claims that drug manufacturers need to fully analyze each drug, including each new use of a drug, before marketing and selling it. In particular, the FDA contends that permitting manufacturers to promote off-label uses would:

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- Discourage manufacturers from seeking FDA approval of new uses of drugs and, consequently, from studying the uses of, and obtaining definitive data on, prescription drugs;
- Cause doctors to prescribe patient treatment based on incomplete or inconclusive information; and
- Potentially cause harm to patients from unstudied uses that actually lead to bad results, or that are merely ineffective.

Doctors regularly prescribe drugs for uses that are outside of those set forth in the drug's FDA-approved labeling. One of the most basic examples of off-label use involves the aspirin tablet. While the FDA approved it as a pain reliever over 100 years ago, most doctors began prescribing it as a means to prevent heart attacks — an off-label use — a little more than 15 years ago and continue to prescribe it off-label today. Doctors have also prescribed Beta Blockers, which the FDA originally approved to lower blood pressure, off-label for many years to decrease the risk of death after a heart attack. The FDA subsequently approved Beta Blockers for the additional use. Similarly, most people do not know that Viagra was not originally approved to treat erectile problems. Instead, the FDA initially approved it to treat chest pain, and only later approved it to treat erectile dysfunction, after substantial off-label use. The same is true with AZT, which the FDA originally approved as a cancer treatment, but doctors frequently prescribed it off-label to delay the onset of AIDS in HIV-infected people. The FDA subsequently approved it for such treatment.

The number of drugs used off-label, and the frequency in which they are prescribed off-label, is staggering. It is estimated that as many as 40 percent of all prescriptions are written for off-label uses. According to a 2003 Knight Rider study, approximately 115 million off-label prescriptions are written per year, nearly double the amount five years earlier. Studies have shown that the following drugs are used off-label at least 50 percent of the time: Accutane (acne), anti-seizure medications such as Topomax, Thalamid (leprosy), anti-psychotic medications such as Seroquel, Risperdal (schizophrenia), and Bextra (arthritis). In addition, it is estimated that physicians prescribe off-label treatment to over 80 percent of all AIDS patients and that 60 percent of cancer physicians prescribe drugs off-label to their patients.

Whereas prior off-label promotion investigations generally focused on the nature of communications made by a pharmaceutical company's sales representatives to physicians to use a particular medicine for an unapproved use, these days it is just as likely that prosecutors will investigate the perks that such companies have commonly provided to physicians, such as grants, continuing medical education seminars, lavish conferences, free samples and fees for writing medical journal articles. In such actions, prosecutors generally argue that these practices are fraudulent promotion schemes that corrupt the information process relied on by doctors in their medical decision making and, consequently, put patients at risk. Prosecutors may also argue that such schemes result in payment of false or fraudulent claims under the federally funded Medicaid/Medicare programs and deprive such programs of the informed, impartial judgment of doctors. Consequently, patients who receive a drug for an unapproved and unproven use have no assurance that their doctors are exercising their independent and fully informed medical judgment, or that their doctors have not been improperly influenced by misleading statements made by, or inducements provided by, a pharmaceutical company.

These cases are generally prosecuted under one or more of the following laws: the Food, Drug, and Cosmetic Act, 21 U.S.C. §321 et seq., which prohibits distribution of misbranded drugs.; the Anti-Kickback Statute, 41 U.S.C. §1320a-7b, which prohibits the giving or receiving of "remuneration" in return for purchases, orders, prescriptions, referrals or recommendations; and the False Claims Act, 31 U.S.C. §3729 et seq., which imposes liability on any person who knowingly makes, uses, or causes to be made or used, a false record or statement to get a false or fraudulent claim paid or approved by the government.

Some of the recent, high-profile investigations and prosecutions involving off-label promotion include the following:

- Serostim — In October 2005, Serono S.A. pled guilty to felony charges and paid $704 million related to its off-label marketing activities for Serostim, its "AIDS wasting" drug. The government alleged that Serono provided kickbacks to doctors and caused the submission of false claims for reimbursement under Medicaid.
- Evista — In 2005, Eli Lilly pled guilty to a misdemeanor charge and paid $36 million to settle off-label promotion charges under The Food, Drug, and Cosmetic Act concerning the drug Evista, its osteoporosis drug. According to the government, Eli Lilly promoted Evista off-label to treat heart disease and breast cancer in women.
- Neurontin — In May 2004, Pfizer's Warner-Lambert unit pled guilty to felony charges and paid $430 million related to its off-label marketing of Neurontin, its epilepsy drug The government alleged kickbacks and fraudulent marketing activities, including paying doctors to attend conferences and treating them to trips to vacation resorts, planting company agents in the audience at medical seminars to refute unfavorable comments about Neurontin, paying doctors to allow sales representatives to sit in on patient visits and paying writers and doctors to prepare favorable papers.
- Lupron — In 2002, TAP Pharmaceuticals paid a total of $850 million to resolve off-label marketing and price manipulation charges related to Lupron, its prostrate cancer drug.

What should pharmaceutical companies be doing? Compliance counsel should conduct an off-label assessment in which they examine the company's compliance program and sales and marketing procedures to make sure they clearly define off-label promotion and distinguish permissible promotion activities from impermissible ones. Compliance counsel should also examine whether the company's marketing plan and promotional materials contain information, or suggest reliance, on off-label uses of drugs. The compliance program should be designed to identify, detect and discipline those who engage in unlawful off-label promotion. It is not sufficient for pharmaceutical companies to merely have the proper written policies and procedures. Instead, compliance counsel must also "monitor" and enforce the company's compliance programs and other corporate

codes, plans and policies relating to off-label promotional activities.

Compliance counsel must establish internal controls that regulate the company's sales and marketing practices, and also regularly test the internal controls to ensure that they work properly and effectively. Compliance counsel must also train (and continually retrain) their employees, especially management and those who communicate with doctors, as to what is and is not permitted in marketing the companies' products and instruct them regarding the relevant statutes and regulations.

Because the risk of enforcement action today is so great, pharmaceutical companies must do more than have a great compliance program. They should strive to create a company-wide culture of compliance that permeates each and every aspect of their business. Compliance counsel find themselves in the enviable, but difficult, position of creating and instilling a compliance "mind-set" in companies, many of which have never had such formal education. Whether it is to implement a cutting edge compliance program or defend a company under attack from the accusations of a whistleblower or governmental agency, it is clear that compliance counsel have attained a new level of importance to their corporations. ■