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Enforcement Related to Off-Label Marketing and Use of Drugs and Devices: Where Have We Been and Where Are We Going?

John N. Joseph, David Deaton, Houman Ehsan,
and Mark A. Bonanno

ABSTRACT: Off-label drug or medical device “use” is the practice of prescribing drugs or medical devices to patients for a purpose not included on the federally approved label. Off-label “marketing” is the practice of attempting to influence physicians to prescribe drugs or devices for off-label purposes. The federal Food and Drug Administration (FDA) maintains regulatory authority over the proper labeling of drugs and medical devices. Although not illegal, off-label use of certain drugs has led to controversy in recent years, especially in light of alleged behind-the-scenes marketing practices intended to increase off-label prescribing. Off-label marketing practices are prohibited and could result in criminal charges against a manufacturer, depending upon the circumstances. Yet a vast gray area exists for subtle marketing practices, such as circulating published medical studies about off-label uses to physicians. This article summarizes the legal and medical standards associated with off-label use and marketing of drugs, provides summaries of recent enforcement activities regarding off-label marketing, and explains the current federal regulatory issues surrounding off-label marketing practices. The authors provide practical pointers on regulatory compliance and the risks associated with fraud and abuse laws for drug companies and practitioners.

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OFF-LABEL MARKETING

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Introduction

Lured by the opportunity to apply his scientific research skills, David Franklin got a job as a medical liaison for a pharmaceutical company. He held a doctorate in biology, and was employed to relay medical information about the company's drug products to physicians. Soon after he started, however, David grew dissatisfied. The medical liaison position was not the science-based position he believed it would be, but basically a sales position—one where David allegedly was expected to engage in aggressive sales practices. Only a few months after David was hired, he filed a nine-count *qui tam* action alleging the pharmaceutical company had violated the federal False Claims Act.¹

Filing a whistleblower case is an extreme response to a bad employment situation, so what happened? The short answer is that David disagreed with the company's marketing campaign, allegedly designed to convince physicians to prescribe the drug Neurontin[®] for conditions for which the drug was not approved by the Food and Drug Administration (FDA). In other words, David's former employer allegedly was marketing Neurontin for "off-label" uses. The drug was prescribed for off-label uses in such volume that David believed the company violated the law. The government agreed (and pursued a separate criminal proceeding parallel to the civil case). The company ultimately settled the federal allegations.²

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- 1 Complaint, U.S. *ex rel.* David Franklin v. Parke-Davis, No. 96-11651PBS (D. Mass. Aug. 13, 1996) (on file with authors).
 - 2 Verdict/Settlement, U.S. *ex rel.* David Franklin v. Parke-Davis, No. 96-11651PBS (D. Mass. May 13, 2004); *see also* Press Release, Dep't of Justice, Warner-Lambert to Pay \$430 Million to Resolve Criminal and Civil Health Care Liability Relating to Off-Label Promotion (May 13, 2004), available at www.usdoj.gov/opa/pr/2004/May/04_civ_322.htm.

The long answer to what happened is more complicated. David's case was controversial. The laws related to off-label promotion are broad and have raised significant First Amendment concerns. With FDA trying to keep pace with court decisions by issuing revised rules and guidance, there are few practical guideposts for drug or device manufacturers interested in addressing the off-label use of their products. The *Franklin* case also raised novel issues regarding the use of false claims allegations as a regulatory tool to police the marketing of prescription drugs.

This article discusses the legal and medical standards associated with off-label use and marketing of drugs and devices, and summarizes recent enforcement activities of off-label marketing practices.³ This discussion is followed by a brief description of the FDA's current position on the subject, including proposals not yet finalized. Finally, the authors describe practical considerations.

Legal and Medical Standards

FDA regulates, among other things, the introduction of prescription drugs and medical devices into commerce. Upon application from a manufacturer, with supporting scientific research into safety and efficacy for a specific proposed use, FDA decides whether to approve or clear the particular drug or device for the applied-for use or indication.⁴ With respect to a new drug, FDA's paramount concerns for approval are patient safety and benefit from the intended use.⁵ The package insert that physically accompanies a drug sets forth the approved uses for that product; in FDA's parlance, the package insert is the "approved professional labeling."⁶ Manufacturer promotion to prescribers and customers is strictly limited to the particular FDA-approved, or "on-label," use or uses. Promotion of a drug for a use that is not on-label—off-label promotion—is strictly prohibited. The government has levied significant civil and criminal sanctions on manufacturers that allegedly have engaged in off-label promotion, as outlined below.

3 The issues discussed in this article apply to both prescription drugs and medical devices. Because the pharmaceutical industry has seen a greater number of cases addressing off-label use, the majority of this article uses examples from the pharmaceutical industry.

4 For medical devices, the approval process varies depending on the risk classification of the device. This article uses the term "approved" to include devices "cleared" by FDA.

5 21 U.S.C. §§ 355(a), 355(d).

6 Final Guidance on Industry-Supported Scientific and Educational Activities, 62 Fed. Reg. 64074, 64075 (Dec. 3, 1997).

Although the rules prohibiting off-label promotion of prescription drugs and devices seem relatively straightforward, the concept is murky. Asymmetrically, while manufacturers cannot promote potential off-label uses to prescribers, prescribers (e.g., providers, hospitals, physicians) routinely prescribe for off-label uses that they believe, based on their medical judgment, will be beneficial. FDA has long acknowledged the value of off-label uses in medical treatment.⁷ Through government-sponsored healthcare programs like Medicare and Medicaid, the federal government reimburses providers for many off-label uses of FDA-approved drugs.⁸ Indeed, FDA recognizes the “important role” that “drug and device manufacturers have... in legitimate scientific and educational discussions, including discussions of unapproved products and unapproved uses.”⁹ Manufacturers typically have the most comprehensive access to data for their products, and in theory would be best suited to disseminate information to practitioners. The difficulty comes in predicting when disseminating information about off-label use becomes prohibited off-label promotion.

FDA’s role and regulatory power over off-label promotion

FDA regulates the manufacture, labeling, and promotion of drugs and medical devices. Congress delegated broad powers to FDA under the Food, Drug, and Cosmetic Act (FDCA).¹⁰ The agency’s mission includes promoting and protecting the public health by balancing two fundamental interests. On the one hand, FDA must ensure that drugs and devices are safe and effective, which protects against the introduction of dangerous or ineffective products into the marketplace. On the other hand, FDA must not unduly delay the availability of safe and effective products to patients in need.¹¹ (For a related discussion concerning patients’ efforts to gain access to unapproved therapies, see *Patient Access to Unapproved Therapies: The Leading Edge of Medicine and Law*, page 45.)

FDA’s safety requirements vary greatly depending on the disease condition the drug or device is aimed at treating and the availability of alternatives for patients. Thus, if the targeted condition is serious, a drug can be quite dangerous but still be approved by FDA for that indication if tests show that the drug effectively treats the targeted con-

7 See 59 Fed. Reg. 8798, 8803 (Mar. 19, 1987).

8 Many off-label uses are included in medical compendia or recognized in peer-reviewed studies and are reimbursable under these federal programs. See 42 U.S.C. §§ 1395x(t)(2)(B), 1396r-8(k)(6).

9 62 Fed. Reg. 64074, 64081 (Dec. 3, 1997).

10 21 U.S.C. § 301 *et seq.*

11 See FDA, FDA’s Mission Statement, available at www.fda.gov/opacom/morechoices/mission.html (last visited Oct. 21, 2008).

dition. For example, FDA is willing to accept significantly more toxicity in a drug aimed at treating aggressive cancer than in a drug aimed at treating a childhood ear infection.¹² Hence, FDA's determination that a drug is "safe" for marketing for a specific use is not equivalent to a determination that the drug is safe generally. Context is important in the drug approval process.

Arguably, then, FDA's mission would be undermined if manufacturers were permitted to seek approval for one indication, then to market the product broadly for all other potential indications. A manufacturer could identify the indication for which it could obtain FDA approval most quickly and cheaply—regardless of how limited the use for that indication. Therefore, off-label marketing restrictions are an essential component of FDA's ability to regulate drugs and devices effectively; these restrictions ensure that FDA reviews safety and effectiveness data for each indication prior to a manufacturer's promotion. Proponents of off-label marketing restrictions argue that eliminating such restrictions would

- diminish or eliminate a manufacturer's financial incentive to study a drug's use and obtain definitive data,
- result in harm to patients from unstudied uses that are ineffective or would lead to bad results,
- diminish the use of evidence-based medicine, and
- could ultimately erode FDA's efficacy standard by allowing manufacturers to end-run the efficacy requirements by marketing for a multitude of uses after approval without proving efficacy for the additional marketed uses.¹³

Accordingly, FDA has several methods of regulating off-label marketing. For example, an approved or cleared drug or device marketed for an off-label use may be "misbranded" under the FDCA. Under 21 U.S.C. Section 352, FDA may deem a drug or device misbranded if the label does not bear adequate directions for use.¹⁴

In an enforcement action under Section 352, the premise of the misbranding theory is that a drug that is promoted and intended for off-label use cannot bear adequate directions for use, because an

12 Michelle Meadows, *Why Drugs Get Pulled Off the Market*, FDA CONSUMER MAG., Jan–Feb 2002, available at www.fda.gov/FDAC/features/2002/102_drug.html.

13 Janet Woodcock, *A Shift in the Regulatory Approach* (June 23, 1997), available at www.fda.gov/CDER/present/diamontreal/regappr/index.htm. Dr. Woodcock was the director of the FDA's Center for Drug Evaluation and Research (CDER), and is currently the Deputy Commissioner and Chief Medical Officer of the FDA.

14 FDA can grant technical exemptions to the labeling requirement while seeking administrative action against manufacturers it deems to be engaging in unlawful off-label promotion. See 21 U.S.C. § 352(f).

FDA-approved label has directions for approved uses only. For example, in *United States v. Articles of Drug*, the United States brought action seeking to seize large quantities of drugs on the ground that the labeling did not contain adequate directions for use and did not meet a regulatory exemption.¹⁵ Every drug has an approved indication for use set forth under the heading “Indication and Usage” on the FDA-approved label. Unapproved use is any use of the drug not identified in the “Indication and Usage” section. The federal district court held that the label met the adequate directions for use requirement because of the inclusion of: (1) a cautionary legend on the drugs’ labels stating federal law prohibits dispensing without prescription; and (2) sufficient directions to a physician, so the drugs could be prescribed safely and for their intended purposes. On appeal, however, the Fifth Circuit held that a drug’s labeling must contain adequate directions for a consumer to engage in self-medication. Because prescription drugs by definition can be used only under a physician’s supervision, such drugs must qualify under a regulatory exemption (i.e., have an approved label for the use). Misbranded drugs could be subject to administrative action against the manufacturer, seizure of the drug, and probable civil lawsuits against the manufacturer by patients who consumed the drug.

Off-label prescribing by physicians

Although FDA regulates promotion of drugs and devices by manufacturers, as a matter of policy, the agency generally does not interfere with the practice of medicine.¹⁶ Physicians may prescribe approved or cleared drugs or devices for off-label uses in the exercise of their professional judgment. Although FDA may take action if safety issues with the use of any drug or device become a public health concern (as discussed above), once a drug or device has been approved or cleared for sale for one purpose, physicians may prescribe it for any other purpose that, in their professional judgment, is safe and effective.¹⁷

Off-label prescribing is most common with older medications that have developed into new uses for which manufacturers have not yet submitted applications and studies required by FDA.¹⁸ For example,

15 *United States v. Articles of Drug*, 625 F.2d 665, 666 (5th Cir. 1980).

16 See 21 U.S.C. § 396; see also *Buckman Co. v. Plaintiffs’ Legal Comm.*, 531 U.S. 341, 350–51 & n.5 (2001) (“FDA is charged with the difficult task of regulating the marketing and distribution of medical devices without intruding upon decisions statutorily committed to the discretion of health care professionals”). *Id.* at 350.

17 See, e.g., 59 Fed. Reg. 59820, 59821 (Nov. 18, 1994) (noting that the agency has restated this policy on numerous occasions).

18 Randall S. Stafford, *Regulating Off-Label Drug Use—Rethinking the Role of the FDA*, 358 NEW ENG. J. MED. 1427–1429 (2008).

FDA approved Risperidone (Risperdal®) in 1993 for the treatment of schizophrenia, but the drug also is used for treating agitation in Alzheimer's patients.¹⁹ There are several reasons for this trend toward unapproved additional uses. First, the cost of clinical testing and submitting a supplemental application for a new indication often outweighs the potential revenue from marketing the drug for an additional indication. Second, if the off-label use is widespread, the manufacturer stands to gain little additional benefit from marketing the new indication. Third, if generic versions of the drug are available, it may not be economically feasible to obtain an additional indication, because the company would incur additional marketing costs (generics are not typically marketed) and the benefit of the new indication would be spread across the various generic versions.

Off-label use of pharmaceuticals is relatively widespread. A 2006 study estimated that more than 20% of all prescriptions written by doctors were for unapproved uses.²⁰ The Government Accountability Office (GAO) found that about 25% of anticancer drugs were prescribed for off-label uses.²¹ Off-label prescribing was higher for certain subgroups of patients. For example, 56% of cancer patients were given at least one drug off-label.²² Another study found that 81% of HIV patients received at least one drug off-label as part of their regimen.²³ The off-label use of medications is especially prevalent in pediatrics because most drugs are not tested in children.²⁴

In some cases, there can be extensive medical experience supporting the off-label use of a drug or device. For example, FDA approved Trazodone (Desyrel®) in 1981 for the treatment of depression. The label noted that "the mechanism of DESYREL's antidepressant action in man is not fully understood."²⁵ FDA has never evaluated, much less approved, Trazodone for the treatment of insomnia. Yet, according to a 2005 NIH conference statement, Trazodone is the most commonly prescribed insomnia medication in the United States.²⁶

19 Charles D. Molsinger et al., *Use of Atypical Antipsychotic Drugs in Patients with Dementia*, 67 AM. FAM. PHYSICIAN 2335 (2003).

20 David C. Radley et al., *Off-Label Prescribing Among Office-Based Physicians*, 166 ARCHIVES INTERNAL MED. 1021 (2006).

21 U.S. GEN. ACCOUNTING OFFICE, OFF-LABEL DRUGS: REIMBURSEMENT POLICIES CONSTRAIN PHYSICIANS IN THEIR CHOICE OF CANCER THERAPIES 4 (1991), available at <http://archive.gao.gov/d18t9/144933.pdf>.

22 *Id.*

23 Carol L. Brosgart et al., *Off-Label Drug Use in Human Immunodeficiency Virus Disease*, 12 J. ACQUIRED IMMUNE DEFICIENCY SYNDROMES & HUM. RETROVIROLOGY 56 (1996).

24 See e.g., Nancy Monestime-Williams et al., *Off-Label Prescribing of Medications for Children*, 103 J. S.C. MED. ASS'N 130 (2007).

25 Desyrel label, available at www.fda.gov/medwatch/SAFETY/2004/Desyrel_PI.pdf.

26 NIH, NIH State-of-the-Science Conference Statement on Manifestations and Management of Chronic Insomnia in Adults, June 13-15, 2005, <http://consensus.nih.gov/2005/2005InsomniaSOS026html.htm>.

In short, off-label prescribing is permitted as part of the legitimate and effective practice of medicine. Unfortunately, aside from FDA's published policy that it will not intrude upon a physician's medical judgment, there is little regulatory or other legal guidance for health-care practitioners who prescribe for off-label uses. Practitioners often are left to rely on ethical guidance to determine when it is acceptable to subject a patient to a potentially unknown/unsubstantiated risk for a potentially unknown/unsubstantiated benefit. For example, the American Medical Association (AMA) adopted a policy for its members that provides, in part:

[A] physician may lawfully use an FDA-approved drug product or medical device for an unlabeled indication when such use is based upon sound scientific evidence and sound medical opinion ...

[W]hen the prescription of a drug or use of a device represents safe and effective therapy, third party payors, including Medicare, should consider the intervention as reasonable and necessary medical care, irrespective of labeling, [and] should fulfill their obligation to their beneficiaries by covering such therapy.²⁷

FDA's stated policy and the AMA's ethical guidelines do not have the effect of law, however, and by themselves do not prevent third-party payors from attempting to deny payment for off-label use by designating it as "experimental." For example, some managed care organizations and private health insurers denied reimbursement for off-label use of drugs in oncology settings, designating the treatments experimental or investigational.²⁸ Congress began to address this issue for cancer drugs in the 1993 Omnibus Budget Reconciliation Act (OBRA), which expanded Medicare coverage for off-label use of anti-cancer drugs as long as the drugs were included in certain standard medical compendia.²⁹

Practitioners take some malpractice risk if something goes wrong with a prescribed off-label use. For example, if a patient suffers a serious adverse reaction to a drug taken for an unapproved use, the practitioner may have difficulty establishing that the treatment was within the standard of care. However, practitioners generally can point to good-faith reliance on FDA and AMA policies regarding off-label use as the basis for their actions.

27 Am. Med. Ass'n, Policy H-120.988: Patient Access to Treatments Prescribed by Their Physicians, available at www.ama-assn.org/ by using "Policy Finder".

28 Am. Soc'y of Clinical Oncology, *Reimbursement for Cancer Treatment: Coverage of Off-Label Drug Indications*, 24 J. CLIN. ONCOL. 3206 (2008).

29 *Id.*

In summary, although the practitioner prescribing off-label uses may be mostly free from FDA intervention, reimbursement and malpractice risks can be just as critical to the physician's practice.

FDA's position on what constitutes improper off-label promotion

As noted earlier, the most difficult task for a manufacturer is knowing what distinguishes direct or indirect promotion for off-label uses (which are not permitted by FDA) as opposed to communicating about off-label uses in a strictly non-promotional and scientific context (which is permitted commercial speech).

As noted above, FDA categorizes prohibited off-label marketing as violating statutory prohibitions against either misbranding (introducing into commerce devices or drugs lacking adequate directions for use)³⁰ or distributing unapproved new drugs under the FDCA.³¹ Under either theory, the main factual issue is whether the manufacturer is promoting an "intended use" for the device or drug that has not been approved by FDA.³²

According to FDA's interpretation, intended use refers to the manufacturer's objective intent, as determined by its expressions and the circumstances surrounding the distribution of the product. Thus, in FDA's view, not only product labeling, but also information disseminated by or on behalf of manufacturers in other contexts (e.g., scientific and educational meetings, symposia, reprints of journal articles, continuing medical education, etc.) can establish an intended use.³³ According to FDA, it is of no legal consequence if any information alleged to constitute off-label promotion by a manufacturer is truthful, fair, and balanced.³⁴ In FDA's view, it is legal for independent parties to disseminate the same type of information, and for providers to use such information in medical decision-making. Conversely, FDA takes the position that it is improper, and in certain instances even criminal, for drug manufacturers to disseminate that same truthful information. As discussed later in this article, however, court rulings based on manufacturers' First Amendment rights have tempered this FDA stance.

30 21 U.S.C. §§ 331(a), 331(b), 352(f)(1), 355(a); 21 C.F.R. §§ 201.5, 801.5.

31 21 U.S.C. § 331(d).

32 See 21 U.S.C. § 321(k)-(n).

33 21 C.F.R. §§ 201.128, 801.4; 62 Fed. Reg. 64074, 64075 (Dec. 3, 1997).

34 Of course, as a practical matter, if these were the only facts, the equities in favor of prosecution would be low. *But see* *United States v. Caputo*, 288 F. Supp. 2d 912, 920-23 (N.D. Ill. 2003), *cert. denied*, 77 U.S.L.W. 3197 (2008) (government could restrict dissemination of non-scientific, off-label information and other forms of off-label promotion because "permitting Defendants to engage in *all* forms of truthful, non-misleading promotion of off-label use would severely frustrate FDA's ability to evaluate the effectiveness of off-label uses." *Id.* at 922).

Enforcement Activities

At one time, enforcement of drug marketing was conducted primarily through the FDA in an administrative setting, with much of the focus on traditional labeling issues. This is no longer the case. Federal investigations are conducted jointly by agents of the FDA and the Department of Justice (DOJ). DOJ agents and prosecutors are fueled by their perception that enormous financial recoveries, including treble damages, can be—and have been—achieved through the vehicle of the False Claims Act.³⁵ The government’s legal argument is that off-label marketing, rather than independent medical judgment, “causes” the prescription of unapproved prescription drugs and therefore provider claims for federal reimbursement for off-label uses are “false” under the False Claims Act. In the government’s view, treble damages and an \$11,000 penalty *per claim* are due. With the “nuclear option” of potential federal program exclusion³⁶ or even criminal prosecution on the table, significant settlements, corporate Deferred Prosecution Agreements, and Corporate Integrity Agreements may appeal to manufacturers.

The consequences of criminal exposure can be severe—and difficult to prevent, even with a disciplined compliance program. Under the FDCA, for instance, a misdemeanor conviction does not require *any* proof of intent to defraud or mislead, essentially imposing strict liability for violations of the act. A misdemeanor conviction carries a maximum sentence of one year in jail plus a fine.³⁷ Felony liability under the FDCA, which does require proof of intent to defraud or mislead, carries a maximum sentence of five years in jail plus a fine.³⁸ If promotional practices can be shown to be *de facto* kickbacks to providers, e.g., payments to physician-speakers in amounts well above fair market value, then criminal liability under the federal Anti-Kickback Statute is possible as well.³⁹

35 31 U.S.C. § 3729(a); 64 Fed. Reg. 47099, 47104 at § 85.3(a)(9) (Aug. 30, 1999).

36 42 U.S.C. § 1320a-7.

37 21 U.S.C. § 333(a)(1).

38 21 U.S.C. § 333(a)(2).

39 The corporate penalties for a federal Anti-Kickback Statute (AKS) violation include a \$500,000 fine plus restitution and a probable corporate integrity/compliance plan as a condition of probation. 42 U.S.C. § 1320a-7b(b)(2)(A); 18 U.S.C. § 3571. Violations also may result in the imposition of civil monetary penalties, 42 U.S.C. § 1320a-7a(a)(7), and, most significantly, program exclusion for the provider. 42 U.S.C. § 1320a-7. For individual offenders, maximum criminal penalties are set by statute; actual prison sentences are set by federal Sentencing Guidelines. The maximum individual criminal penalty for just one healthcare-related kickback is five years in jail and a \$250,000 fine. 42 U.S.C. § 1320a-7b(b); 18 U.S.C. § 3571.

Global criminal and civil resolutions

Since about 1999, the law enforcement community, which once limited its off-label investigations to sales of dubious “snake oils,” has focused on pharmaceutical manufacturers—both large and small. The following is a discussion of the major settlements that provide the backdrop for today’s investigations.

Cephalon: Actiq[®], Provigil[®], Gabitril[®] (E.D. Pa.)

In November 2007, Cephalon pleaded guilty to a misdemeanor violation of the FDCA and entered into a \$425 million settlement with the government to resolve an investigation into off-label marketing of Actiq, a berry-flavored lollipop narcotic approved for pain relief in connection with cancer treatments.⁴⁰ The investigation was initially triggered by the death of a 20-year-old woman who overdosed, and it was spurred by Cephalon’s use of aggressive marketing tactics of Actiq.⁴¹ According to the Connecticut Attorney General, Cephalon engaged in “questionable” practices to increase sales of Actiq. Alleged marketing activities that caused concern included:

- Setting high sales quotas and encouraging prescriptions with larger doses. Specifically, although the Actiq label says patients initially should be prescribed no more than six lollipops containing a 200-microgram dose of fentanyl (the smallest of six possible dosages) to minimize the risk of overdosing, Cephalon allegedly encouraged doctors to start patients on 24 lollipops containing 400 micrograms of fentanyl each.
- Targeting non-cancer doctors, especially neurologists, with small medical studies done without control group data, suggesting that Actiq could be used to treat migraine headaches and back pain. Internal Cephalon marketing documents encouraged sales reps to refer to Actiq as an “ER” on a stick.
- The authors of the studies were paid lecturers for Cephalon, and were flown into seminars to present their “findings.”
- The use of free Actiq coupons for doctors who were not cancer doctors and who stated that they were unlikely to treat a cancer patient.

40 See Stephen McGuire, *Cephalon Pays \$425 Million to Settle Claims of Off-Label Marketing*, MED. MARKETING & MEDIA, NOV. 12, 2007, available at www.mmm-online.com/Cephalon-pays-425-million-to-settle-claims-of-off-label-marketing/article/96321/. The investigation and resolution also covered aggressive off-label marketing tactics in connection with two other Cephalon drugs, the narcolepsy pill Provigil and the epilepsy treatment Gabitril.

41 FDA approved Actiq in 1998 for use by cancer patients who suffer intense pain for which other narcotics proved ineffective. Surveys suggested that more than 80% of patients who use the drug do not have cancer.

Because of Cephalon's aggressive marketing tactics, doctors prescribed the fentanyl-based narcotic to relieve non-cancer related pain, such as migraine headaches and back pain. The ever-increasing use of Actiq concerned doctors and government regulators because of the highly addictive nature of fentanyl.⁴² Besides the guilty plea to a single misdemeanor charge and \$425 million settlement, the Office of the Inspector General for the Department of Health and Human Services (HHS-OIG) imposed a Corporate Integrity Agreement on Cephalon. Although the settlement resolved the federal investigation into Cephalon's marketing practices, a statement issued at the time of the settlement by the Connecticut Attorney General's Office, which also had been investigating Cephalon for off-label marketing, indicated that the Connecticut investigation would continue.

*Specialty Distribution Services (SDS): Human Growth Hormone (HGH)
(D. Mass.)*

In September 2007, SDS, a subsidiary of Express Scripts, admitted that it had distributed HGH for purposes other than those approved by FDA.⁴³ The distribution of anabolic steroids and/or human growth hormone for muscle enhancement purposes may involve conduct designed both to defraud the United States and to violate federal law.⁴⁴ Since 1938, federal law has prohibited the distribution of anabolic steroids and/or human growth hormone outside a legitimate doctor-patient relationship.⁴⁵ In addition, prescription drugs such as anabolic steroids and/or human growth hormone can be legally distributed only in those instances in which a physician, based upon an individualized determination of a proper course of treatment, authorizes the drug's distribution to a patient under his or her supervision.⁴⁶ Distribution of

42 See Actiq label, available at www.fda.gov/cder/foi/label/2007/020747s0271bl.pdf.

43 Associated Press, *Firm Must Pay Fine, Cooperate with Ongoing Investigations*, ESPN, Sept. 19, 2007, available at <http://sports.espn.go.com/espn/news/story?id=3025958> [hereinafter *Associated Press*]; Michael S. Schmidt, *Company Agrees to a Fine Over Shipments of H.G.H.*, N.Y. TIMES, Sept. 19, 2007, available at www.nytimes.com/2007/09/19/sports/othersports/19doping.html [hereinafter *Schmidt*].

44 UNITED STATES ATTORNEYS' MANUAL, CIVIL RESOURCE MANUAL, § 19, HUMAN GROWTH HORMONE/STEROID STATUTORY OVERVIEW, available at www.usdoj.gov/usao/eousa/foia_reading_room/usam/title4/civ00019.htm [hereinafter *UNITED STATES ATTORNEYS' MANUAL*].

45 *Id.*

46 See *DeFreese v. United States*, 270 F.2d 730, 733 & n.5 (5th Cir. 1959), *cert. denied*, 80 S. Ct. 810 (1960); *Brown v. United States*, 250 F.2d 745, 746-47 (5th Cir. 1958), *cert. denied*, 78 S. Ct. 779 (1958); see also *United States v. Zwick*, 413 F. Supp. 113, 115 (N.D. Ohio 1976) (holding that it is not proper for the physician dispensing and prescribing anorectic controlled drugs to adopt a unitary approach to the treatment of obesity in that no standard approach to treatment exists).

these drugs outside these restrictions has resulted in the prosecution and conviction of laypersons, pharmacists, and physicians.⁴⁷

In 1990, Congress amended the FDCA in an effort to crack down on illegal use of anabolic steroids, particularly HGH.⁴⁸ Specifically, Congress enacted higher criminal penalties for offenses involving the illegal distribution of anabolic steroids and HGH. This new legislation, enacted as part of the Anabolic Steroids Control Act,⁴⁹ resulted in a reconfiguration of the statutory scheme regulating the distribution of both anabolic steroids and HGH. The act reclassified anabolic steroids as Schedule III controlled substances.⁵⁰ It also amended the FDCA to criminalize, as a five-year felony, the distribution and possession with intent to distribute of human growth hormone

for any use ... other than the treatment of a disease or other recognized medical condition, where such use has been authorized by the Secretary of Human Services ... and pursuant to the order of a physician⁵¹

The amended FDCA makes the prosecution of HGH off-label cases different from that of other drugs, because doctors may not prescribe HGH for any reason other than to treat a disease or other recognized medical condition. According to the *United States Attorneys' Manual*, prosecuting for the distribution of human growth hormones is different from prosecuting virtually any other drug distribution under the FDCA. For example, proof of interstate distribution is unnecessary. Additionally, the *mens rea* requirement for a felony is "knowing distribution" or "knowing possession with intent to distribute," not "intent to defraud or mislead."⁵² Thus, prosecuting non-physicians, including manufacturers, for distributing HGH is akin to prosecuting a narcotics case under the Controlled Substances Act. As a result, establishing liability in such cases is simpler than for other FDCA offenses.⁵³

It is in this context that SDS entered into a Deferred Prosecution Agreement with the U.S. Attorney's Office for the District of Massachusetts. As part of the deal, SDS paid the government \$10.5 million and agreed to cooperate with the government investigation for the

47 See, e.g., *United States v. Shields*, 939 F.2d 780 (9th Cir. 1991), *superseded after remand* by *United States v. Von Mitchell*, 984 F.2d 338 (9th Cir. 1993); *United States v. Siler Drug Store*, 376 F.2d 89 (6th Cir. 1967); *DeFreese v. United States*, 270 F.2d 730, 733 & n.5 (5th Cir. 1959), *cert. denied*, 80 S. Ct. 810 (1960); *Brown v. United States*, 250 F.2d 745, 746-47 (5th Cir. 1958), *cert. denied*, 78 S. Ct. 779 (1958).

48 See 21 U.S.C. § 333(e).

49 Pub. L. No. 101-647, tit. XIX, §§ 1901-05.

50 See 21 U.S.C. § 812(c).

51 *Id.* § 333(e)(1).

52 UNITED STATES ATTORNEYS' MANUAL, at § B.

53 *Id.*

next three years. Although not as large as other off-label marketing settlements, this case is notable for two reasons: (1) it exemplifies the extreme regulatory position in the off-label context; and (2) several professional athletes and entertainers have been accused of abusing HGH for cosmetic or performance enhancement purposes—the Massachusetts investigation arose out of SDS’s deliveries of HGH to a prominent Boston athlete in 2002 and 2003.⁵⁴

Orphan Medical: Xyrem® (E.D.N.Y)

In July 2007, Orphan Medical, collectively with its parent corporation, Jazz Pharmaceuticals, resolved an Eastern District of New York off-label investigation by pleading guilty to a felony charge of misbranding in violation of 21 U.S.C. Sections 331(a) and 333(a)(2) and agreeing to pay nearly \$20 million in fines and penalties.⁵⁵ The settlement resulted from the government’s investigation arising out of a qui tam action brought by a former Orphan Medical sales representative. This case is notable because it involved the illegal marketing of Xyrem, also known as gamma-hydroxybutyrate or GHB, the highly controversial drug commonly known as the “date rape drug.” Orphan Medical reportedly marketed the drug for numerous unapproved uses, including fatigue, pain, and psychiatric disorders.

Xyrem was approved in 2002 for cataplexy, a condition characterized by weak or paralyzed muscles in connection with narcolepsy. In 2005, Xyrem was approved for a condition known as Excessive Daytime Sleepiness, or EDS. In pleading guilty to the felony misbranding charge, Orphan admitted that it paid a psychiatrist tens of thousands of dollars to give seminars around the country to promote Xyrem for off-label uses. FDA required black-box warnings on the label, stating that Xyrem’s safety had not been established for children and that there was only limited data for elderly patients. Despite that, an Orphan-paid psychiatrist allegedly told his audiences that Xyrem was safe to prescribe to children and the elderly.⁵⁶ The psychiatrist, with the full

54 *Associated Press; Schmidt*. In an unrelated investigation out of Albany, New York, the Albany County District Attorney’s Office investigated and charged Specialty Pharmacy, an Orlando, Florida business, and its corporate officials with illegally dispensing performance-enhancing drugs to professional athletes. *Schmidt*.

55 Press Release, U.S. Attorney’s Office for the E. Dist. of N.Y., Jazz Pharmaceuticals, Inc. Agrees to Pay \$20 Million to Resolve Criminal and Civil Allegations in “Off-Label” Marketing Investigation (July 13, 2007), available at www.drugs.com/news/jazz-pharmaceuticals-inc-agrees-pay-20-million-resolve-criminal-civil-allegations-off-label-6486.html.

56 *Id.*; see also Press Release, U.S. Attorney’s Office for the E. Dist. of N.Y., Psychiatrist Charged with Conspiracy to Illegally Market the Prescription Medication Xyrem, Also Known as “GHB,” for Unapproved Medical Uses on Behalf of Its Manufacturer (Apr. 5, 2006), available at www.usdoj.gov/usao/nye/pr/2006/2006apr05.html [hereinafter *Press Release, U.S. Attorney’s Office for the E. Dist. of N.Y.*].

knowledge and approval of Xyrem's sales force, made other misleading statements, including minimizing the potential side effects and dangers of overdose. This paid surrogate even suggested that GHB was not really the date rape drug. The government alleged that in conjunction with his off-label promotion, the psychiatrist, with the knowledge of Orphan representatives, advised doctors how to bill to conceal the off-label uses and thus ensure reimbursement from insurers.

Xyrem sales representatives allegedly used the psychiatrist in connection with efforts to promote Xyrem for a number of off-label uses, including fatigue, insomnia, chronic pain, EDS (prior to its approval), weight loss, depression, bi-polar disorders, and movement disorders such as Parkinson's Disease. Orphan allegedly sent drug representatives across the country to visit doctors who did not specialize in treating narcolepsy. Orphan rewarded physicians who were prescribing Xyrem, and made unrestricted educational grants to induce physicians to prescribe Xyrem for off-label uses. Xyrem representatives also disseminated written materials relating to off-label uses of Xyrem that did not meet FDA standards.

Orphan/Jazz pleaded guilty to a felony violation of the FDCA and agreed to pay \$5.5 million in criminal penalties, \$12.2 million in reimbursement to private and public health insurers to cover payments for off-label scripts, and \$3.75 million to resolve the government's civil False Claims Act case. Jazz also entered into a five-year Corporate Integrity Agreement with the OIG.⁵⁷ In addition, a former Orphan sales manager pleaded guilty to a single felony count of introducing a misbranded drug into interstate commerce, and the paid psychiatrist was indicted on conspiracy charges. The psychiatrist, Dr. Peter Gleason, referred to as a "carnival snake oil salesman" by the prosecutors, has responded to the indictment by fighting the charges and insisting that Xyrem is both safe and effective for off-label uses.⁵⁸ Dr. Gleason also claims that the federal charges are unconstitutional because they violate his free speech rights.

Purdue Frederick Company: OxyContin® (W.D. Va.)

In May 2007, the Purdue Frederick Company, as well as its president, chief legal officer, and former chief medical officer, pleaded guilty to charges of misbranding with intent to mislead under the provisions of

57 A copy of the Jazz Corporate Integrity Agreement can be found at www.oig.hhs.gov/fraud/cia/agreements/Jazz%20CIA.pdf.

58 Press Release, U.S. Attorney's Office for the E. Dist. of N.Y.

the FDCA.⁵⁹ Although the company pleaded guilty to a felony charge, the individual corporate officials pleaded guilty to misdemeanor charges. The investigation stemmed from the company's fraudulent marketing of OxyContin. The company's liability stemmed from false claims that OxyContin was less addictive, less subject to abuse, and less likely to cause withdrawal symptoms than other pain relievers; FDA had vetted none of these statements. According to the investigation, the use of OxyContin may have contributed to a number of deaths. Purdue misbranded OxyContin as follows:

- Using various visual aids and training materials, Purdue sales representatives fraudulently told healthcare providers that OxyContin was less likely to be abused and was less addictive because OxyContin had a less euphoric effect than short-acting opioids. These presentations also were used in role-play training at Purdue's headquarters.
- Despite information suggesting that OxyContin was addictive even at low doses, Purdue supervisors and employees drafted an article about a study on the use of OxyContin in osteoarthritis patients that suggested OxyContin was not addictive and could be stopped abruptly without any negative effects. Purdue sales representatives were encouraged to use the published article as part of their marketing efforts.
- Purdue sales representatives falsely led providers to believe that the delayed release of OxyContin made it less euphoric and therefore less addictive and less likely to be abused. The false statements were based on language in the package insert stating, "Delayed absorption, as provided by OxyContin tablets, is believed to reduce the abuse liability of a drug."⁶⁰ Supervisors told sales representatives they could tell healthcare providers that OxyContin potentially creates less chance for addiction than immediate-release opioids, ignoring reports of OxyContin abuse and diversion.

59 Press Release, U.S. Attorney's Office for the W. Dist. of Va., The Purdue Frederick Company, Inc. and Top Executives Plead Guilty to Misbranding OxyContin; Will Pay Over \$600 Million (May 10, 2007), *available at* www.usdoj.gov/usao/vaw/press_releases/purdue_frederick_10may2007.html. Purdue, through its own press release, emphasized that the misbranding charges did not mean that FDA-approved prescribing information was incorrect, but only that statements of some employees went beyond the approved FDA information in promoting OxyContin to some healthcare professionals. See Press Release, Purdue Pharma L.P., Purdue Pharma L.P.'s Agreement with the Government, *available at* www.purduepharma.com/pressroom/news/wdvaresolution/Terms_of_WDVA_Agreement.pdf.

60 FDA, LCDR Kristina C. Arnwire, Acting Team Leader, Div. of Medication Error Prevention, Office of Surveillance & Epidemiology, Reported Manipulation of OxyContin Tablets (May 5, 2008), *available at* www.fda.gov/ohrms/dockets/ac/08/slides/2008-4356s1-04-FDA-corepresentations.ppt.

The price to settle the OxyContin charges was substantial; the company and the individuals paid more than \$634 million in fines, penalties, and civil settlements. Specifically, pursuant to the plea agreements, \$276.1 million was forfeited to the federal treasury, \$160 million was paid to Medicaid-participating states, \$130 million was set aside for liability to private payors, \$5.3 million was paid to the Virginia Attorney General's Medical Fraud Control Unit to fund future fraud investigations, and \$20 million was paid to the Virginia Prescription Monitoring Program. The company also entered into a Corporate Integrity Agreement⁶¹ requiring it to implement an effective compliance program and engage an independent review organization to monitor the company's compliance for five years.

Pharmacia & Upjohn Company: Genotropin® (D. Mass.)

In April 2007, Pharmacia entered into a three-year Deferred Prosecution Agreement regarding an off-label matter and paid the government \$15 million.⁶² Like the SDS case described above, Pharmacia had promoted its drug Genotropin, a Human Growth Hormone, for off-label uses such as anti-aging, cosmetic, or other athletic performance enhancement purposes. Pharmacia's conduct was brought to the federal government's attention through a disclosure by Pfizer, Pharmacia's parent company.⁶³ Pfizer disclosed the conduct, which predated Pfizer's acquisition of Pharmacia. This case illustrates that acquisitions can lead to off-label disclosures and investigations—the fact that the new owner did not engage in unlawful conduct did not insulate the new owner from liability.

InterMune: Actimmune® (N.D. Cal.)

In October 2006, InterMune entered into a Deferred Prosecution Agreement, as well as a five-year Corporate Integrity Agreement with the OIG related to its marketing of Actimmune for the treatment of

61 A copy of the Purdue Corporate Integrity Agreement can be found at www.oig.hhs.gov/fraud/cia/docs/CIAPurdue.pdf.

62 See Press Release, U.S. Attorney's Office for the Dist. of Mass., Pfizer Subsidiary Agrees to Plead Guilty for Offering Kickback and Pay \$19.68 Million Criminal Fine; Second Subsidiary Agrees to Pay Additional \$15 Million Penalty to Resolve Allegations of Illegal Promotion of Human Growth Hormone (Apr. 2, 2007), available at <http://boston.fbi.gov/dojpressrel/pressrel07/kickbackplea040207.htm>. A related company, Pharmacia & Upjohn Company, Inc., was involved in a concurrent anti-kickback investigation. The anti-kickback side of the case, which dealt with Pharmacia's contract with a patient assistance program manager, resulted in a felony guilty plea, an additional criminal fine of \$19.7 million, and the permanent exclusion of that Pharmacia company from all federal healthcare programs. *Id.*

63 Press Release, Pfizer NV/SA, Pharmacia Subsidiaries Reach \$34.7 Million Settlement with DOJ and Resolve Allegations of Improper Activities Prior to Acquisition by Pfizer (Apr. 2, 2007), available at www.pfizer.be/Media/Press+bulletins/In+General/Pharmacia+subsidiaries+reach+settlement+with+DOJ.htm.

idiopathic pulmonary fibrosis (IPF), a fatal disease.⁶⁴ Actimmune had been approved by FDA only for the treatment of chronic granulomatous disease⁶⁵ and malignant osteopetrosis,⁶⁶ not IPF. InterMune's marketing materials included press releases touting clinical trial results tending to indicate that Actimmune benefited patients with IPF. According to the government, however, these clinical trials did not demonstrate any statistically significant benefit. InterMune paid nearly \$37 million (roughly \$30 million to the federal government and almost \$7 million to state governments) to settle the matter.

More recently, in March 2008, the government indicted former InterMune CEO Scott Harkonen on charges of wire fraud and felony violations of the FDCA for his role in the off-label marketing of Actimmune.⁶⁷ Specifically, the government alleged that Harkonen, as a doctor and chief executive officer of InterMune, directed that Actimmune be marketed to treat IPF. In marketing Actimmune for this unapproved treatment, Harkonen claimed that Actimmune was safe and effective for use in treating IPF. More problematic was Harkonen's claim that Actimmune helped IPF patients live longer by reducing mortality by up to 70%, a claim without FDA-approved support. According to the indictment, Harkonen and other InterMune executives were told explicitly that it was unlikely FDA would approve Actimmune for the treatment of IPF given the failure of InterMune's studies to show that it was effective for IPF. It cost \$50,000 to treat an IPF patient for one year with Actimmune, and prescriptions to treat patients with IPF generated the vast majority of Actimmune sales. Thus, considerable sales were falsely billed, increasing the risk of enforcement.

*Schering Sales Corporation and Schering-Plough Corporation:
Temodar[®], Intron[®] A (D. Mass.)*

One off-label settlement that has provoked some criticism due to its potential impact on the dissemination of scientific data about potentially beneficial off-label uses of drugs is the March 2008 settlement between Schering Sales Corporation and the government. Schering pleaded guilty to a felony conspiracy to make false statements to FDA

64 Press Release, U.S. Dep't of Justice, Biopharmaceutical Firm InterMune to Pay U.S. Over \$36 Million for Illegal Promotion and Marketing of Drug Actimmune (Oct. 26, 2006), available at www.usdoj.gov/opa/pr/2006/October/06_civ_728.html. A copy of the InterMune Corporate Integrity Agreement can be found at www.oig.hhs.gov/fraud/cia/docs/InterMuneCIA.pdf.

65 Chronic granulomatous disease is a hereditary disease that impairs the function of white blood cells in the immune system.

66 Malignant osteopetrosis is a hereditary disease that adversely affects bone development and function.

67 Press Release, U.S. Dep't of Justice, Former InterMune CEO W. Scott Harkonen Indicted for Wire Fraud and FDA Violations (Mar. 18, 2008), available at www.usdoj.gov/opa/pr/2008/March/08_civ_217.html.

and the Health Care Financing Administration involving among other things, off-label promotion of Temodar and Intron A.⁶⁸ The underlying investigations were initiated as a result of three qui tam actions. The Schering companies paid a combined total of \$435 million to settle the civil qui tam and criminal investigations against them, and Schering Sales Corporation was permanently excluded from participating in federal healthcare programs.

The off-label portion of these federal investigations stemmed from the marketing of Temodar and Intron A for unapproved uses.⁶⁹ Specifically, Temodar was developed and approved for a particular type of brain cancer resistant to other drugs. Schering, however, allegedly marketed Temodar for other uses, including other brain cancers and cancers that had spread to other parts of the body. Similarly, Schering allegedly promoted the use of Intron A for the treatment of certain superficial bladder cancers when it was approved only for use in treating Hepatitis C, AIDS-related Kaposi's sarcoma, melanoma, and lymphoma.

The government's allegations centered on direct statements made by Schering officials to FDA designed to reassure the agency that certain off-label promotional activities of Schering sales representatives were an isolated occurrence. However, the off-label promotion of Temodar and Intron A allegedly were directed from headquarters as part of a national corporate marketing plan.⁷⁰ The government further alleged that Schering later made statements to FDA causing the agency to believe that Schering was addressing this illegal conduct when it was expecting to pursue a national marketing strategy based on promoting off-label usage of these drugs.⁷¹

68 Press Release, U.S. Attorney's Office for the Dist. of Mass., Schering to Pay \$435 Million for the Improper Marketing of Drugs and Medicaid Fraud (Aug. 29, 2006), available at <http://www.usdoj.gov/usao/ma/Press%20Office%20-%20Press%20Release%20Files/Schering-Plough/press%20release.pdf> [hereinafter *U.S. Attorney's Office for the Dist. of Mass.*]. The settlement also required Schering to enter into an agreement to augment its existing Corporate Integrity Agreement. See Addendum to the Corporate Integrity Agreement Between the Office of Inspector General of the Department of Health and Human Services and Schering-Plough Corporation (Aug. 25, 2006), available at www.oig.hhs.gov/fraud/cia/agreements/Schering_Plough_Corporation_08252006_addendum.pdf. Subsequent to the settlements with the government, Schering became involved in several class action lawsuits arising in part out of the company's alleged off-label marketing practices. See Charles Toutant, *Schering-Plough Defends Suits Over Marketing of "Off Label" Drug Uses*, N.J. L. J., Aug. 31, 2007, available at www.law.com/jsp/article.jsp?id=1188464549972.

69 The other object of the federal investigations involved a non-off-label issue related to allegations of Medicaid fraud associated with the pricing of Schering's Claritin RedTabs.

70 *U.S. Attorney's Office for the Dist. of Mass.*

71 *Id.*

The Schering national marketing plan for Temodar and Intron A sought to induce doctors to prescribe these drugs for unapproved off-label uses through various strategies, including

- sham advisory boards,
- improper preceptorships,
- lavish entertainment, and
- improper distribution of peer reviewed clinical trials.

It is the last point that has been a source of frustration for critics of off-label prosecution. Whether there is reliable scientific data supporting the off-label use of Temodar and Intron A is of no import to the government. However, to the extent that the settlement results in a decrease in treatment with drugs that have some supported benefit for off-label uses, the government could be construed as chilling this beneficial use.⁷² Critics of the government's approach argue that, to the extent that sales remain the same or grow, Schering's conduct does not appear to have been material to the overall sales of Temodar and Intron A.⁷³ The crux of this argument is based on free speech rights.

Eli Lilly: Evista® (S.D. Ind.)

The December 2005 Eli Lilly settlement further highlights that companies cannot market drugs for off-label uses even if scientific data support those uses. Eli Lilly pleaded guilty to a misdemeanor violation of the FDCA and paid \$36 million to the government: \$24 million in equitable disgorgement tied to a consent decree of permanent injunction, \$6 million in a criminal fine, and \$6 million in asset forfeiture.⁷⁴ The settlement ended the government's investigation into Eli Lilly's marketing of the osteoporosis drug Evista for off-label uses. Specifically, Eli Lilly allegedly promoted Evista for preventing and reducing the risk of breast cancer and reducing the risk of heart disease, both off-label uses. (Ironically, in late 2007, FDA approved Evista for use as a breast cancer preventative.⁷⁵)

Evista's brand team allegedly engaged in off-label promotion after FDA initially rejected proposed labeling concerning use of the drug to prevent breast cancer. According to the government's investigation,

72 *Critics Blast Off-Label Component of Schering-Plough's Global Settlement*, 5 RX COMPLIANCE REP., Oct. 4, 2006, at 6, available at www.wlf.org/upload/100406rxcomp.pdf.

73 *Id.*

74 Press Release, U.S. Dep't of Justice, Eli Lilly and Company to Pay \$36 Million Relating to Off-Label Promotion (Dec. 21, 2005), available at www.usdoj.gov/opa/pr/2005/December/05_civ_685.html.

75 *FDA Approves Eli Lilly's Osteoporosis Drug Evista to Prevent Breast Cancer*, *Company Says*, MED. NEWS TODAY, Sept. 19, 2007, available at www.medicalnewstoday.com/articles/82754.php.

the Evista brand team resorted to the off-label strategy after disappointing revenues for Evista's first year. Some of the alleged sales tactics employed by the Evista sales representatives included:

- Personal one-on-one sales pitches regarding potential off-label uses of Evista, where sales personnel asked "bait" questions to trigger an inquiry from the doctor regarding unapproved off-label uses.
- Sales representatives sending unsolicited letters to physicians on their sales routes touting Evista's potential efficacy for unapproved uses.
- Organizing a "market research summit" where Evista was discussed with doctors for unapproved off-label uses, including the prevention of breast cancer.
- Producing and distributing a promotional video demonstrating "Evista Best Practices," in which Evista sales representatives explicitly state that Evista is the best drug for preventing osteoporosis (its approved use), as well as for preventing breast cancer and heart disease (off-label uses).
- Training Evista sales representatives to use reprinted medical articles to unfairly highlight the results of using Evista to treat unapproved indications by hiding the disclosure page that revealed that the article's authors were employed by Eli Lilly and that Evista's effectiveness in reducing the risk of breast cancer had not yet been established.

In addition to pleading guilty to misdemeanor charges of misbranding, Eli Lilly agreed to a civil consent decree that required equitable disgorgement of \$24 million. The terms of the consent decree and permanent injunction are similar to a Corporate Integrity Agreement in that they require Eli Lilly to refrain from promoting Evista for off-label uses, to implement compliance procedures, and to hire an independent review organization to monitor Eli Lilly's compliance with the terms of the decree. Thus, even if the drug's off-label claims are accurate, a company runs a significant risk when marketing its drug for an off-label indication before FDA approves the drug for that use.

Serono Labs: Serostim[®] (D. Mass.)

Serono Labs pleaded guilty to felony criminal charges in connection with its AIDS wasting drug Serostim in October 2005.⁷⁶ The case was not a strict off-label marketing case; rather, Serono pleaded guilty

⁷⁶ Press Release, U.S. Dep't of Justice, Serono to Pay \$704 Million for the Illegal Marketing of AIDS Drug (Oct. 17, 2005), available at www.usdoj.gov/opa/pr/2005/October/05_civ_545.html.

to conspiring with medical device manufacturer, RJL Sciences,⁷⁷ to market RJL's bioelectrical impedance analysis (BIA) computer software for use in calculating body cell mass and diagnosing AIDS wasting—uses for which the FDA had not approved the software. Serono had experienced a decline in Serostim sales because of the market introduction of protease inhibitors (protease inhibitors are a mainstay of HIV anti-viral therapy and can help reduce the effects of AIDS wasting).⁷⁸ Serono partnered with RJL to market RJL's product as a means of diagnosing AIDS wasting by calculating body cell mass. The purpose of the agreement, from Serono's perspective, was to increase the overall patient base diagnosed with AIDS wasting and thereby boost Serostim sales. AIDS wasting however, is not diagnosed by body cell mass but by changes in weight and lean body mass. Serono paid a total of \$704 million to the government: a \$137 million criminal fine and \$567 million to settle civil liabilities. Further, Serono agreed to be excluded from all federal healthcare programs for five years and to enter into a Corporate Integrity Agreement⁷⁹ with HHS. Serono Labs and its related companies settled a civil class action suit related to Serostim for \$24 million in late 2007. This case illustrates that the government will not limit enforcement discretion to traditional "marketing" activities.

Warner-Lambert Company: Neurontin® (D. Mass.)

In May 2004, Warner-Lambert pleaded guilty to a felony violation of the FDCA and paid the government \$430 million to settle the investigation related to Warner-Lambert's marketing of the anti-seizure drug Neurontin.⁸⁰ (This settlement was in addition to the settlement of the civil False Claims Act case instituted by qui tam relator David Franklin highlighted in the Introduction to this article.) The company allegedly marketed Neurontin for a number of unapproved uses, including bipolar disorder, pain disorders, amyotrophic lateral sclerosis, attention deficit disorder, migraines, withdrawal-related seizures, restless leg syndrome, and as a first-line, isolated treatment for epilepsy.

77 RJL and its president had pleaded guilty for their role in the conspiracy in April 2005. See William M. Bulkeley, *RJL Sciences and Its President Plead Guilty in Medical-Device Case*, WALL ST. J., Apr. 20, 2005, available at www.aegis.com/news/wsj/2005/wj050408.html.

78 William A. McGrath, *Serono Settlement Should Highlight Need for Compliance, Not Chill Legitimate Off-Label Communication*, 13 FDA ADVERTISING & PROMOTION, Dec. 2005, at 14, available at www.wileyrein.com/docs/publications/12471.pdf.

79 A copy of the Serono Corporate Integrity Agreement can be found at www.oig.hhs.gov/fraud/cia/agreements/SeronoHoldings_101405.pdf.

80 Press Release, U.S. Dep't of Justice, Warner-Lambert to Pay \$430 Million to Resolve Criminal & Civil Health Care Liability Relating to Off-Label Promotion (May 13, 2004), available at www.usdoj.gov/opa/pr/2004/May/04_civ_322.htm. A copy of the Warner-Lambert settlement agreement can be found at www.usdoj.gov/civil/foia/elecread/2004/Warner-Lambert%202004.pdf.

Among the numerous off-label marketing practices in which Warner-Lambert allegedly engaged, the company:

- Promoted Neurontin for use as a sole drug in the treatment of epileptic seizures, even though FDA had rejected the monotherapy indication;
- Promoted Neurontin for the treatment of bipolar disease, even though a scientific study had not demonstrated efficacy against a placebo;
- Encouraged sales representatives to proactively pitch Neurontin for off-label uses to physicians;
- Through its sales representatives, made false or misleading statements about FDA approval of Neurontin in response to physician questions; and
- Used sham consultants' meetings and sham independent medical education to promote Neurontin for off-label uses.

The \$430 million settlement was comprised of \$240 million in a criminal fine, \$83.6 million (plus interest) in False Claims Act liability, and \$106.4 million in state Medicaid and consumer fraud liabilities. Pfizer, which had acquired Warner-Lambert after the charged off-label marketing occurred, entered into a Corporate Integrity Agreement⁸¹ to ensure that the compliance program it had implemented upon acquiring the company would continue to be effective.

Genentech: Protropin® (N.D. Cal.)

In April 1999, Genentech reached a settlement agreement with the government regarding marketing of the HGH Protropin, which FDA had approved for treating children with growth hormone deficiency.⁸² In the settlement, Genentech pleaded guilty to a misdemeanor violation of the FDCA, paid a \$30 million criminal fine, and paid an additional \$20 million in civil restitution to Medicaid and CHAMPUS (a federal military insurance program) for improper reimbursements. Further, the company admitted that it had marketed the drug for off-label uses, including for use in children who were short but not growth hormone deficient, children with a certain form of juvenile obesity, and some burn victims. As an additional component of the settlement,

81 A copy of the Pfizer Corporate Integrity Agreement can be found at www.oig.hhs.gov/fraud/cia/agreements/pfizer_5_11_2004.pdf.

82 See *Genentech Confirms Settlement Agreement with U.S. Government*, BUSINESS WIRE, Apr. 14, 1999, available at http://findarticles.com/p/articles/mi_m0EIN/is_1999_April_14/ai_54376955; Tamar Nordenberg, *Maker of Growth Hormone Feels Long Arm of Law*, FDA CONSUMER, Sept. 1999, available at http://findarticles.com/p/articles/mi_m1370/is_5_33/ai_55928683.

the government acknowledged that the off-label marketing of Protopin had occurred from 1985 to 1994, and ceased in 1994 after the company implemented stricter compliance and training programs.

Civil Settlements

In certain instances where intent rises only to the level of “reckless disregard” or “deliberate ignorance,” the government enters civil resolutions that do not globally resolve all potential claims. These cases address the same promotional conduct and usually involve a Corporate Integrity Agreement.

Bristol-Myers Squibb Company (BMS) and Otsuka America Pharmaceutical: Abilify® (D. Mass. & S.D. Fla.)

In September 2007, BMS entered into a civil settlement agreement to pay \$515 million to settle a wide range of government investigations dating back as far as 1994⁸³ that included alleged off-label promotion of Abilify. FDA approved Abilify, an atypical anti-psychotic drug, for the treatment of adult schizophrenia and bi-polar disorder. Abilify carried a black box warning regarding use in treating dementia-related psychosis. The government alleged that notwithstanding lack of FDA approval for pediatric and geriatric patients, BMS instructed its sales force to call on child psychologists and pediatricians to promote Abilify for the treatment of dementia and psychosis. Allegedly, BMS also created a specialized sales force designed to service nursing homes and long-term care facilities, where dementia is much more widespread than the approved conditions of schizophrenia and bi-polar disorder. Of the \$515 million BMS paid, \$328 million went to the federal treasury, of which \$25 million represented disgorgement of profits allegedly derived from off-label marketing of Abilify. More than \$187 million went to Medicaid-participating states.⁸⁴ In addition, BMS agreed to enter a five-year Corporate Integrity Agreement⁸⁵ with HHS-OIG.

83 Press Release, U.S. Dep’t of Justice, Bristol-Myers Squibb to Pay More Than \$515 Million to Resolve Allegations of Illegal Drug Marketing and Pricing (Sept. 28, 2007), available at www.usdoj.gov/opa/pr/2007/September/07_civ_782.html. This settlement resolved seven qui tam actions filed in Massachusetts and Florida. Other components of the settlement involved investigations into the pricing of BMS drugs and remuneration offered to physicians to induce them to write prescriptions for BMS drugs.

84 In March 2008, shortly after the BMS settlement, Otsuka, which had partnered with BMS to co-promote Abilify, settled its case with the government related to the off-label marketing for \$4 million. Press Release, U.S. Dep’t of Justice, Otsuka to Pay More than \$4 Million to Resolve Off-Label Marketing Allegations Involving Abilify (Mar. 27, 2008), available at www.usdoj.gov/opa/pr/2008/March/08_civ_244.html.

85 A copy of the BMS Corporate Integrity Agreement can be found at www.oig.hhs.gov/fraud/cia/agreements/BMS_CIA.pdf. Otsuka also entered into a Corporate Integrity Agreement, which can be found at www.oig.hhs.gov/fraud/cia/agreements/otsuka_america_pharmaceutical_inc_03252008.pdf.

Cell Therapeutics (CTI): Trisenox® (W.D. Wash.)

In April 2007, CTI settled an off-label marketing investigation related to their anti-cancer drug Trisenox.⁸⁶ The investigation was triggered by a qui tam action alleging Trisenox was promoted and prescribed to treat patients with cancers for which Trisenox was not an approved treatment. FDA approved Trisenox A in 2000 for the limited use of treating patients with acute promyelocytic leukemia, which affects approximately 400 people annually. According to the qui tam allegations and the federal investigation, CTI allegedly used sham consulting agreements to pay doctors \$500 to \$1000 to attend dinners and conferences to learn about various off-label uses of Trisenox. Doctors who prescribed Trisenox frequently were eligible for and received additional payments of up to \$1500 in alleged illegal kickbacks for speaking at conferences promoting Trisenox. The government alleged that CTI misled doctors into believing that Trisenox was medically accepted for a number of different cancers in addition to its approved use.

The government alleged that these meetings caused thousands of false claims for prescriptions for unapproved uses to be submitted and paid through Medicare. In the settlement, CTI paid \$10.5 million to the government to resolve the civil qui tam allegations of off-label marketing, as well as allegations that it used illegal kickbacks to encourage physicians to prescribe Trisenox. CTI denied any wrongdoing and has since filed a lawsuit against its consultant, the Lash Group, alleging that the company provided negligent advice.

Gilead Sciences: Viread® (N.D. Cal. & 9th Cir.)

In a recent case, private civil exposure to a manufacturer came in the form of a securities action instead of a civil false claims action. In *Gilead*,⁸⁷ a group of individual investors brought a securities fraud action “alleg[ing] violations of sections 10(b) and 20(a) of the Securities Exchange Act of 1934, 15 U.S.C. 78j(b), 78t(a), and SEC Rule 10b-5, 17 C.F.R. § 240.10b-5.”⁸⁸ The plaintiffs’ complaint stated that Gilead, a biopharmaceutical company whose biggest commercial product is

86 See John Cook, *Cell Therapeutics to Pay \$10.5 Million*, SEATTLE POST-INTELLIGENCER, Apr. 17, 2007, available at http://seattlepi.nwsourc.com/business/311948_cell18.html; Kirsten Orsini-Meinhard, *Cell Therapeutics to Pay \$10.5 Million to Settle Feds’ Suit*, SEATTLE TIMES, May 2, 2007, available at http://seattletimes.nwsourc.com/html/business/technology/2003670653_cell18.html. As a part of the settlement, Cell subsequently entered into a Corporate Integrity Agreement, which can be found at www.oig.hhs.gov/fraud/cia/agreements/cell_therapeutics_inc_12222007.pdf.

87 *In re Gilead Scis. Secs. Litig.*, 536 F.3d 1049 (9th Cir. 2008), *rev’g*, Nos. C03-4999 MJJ, C03-5391 MJJ, C04-0100 MJJ, C03-5088 MJJ, C03-5592 MJJ, C03-5113 MJJ, C03-5805 MJJ (N.D. Cal. May 12, 2006).

88 *Id.*

the HIV drug Viread, “misled the investing public by representing that demand for [Viread] was strong without disclosing that unlawful [off-label] marketing was the cause of that strength.”⁸⁹ The plaintiffs alleged that FDA approved Viread for use in approximately 40% of HIV patients, but that Gilead repeatedly violated FDA’s off-label marketing regulations in an effort to have Viread prescribed to the remaining HIV patients.⁹⁰ These efforts allegedly lead to between 75 and 95% of Viread’s sales deriving from off-label uses.⁹¹ On March 14, 2002, FDA sent an “Untitled Letter” to Gilead accusing the company of understating the risks of Viread, a form of off-label marketing, and ordered Gilead to “immediately cease” the practice.⁹² The plaintiffs claimed that Gilead’s off-label marketing only increased after FDA’s demand. By the summer of 2003, Gilead raised the price of Viread and announced “that it anticipated [that] its second quarter financial results would exceed analysts’ expectations....”⁹³

FDA issued a Warning Letter that chastised Gilead for statements made by one of its sales representatives at the 15th National HIV/AIDS Update Conference in March and April of 2003. The letter stated that the employee “made oral statements that minimized the risk information and broadened the indication for Viread.” FDA ordered Gilead to make corrective disclosures, which Gilead did on November 7, 2003. Prior to Gilead’s disclosure, FDA made its Warning Letter public on August 7, 2003. According to the plaintiffs, Viread suffered a drop in sales starting in August. Gilead’s officers sold a large number of shares, while the public did not fully understand the significance of the FDA Warning Letter until Gilead’s press release on October 28, 2003, “detailing [its] third quarter financial results.”⁹⁴

The district court dismissed the case, holding that the investors failed to allege loss causation. The plaintiffs appealed. On appeal, the court found that “the complaint sufficiently allege[d] a causal relationship between (1) the increase in sales resulting from the off-label marketing, (2) the Warning Letter’s effect on Viread orders, and (3) the Warning Letter’s effect on Gilead’s stock price.”⁹⁵

89 *Id.* at 1052.

90 *Id.* at 1051. According to the complaint, the off-label marketing took three forms: (1) marketing to HIV patients co-infected with Hepatitis B, which was not an approved use; (2) marketing Viread as a first-line or initial therapy for HIV infection, even though Viread was approved only as adjunct therapy; and (3) marketing against Viread’s safety profile (i.e., that Viread was safer than the label indicated).

91 *Id.*

92 *Id.*

93 *Id.* at 1052.

94 *Id.* at 1054.

95 *Id.* at 1057.

Although *Gilead* has not yet been adjudicated on its merits, the appellate court's ruling highlights how the business risk to pharmaceutical and medical device companies from off-label promotion of drugs can vary. Off-label use could lead to civil lawsuits from investors, third-party payors or individual patients, depending on the circumstances.

The criminal and civil cases highlighted above clearly indicate that off-label marketing practices can result in significant monetary penalties. A fair amount of controversy exists regarding the use of statutes such as the criminal or civil False Claims Act to police the pharmaceutical industry. Another source of controversy stems from the lack of clear regulatory guidance for off-label use and marketing, which is discussed in more detail below.

Administrative Guidance

Regulation of off-label marketing can seem complex and ambiguous. At one extreme, intentional off-label promotion of a drug or device without scientific support for its promoted use has—and continues to be—prohibited. This scenario implicates one of FDA's fundamental missions—to protect the public's safety in the use of prescription drugs. Although this situation can occur, it is rare for a drug or device manufacturer to engage in such unsubstantiated off-label promotion. Simply put, it would be difficult to convince physicians to prescribe a drug for a specific indication if no scientific evidence exists to support that use.

At the other extreme, a manufacturer's best defense against the accusation of off-label promotion is not to market its product. Such a course of conduct is not viable from a marketing perspective, and a regulatory scheme that would foster such a conservative approach raises significant commercial free speech concerns.

In practice, if a drug or device has exceptional therapeutic value, or a substantial market potential for a use not included in the initial label, the manufacturer is almost certain to seek a label revision to include the additional indication and subsequently will market the drug or device accordingly. Minoxidil serves as one such example. FDA approved Minoxidil as an oral antihypertensive⁹⁶ under the trade name Loniten[®] in 1979.⁹⁷ After Minoxidil entered the market, the drug was associated with hair growth. Obviously, treatment for baldness was

96 Medication used to treat high blood pressure.

97 MedlinePlus, Drugs, Supplements, and Herbal Information, www.nlm.nih.gov/medlineplus/druginfo/medmaster/a682608.html (last visited Oct. 25, 2008); Loniten, www.fda.gov/cder/foi/label/2002/18154s23lbl.pdf (last visited Oct. 25, 2008). See also www.fda.gov/cder/foi/label/2002/18154s23lbl.pdf (Loniten label) (last visited Nov. 3, 2008) and www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm (search Loniten approval history).

not a labeled indication for Loniten. Nevertheless, in 1988, UpJohn received FDA approval for Rogaine[®], a topical form of Minoxidil for hair growth.⁹⁸

In between these extremes lies almost every real-world situation. The most common scenario involves the dissemination by a manufacturer of scientific data and publications in support of emerging or potential off-label uses. It is precisely in this situation that FDA's recent position is not clear, because over the last decade, the regulatory structure for off-label marketing has been, and remains, in a state of flux. The best a manufacturer can do is to review the history of FDA's position, understand how and why it changes over time, and try to anticipate what may be waiting on the horizon.

Before 1997, there was a long-standing prohibition on the dissemination of information about unapproved uses of drugs and devices by manufacturers, subject to very limited exceptions. Two events changed this approach to regulating off-label marketing. First, in 1997, Congress enacted the Food and Drug Administration Modernization Act (FDAMA),⁹⁹ amending the FDCA.¹⁰⁰ Section 401 of FDAMA described certain conditions under which a drug or medical device manufacturer could choose to disseminate medical and scientific information discussing unapproved uses of approved drugs (as well as cleared or approved medical devices) to healthcare professionals and certain entities (including pharmacy benefits managers, health insurance issuers, group health plans, and federal or state governmental agencies).¹⁰¹

Second, in a July 30, 1998, District of Columbia district court opinion, the Washington Legal Foundation (WLF) successfully convinced the court that FDA's regulation of off-label marketing violated manufacturers' First Amendment rights.¹⁰² The WLF argument focused on the fact that a manufacturer's lawful claims about a drug do not match the scope of a physician's lawful prescriptions. However, WLF did not argue that a manufacturer could disseminate inaccurate or misleading information, an allegation in many of the enforcement actions described above. In ruling that the FDA's Guidance Documents are more extensive than necessary to serve the asserted government interest and unduly burden important speech,¹⁰³ the court struck down

98 FDA, Drugs@FDA, www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm (last visited Oct. 25, 2008); Rogaine, www.fda.gov/cder/foi/label/2005/019501s020,025lbl.pdf (last visited Oct. 25, 2008).

99 Food and Drug Administration Modernization Act of 1997 (FDAMA), Pub. L. No. 105-115 (Nov. 27, 1997), at § 401, *codified at* 21 U.S.C. § 360aaa *et seq.*

100 Food, Drug and Cosmetic Act, 21 U.S.C. § 301 *et seq.*

101 Sec. 401, Food and Drug Administration Modernization Act of 1997, Pub. L. No. 105-115 (1997), *codified at* 21 U.S.C. § 360aaa *et seq.*

102 Wash. Legal Found. v. Friedman, 13 F. Supp. 2d 51 (D.D.C. 1998).

103 *Id.* at 71-72.

FDA's (1) Guidance to Industry on Dissemination of Reprints of Certain Published, Original Data;¹⁰⁴ (2) Guidance for Industry Funded Dissemination of Reference Texts;¹⁰⁵ and (3) Final Guidance on Industry Supported Scientific and Educational Activities.¹⁰⁶

Shortly before publication of the court's opinion, in June 1998, FDA issued a proposed rule for dissemination of information on unapproved and new uses for drugs and devices.¹⁰⁷ The proposed rule would create a new Code of Federal Regulations Part, entitled "Dissemination of Information on Unapproved/New Uses for Marketed Drugs, Biologics, and Devices," to implement section 401 of the FDMA.¹⁰⁸ These changes were only the beginning of the flux in regulatory structure. Congress had built a sunset provision into FDAMA Section 401, that effectively nullified the changes to the FCDA by September 26, 2006, or seven years from the date FDA promulgated accompanying regulations. Before FDA managed to finalize its rule, however, it was dealt another setback by the courts.

In 2000, the WLF renewed its action against the FDA in *WLF v. Hennery*.¹⁰⁹ The court granted a permanent injunction declaring the FDAMA and its implementing regulations unenforceable, and denied the FDA's motion to confine application of an injunction to express provisions of guidance documents.¹¹⁰ The FDA appealed. The Court of Appeals dismissed the appeal and vacated the injunction for lack of constitutional controversy after FDA conceded the position that the FDAMA did not provide it with independent authority to proscribe speech, and WLF responded that it no longer had constitutional objection to FDAMA or guidance.

Subsequent to the *Hennery* decision, FDA published a clarification on the applicability of FDAMA section 401, establishing a "safe harbor" for a manufacturer that complies with the FDAMA before and while disseminating journal articles and reference publications about new uses of approved or cleared products.¹¹¹ FDA retained the right, in the context of case-by-case enforcement, to determine from a manufacturer's written materials and activities how the manufacturer intended its products to be used. FDA also recognized that if the agency brought an enforcement action, a manufacturer could raise a First Amendment defense.

104 61 Fed. Reg. 52800 (Oct. 8, 1996).

105 *Id.*

106 62 Fed. Reg. 64074 (Dec. 3, 1997).

107 63 Fed. Reg. 31143 (June 8, 1998).

108 *Id.*

109 *Wash. Legal Found. v. Hennery*, 202 F.3d 331 (D.C. Cir. 2000), *motion denied*, 128 F. Supp. 2d 11 (D.D.C. 2000). Note that *Hennery* is a continuation of *Friedman*, and substituted Dr. Hennery because she was the new FDA Commissioner.

110 *Id.*

111 65 Fed. Reg. 14286 (Mar. 16, 2000).

Thus, by the time the implementing regulations were codified at 21 C.F.R. Part 99 in 2001, more than three years after the passage of the FDMA, the force behind the rules had dramatically changed. Nevertheless, the final rule provided in relevant part:¹¹²

A manufacturer may disseminate to a health care practitioner, a pharmacy benefit manager, a health insurance issuer, a group health plan, or a Federal or State Government agency written information concerning the safety, effectiveness, or benefit of a use not described in the approved labeling for an approved drug or device or in the statement of intended use for a cleared device, provided that the information:

(1) is about a drug or device that has been approved, licensed, or cleared for marketing by FDA;

(2) is an unabridged reprint or copy of a peer-reviewed article (excludes: letters to the editor; abstracts of a publication; anything regarding Phase 1 trials in healthy people; flagged reference publications that contain little or no substantive discussion; and observations in four or fewer people that do not reflect any systematic attempt to collect data, unless the manufacturer demonstrates to FDA that such reports could help guide a physician);

(3) is an article about a clinical investigation with respect to the drug or device;

(4) does not pose a significant risk to the public health;

(5) is not false or misleading (considered misleading if, among other things, the information includes only favorable publications when unfavorable publications exist, excludes articles, or the information presents conclusions that clearly cannot be supported by the results of the study);

(6) is not derived from clinical research conducted by another manufacturer unless that manufacturer gives permission; and

112 These regulations did not apply to unsolicited requests for information by a healthcare provider.

(7) with some exception, that sixty days before disseminating any such written information, a manufacturer submit to the FDA an identical copy of the information to be disseminated, and an explanation of the manufacturer's method of selecting the articles.¹¹³

As noted earlier, section 401 of FDAMA ceased to be effective on September 30, 2006. Thus, these implementing regulations are no longer applicable. The controversy continues. On January 30, 2008, the WLF issued a report claiming that FDA regulation of prescription drug promotion "is being conducted in a manner that routinely violates both the First Amendment and FDA's statutory mandate."¹¹⁴ The WLF's conclusion could indicate another round of litigation ahead:

FDA routinely orders suppression of truthful speech, demands that manufacturers engage in "corrective advertising" in the absence of any evidence that consumers have been misled by supposedly misleading advertising, and violates federal administrative law by using compliance letters (rather than established notice-and-comment procedures) to adopt new agency policies regarding product promotion.¹¹⁵

In February 2008, FDA released draft guidance that would renew the procedures for dissemination of scientific literature on off-label uses.¹¹⁶ Under the draft guidance, FDA would permit drug and device companies to disseminate articles to doctors if the articles were peer-reviewed and came from a journal with an expert editorial board. However, the draft guidance does contain a significant change. FDA would drop the requirement that drug and device makers provide the studies to FDA beforehand or promise to seek approval of the discussed use, but the article must be accompanied by a prominent warning that the use described is not approved or cleared by FDA. Other highlights of the draft guidance include:

- FDA regulations generally prohibit manufacturers from distributing products not approved as safe and effective or cleared through a substantial equivalence determination.

113 21 C.F.R. Part 99. The requirement that a manufacturer essentially seek approval of the off-label use to lawfully disseminate articles about the use was the most burdensome aspect of C.F.R. pt. 99.

114 Press Release, Wash. Legal Found., Report Concludes that Regulation of Drug Promotion Violates First Amendment and Federal Law (Aug. 7, 2006), available at www.wlf.org/upload/080706RS.pdf.

115 Wash. Legal Found., CaseDetail: Report on FDA First Amendment Abuses (Aug. 7, 2006), available at www.wlf.org/Litigating/casedetail.asp?detail=440.

116 See FDA, [Draft] 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 (Feb. 2008), available at www.fda.gov/oc/op/goodreprint.html.

- FDA claims its legal authority to determine whether distribution of medical or scientific information constitutes promotion of an unapproved new use, or whether such activities cause a product to be misbranded or adulterated, has not changed.
- FDA recognizes the important public policy reasons for allowing manufacturers to disseminate truthful and non-misleading medical journal articles, and medical or scientific reference publications, on unapproved uses to healthcare professionals and entities.
- Off-label uses may be important and even may constitute a medically recognized standard of care. Accordingly, the public health may be advanced by healthcare professionals' receipt of medical journal articles, and medical or scientific reference publications, on unapproved or new uses, if the materials are truthful and not misleading.
- FDA will allow distribution of scientific or medical journal articles that meet a more rigorous set of quality standards than before. For example, the article must be published by an organization with an editorial board independent of the organization, with a publicly stated disclosure policy for conflict of interest. The publication should not be:
 - (1) primarily distributed by a drug or device manufacturer (but should be generally available);
 - (2) written, edited, excerpted, or published specifically for, or at the request of, a drug or device manufacturer; or
 - (3) edited or significantly influenced by a drug or device manufacturer or any individuals having a financial relationship with the manufacturer.

The draft guidance is not without controversy. Representative Henry Waxman (D-California) claims that the proposed guidelines will leave consumers at risk and sent a letter to FDA stating that the new proposal “would open the door to abusive marketing practices that will jeopardize safety, undermine public health, and lead to an increase in unapproved uses of powerful drugs.”¹¹⁷ Representative Waxman also argued that the new FDA off-label use proposal would discourage drug companies and medical device makers from conducting definitive scientific studies and seeking formal FDA approval for alternative uses of drugs and devices if they could profit from off-label uses without such studies. Other critics

117 Letter from Henry A. Waxman, Chairman, House of Representatives Committee on Oversight and Government Reform (Nov. 30, 2007), *available at* <http://oversight.house.gov/documents/20071130102744.pdf>.

say the proposed guidance, as currently written, will allow companies to selectively use peer-reviewed journal articles that support off-label use of their products as marketing tools.¹¹⁸

Conclusion

The future of FDA's draft guidance, and its role in regulating the dissemination of information relating to the off-label use of approved and cleared drugs and devices, remains uncertain. The agency must balance the risk of drug or device misuse or suboptimal use against the reality that off-label drug or device use may represent the standard of care and the best medical option for patients; the needs of healthcare practitioners to have access to the latest medical information; and the First Amendment rights of manufacturers. As FDA attempts to reach this balance, drug and device manufacturers face a world of uncertainty. Although the trend over the past decade has been to allow greater dissemination of reliable scientific information on off-label use, the *Gilead* case and others discussed above highlight the dangers a drug or device manufacturer faces if FDA accuses it of off-label promotion.

What does the current status of the law and recent enforcement activity mean in everyday, operational terms? Of course, a manufacturer's *express* marketing and promotional activities may not tout a particular off-label use. Sales representatives "detailing," advertisements, and promotional conferences with physicians should not affirmatively initiate communications about off-label uses. Prescribing attendees to a sales pitch or conference cannot receive payment in cash or kind, lest a kickback be inferred.

Even activities not expressly categorized or budgeted as promotional may—in FDA's or DOJ's view—cross the line into off-label promotion if those activities address off-label uses and are in some way pretexts for promotion. Thus, the government has raised concerns where:

- the size of the sales force appears disproportionate to the size of the on-label market;
- providers targeted for detailing do not, or do not primarily, treat the on-label disease state(s);
- medical literature disseminated about an off-label use is not based on good science or is otherwise misleading, unfair, or unbalanced;

118 See e.g., Angie Drakulich, FDA to Allow Off-Label Information, Draft Guidance May Be Too Soon, Too Simple, *ePT—The Electronic Newsletter of Pharmaceutical Technology* (Feb 21, 2008), available at <http://pharmtech.findpharma.com/pharmtech/article/articleDetail.jsp?id=492953> (last visited Nov. 3, 2008).

- marketing is not consistent with the drug's or device's safety profile (i.e., marketing the product as being safer than the label indicates);
- customers are solicited or encouraged by the manufacturer to ask medical questions about off-label uses (even if the resulting answers are scientifically accurate);
- CMEs concern off-label uses and the content, faculty, and/or number of CMEs is dictated by the manufacturer;¹¹⁹
- the manufacturer's marketing budget is used to support ostensibly non-promotional events, like CMEs;
- the manufacturer conducts return-on-investment analyses (ROI) with respect to either ostensibly independent CMEs on off-label topics or ostensibly non-promotional advisory boards/consultants;
- "investigator-initiated" studies of off-label uses are suggested or encouraged by the manufacturer or its sales representatives;
- manufacturer-initiated studies of off-label uses are completed and disseminated without an intent to seek approval for the off-label use (sometimes called a "publication strategy");
- studies with "bad" results are not published or otherwise made available;¹²⁰
- educational grants, invitations to conferences, and other perks are distributed to high-level, off-label device users selectively; and/or
- feedback from paid consultants and advisory boards is not really needed, collected, or reviewed, but such arrangements are used merely as opportunities to educate (and perhaps reward with honoraria) opinion leaders about an off-label use. (This practice could create kickback concerns, too.)

119 For guidance in this area, see Accreditation Council for Continuing Medical Education (ACCME), Standards for Commercial Support, Standards to Ensure the Independence of CME Activities (Sept. 2004), *available at* http://www.accme.org/dir_docs/doc_upload/68b2902a-fb73-44d1-8725-80a1504e520c_uploaddocument.pdf.

120 For suggested publication and disclosure policies, see, e.g., the PhRMA "Principles of Conduct of Clinical Trials and Communication of Trial Results," *available at* www.phrma.org/files/Clinical%20Trials.pdf; the International Committee of Medical Journal Editors (ICMJE) "Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication," *available at* www.icmje.org/; the "Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases" issued by the four major international pharmaceutical associations, *available at* <http://www.phrma.org/files/2005-01-06.1113.PDF>; and the revised CONSORT (Consolidated Standards of Reporting Trials) statement developed by investigators and editors to help authors, *available at* www.consort-statement.org/?o=1011.

Accordingly, to reduce the risk of exposure, compliance audits of vendor sales and marketing practices, or of provider purchasing practices, should take into account these red flags.

Similar common sense precautions are recommended for health-care professionals who prescribe medications. In particular, prescribing professionals ought to carefully examine their financial relationships with drug and device manufacturers, because financial relationships often form the basis for impugning the integrity of the medical professional in off-label cases.

Finally, from a fraud and abuse perspective, both manufacturers and providers need to be mindful of evolving enforcement activity. In particular, if federal prosecutors treat certain off-label promotional activities as false claims, there will be a significant financial incentive for disgruntled employees to file qui tam actions. Although it remains to be seen how viable a false claims theory will be as an enforcement tool, in addition to the criminal and civil penalties that exist under the FDCA itself, off-label “education,” “promotion,” and “marketing” of FDA-approved drugs and devices will require continued due diligence in an evolving regulatory landscape.

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