I suggest the following simple ten ways to avoid malpractice in litigation:

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IN THIS ISSUE
Michael F. Healy and Kelly Savage Day of Sedgwick Detert Moran & Arnold LLP review current law and regulation relating to off-label marketing of pharmaceutical drugs and discuss best practices to manage the risks of off-label activities.

Managing Risks Associated with Off-Label Promotion of Pharmaceuticals

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Off-label use—the practice of prescribing a medication for a purpose other than that for which the medication is officially approved—is legal and quite common in the United States. Over one-fifth of all drugs are prescribed off-label. For cardiac medications, off-label use is estimated at 46 percent. Other studies have indicated that 81 percent of AID patients are prescribed drugs off-label and that the majority of cancer drug treatment is off-label.

Even though off-label use is legal, most types of off-label promotion are strictly prohibited. The federal Food and Drug Administration ("FDA") generally forbids manufacturers from marketing drugs for unapproved uses. The FDA does, however, allow manufacturers to provide physicians with scientific and educational information about off-label uses, but such information should comply with strict FDA guidelines.

Pharmaceutical companies engaging in improper off-label marketing can not only suffer enormous monetary liability, but also may face significant limitations on their future business practices and serious damage to their reputation. The Department of Justice and state Attorneys General have been very active in bringing enforcement actions against manufacturers they believe have engaged in illegal promotion of off-label use. Just last year, Pfizer agreed to pay the largest health-care fraud settlement in history – $2.3 billion – to resolve criminal and civil suits arising from promotion of its antipsychotic drug Zyprexa for such off-label uses as treating dementia (including Alzheimer’s dementia) in elderly people. In at least one case, the Justice Department brought a criminal action against an industry executive, who now faces substantial prison time. Finally, plaintiffs’ attorneys increasingly are piggy-backing on actions brought by federal and state governments by filing civil suits against drug manufacturers and life sciences companies arising from the same allegations of off-label marketing.

In this article, we briefly review current law and regulation relating to off-label marketing and discuss best practices to manage the risks associated with off-label promotion.

Current Law and Regulation Regarding Off-Label Promotion

Once the FDA has approved a medication for a specific purpose, medical providers generally may prescribe the medication for other treatment regimens that are not included

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1 We give special thanks to Joanna Luminoso, a junior associate at Sedgwick, Detert, Moran & Arnold LLP, whose research assistance contributed to this article.
2 See Radley et al., Off-label Prescribing Among Office-Based Physicians, 166 ARCH. INTERN. MED. 1021 (2006).
3 Ibid.
4 “Patients Take Off-Label Drugs for Opportunistic Infections,” AIDS Weekly (Oct. 24, 1994.)

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6 On March 18, 2008, W. Scott Harkonen, the former Chief Executive Officer of InterMune, Inc., was indicted on wire fraud and felony FDCA charges for his role in marketing Actimmune as a treatment for idiopathic pulmonary fibrosis, an off-label use. Harkonen authorized the issuance of a press release announcing the results of a clinical trial of Actimmune for the treatment of idiopathic pulmonary fibrosis (“IPF”) on Aug. 28, 2002. Although the clinical trial in fact failed, the press release’s headline falsely stated that “InterMune Announces Phase III Data Demonstrating Survival Benefit of Actimmune in IPF,” with the subheading “Reduces Mortality by 70% in Patients With Mild to Moderate Disease.” On September 29, 2009, after a seven-week jury trial, Harkonen was acquitted on the felony FDCA charges but convicted on the wire fraud charge for authorizing the issuance of a misleading press release in August 2002. If the conviction is upheld on appeal, Harkonen could be sentenced to up to 20 years in prison.
in the product’s approved labeling. With limited exceptions, however, the FDA prohibits all marketing of drugs for off-label uses.

Under the federal Food, Drug, and Cosmetic Act (“FDCA”), any approved drug marketed for an unapproved use is both: (1) an unapproved drug regarding that use, and (2) misbranded, because the labeling does not include “adequate directions for use.”7 Promotion of drugs for unapproved uses is a strict liability criminal offense, with a penalty of up to one year in prison, a fine of up to $100,000 for individuals and $200,000 for corporations, or both.8 If the off-label promotional activity involves “intent to defraud or mislead,” the penalties increase to up to three years in prison, a fine of up to $250,000 for individuals and $500,000 for corporations, or both.9 Moreover, the fines may be increased beyond these limits depending on the financial gain to the manufacturer or loss to the government.10

Despite these penalties, the FDA recognizes that off-label uses or treatment regimens may be quite beneficial to patients and may even constitute the medically-recognized standard of care.11 Accordingly, the FDA permits manufacturers to provide health-care providers12 with truthful information about unapproved new uses of approved medications, so long as the information is provided as part of a so-called “scientific exchange” and not via marketing or sales promotion.

There are three main ways in which such a scientific exchange may occur. First, manufacturers may respond to unsolicited questions about unapproved uses from physicians and other health-care providers. When doing so, the manufacturer should follow certain rules. Otherwise, the manufacturer risks having the discussion characterized as illegal marketing rather than a scientific exchange.

Unsolicited questions should be truly unsolicited, not cued. In other words, sales representatives should not prompt doctors to ask questions about off-label uses. In addition, the response should be tailored to the scope of the question. Moreover, the response should provide objective, neutral, and balanced information — touting the benefits of off-label uses without disclosing all known risks constitutes illegal promotion. Second, under certain conditions, off-label use may be discussed at professional conferences that are independent from the promotional influence of the supporting company.13 In determining whether a conference is truly independent of the trials. Finally, with the growth of the generic industry, there is little incentive for brand-name manufacturers to spend the money to obtain FDA approval for new uses of drugs that are, or soon will be, off-patent.

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7 21 U.S.C. §§ 331(b), 352(f); 21 C.F.R 201.100(c)(1); see also, Guidance for Industry on 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 79 Fed. Reg. 1694 (Jan. 13, 2009) and http://www.fda.gov/oc/op/goodreprint.html (“Good Reprint Practices”).
11 See Good Reprint Practices, supra. Indeed, because medicine progresses far more rapidly than FDA regulatory evaluation, cutting-edge medical advances are almost always off-label. Thus, off-label use is frequently the recognized medical standard of care. In addition, there are many rare medical conditions that lack any on-label treatment because the small number of potential users does not justify the enormous expense of clinical

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substantive influence of the manufacturer, the FDA evaluates whether and to what extent the company is in a position to influence the presentation of information related to its products or otherwise transform an ostensibly independent program into a promotional vehicle. The FDA examines the following factors as part of this evaluation: (1) who controls the content and the selection of speakers; (2) disclosures about any company funding, any relationships between the speakers and the sponsoring company, and whether any unapproved uses will be discussed; (3) the focus of the program; (4) the relationship between the conference provider and the supporting company; (5) provider involvement in company sales or marketing; (6) the provider’s demonstrated history of meeting standards of balance, objectivity, and scientific rigor; (7) audience selection; (8) opportunities for meaningful discussion and questioning; (9) dissemination of material about a sponsoring company’s products; (10) ancillary promotional activities; and, finally, (11) whether any complaints have been raised by the provider, presenters, or attendees regarding attempts by the supporting company to influence content.

Finally, provided FDA guidelines are followed, manufacturers may provide health-care providers with medical journal articles and medical or scientific reference publications on unapproved uses of drugs. But to avoid potential federal regulatory enforcement actions, manufacturers should adhere to the so-called “Good Reprint Guidelines” published by the FDA in January 2009 (the “Guidelines”). Under the Guidelines, manufacturers may disseminate scientific and medical journal articles, reference publications, and reprints (“Reprints”) so long as the following requirements are met:

1. Requirements for Journal/Publication:
   - The publisher should have an editorial board that uses qualified and independent experts;
   - The publisher should adhere to a publicly-stated policy of full disclosure of any conflict of interest or biases for all authors, contributors, or editors;
   - The journal should be peer-reviewed;
   - The publication should not be in the form of a manufacturer-funded supplement;
   - The publication should be generally available in bookstores for medical/scientific textbooks;
   - The publication should not be primarily distributed by the manufacturer;
   - The publication should not be edited or otherwise influenced by the manufacturer; and
   - The reference publications must discuss study data.

2. Requirements for Information in the Reprint:
   - The Reprint should address scientifically sound, adequate, and well-controlled clinical trials, including historically-controlled studies, pharmacokinetic (“PK”) and pharmacodynamic (“PD”) studies, and metaanalyses testing a specific clinical hypothesis;

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14 Id. at 64095.
15 Id. at 64096-99. The Accreditation Council for Continuing Medical Education guidance in this area is also worth considering. See, 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.
16 See Good Reprint Practices, supra.
The Reprint must not be false or misleading. For example:
- The study should not be called “definitive” if it is inconsistent with the weight of credible evidence; and
- The Reprint should involve a clinical investigation that the FDA has previously indicated is not adequate and well-controlled.

The Reprint should not contain annotations, markings, or highlighting;

The information in the Reprint should not pose a significant risk to the public health, if relied upon; and

No abstracts, “Letters to the Editor,” or, Phase One studies of healthy subjects.

3. What Should be Provided with the Reprint:

• The approved labeling; and
• A comprehensive bibliography of publications discussing adequate and well-controlled clinical studies published in medical journals or medical or scientific texts about the use of the drug covered by the information disseminated.

4. What the Manufacturer Should Disclose (by a prominently displayed and permanently affixed statement):

• That the FDA has not approved the drug or device for the uses described;
• The manufacturer’s interest in the product that is the subject of the Reprint;
• Any author(s) known to the manufacturer as having a financial interest in the product or manufacturer or who is receiving compensation from the manufacturer, along with the author’s affiliation;
• Any person known to the manufacturer who has provided funding for the study; and
• All significant risks known to the manufacturer concerning the unapproved use not discussed in the Reprint.  

5. How the Reprint Should (and Should Not) be Distributed

- The Reprint should be distributed separately from information that is promotional in nature – thus, no marketing pieces (including carriers, stickers, flyers, and the like);
- Sales representatives should not discuss the Reprint when visiting health-care providers. Instead, to the extent that recipients of Reprints have questions, the sales representative should refer their inquiries to a medical/scientific officer or department, and the officer or department to which the referral is made should be separate from the sales and/or marketing departments;
- Although Reprints may be distributed at conferences in settings appropriate for scientific exchange, Reprints should not be distributed in promotional exhibit halls or during promotional speakers’ programs.

Best Practices to Mitigate Potential Liability for Off-Label Promotion

Many civil and criminal charges have been brought against drug manufacturers for off-label activities. In fact, almost every leading pharmaceutical manufacturer is likely being investigated for off-label promotion practices. Against this ominous backdrop, here are a number of practical suggestions for

17 This requirement is not limited to risks that are publicly known.
limiting potential liability from illegal off-label marketing: (1) create a culture of compliance that focuses on communication, confirmation, and correction; (2) train and monitor sales staff; (3) develop policies and procedures for communication about off-label uses; (4) develop policies for responding to unsolicited questions about off-label uses; (5) develop policies and procedures with respect to trade shows; (6) develop policies and procedures regarding distribution of reprints; (7) develop policies and procedures regarding grants; and (8) watch out for smoking guns.

By taking the proactive steps recommended in this article, manufacturers can protect themselves and their companies in the future.

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18 Such activities should include: (1) educating sales managers and representatives about off-label activities and how to avoid illegal off-label promotion; (2) testing the effectiveness of educational materials and training; (3) compensating sales managers and representatives in a way that does not provide an incentive to engage in off-label; (4) being on the lookout for “homemade materials,” (5) monitoring sales levels for suspicious results; and (6) auditing sales managers and representatives often to measure compliance.

19 Be truthful, accurate and objective – present information in a balanced, scientific manner. When discussing clinical trials, limit discussions to study data and avoid conclusive statements or interpretations. Do not make claims of safety or effectiveness regarding unapproved uses. Avoid using testimonials and success stories regarding off-label uses. Avoid redistributing press releases to actual or potential customers (this likely will be deemed promotional activity). Consider searching for – and stopping – employee posts and discussions on websites and in online chatrooms. These sorts of unmonitored, unapproved communications potentially can provide useful intelligence for plaintiffs’ attorneys.

20 Be sure sales representatives avoid “prompting” or “cuing” questions about off-label use. Consider “scripting” sales representatives’ answers to such questions, and have sales representatives refer any substantive issues to the Medical Affairs department. Medical Affairs should be an independent, scientifically objective unit. Narrow broad, open-ended, questions before responding, because all responses should be confined to the specific question asked. Clearly disclose that the drug has not been approved for the use in question. Keep any discussion balanced and objective – scientific rather than promotional; and document all responses to unsolicited requests.

21 Train employees extensively regarding permitted and prohibited statements and activities. Consider having Medical Affairs personnel present to respond to questions about off-label uses at trade shows.

22 Strictly comply with the FDA Good Reprint Practices discussed above. Make sure the company has sufficient infrastructure and controls to manage off-label reprints, including: (1) resources to ensure publication and disclosure requirements are met; (2) procedures to assess whether the benefits from a Reprint outweigh the risks/costs resulting from the necessary disclosures; and (3) auditing to ensure compliance.

23 Grant money should be provided to independent scientific researchers and organizations, not to “wholly-owned” grantees. Companies should also ensure that grants for educational conferences and symposia (e.g., Continuing Medical Education programs) are to independent organizations.

24 Regulators often become suspicious when: (1) the overall size of the sales force appears disproportionately large as compared to the size of the on-label market; (2) health-care providers targeted for sales calls do not treat the on-label disease (or treat the on-label disease only minimally); (3) the company’s marketing budget supports ostensibly nonpromotional events like Continuing Medical Education conferences; (4) the manufacturer conducts profitability analyses with respect to off-label activities; (5) the company initiates, performs, and disseminates the results of studies concerning off-label uses with no intent to seek approval for the off-label use (a “publication strategy”); (6) the manufacturer fails to publish or make available internal studies of off-label uses yielding adverse results; (7) educational grants, conference invitations, and other favors are selectively provided to heavy off-label users; and (8) agreements with paid consultants and advisory boards are used as opportunities to educate (and reward) opinion leaders about off-label uses.
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