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GUIDELINES FOR OFF-LABEL COMMUNICATION

By **Milton Liebman**

A clear picture of what is permitted in providing information to healthcare professionals about off-label use of approved prescription drugs is not available. It doesn't exist. Food & Drug Administration (FDA) has said some off-label drug information is acceptable. But it has not issued regulations or given firm guidance on dissemination of off-label information that may resolve concerns that manufacturers have.

"Off-label confusion" might better describe guidance on off-label communications.

However, off-label information is legal and in common practice, though "off-label confusion*", might be the better term. A conference on **Guidelines for Disseminating Off-Label Information**, then, is just what was needed to help explore the uncertainties involved in the practice. One of a series of pharma-ceutical conferences by the Center for Business Intelligence, it was held in Washington, D.C. October 20, 2003.

Two Major Trends

William Vodra, partner in the Washington, D.C. law firm Arnold & Porter, outlined two major legal trends in off-label promotion. The first is that the courts have pushed back the authority of the FDA. The second is that other constraints have emerged from other government agencies.

In a decision of the U.S. District Court (DC) in the Washington Legal Foundation vs. Henney case (July 1999), the court struck down three FDA policy documents and portions of the FDA

Modernization Act (FDAMA) that imposed severe restrictions on manufacturers' dissemination of scientific information about their products as violations of the First Amendment.

In the opinion of the Coalition for Healthcare Communications, the District Court's rulings set the current parameters. The company holding an approved NDA (or PMA for medical devices) may distribute in any manner to any healthcare provider any independently prepared medical textbook, compendium, peer-reviewed journal article that includes off-label information about the drug or device.

Conference participant Jack E. Angel, executive director of the Coalition, referred to the general requirements that must be met. These include disclosure of any financial arrangements between authors, publisher, and the pharmaceutical company; inclusion of approved labeling with the distributed information; and disclosure that use of the drug or device is not FDA-approved. Off-label use should not be promoted, and the distributed material should not be false or misleading. There are further requirements specific to journal articles and to texts.

The other restraints that have emerged include enforcement action by the Office of the Inspector General (OIG) of Health & Human Services, Department of Justice (DoJ), and state attorney generals. Actions by these government agencies have been widely publicized.

New Risks From Off-label Promotion

The federal False Claims Act has been broadly invoked the past two years against actions taken by pharmaceutical firms, Vodra said. The Act allows the U.S. to sue to recover improperly paid

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monies, together with civil penalties. Whistleblowers can sue on behalf the government (qui tam proceeding) and be handsomely rewarded with as much as 30-plus percent of the recovery. They have access to internal company documents and often are not identified during the evidence-gathering stages.

Beware of the Whistleblower!

QUI TAM - Latin abbreviation for "Who sues on behalf of the King as well as for himself." An action under a statute that establishes penalties for certain acts or omissions that can be brought by an informer and in which a portion of the penalties, fines, awards can be awarded the whistleblower.

A current case in point is U.S. (Franklin) v. Parke-Davis. Franklin worked for Parke-Davis for five months as a "medical liaison" and initiated the qui tam action. He was used only for product promotion, he said, during which time P-D instructed him to make false claims about off-label uses of Neurontin, to recommend doses above approved levels, and guide doctors in how to conceal that prescriptions were off-label in order to obtain reimbursement from VA and Medicaid. He claimed 50 percent of prescriptions were written for off-label use and 50 percent of those were reimbursed by the federal government. (Neurontin is indicated as adjunctive therapy in the treatment of partial seizures; it was used frequently for therapy for bipolar disorder and other conditions.)

The federal government does not reimburse for drugs used for an off-label indication, unless it is listed in a compendium. In this case the government will not have to prove whether P-D made false claims because the courrt ruled that even truthful company statements can result in liability if they are a substantial factor that led the government to pay for off-label drug use, Vodra said.

Under the False Claims Act a manufacturer may be sued based on the failure to abide by FDA rules against off-label promotion, Vodra pointed out, "where the manufacturer knowingly causes a false statement to be made to get a claim paid."

There is no requirement that a manufacturer make a false statement to physicians in order to incur liability. It may exist if a true statement was a "substantial factor" in submission of a false claim.

There are state statutes that deal with false and deceptive advertising or promotion enforceable by the state Attorney General or subject to private suit or class action. Under deceptive trade practice suits, no physical harm need occur. The claim is made that purchase of the product was induced by unfair practice.

Extra Claim for Bextra

There is a current case in which The Conference of California Seniors (CCS) has sued Pfizer and Pharmacia for violating state false advertising laws. The suit charges that a clinical study in the May 2003 issue of the Journal of the American Dental Association described the use of the Cox-2 inhibitor Bextra for an unapproved indication—treatment of pain after oral surgery. (Bextra does not have an indication for acute pain).

The study was financed by the manufacturer, whose employees authored a report on the favorable results of the study. CCS charged that the publication constituted unfair and deceptive advertising. The Association of Medical Publications (AMP) filed a "friend of the court" brief outlining the concerns of publishers given this accusation.

The fact that the clinical study was accepted and published by a peer-reviewed, association journal did not appear to concern the CCS, although the case could well infringe First Amendment rights of the scientific press. No decision has been yet handed down, but the case illustrates the unusual twists and turns that can lead to a state false advertising suit claiming use of off-label information.

Vodra warns that marketers must consider these and a number of other legal risks.

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Where the Rubber Meets the Road

A high risk factor in off-label communications is the training and control of the sales force.

To have a successful program, it is essential that management be involved, stated Kathleen A. Knight, vice president, deputy general counsel, Alcon Laboratories, Inc. A set of guidelines must be drafted that considers the character of the organization, the business needs, the rules to follow and the reasons behind them. Management must issue the company-specific guidelines and be committed to enforcement.

As Vodra said, research, marketing, sales, R&D, regulatory and legal should all be involved. Review the program in view of the company's current practices.

Knight, a no-nonsense lawyer, initially motivates rigid compliance by Fear and Guilt. In motivating through fear, Knight stresses all of the actions that government agencies can take if sales representatives step out of guidelines, and how those actions can hurt a company. She emphasizes that the FDA can respond when regulations are not followed with warning letters that may be used as an exhibit in a court case, or by seizure of the drug, thereby removing it from the market. Legal actions that state Attorney Generals can and do take include prosecution under false and deceptive advertising statutes and consumer fraud laws.

Knight prefers ethics as a motivator. She believes that, by "appealing to their soul," she can convert them to compliance for the long term.

Regulators are focusing increasingly on sales force activities as John Kamp of the Wiley Rein & Fielding law firm attests. "Direct to consumer advertising has passed the test," he said "For the most part it works. The big public criticism is likely over."

He suggested that other areas in marketing will get a closer look, and "a focus on detailing is most likely because that's where the money is." And that supports the need for field force training and compliance.

But, off-label communications clearly tops the "most wanted" list.

Seven Steps to Safety?

If you are planning to market an approved product for an unapproved indication, keeping a trusted lawyer nearby might be a logical first step to assure safety. Vodra offers seven steps for marketers:

1. Assess the full weight of clinical evidence available about the effectiveness of the off-label use. Poll the experts in the therapeutic area. Is the company going to file an NDA for this use? Why take risks if the drug may not be therapeutically acceptable?
2. Is the potential commercial benefit worth the risk in relation to the types and level of promotional activities you have in mind? Why take any risks if there is no obvious commercial benefit?
3. Assess the safety downside, the new risks, side-effects, reactions or outcomes in patients who do not respond, etc.
4. Product liability risks from off-label use must be assessed. This includes relevant information in, and what is missing from, the current labeling. The missing information must be readily found in material being distributed and the off-label status clearly disclosed.
5. There can be marketing risks based on specific off-label activities such as dissemination of reprints, preparation of materials, etc. How many different types of activity will be undertaken? If sales representatives are involved, a key question is, can they be properly trained and controlled?
6. If there is an approved product on the market for the proposed use, how is that company likely to react? Take into account that the product cannot be reimbursed by government for off-label use. Will internal documents be created that may cause discomfort if made public?
7. Use a formal, internal company-wide process involving R&D, clinical medicine, regulatory affairs, and legal. If there are any significant risks, take them to higher management. Risk tolerance may differ at the corporate level.

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