# Off-Label Marketing Investigations in the Pharmaceutical Industry

*Managing Principal Paul Greenberg and Vice President Tamar Sisitsky discuss the challenges of isolating the impact of off-label marketing on sales*

Purchases of prescription pharmaceuticals are driven partially by science and partially by marketing. Physicians prescribe a drug based on its clinical characteristics, including expected patient-specific safety, efficacy, and side-effect profiles. In addition, drug selection is based, in part, on efforts by the manufacturer to increase product visibility.

## Science or Marketing?

Disentangling that portion of a drug's sales that results from science versus marketing has long been a challenge in pharmaceutical industry disputes involving issues such as transfer pricing, intellectual property, antitrust, and breach of contract. Recently, efforts to parse out the effects of science and marketing on pharmaceutical sales have moved into a new arena. Government investigations are increasingly focused on incremental sales obtained by pharmaceutical manufacturers' marketing of drugs for various "off-label" uses — indications that the FDA has not formally approved.

Physicians have long prescribed medications for off-label uses, and such experimentation is both legal and an accepted part of medical practice. According to a November 2003 Knight Ridder report, the number of off-label prescriptions increased 96% between 1997 and 2003. During that same period, off-label sales of drugs accounted for 23% of the total retail value of all drug sales. Research appearing in *The New Jersey Law Journal* in 2006 indicates that 60% of oncology patients and 80% of AIDS patients have received off-label medications.

The issue in the government investigations is not the physician's prescribing behavior but the manufacturer's marketing behavior. FDA rules allow for some publicizing of scientific information concerning a drug's benefits, but there often is no bright line separating science from marketing. Drug manufacturers are barred from directly promoting off-label uses to physicians, but they are permitted to answer questions or provide information if asked by medical practitioners. In

### SETTLEMENTS IN OFF-LABEL INVESTIGATIONS

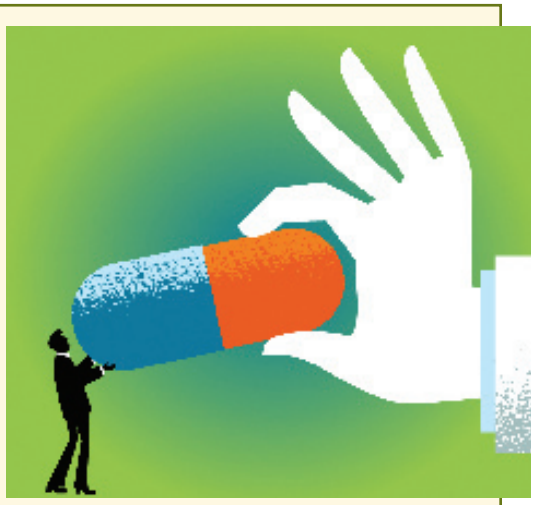
***Genentech:*** $50 million settlement with the U.S. Department of Justice for off-label marketing of **Protropin**, a synthetic growth hormone, for use in treating burns and a kidney disorder (1999).

***Pfizer:*** $430 million settlement associated with off-label marketing of epilepsy drug **Neurontin** for various psychiatric disorders, back pain, and headache (2004).

***Eli Lilly:*** $36 million to settle charges related to off-label marketing of osteoporosis drug **Evista** for breast cancer prevention (2005).

***Serono:*** $704 million to resolve charges for off-label marketing of **Serostim**, an FDA-approved drug for the treatment of AIDS wasting, for treatment of loss of body cell mass (2005).

***Schering-Plough:*** $435 million to resolve charges regarding off-label marketing of **Temodar**, approved to treat certain types of brain tumors, to treat other kinds of brain cancers, and hepatitis drug **Intron A** for superficial bladder cancer (2006).



***InterMune:*** $36 million to settle charges related to off-label marketing of immune disorder drug, **Actimmune**, for treatment of idiopathic pulmonary fibrosis (2006).

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addition, manufacturers often sponsor continuing medical education seminars where off-label use of various drugs can be discussed, including the results of clinical trials for off-label indications. Manufacturers argue that these events are designed to keep up with the latest scientific developments and respond to the results of physician experimentation; critics see them as violations of the FDA's ban on off-label promotional activity. A complex challenge exists in trying to isolate the impact on sales of marketing as opposed to a range of other possible influences.

### KEY ISSUES IN OFF-LABEL MARKETING INVESTIGATIONS

**The government has indicated that the following could be considered potential evidence in off-label investigations:**

- **Rates of off-label prescriptions before and after physician conferences hosted by the manufacturer.**
- **Market research recording doctors' state of mind after marketing meetings.**
- **Role of the manufacturer in prescribing activity.**
- **A small market for approved use relative to a large sales force.**
- **Financial incentives for off-label use.**
- **Failure to identify company funding for research, articles, presentations.**
- **Health consequences from off-label use.**

*Source: "Fraud Issues in Off-Label Promotion," PharmaCongress presentation by Virginia Gibson, Assistant U.S. Attorney, October 2, 2003.*

## Damages Approaches

Estimating the incremental sales at issue requires knowing not only the portion of a drug's prescriptions that was off-label, but also the portion that can be tied to the improper marketing. Pharmaceutical industry data, including internal company financials, public and private administrative claims data concerning patient health care use, and third-party market research, can inform the total amount of a drug's off-label sales. However, even with access to all of these data sources, defining what is off-label may be ambiguous to the extent that the label does not map neatly to available disease classifications (e.g., ICD-9, which is often used for reimbursement) and patterns of use (e.g., recommended daily dose). Moreover, determining the portion of total off-label sales due to the conduct at issue in these investigations requires knowing the percentage of off-label sales that would have occurred in the absence of any off-label marketing. This "background rate" recognizes that an accepted part of medical practice is for physicians to prescribe medications for non-indicated uses.

In some early cases (such as the 1999 *Genentech* case), the government did not distinguish between off-label sales directly resulting from illegal promotion and such background-rate off-label sales. More recently, the government did attempt to account for these distinctions in the 2004 Neurontin case (*United States v. Warner-Lambert Company LLC*), concluding that slightly over a quarter of Neurontin sales would have been for off-label uses even without improper promotional activity.

## Future Directions

As costly as past and ongoing off-label marketing investigations have been, they may represent only the beginning of an upward trend. Michael K. Loucks, First Assistant U.S. Attorney for the District of Massachusetts, recently encouraged companies to file off-label suits against their competitors to protect their lawfully gained labels. He described such suits as in the "economic self interest" of companies that had made "an honest effort to market products lawfully." Such lawsuits have not occurred to date, but should they start to be filed, they would represent a significant expansion of off-label investigations.

Mr. Loucks also recently indicated that with the advent of Medicare Part D and Medicare's expanded payments for prescription drugs, the government will maintain its focus on pharmaceutical marketing activity.

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