

Legal and Economic Perspectives Concerning US Government Investigations of Alleged Off-Label Promotion by Drug Manufacturers

Paul E. Kalb¹ and Paul E. Greenberg²

1 Sidley Austin LLP, Washington, District of Columbia, USA

2 Analysis Group, Inc., Boston, Massachusetts, USA

Over the past few years, many pharmaceutical manufacturers have settled claims brought by the US Department of Justice (USDOJ) alleging that the drug companies engaged in illegal, off-label product promotion. Between 2003 and 2007, 11 investigations involving off-label promotion in the US were settled. Six of those investigations settled in 2007 alone.^[1] In addition, Pfizer Inc. recently announced a reserve in the amount of \$US2.3 billion related to the alleged off-label promotion of the cyclo-oxygenase-2 inhibitor Bextra[®] (valdecoxib), as well as issues relating to several other drugs, and Eli Lilly and Company recently settled claims, for approximately \$US1.4 billion, that it promoted its atypical antipsychotic drug Zyprexa[®] (olanzapine) for unapproved uses.^[2]

In this editorial, Paul E. Kalb, MD, JD, and Paul E. Greenberg, MA, MS, offer legal and economic perspectives on the issue.

1. A Lawyer's Perspective

Following US FDA approval, many drugs are studied by clinical investigators for uses other

than those approved by the FDA. In some, but by no means all, instances, manufacturers rely on the results of these studies to seek supplemental FDA approvals, but even when they do, there is generally a substantial lag between the time that clinical data are available and FDA approval. Thus, at any given time, there tends to be a large body of data available to clinicians concerning unapproved uses of FDA-approved drugs.

Because the FDA does not regulate the practice of medicine, physicians, constrained only by their professional obligations, may prescribe drugs for uses that have not been approved by the FDA. This practice of off-label prescribing is quite common, especially in rapidly evolving fields such as oncology.¹ In that field in particular, physicians and their patients must weigh not only the risk of treating with a drug (a central concern of the FDA), but also the risk of not treating (which is not a primary focus of the FDA). Physicians' decisions to prescribe off label are informed by the available scientific literature, and it stands to reason that the more truthful, non-misleading data available, the more informed their decisions will be.

1 An *Annals of Oncology* editorial^[3] indicated an off-label use rate of more than 20%. Poole et al.^[4] found that 85% of cancer patients were given at least one drug off label. The US-based National Comprehensive Cancer Network (NCCN) estimates that today 50–75% of all uses of drugs and biologics in cancer care are off label.^[5] A General Accounting Office (GAO) study^[6] found that 56% of cancer patients were given at least one drug off label.

The US Government's crackdown in recent years on 'off-label' promotion is presumably driven by the view that suppressing manufacturer dissemination of information about off-label uses will benefit public health (by, *inter alia*, forcing manufacturers to seek more supplemental FDA approvals). But off-label information is not homogeneous. Thus, it may follow that suppressing untruthful or misleading information advances public health, but there is no reason to believe that suppressing the dissemination of truthful, non-misleading information will have the same effect. Indeed, there is a serious risk that aggressive enforcement against manufacturers who disseminate truthful, non-misleading off-label information will chill the dissemination of such information – as well as associated activities such as investment in Phase IV research and support for Continuing Medical Education (CME) – to the detriment of both physicians and their patients.

2. An Economist's Perspective

Notwithstanding the issues described above, the reality is that government prosecutors continue to pursue many off-label actions; thus, at times, it is necessary to calculate potential damages for purposes of either settlement or trial.^[7] From an economic perspective, two types of damages are often of potential concern: (i) government loss, based on the claim that US federal and state healthcare programmes (e.g. Medicare and Medicaid) must be reimbursed for having sustained elevated reimbursements as a result of the conduct at issue; and (ii) corporate gain, where the damages are premised on the need to disgorge the gain that resulted from the wrongful conduct.

No matter what damages approach is taken, several practical issues must be addressed, including figuring out just how much off-label prescribing actually occurred over a defined time period. This is complicated by the potential range of off-label prescribing, including disease state; targeted patient population (e.g. paediatric); patterns of treatment (e.g. dosing and dose frequency, initial vs subsequent line of therapy,

acute versus chronic use of the drug); and efficacy, safety or adverse effect profile relative to competitors. In the past, US Government investigations alleging illegal off-label promotion by the manufacturer have focused on various combinations of these concerns with respect to specific drugs.

In each of these off-label promotion scenarios, definition of what is off label may be difficult. For example, for chronic diseases with many associated symptoms, treatment on any given day may be characterized as primarily intended to address either the patient's most disconcerting symptom(s) on that day, or the underlying chronic illness giving rise to that specific symptom. The challenge is that the first characterization could well translate into a determination that the drug was used for off-label purposes, but the second could result in an on-label classification of the drug's use on that particular day. This ambiguity over how to separate on- versus off-label prescriptions often can be resolved with attention to administrative claims data, a commonly used source in pharmacoeconomic analysis. US Government (e.g. Medicaid, Medicare) and private payer datasets offer detailed patient claims histories for large segments of the insured population, and offer insight into disease and drug-use patterns over time on a patient-by-patient basis.

Another critical step in an economic analysis of the conduct at issue is to determine what portion of off-label sales is attributable to improper promotion as opposed to confounding factors. Assuming liability is established, quantifying damages requires isolating the impact of illegal off-label promotion on sales. This can be challenging, since purchases of prescription drugs may be driven by many factors, including the following:

- the characteristics of the product versus competing compounds (e.g. safety, efficacy and adverse effect profiles);
- patient needs given medical and prior drug-use history;
- physician experience with the drug;
- extent of scientific support for the drug's use in on-label as well as off-label ways; and

- economic/business conditions (e.g. number of compounds in the therapeutic class, price of product and competing compounds, nature and extent of promotion of product and competing compounds).

Pharmacoeconomics also provides important methodological grounding in this type of situation in its insistence on monetizing all known costs and benefits associated with the use of one drug compared with another. Thus, if a US Government investigator alleges that a drug was promoted off label, such that too many prescriptions were reimbursed, a hypothetical scenario can be constructed in which illegal promotion did not occur. In that construct, the cost of the extra prescriptions of the drug in question would need to be offset by the cost of the next best alternative drug that likely would have been forthcoming in its place. In addition, any reduction in patient benefits associated with the use of that next best drug should also be considered in the analysis.

3. Conclusions

In the pharmaceutical industry, the flow of scientific information about new ways of using existing drugs moves at a faster pace than the regulatory process. This can generate beneficial treatment options for patients on a separate timetable from potential regulatory review. This reality has important public-policy implications, particularly with respect to the dissemination of truthful and non-misleading off-label scientific information. In addition, this reality has important implications for economic assessments of damages, to the extent that the US Government chooses to continue to prosecute these types of cases.

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Correspondence: *Paul E. Greenberg*, Analysis Group, Inc., 111 Huntington Avenue, 10th Floor, Boston, MA 02199, USA.

E-mail: pgreenberg@analysisgroup.com