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Economic Analysis In Off-Label Promotion Cases

Law360, New York (February 09, 2009) -- In an increasing number of government investigations, the central allegation is that a pharmaceutical manufacturer promoted one of its products off-label. Many of these investigations have resulted in hundreds of millions of dollars in payouts by drug companies.

The sheer number of these investigations and magnitude of settlements, as well as the complex regulatory, scientific and business environment in which prescription drug sales occur, suggest a key role for economic analysis.

Newly announced U.S. Food and Drug Administration regulations that permit pharmaceutical companies to distribute copies of medical journal articles describing unapproved drug uses are likely to add further to this complexity.

In some investigations, the focus has been the disease or medical condition for which a drug was allegedly promoted, while in other investigations, the target population has been of primary interest (e.g., pediatric, elderly).

At times, the leading concern has been the alleged promotion of off-label patterns of treatment (e.g., initial versus subsequent line of therapy, acute versus chronic use of the drug), while in other instances off-label promotion of higher-than-indicated doses has invited close scrutiny.

In still other matters, the government's primary focus has been the promotion of a beneficial property of a drug that is alleged to help its manufacturer establish a more competitive footing compared with alternative interventions (e.g., breast cancer prevention property, equivalent or more favorable safety profile relative to comparator products).

Even if off-label promotion by drug manufacturers is not permitted, a physician can prescribe a medication for a non-approved use if it is medically appropriate. In practice, physicians often choose to prescribe medications for unapproved uses for a variety of reasons.

Off-label prescribing is common when there is substantial unmet need — for example when treating painful conditions, cancer and mental illness — and the physician has tried other available on-label therapies. In such instances, resolving patient symptoms may be best achieved with off-label prescribing.

Government charges of manufacturer wrongdoing with respect to off-label promotion can include civil false

claims as well as criminal violations.

From an economic perspective, these legal theories generally translate into two types of damages: (1) government loss, based on the claim that federal and state health care programs (e.g., Medicare and Medicaid) sustained elevated reimbursements as a result of the conduct at issue; and (2) corporate gain, where the damages are based on the gain that resulted from the wrongful conduct.

In instances where liability can be established, a central economic issue under both legal theories involves separating out off-label sales due to off-label promotion from those that would have occurred anyway even in the absence of the conduct at issue.

This often requires analysis of numerous confounding factors in the marketplace which, taken together, may have contributed substantially to the observed level of off-label prescribing.

But before any causation analysis can be implemented, it is necessary to distinguish on- versus off-label sales. Doing so requires careful attention to the available data.

In many therapeutic classes, there exist detailed surveys of physicians' prescribing habits. This includes widely cited data sources such as NDTI (IMS) and PDDA (Verispan), which collect information on the primary medical reason for recommending a specific drug during a patient encounter. Such data sources can provide some insight concerning the range of drug uses.

While these off-the-shelf sources are often relied upon in government investigations to assess the rate of off-label prescribing, at times they may be inadequate because they do not take full account of the patient's medical history. Instead, they focus solely on stated clinical considerations the day the drug was recommended.

For chronic diseases with many associated symptoms, on any given day, treatment may be characterized as primarily intending to address either the patient's most disconcerting symptom(s) on that particular day, or the underlying chronic illness giving rise to that specific complaint.

But whereas the first characterization could well translate into a determination that the drug was used for off-label purposes, the second designation could result in on-label classification of the drug's use.

Such ambiguity can be settled with attention to the patient's full medical profile, which can be accomplished using several different approaches.

One strategy, where such data are available, is to rely on company surveys specifically designed to assess on- versus off-label use over time.

Another approach is to examine administrative claims data (e.g., Medicaid, Medicare, private payer), which capture patient encounters with the healthcare system that trigger insurance claims for the payer. These data contain patient medical histories, including disease and drug use patterns.

By bringing to bear a rich longitudinal perspective, these data make it possible to go beyond the limits of market research like NDTI and PDDA. Instead, analysis of actual patient health care use over time allows for more informed classification of on- versus off-label use.

The next 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.

Other drivers of off-label prescribing could include unmet need for the conditions in question, emerging scientific information about the drug, changing reimbursement rules, label changes in other countries for the drug under investigation, and label changes in the U.S. of therapeutically equivalent drugs.

Here, economists draw upon a number of techniques, from yardstick approaches to more elaborate statistical methods. A yardstick approach can be useful in establishing levels of off-label sales for the period in question by identifying a benchmark time period or a comparison set of similar products in the same therapeutic class.

The goal with both yardstick measures is to develop an estimate of the background rate of off-label prescribing that would have occurred in the absence of the conduct at issue in the investigation.

Alternatively, more sophisticated statistical analysis, such as regression modeling, may be helpful to accomplish the same objective where no such yardstick measure exists.

Using these methods, it is possible to estimate sales stemming from off-label promotion, a key input into the estimation of damages in connection with both criminal and civil charges.

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