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What Attorneys Should Know About FDA's MedWatch Data

Law360, New York (January 29, 2014, 5:11 PM ET) -- Following the introduction of new pharmaceuticals, reports of adverse events often surface in the news media. Some drugs, particularly blockbusters, eventually become the subject of lawsuits. Attorneys involved in these cases need to be fully informed about the quality and limitations of the spontaneous adverse event data used by the U.S. Food & Drug Administration, pharmacovigilance researchers and activist groups in monitoring post-marketing drug safety. Ignoring the limitations of this data may result in erroneous inference about the causal relationship between drug use and reported adverse events.

A recent example illuminates the pitfalls of such an assumption and centers on the smoking cessation drug varenicline marketed by Pfizer in the United States since 2006 as Chantix. Following mounting claims by users and plaintiff attorneys that Chantix had caused serious side effects such as depression and suicidal thoughts, the FDA required Pfizer to include a black-box warning about these risks on its product package in 2009. However, in September 2013, the results of a new randomized clinical trial involving Chantix were announced, showing that users of the drug were no more likely to experience depression or thoughts of suicide than were those taking a placebo.[1]

How could these recent clinical trial results differ so radically from the spontaneous adverse event reports in the FDA's MedWatch data? Often, this difference arises out of a misuse and/or misunderstanding of the information available through post-marketing surveillance data and the appropriate methods required to properly analyze and interpret such data. Litigators and triers of fact must understand the limitations of spontaneous adverse event data and their implications to correctly evaluate the merits of their use.

Drug Approval and Causal Relationships

Before a new drug is launched, it must go through several phases of development, including multiple rounds of testing of its efficacy and safety, and a strict regulatory approval process. In the United States, drugs cannot legally be sold without the FDA's approval, which is awarded only after a series of Phases I-III clinical trials establish that the drug is safe and efficacious. Based on the outcome of these trials, the FDA assesses whether the drug works as intended, whether its therapeutic benefits outweigh known risks,[2] and, based on these observations, whether or not to approve the drug. These clinical trials are well controlled and randomized and are considered the gold standard when it comes to evaluating safety and efficacy.

Accurately assessing the efficacy and safety of a drug in a post-marketing setting requires establishing a causal link between the drug and the safety outcome of interest amid complex real-world drug utilization patterns. For example, suppose we observe a patient suffering a myocardial infarction after

taking "Drug A." That information in itself is not sufficient to prove causality because “confounding factors,” such as smoking, may have caused or significantly contributed to the event.[3] Since smoking significantly increases the risk for myocardial infarction, it is difficult to isolate the cause of the heart attack: Is it due to smoking, to use of the drug, to both, or to neither?

The influence of confounding factors must be evaluated to appropriately determine causation. Establishing causality in the real world absent a protocol-driven clinical trial framework is difficult because the patient may not use the drug as directed, may use other drugs and may have comorbidities, all of which can contribute to the adverse event. The goal of pharmacoepidemiology is to tease out the role of the drug of interest amid a host of confounders.

Potential Misuse of MedWatch Data in Drug Safety Litigation

At the core of post-marketing monitoring is a spontaneous reporting system for collecting reports on adverse events and quality problems (i.e., MedWatch) and a database that maintains information on adverse drug reactions (the FDA Adverse Event Reporting System, or "FAERS" — formerly known as "AERS").

A single, one-page form is available online for anyone, including health care professionals, family members, patients and manufacturers to report, on a voluntary basis, any suspected adverse events to the FDA or drug manufacturers. The FDA has relied on this data as one of many factors in deciding whether to issue product safety alerts, update a product’s label, restrict access to a drug, request additional information or analysis from the manufacturer or remove a product from the market.

While FAERS data play an important role in safety signal generation and serve as a useful surveillance and regulatory instrument, important biases and caveats have been identified by the FDA and the pharmacovigilance research community and spelled out in the academic and scientific literature. There are several flaws and biases, including the varying quality and unverified nature of voluntary reports, significant under-reporting, duplicative reports, more intense reporting for new drugs (the “Weber effect”), increased reporting spurred by publicity, black-box warnings and product withdrawals as well as the lack of any information about the underlying rate of use.[4]

Because of their shortcomings, establishing a causal link between a drug and a particular adverse event based on voluntary spontaneous reports can be especially challenging. In litigation, however, this data has been misused to imply a causal relationship between a drug and an adverse event. For example, safety signals have been implied based on a count of adverse events concomitant with a particular drug use over time. However, without information about the rate and risk of adverse events, a review of concomitant therapies, an examination of the timing of the adverse event, the dosage used and many other elements, such reports do not provide a scientifically valid basis for any affirmative conclusion.

Are 100 reported adverse events a lot? What if 100 patients took the drug? How about a million patients? Similarly, if a drug’s sales went from 1,000 to 1 million and adverse event reports increased from 1 to 100, should that cause increased concern? Probably not, since the rate of adverse events would be decreasing, not increasing, despite a higher count of adverse events. A count of adverse events is clearly an insufficient basis from which to draw any conclusions on safety.

Beyond the obvious limitations of a crude count, the potential for confounding factors further complicates any interpretation of spontaneous adverse event reports. Specifically, even if it were possible to calculate a rate of reported adverse events among patients using a particular drug, there is

no way to know whether that rate is higher, lower or exactly what would be expected given the health profile of the population taking the drug. It may also be higher, lower or the same as the rate of adverse events among patients taking an alternative therapy.

Absent appropriate context,[5] one cannot generate a reliable hypothesis about the potential relationship between a drug and an adverse event based solely on its spontaneous reports, let alone establish a causal relationship between the drug of interest and the adverse events reported. Significant further analysis is needed.

Appropriate Analysis of Post-Marketing Surveillance Data

Pharmacovigilance — a branch of pharmacoepidemiology referring to the science of detecting and assessing spontaneous adverse event reports associated with drug use — often involves an analysis of reports from FAERS.[6] A correct pharmacovigilance analysis will use the spontaneous reports about a given drug as a starting point as opposed to an end point and will seek to identify and then test potential safety signals. In addition to providing an early, albeit incomplete and potentially biased, tool to examine the nature of adverse drug reactions ("ADR") and generating safety signals, FAERS data can also be useful as a point of entry to identify risk factors for ADRs.

The identification of a signal often results from a systematic examination of the reported adverse events using statistical tools.[7] For a given drug and adverse event, analysts seek to compare the reporting rate of the adverse event in different populations to identify any indication that the drug is leading to a higher-than-expected rate of the adverse event.

The most often cited and used data analytic methods include, among others, the proportional reporting ratio ("PRR"), the multi-item gamma poisson shrinker ("MGPS") algorithm, and reporting odds ratios ("ROR").[8] While their names may suggest exotic mathematical exercises, these methods follow a simple three-step process. First, a comparator patient population is constructed with an expected frequency of a specific adverse event/drug combination. Second, this constructed frequency is compared to the observed frequency of adverse events. Finally, the results are statistically examined for any potential safety signal.

Despite the limitations of the FAERS data, these more sophisticated data analytic methods improve the interpretability of this data and the scientific validity of hypothesis generation regarding potential adverse event/drug relationships. Following the identification of a potential safety concern through a signal detection analysis, further scientific evaluation, including options such as large population-based epidemiological studies and Phase IV safety clinical trials, provide the next levels of evidence in assessing the strength of causal association between the use of a drug and the subsequent adverse event.

In conclusion, although FAERS data about a specific drug can be useful in helping drug safety researchers and policymakers generate hypotheses on potential drug safety signals, when coupled with appropriate analytical methods, attorneys should understand the limitations and potential misuse of those data, particularly in a litigation context.

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[1] Anthenelli, Robert M., et al, "Effects of Varenicline on Smoking Cessation in Adults with Stably Treated Current or Past Major Depression: A Randomized Trial," Annals of Internal Medicine, 2013: 159(6), pp. 390–400.

[2] "Development & Approval Process (Drugs)" U.S. Food and Drug Administration, http://www.fda.gov/Drugs/DevelopmentApprovalProcess/default.htm, visited on June 9, 2011.

[3] Confounders may be considered a confusion of effects, or extraneous factors that distort the apparent effect of the drug. (Rothman, Kenneth and Sander Greenland, Modern Epidemiology)

[4] See, e.g., Food and Drug Administration, "Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment," available at http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126834.pdf; Stephenson, Wendy P., and Manfred Hauben, "Data Mining for Signals in Spontaneous Reporting Databases: Proceed with Caution," Pharmacoepidemiology and Drug Safety, 2007:16, pp. 359–365; and Almenoff, June, et al., "Perspectives on the Use of Data Mining in Pharmacovigilance," Drug Safety, 2005:28(11), 981–1007.

[5] Assessment of a potential relationship between a drug and an adverse event must be undertaken within the appropriate context — e.g., the population taking the drug or a specific subset of that population. (See, e.g., Pariente, Antoine, et al., "A Potential Competition Bias in the Detection of Safety Signals from Spontaneous Reporting Databases," Pharmacoepidemiology and Drug Safety, 2010:19, pp. 1166–1171.)

[6] See, e.g., Food and Drug Administration, "Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment," available at http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126834.pdf; Ahmad, Syed Rizwannuddin, "Adverse Drug Event Monitoring at the Food and Drug Administration," Journal of General Internal Medicine, 2003:18, pp. 57–60; and Stephenson, Wendy P., and Manfred Hauben, "Data Mining for Signals in Spontaneous Reporting Databases: Proceed with Caution," Pharmacoepidemiology and Drug Safety, 2007:16, pp. 359–365. An assessment of data from SRS is often performed "as a supplement to qualitatively examining individual case reports." (Hennessy, Sean, "Disproportionality Analyses of Spontaneous Reports," Pharmacoepidemiology and Drug Safety, 2004:13, pp. 503–504.)

[7] Food and Drug Administration, "Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment," available at http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126834.pdf.

[8] See, e.g., Food and Drug Administration, "Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment," available at http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126834.pdf; and Stephenson, Wendy P., and Manfred Hauben, "Data Mining for Signals in Spontaneous Reporting Databases: Proceed with Caution," Pharmacoepidemiology and Drug Safety, 2007:16, pp. 359–365.
