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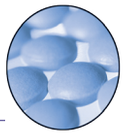

Product Liability in the Pharmaceutical Industry:

A Growing Role for Quantitative Analysis

by Pierre Y. Cremieux, Ph.D. and Paul E. Greenberg, M.A., M.B.A.

A variety of medical and legal forces are converging to create a demanding new context for class-action lawsuits involving pharmaceutical product liability. From a medical perspective, this shift began in 1977, with the introduction of the anti-ulcer drug, Tagamet®—the first long-term daily-use medication targeting quality of life rather than survival. Prior to that time, most drugs had been aimed primarily at acute conditions requiring short-term treatments; whole new classes of drugs have since emerged to address chronic illnesses, including conditions like high blood pressure, high cholesterol, osteoporosis, depression, allergies, migraines, and chronic pain. As new pharmacotherapies have become widely used, increasing numbers of patients have consumed them for five or 10 years, or more—far longer than the typical duration of clinical trials required for initial Food and Drug Administration (FDA) approval. With widespread polypharmacy in evidence, unforeseen side effects and drug interactions have also arisen.

Simultaneously with this new chronic pharmacotherapy, plaintiffs' lawyers, having won significant victories in asbestos and tobacco lawsuits, have turned their attention to pharmaceutical litigation. The number of class-action, mass tort lawsuits in this area has increased, spurred, for example, by FDA-initiated drug withdrawals due to safety concerns or by a warning label change on a long-marketed product. These complex class actions at the nexus of epidemiology, economics, and statistics, together with recent legal developments such as *Daubert v. Merrell Dow Pharmaceuticals*,[1] *Kumho Tire Co. v. Carmichael*,[2] and amendments to Rule 702 of the Federal Rules of Evidence, have raised the expectations and standards for expert testimony in such litigation. Trial judges must ensure that all testimony based on scientific knowledge (as well as technical and other specialized knowledge) is not only relevant, but also reliable. Reliability is assessed by investigating:

- whether the expert's technique or theory can be tested in some objective sense, or instead is simply a subjective, conclusory approach that cannot be assessed for reliability;
- whether the technique or theory has been subjected to peer review and publication;
- what the known or potential rate of error of the technique or theory is when applied;
- what the standards and controls are and how they are maintained;
- whether the technique or theory has been generally accepted in the scientific community.

This new context of increased litigation and higher standards for expert testimony often calls for a rigorous quantitative approach to pharmaceutical class action lawsuits. While quantitative evidence has been used in such cases, today's legal environment demands that available data be analyzed more thoughtfully, systematically, and comprehensively than ever before. Increasing numbers of relevant data sources (e.g., FDA safety data, comprehensive payer datasets, clinical trials results, epidemiological studies, and market research), coupled with appropriate analytical methods that often draw on techniques originating in the fields of economics, epidemiology, and health outcomes research, have become invaluable tools to address issues such as class certification and damage assessment.

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Some Useful Databases

Pharmaceutical mass tort investigations often rely on a variety of industry sources, each of which possesses distinctive characteristics that determine its case-specific relevance.

MedWatch

MedWatch (FDA's safety information and adverse event reporting program) is a compilation of clinical information on product safety issues. Its contents are obtained from voluntary reporting by healthcare professionals and consumers who suspect an association between an adverse event and a drug or medical device they prescribe, dispense, or use. In addition, drug companies are required to report any adverse events associated with their medical products. This data source is readily available and widely used by regulators, sponsors, and marketers, thus contributing to its timeliness. The experiences of all real-life consumers may not be fully represented in MedWatch, however, as adverse events likely are underreported prior to a legal action and overreported immediately thereafter. Nevertheless, it can be a valuable information source in the context of pharmaceutical mass tort litigation.

For example, the characteristics of patients with adverse events who used the drug at issue in a lawsuit can be compared with those of patients with adverse events who took its nearest competitor drug. By comparing the demographic and medical characteristics (e.g., age, gender, comorbid disease profile, concomitant drug use, and nature of adverse event) of two patient groups using appropriate statistical techniques, it may be possible to better understand the causation path between the adverse event and the drug itself.

Administrative Health Insurance Claims Databases

These databases include detailed descriptive information concerning virtually any encounter between a privately- or publicly-insured patient and the healthcare system.[3] This includes, for example, all claims made by providers for inpatient and outpatient care, visits to physicians or other healthcare providers, drugs, and laboratory tests. For the employed population, these data also may include work loss resulting from sick leave, as well as short- and long-term disability. Because insurers record each financial claim in great detail, such databases can provide large, representative samples of systematically- and uniformly-collected, longitudinal patient profiles. Widely respected, peer-reviewed medical, health economic, and managed-care journals often include scholarly analyses based on such data.

In a litigation context, claims data can provide a wealth of information related to patients taking the drug at issue in the litigation, including:

- demographics (e.g., age, gender, marital status, number of dependents);
- financial responsibility for health costs (e.g., patient out-of-pocket costs, amount of reimbursements by payer);
- medical history (e.g., contraindicated comorbid conditions and/or drugs);
- usage of the drug in question (e.g., frequency, dosage, titration); and
- timing and severity of any subsequent adverse event that is alleged to result from usage of the drug.

Using this resource, patient-by-patient facts can be compiled to provide a detailed set of information upon which to investigate issues of class certification and damages.

Pre- and Postmarketing Clinical Trials

Clinical trials are required as part of FDA's new drug application approval process, and may be supplemented by manufacturer-funded investigations to add labeled indications, to document product advantages compared with a variety of alternative drugs, or to establish real-world usage patterns versus pre-existing standards of care. These studies provide detailed data concerning patient response to a drug, often in a carefully-monitored environment.

Clinical trials can last anywhere from several months to a few years, and include less than a hundred to several thousand patients from a carefully selected population. Depending on their design and purpose, they may offer only limited generalizability to real-life drug user populations. Because these types of studies tend to capture only short-term pharmacological effects on a narrow patient population, they may fail to capture adverse events that are confounded by drug and comorbidity interactions based on longer-term drug usage in real-world settings. Despite this limitation, well-controlled clinical trials are widely seen as a "gold standard" for clinical research, and can provide invaluable scientific evidence to evaluate some types of claims in a mass tort drug case.

Open-label clinical trials can provide additional useful patient-level medical data. These types of trials generally are initiated after the drug has been approved, usually include larger patient samples, and often have less strict patient inclusion/exclusion criteria. Because these studies usually are not blinded or placebo-controlled, sophisticated biostatistical, epide-

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miologic, and/or econometric methods often are needed to properly address sample selection biases and other non-random clinical trial characteristics.

Despite possible limitations, clinical trial data can provide the most detailed assessment of patient response to a drug intervention from a medical perspective, and, thus, can be valuable in understanding the relationship between a drug's use and a claimed adverse event consequence.

Epidemiological Studies

Epidemiological studies may be conducted to test or confirm previously suspected associations between adverse events and drugs. When pharmaceutical companies originate and monitor such population-based studies to develop scientifically rigorous data on a large, representative sample with a longitudinal dimension, they can provide a rich alternative to either the MedWatch system or administrative claims data. Academic researchers and government agencies also may initiate epidemiological studies to assess a variety of policy issues (e.g., determinants of the quality of medical care provided to different patients for a particular disease).

Because all of these studies are based on survey responses (unlike administrative claims, which are archival in nature), data concerning both treated and untreated sufferers of a particular disease can be compiled using this population-based approach. This source may provide an additional benchmark for comparison with the group of patients using the drug. Of course, the survey nature of these data may require appropriate statistical adjustments to address possible response biases. Similarly, attention to the survey design will be important to ensure data reliability.

Market Research Sources

The pharmaceutical industry generates many market research sources, some of which are designed primarily as a strategic input and basis for decisionmaking by manufacturers (e.g., IMS, Scott Levin), while others are developed by constituent groups within the healthcare sector (e.g., National Community Pharmacists' Association, Healthcare Distribution Management Association, and National Association of Chain Drug Stores). Unlike the sources noted above for which patient-level details are provided, market research sources often report more aggregated information (e.g., retail drug store purchases and sales, manufacturer promotional activities, physician prescribing patterns, and industry trends). These data sources often are available over longer time periods than patient level data, and may be especially valuable in analyzing legal claims that span long time frames.

Class Certification Considerations

Class certification in a pharmaceutical industry case can be complicated by the unique structure of the healthcare sector. In many industries, consumers simply purchase and pay for a product from a manufacturer with relatively few—or even no—intermediaries (e.g., a car from an automobile dealership affiliated with the manufacturer, or a sandwich from a local deli). In contrast, a variety of intermediaries stand between a drug's consumer and its manufacturer, including the prescribing physician, the dispensing pharmacist, and the reimbursing authority that pays all or part of the price (e.g., private insurer or government agency). There may be myriad paths through which consumers receive, and pay for, a product at issue in the lawsuit. This idiosyncratic industry structure bears on the question of whether issues common to the prospective class predominate over individual issues that should be considered on a matter-specific basis.

In addition to market-structure-based investigations, statistical analyses of patient medical conditions may further inform whether a class should be certified. Individuals joined in a proposed class may appear to have many similarities, including having all taken the same drug and suffered an adverse event. This apparent similarity, however, may obscure highly varied causation paths and other significant points of distinction.

For example, many members of an aging population, suffering from multiple health problems, present complicated comorbidity profiles and health histories. The duration, frequency, and dosage of a drug can vary substantially among individuals, producing a wide array of medical effects. The adverse events themselves may vary substantially in type and medical severity, as individual patients often respond differently to seemingly identical treatments. Many patients take several drugs regularly, vastly complicating the isolation of a single causal pathway for a given adverse event profile. There also may be substantial variation in out-of-pocket drug expenditures among patients throughout the country.

Careful consideration of each of these factors, with appropriate attention to the types of datasets described above, may provide critical input in determining the appropriateness of certifying a class of patients. In the absence of rigorous, quantitative analysis, determinations may be made on the basis of qualitative, emotional, or unduly aggregated considerations.

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Quantifying Damages

Data and methods relied on to determine the size, membership, and characteristics of the class can be a starting point for assessing the magnitude of drug-related injury. A further consideration for damages assessment is to distinguish those consumers who benefited as a result of the use of the drug from those who were harmed.

To assess the monetary value of the harm, methods grounded in the economics, epidemiology, and health outcomes research literature can be useful. For example, administrative claims databases could be used to calculate excess direct and indirect costs due to an adverse event resulting from the use of a specific drug. Direct costs could include the added expenses incurred for physicians' services, hospital stays, drugs, laboratory tests, and support therapy to treat the adverse event; indirect costs could include work loss that results from the adverse event.

Regardless of the precise approach taken, calculations of damages should be based on sound econometric and epidemiological methodology applied to appropriate databases.

Admissible and Convincing Testimony

Widely-recognized statistical techniques applied systematically to large databases can offer great advantages in pharmaceutical mass tort cases. Such techniques meet the higher standards of admissibility that have evolved during the past decade. They possess the requisite sophistication for addressing the highly complex issues of class certification, chains of causation, and economic harm that dominate class action suits. And, because they are grounded in economics, epidemiology, and health outcomes research, such specialized quantitative analyses promise to be far more convincing to triers of fact than those based on less rigorous and less specialized analysis.

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Analysis Group is an economic, financial, and strategy consulting firm.

[1] 509 U.S. 579 (1993).

[2] 526 U.S. 137 (1999).

[3] Paul E. Greenberg & Howard G. Birnbaum, *Administrative Claims Data: A Valuable Tool in Pharmaceutical Litigation*, FDLI UPDATE, Jan./Feb. 2004, at 12.

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