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A NEW WAY TO KEEP JUNK SCIENCE OUT OF THE COURTROOM

Can you say pharmacoepidemiology?

In more and more multidistrict litigations involving pharmaceutical products, discovery is bifurcated on the question of general causation; that is, the court determines whether plaintiffs' general causation theories survive *Daubert* before reaching the question of whether any plaintiff can prove specific causation. Although this approach has advantages and disadvantages for both sides, it is generally an efficient way to dispose of meritless litigation when plaintiffs' causation theories are questionable and may not pass *Daubert*, thus eliminating the need for case-specific discovery as to hundreds of plaintiffs. But, this approach only works if plaintiffs are required to prove general causation using reliable and accepted scientific methodologies. All too often, plaintiffs attempt to bypass *Daubert* with far less.

For instance, in recent litigation involving hundreds of cases claiming injury from a prescription drug, plaintiffs' attorneys paid their pharmacovigilance expert more than half a million dollars for a "signal detection" analysis based on post-marketing adverse event reports (AERs), which courts have repeatedly rejected as an unreliable basis for proving general causation. Worse yet, the expert testified that her "analysis" began years before any case was ever filed and far before the creation of the MDL, assuredly adding to the hefty price tag. Plaintiffs' willingness to spend this kind of money on analyses of AER data, which should by no means get them past their general causation hurdle, highlights the need for a requirement that plaintiffs, as a threshold matter, invest their resources in data analyses that might actually be meaningful to the court's gatekeeping role. The appropriate substitute is a pharmacoepidemiology analysis.

What is Pharmacoepidemiology?

Pharmacoepidemiology is the study of the use and effects of drugs in large groups of people. Pharmacoepidemiologic studies use peer-reviewed, published and generally accepted statistical methodologies to analyse medical information contained in large healthcare (medical records or claims) databases to determine whether the risk of an adverse event is higher on drug than off. Healthcare databases with clinical and prescription data are a valuable resource for large population studies that are specifically focused on the potential association between a drug and an adverse event. Typically, these data are not subject to the well-known pitfalls and limitations of FDA's adverse event reporting system, including the problem of extreme duplication in the FDA's AERs database, reporting biases as a result of adverse publicity (often initiated by plaintiffs' lawyers) and litigation.

Why Should Plaintiffs be Forced to do Pharmacoepidemiologic Analyses?

It is nothing new to say that plaintiffs should be required to present epidemiologic evidence of a statistically significant association between a drug and an adverse event as a threshold matter. Courts have consistently recognized the importance of epidemiologic studies to prove general causation. At least one federal court has made clear that "confirmatory epidemiological data" is necessary to prove general causation.[1] A pharmacoepidemiologic study fills in the evidentiary gap when plaintiffs cannot come forward with evidence of an association — either through controlled clinical study data or epidemiologic studies reported in the literature.

Properly conducted pharmacoepidemiologic studies using healthcare databases are an efficient, reasonable and cost-effective way (if conducted using reliable and generally accepted statistical methodology) to determine whether the adverse event alleged by plaintiffs is significantly associated with the prescription drug as alleged. In fact, leading statistician Brian Strom has recognized the advantages that existing healthcare databases offer, including their sample size (ranging from hundreds of thousands to millions of patients), the speed with which results may be obtained — as the data are already computerized — and the low cost, given the available sample size "relative to prospective studies."[2] A healthcare database can be purchased for as little as $15,000–30,000.

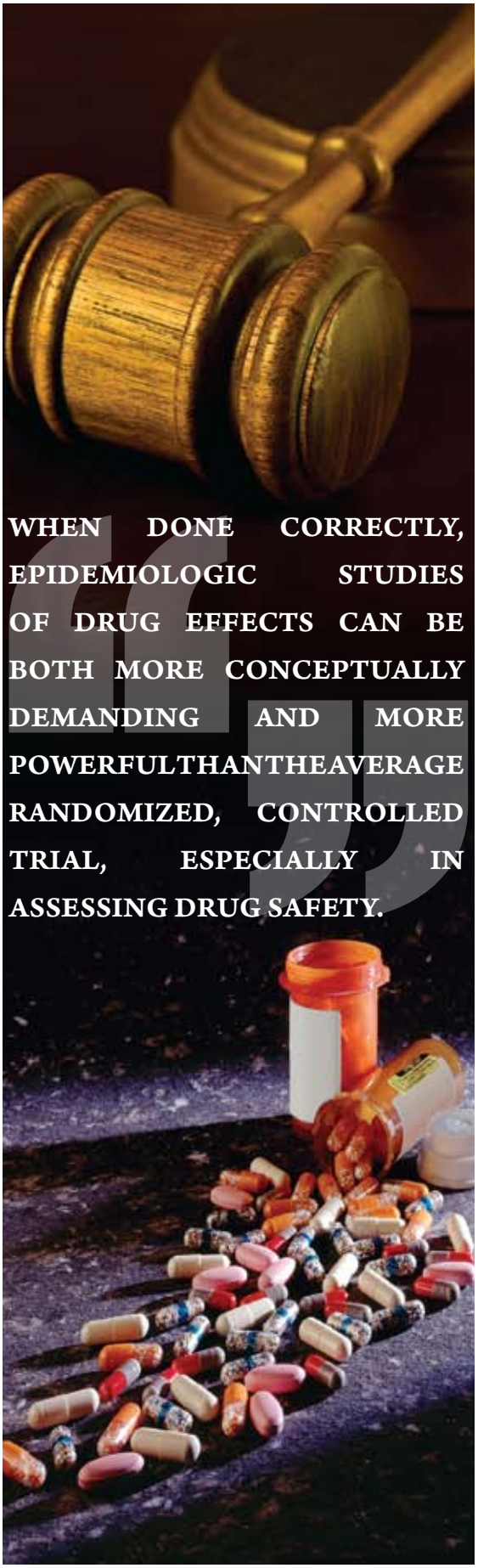
Perhaps more important, properly conducted pharmacoepidemiologic studies provide a far superior and reliable method of assessing whether a drug is truly associated with an increased risk for the specific adverse event alleged than the alternatives most often used by plaintiffs. In particular, they surpass analyses based on spontaneously reported adverse events, anecdotal case reports, improperly conducted meta-analyses and, arguably, even clinical studies (often criticized by plaintiffs as "underpowered" to detect the often "rare risk" raised in litigation). A 2007 article in the *New England Journal of Medicine* recognized these benefits: "When done correctly,

epidemiologic studies of drug effects can be both more conceptually demanding and more powerful than the average randomized, controlled trial, especially in assessing drug safety."[3]

Pharmacoepidemiologic analyses are likewise superior to "pooled analyses" of clinical trial data for multiple drugs from the same class. Although such analyses provide more data, they lack reliability and often lead to skewed results because the drugs are often only pooled according to approved indication, without regard to chemical structure, mechanism of action, pharmacologic properties or any other similarities. For example, this year FDA mandated an all-antiepileptic drug (AED) labelling change to include a warning regarding increased risk of "suicidality." This labelling change across all AEDs was based on a pooled or combined analysis of placebo-controlled clinical studies for 11 different antiepileptic medications whose only common factor was FDA approval for seizure disorder. Despite the fact that only two of the 11 drugs showed a statistically significant increased risk for "suicidality," thus skewing the results for the other nine, a class-wide warning was mandated for these and all drugs approved for seizure disorder. Plaintiffs' experts relied heavily on FDA's overall findings in the pooled analysis to support their general causation opinions as to a single drug for which no statistically significant increased risk was found.

Although FDA's pooled analyses in the public health arena have some merit, in the context of litigation, this type of analysis cannot be used to attribute causation to any single drug included in the dataset. Nor should FDA's "pooled data" methodology for public health purposes supplant plaintiffs' burden under *Daubert* to show by scientifically reliable methodology that the subject drug is statistically significantly associated with the risk alleged and that the association is causal. As courts have recognized, FDA takes regulatory action "upon a lesser showing of harm to the public than the preponderance-of-the evidence or more-likely-than-not standard used to assess tort liability."[4] These studies are not used by regulators to establish actual cause and effect — or even association on an individual drug basis — and plaintiffs should not be permitted to make more of the "pooled data" findings to argue causation than FDA.

Recently, the FDA has also noted the value that healthcare databases and pharmacoepidemiologic studies play in drug safety and is undertaking efforts to ensure that these data sources are used efficiently and effectively. In 2008, the Center for Drug Evaluation and Research and the Center for Biologics Evaluation and Research at FDA organized a public workshop and requested comments on "Developing Guidance on Conducting Scientifically Sound Pharmacoepidemiologic Safety Studies Using Large Electronic Healthcare Data Sets" to "exploit such databases more efficiently" and develop guidance and best practices for study design to detect health risks in regulatory assessment.[5]

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Given that pharmacoepidemiologic studies are cost-effective and more reliable than many alternatives, it can be argued that, without other evidence of a statistically significant association between the drug and the alleged adverse event, well-financed plaintiffs' lawyers should be required to invest in this type of scientific data analysis. It is well known that the prelitigation investment by plaintiffs' counsel in pharmaceutical product cases is substantial, often involving the engineering of Citizens' Petitions and associated publicity, retention and extensive use of expert services and concerted efforts to scour and analyse FDA's AER database for possible allegations of "missed signals" and internal "causality" determinations, all in an effort to manufacture a case that will ultimately reach a jury. Relatively speaking, the acquisition of a healthcare database is neither expensive nor difficult, and a pharmacoepidemiologic study using the database can be conducted with equal or less investment of time and money than these other efforts routinely undertaken by plaintiffs' lawyers to position themselves for big litigation.

Absence of Evidence is Not Evidence of Absence

The availability of healthcare databases for pharmacoepidemiologic study is a strong counterpunch to plaintiffs' well-worn excuse that "absence of evidence is not evidence of absence." The suggestion that "there could be something there" will not carry the day for plaintiffs, and the weight of authority is behind this. In one federal case, the plaintiffs' experts had no epidemiologic evidence of an association between Celebrex at a dose of 200 mg/day and heart attacks or stroke — the claimed events at issue in the litigation. Plaintiffs' experts attempted to extrapolate from observational studies involving other doses to prove general causation. In concluding that the extrapolation was unreliable, the court noted: "Instead of citing evidence that supports such extrapolation, plaintiffs complain that evidence of harm at 200 mg/day does not exist because Pfizer did not initiate long-term randomized trials at such a dose. Plaintiffs cite no case, however, that suggests that they can satisfy their burden of proof based on lack of evidence; plaintiffs filed these lawsuits and carry the burden of proof." [6] Plaintiffs' arguments about absence of evidence (or that defendants should be doing the work) should be met with little favour and can be readily attacked because of the accessibility of healthcare databases at relatively low cost and little burden.

Defendants' Use of Pharmacoepidemiologic Studies in Litigation

Even though it is unequivocally plaintiffs' burden, if defendants for whatever strategic reasons elect to conduct their own pharmacoepidemiologic study, a well-conducted study that shows no statistically significant association should be dispositive. A court must grant a motion for summary judgment if the moving party shows that there is no genuine issue of material fact such that the moving party is entitled to judgment as a matter of law. Defendants can do this through a favourable pharmacoepidemiologic study. Plaintiffs' attack on defendants' study as insufficient does nothing to satisfy their burden of proof through reliable scientific evidence that a drug can cause an adverse event. In other words, plaintiffs' experts should be required to present pharmacoepidemiologic data supporting their general causation opinions, and plaintiffs cannot rest their case on mere criticisms of the epidemiologic data that contradicts their opinions. Courts have noted that plaintiffs' criticism of the epidemiological studies does not satisfy their burden of proof. Plaintiffs cannot carry their burden simply by claiming defendants' pharmacoepidemiologic analysis was not good enough.

Limitations of Healthcare Database Analyses

Pharmacoepidemiologic studies have limitations. Some recognized limitations of certain "epidemiologic databases" include "lagtime" between data entry and availability, inadequate numbers of patients to study risks of extremely rare events and lack of information on confounding factors in certain databases. Available databases have different strengths and weaknesses; a variety should be researched and considered to determine the one best suited to the case. Another arguable limitation is the potential for litigation bias if the healthcare database analysis is conducted for litigation and has not been published in a peer-reviewed journal. To address this, a court could easily and inexpensively consult independent experts whose role would be to consider litigation-based studies and verify the validity and reliability of the methodology. Consulting experts could give the court reassurance if the study has not been peer-reviewed or published because it is too new or is of limited interest. Even with these limitations, pharmacoepidemiologic studies are still better and more reliable evidence than the alternative sources on which plaintiffs presently rely.

Conclusion

As federal courts continue to struggle with the proper parameters for admissibility of expert testimony on technical and scientific issues, a requirement that plaintiffs come forward with pharmacoepidemiologic evidence to support their claims will go far toward resolving *Daubert* challenges and, ultimately, eliminating meritless claims. **Pharma**

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