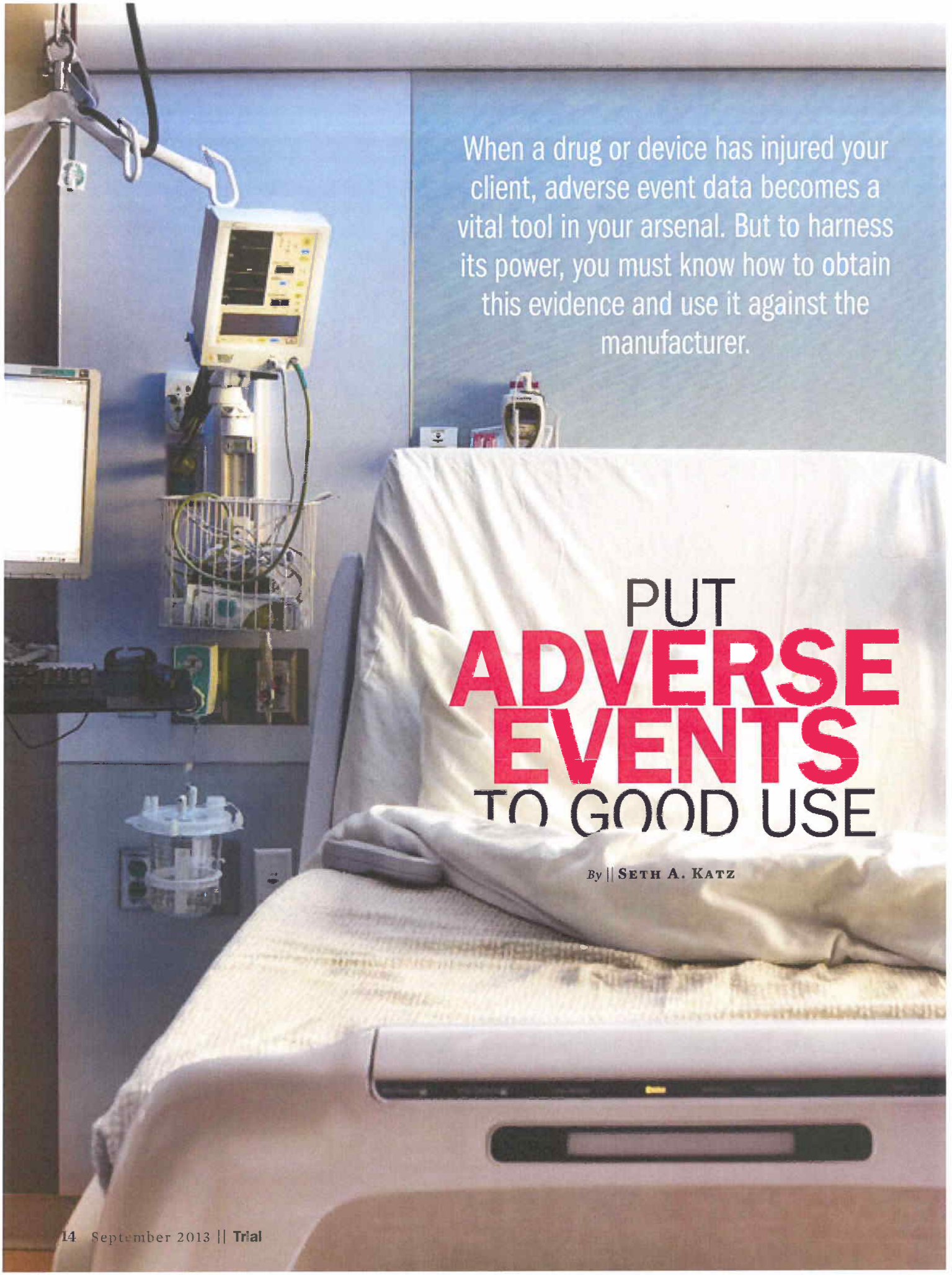
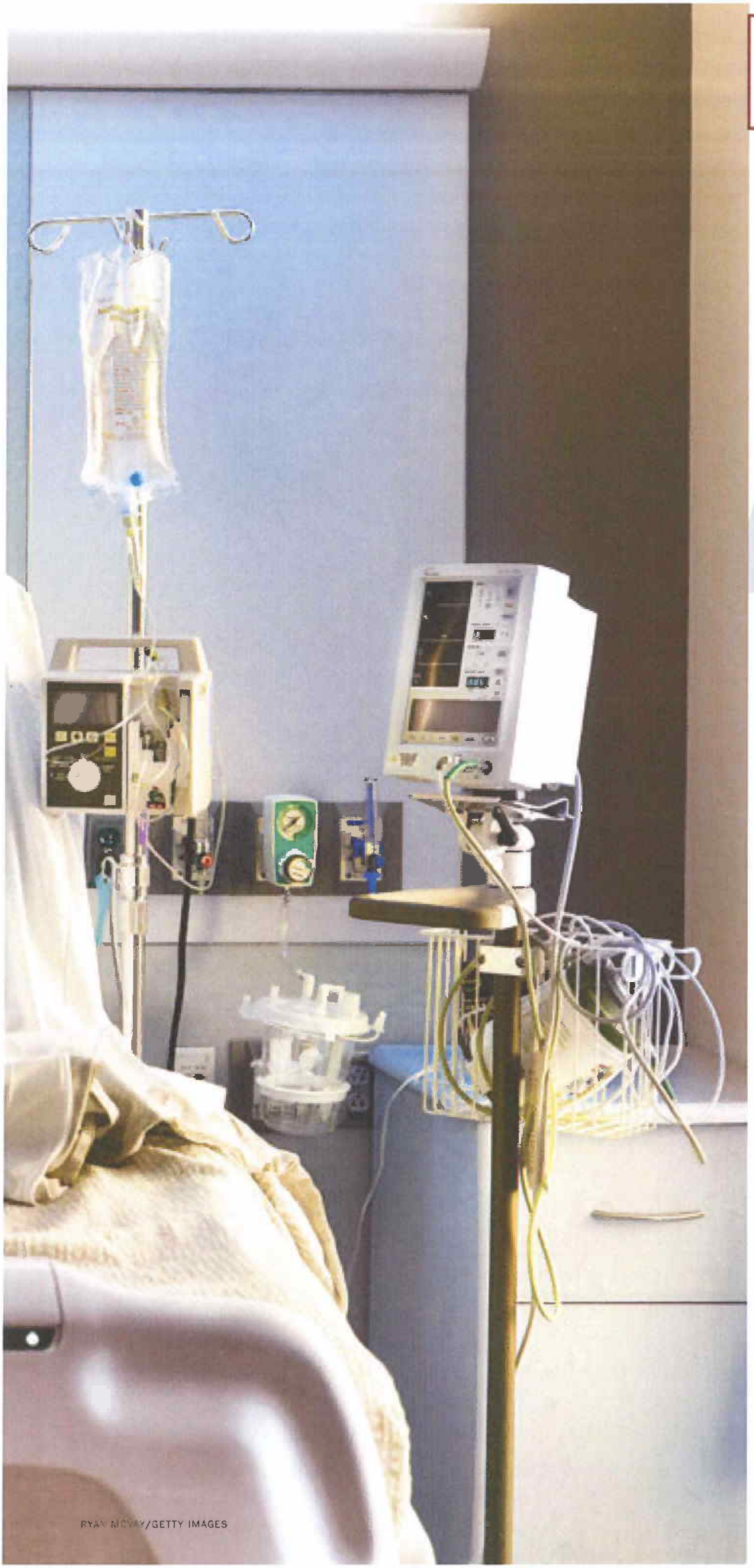


When a drug or device has injured your client, adverse event data becomes a vital tool in your arsenal. But to harness its power, you must know how to obtain this evidence and use it against the manufacturer.

PUT ADVERSE EVENTS TO GOOD USE

By || Seth A. Katz



RYAN MCVAY/GETTY IMAGES

Adverse event information can be a powerful litigation tool in pharmaceutical drug and medical device cases. Because it is aggregated data related to how the drug or device performs in a large user population, you can use it to help prove certain elements of your client's claims.

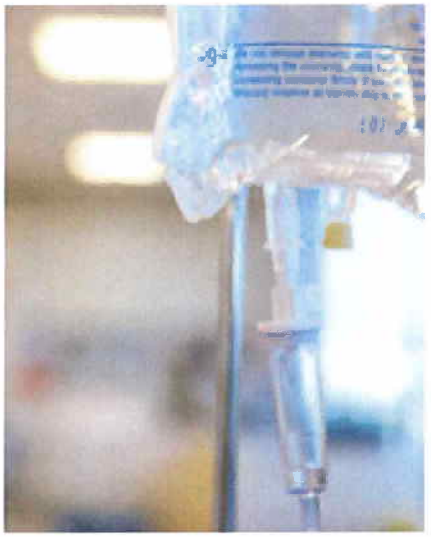
Plaintiff lawyers also should use adverse event data—both the aggregated information and information about a single adverse event—to evaluate potential claims. The data can be telling—it may reveal that the product does not demonstrate the problems or defect that you allege. You need to know how to get this information from the defendant during discovery and how to use the evidence you acquire to your client's advantage.

Adverse event information first comes into play when a manufacturer conducts clinical trials for a drug or device. If an adverse event is seen during a trial, it must be reported to the FDA. While a massive number of people may use the product once the FDA has approved it for sale, only a limited population is exposed to it during clinical trials. Assuming that the manufacturer adequately and accurately reports the adverse events seen during the product's development, this will form the basis for the product's initial label that is used on sale approval. A manufacturer, however, has an obligation to update its

label when it becomes aware of a safety risk. It is important to remember that medical ethics usually prohibit giving a drug to a population that might be susceptible to an adverse event during clinical trials. Therefore, postmarket adverse event reporting is critical to the ongoing evaluation of a product's safety.

Once the product is on the market, the manufacturer is required to file periodic reports with the FDA regarding adverse events.[1] Pharmaceutical companies compile brief doctor or patient statements, known as adverse drug experience (ADE) reports or medical device reports (MDR). The companies must submit all adverse events they become aware of to the FDA.[2] In the case of pharmaceuticals, the ADEs document "any adverse event associated with the use of a drug in humans, whether or not considered drug related."[3] With medical devices, manufacturers must report any event they become aware of that reasonably suggests that the device may have caused or contributed to a death or serious injury or that the device has malfunctioned in a way that would be likely to cause a death or serious injury.[4]

Adverse events are significantly underreported. Estimates are that between 1 and 10 percent of the number of adverse events that occur are actually reported.[5] While drug and device manufacturers are required to report adverse events they become aware of to the FDA, the reporting system for physicians and hospitals is voluntary—no agency or regulator requires hospitals, doctors, or pharmacies to file adverse event reports with the manufacturer or the FDA.[6] The reasons for health care providers' underreporting of adverse events have been studied and include difficulty in accessing report forms, lack of information on how to report, lack of time, different care priorities, uncertainty about the product causing the adverse event, and lack of awareness of the reason for reporting adverse events.[7]



DEFENDANTS COMMONLY CHALLENGE THE ADVERSE EVENT REPORTS' RELIABILITY, BUT THE FACT THAT THE FDA AND THE DRUG COMPANIES RELY ON THESE REPORTS FOR THEIR OWN ANALYSIS CAN BE USED TO REFUTE THIS ATTACK.

It also should not be overlooked that if a manufacturer does not evaluate its product's role in the adverse event honestly and accurately—or even worse, intentionally miscategorizes events to obscure a signal or intentionally fails to acknowledge that its product was the event's cause—that conduct may support a punitive damages claim.

Discovery

Adverse event information falls squarely within Federal Rule of Civil Procedure 26(b)'s breadth. While adverse event information is discoverable, the relevant FDA regulations[8] require that both the patient's and the reporter's identities be protected, so this information needs to be redacted.[9]

It is important to address with defense counsel what will and will not be redacted *before* production. Make sure that the only thing that is redacted is data that truly constitutes patient-identifying information. Names, street addresses, phone numbers, email addresses, and Social Security numbers allow you to identify (and contact) an individual, so this information is likely to be redacted. Knowing that someone in Los Angeles or Miami had an adverse event while taking a particular drug does not enable you to identify the patient or doctor. But the fact that a certain number of adverse events from the same city or zip code were reported to the manufacturer within a short period may reveal information about a cluster of adverse events.

Similarly, a date of birth may help you see a signal that a certain age group is experiencing a particular adverse event at a higher rate than other groups, and this information may be valuable. While it is important to comply with the regulations, it is equally vital that you not agree to give up information that you are entitled to and that can help your case.

Document and information requests. You need to know what to ask for. Drug and medical device manufacturers routinely maintain various types of adverse event data, and you should request them all during discovery:

- MedWatch forms, which the company completes and submits to the FDA when an adverse event is reported
- adverse event database (All drug and device companies maintain a database to track, report, and analyze their products' adverse events.)
- statistical analysis systems (SAS) data from clinical trials, including raw data and "clean" data sets that

the company creates (Companies use SAS data to track information related to their clinical trials, including adverse events.)
- adjudication reports or causality assessments, which are the company's assessment of whether an adverse event is related to the product or some other cause
- adverse event backup or source files (When an adverse event is reported to the company, such as via a physician letter, a file is created that contains the original report and other information related to the company's investigation.)
- periodic adverse drug experience reports (PADER) and period safety update reports (PSUR), which companies must submit to the FDA and foreign regulators identifying adverse event reports for their products that were observed during the reporting time period (These are in addition to the adverse events that have to be reported to the FDA for a shorter time period, such as 15-day reports.)
- pharmacovigilence standard operating procedures (These are the internal rules that the company sets for handling, monitoring, and reporting adverse events.)

Too often, plaintiffs ask for only a few of these documents or fall prey to the manufacturer's argument that the plaintiff does not need all this information.

Production format. Obtaining the defendant manufacturer's adverse event database in a usable format is critical. These databases often run on proprietary software that you cannot operate on your office computer. You do not want to have to purchase the proprietary licensing or build your own software to be able to use the materials you receive. To avoid this problem, determine the database's required software and its features. It is also a good idea to have an understanding of the type of hardware that the manufacturer uses to run the database. The best way to do this is to take a Rule 30(b)(6) deposition of a corporate representative who can testify about the database, its capabilities, and how it can be exported for production.

Receiving a database in an inaccessible format can put you in a compromising position. You have information in your possession that you cannot access, but you may not be in a position to go to the court for relief, especially if the production has been made in a format you requested or agreed to receive. Or if you do have to go to the court, the defendant will argue that it provided what you asked for, it expended significant sums of money and labor in producing it, and reproducing the database in a different format is unduly burdensome.

To prevent these issues, plan ahead. Always discuss the database format with opposing counsel before production, and if you need technical assistance, do not hesitate to hire an information technology vendor. The vendor can work with you and participate in the database production negotiations. You want to guarantee that you will receive the data in a format that will allow you to
- load the database onto a server or computer that you (or your experts) will be able to run to simulate the same functionality the manufacturer had, or perhaps have the production made on a separate computer
- search the database
- sort the data by criteria such as type of adverse event or injury
- understand the database's lexicon (for example, for "gender," does "1" refer to male or female?)
- view any changes made in each database entry based on the manufacturer's investigation of the adverse event report
- export data
- save any searches you run to avoid rerunning the search each time you want to retrieve the data.

Also request periodic data updates. Remember that the manufacturer adds information to its database as new adverse events are identified. Create a schedule for the manufacturer to give you updated information in a format that can be added to the database so that a year or more into the litigation, you are working with a complete record.

Using the Data as Evidence

Once you have received the adverse event information in discovery, how can you use it to prove your case? Adverse

MORE ON ADVERSE EVENTS

Visit the Web pages below for additional information.

AAJ SECTION

Section on Toxic, Environmental, and Pharmaceutical Torts (STEP)
www.justice.org/sections

AAJ LITIGATION GROUP

DePuy Metal on Metal Hip Implant
www.justice.org/litgroups

LITIGATION PACKET

DePuy Hip Implant
www.justice.org/litigationpackets

AAJ EDUCATION PROGRAM

DePuy Litigation Update—2013 Annual Convention
www.PlaybackAAJ.com

event reports sometimes contain third-party statements by people who have no relationship to the lawsuit and will not testify. Defendants often seek to exclude adverse event reports as inadmissible hearsay. However, this information may be admissible for nonhearsay purposes, such as to establish that the defendant had notice of a particular risk (or should have had notice of the risk because it should have seen a signal) and to establish causation.

Notice and signal detection. A pharmaceutical or medical device manufacturer has a duty to warn of dangers it knows about or, in the exercise of reasonable care, should have known about.[10] When offered to establish that a manufacturer had notice that its product was associated with an increased incidence of adverse events, adverse event reports are not hearsay.

In *Brown v. Novartis Pharmaceuticals Corp.*, for example, the court ruled that specific adverse event reports could be admitted to show notice to the defendant, rather than for the truth of the matter asserted.[11] The court noted that any concern that the jury would consider the adverse event report for another purpose can be addressed with a limiting instruction.[12]

The rule allowing adverse events into evidence to show notice is analogous to the general tort rule that evidence of similar accidents at the same location is evidence of notice of a dangerous condition. Some courts require a showing that the circumstances noted in the adverse event report are "substantially similar" to the circumstances in the case at bar. In *Bartlett v. Mutual Pharmaceutical Co.*, the court did not require the incidents underlying the case reports to be similar to the present case "in all respects" but only "substantially similar," finding that, at least when adverse event reports were proffered to establish notice, it was sufficient that the reports involved instances of developing the injury at issue after taking the drug at issue.[13]

TO THE EXTENT THAT A DRUG SAFETY EXPERT HAS REASONABLY RELIED ON ADVERSE EVENT INFORMATION IN FORMULATING HIS OR HER OPINIONS, **TESTIMONY MAY BE ADMISSIBLE EVEN IF THE REPORTS THEMSELVES ARE NOT.**

Courts do not always require that the facts involved in the reported adverse events be similar to those in the plaintiff's case. For example, in *Hogan v. Novartis Pharmaceuticals Corp.*, the court allowed into evidence individual reports and the total number of reports to establish notice, regardless of their similarity to the plaintiff's circumstances.[14]

Another notice argument involves the FDA Adverse Event Reporting System (FAERS) database, through which the agency looks for potential signals of serious risks and new safety information. Any risk or safety signals are reported quarterly on the FDA website.[15]

Similarly, drug manufacturers routinely monitor adverse event reporting as part of their pharmacovigilance. Defendants commonly challenge the reports' reliability, but the fact that the FDA and the manufacturers rely on these reports for their own analysis can be used to refute this attack. Also, do not overlook the fact that a single adverse event can constitute a signal that would require a company to take some action to protect patients.

Causation. Another nonhearsay purpose for adverse event reports is to establish causation. Frequently, the battle arises when they are the basis of an expert's opinion regarding causation.

Federal Rule of Evidence 703 allows experts to base opinions on evidence of a type reasonably relied on by experts in the relevant field. Drug safety experts rely on adverse event reports to formulate opinions and inferences. The FDA has long recognized the usefulness of analyzing adverse event reports to detect safety signals. Statistical review of information in the FAERS database is part of the industry standard for pharmacovigilance, and the drug companies and the FDA conduct this review.

To the extent that a drug safety expert has reasonably relied on adverse event information in formulating his or her opinions, the expert's testimony may be admissible even if the reports themselves are not. Medical professionals also rely on case reports to draw conclusions about what caused a patient's particular illness.[16]

Many courts have allowed experts to rely on adverse event reports as one component of their analysis, even where adverse events standing alone likely would be insufficient to support a causation theory. For example, a trial court in the Levaquin MDL allowed testimony from a plaintiff expert who relied, in part, on adverse event reports

as evidence of causation, but the court gave a jury instruction that adverse event reports, standing alone, do not establish causation.[17]

Similarly, in the phenlypropanolomine (PPA) MDL, the district court admitted non-epidemiological evidence the plaintiffs' experts relied on, such as case reports associating PPA with hemorrhagic stroke in women.[18] The court noted: "The non-epidemiological evidence also gains added legitimacy from the fact that several of [the] plaintiffs' experts base their opinions, in part, on independent PPA-related research."[19]

While the above-cited cases support admission of adverse event data to prove causation, some courts have held that the data alone or in too small a sample is not sufficient to establish causation.[20] However, some courts that have excluded testimony based on adverse event reports also have acknowledged that such testimony may be admissible as a component of causation evidence, especially when supported by epidemiological studies.[21]

Because the law is split on how and when adverse event data can be used to establish causation, you must be familiar with the relevant case law in your jurisdiction. Then you can make the most persuasive arguments in support of admissibility in response to the defendant's motion in limine that you should expect before trial.

Adverse event data plays many roles in pharmaceutical and medical device litigation. Knowledge of how to obtain it and how to get it admitted will go a long way toward your ultimate goal—holding the manufacturer accountable for its actions.

Seth A. Katz *practices law with Burg Simpson Eldredge Hersh & Jardine in Englewood, Colo. He can be reached at skatz@burgsimpson.com.* *He wishes to thank Meghan Quinlivan, an associate at Burg Simpson, for her research assistance with this article.*

Notes

1. *See* 21 C.F.R. §314.80(c) (2013) (reporting requirements for pharmaceuticals); 21 C.F.R. §803.1 & 21 C.F.R. §§803.50–803.58 (2013) (reporting requirements for medical devices).
2. 21 C.F.R. §314.80(c).
3. *See* 21 C.F.R. §314.80(a) (2013).
4. 21 C.F.R. §§803.1(a) & 803.3 (2013).
5. *See e.g.* Lorna Hazell & Saad A.W. Shakir, *Under-Reporting of Adverse Drug Reactions: A Systematic Review*, 29 Drug Safety 385, 387 & 390 (2006) (finding a median underreporting rate of 94 percent across 37 studies from 12 countries including the United States, Canada, the United Kingdom, France, Sweden, and Norway).
6. *See* U.S. Food & Drug Admin., FDA Adverse Event Reporting System (FAERS), www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm (Sept. 10, 2012) ("Reporting of adverse events and medication errors by healthcare professionals and consumers is voluntary in the United States.").
7. *See* Hazell & Shakir, *supra* n. 5; *See also* Karen J. Belton, *Attitude Survey of Adverse Drug-Reaction Reporting by Health Care Professionals Across the European Union. The European Pharmacovigilance Research Group*, 52 European J. of Clinical Pharmacology 423 (1997); Karen J. Belton et al., *Attitudinal Survey of Adverse Drug Reaction Reporting by Medical Practitioners in the United Kingdom*, 39 British J. of Clinical Pharmacology 223 (1995).
8. 21 C.F.R. §20.63 (2013).
9. *See e.g. Harris v. Upjohn Co.*, 115 F.R.D. 191, 192–93 (S.D. Ill. 1987); *In re Eli Lilly & Co., Prozac Prods. Liab. Litig.*, 142 F.R.D. 454, 459 (S.D. Ind. 1992); *Eli Lilly & Co. v. Marshall*, 850 S.W.2d. 155, 160 (Tex. 1993).
10. *See e.g. Lindsay v. Ortho Pharm. Corp.*, 637 F.2d 87, 91 (2d Cir. 1980).
11. 2012 WL 3066588 at **9–10 (E.D.N.C. July 27, 2012).
12. *Id.*; *see also e.g. Worsham v. A.H. Robins Co.*, 734 F.2d 676, 690 (11th Cir. 1984); *Mahaney ex rel. Est. of Kyle v. Novartis Pharms. Corp.*, 835 F. Supp. 2d 299, 312–13 (W.D. Ky. 2011); *Bartlett v. Mut. Pharm. Co., Inc.*, 760 F. Supp. 2d 220, 234, n. 7 (D.N.H. Jan. 5, 2011), *rev'd on other grounds*, 2013 WL 3155230 (U.S. June 24, 2013); *In re Fosamax Prods. Liab. Litig.*, 2013 WL 174416 at *4 (S.D.N.Y. Jan. 15, 2013).
13. 2010 WL 3092649 at *1 (D.N.H. 2010), *rev'd on other grounds*, 2013 WL 3155230 (U.S. June 24, 2013); *see also Mahaney*, 835 F. Supp. 2d at 312–13.
14. 2011 WL 1533467 at *13 (E.D.N.Y. Apr. 24, 2011).
15. U.S. Food & Drug Admin., *Potential Signals of Serious Risks/New Safety Information Identified from the FDA Adverse Event Reporting System (FAERS)*, www.fda.gov/Drugs/GuidanceComplianceRegulatory Information/Surveillance/AdverseDrug Effects/ucm082196.htm#QuarterlyReports.
16. *McClellan v. I-Flow Corp.*, 710 F. Supp. 2d 1092, 1113 (D. Or. 2010) (Case reports "are routinely reviewed and relied upon by physicians in the normal course of their profession, as evidenced by a review of the medical literature."); *see also Bartlett*, 2010 WL 3092649 at *1.
17. *See Schedin v. Ortho-McNeil-Janssen Pharms., Inc.*, 808 F. Supp. 2d 1125, 1139 (D. Minn. 2011), *rev'd in part on other grounds, sub nom. In re Levaquin Prods. Liab. Litig.*, 700 F.3d 1161 (8th Cir. 2012).
18. *See In re Phenylpropanolamine (PPA) Prods. Liab. Litig.*, 289 F. Supp. 2d 1230, 1242 (W.D. Wash. 2003).
19. *Id.*; *see also Brown*, 2012 WL 3066588 at **9–10; *Kendall v. Hoffman-LaRoche, Inc.*, 2010 WL 3034453 at *31 (N.J. Super. App. Div. Aug. 5, 2010) (per curiam), *aff'd*, 209 N.J. 173 (N.J. 2012).
20. *See e.g. McClain v. Metabolife Intl., Inc.*, 401 F.3d 1233, 1253–54 (11th Cir. 2005) (barring the testimony of an expert witness who relied on case reports, finding that because of their anecdotal nature, the case reports by themselves are not sufficient to prove causation); *Glastetter v. Novartis Pharms. Corp.*, 252 F.3d 986, 989–90 (8th Cir. 2001) (per curiam) (refusing to admit evidence of adverse events to prove causation based on the small number of events because "'causal attribution based on case studies must be regarded with caution'") (quoting *Reference Manual on Scientific Evidence* 475 (Fed. Jud. Ctr. 2000)).
21. *See e.g. Caraker v. Sandoz Pharms. Corp.*, 188 F. Supp. 2d 1026, 1035 (S.D. Ill. 2001) (a *Daubert* ruling finding that the experts' "ruling in" methodology was insufficient in light of a lack of epidemiological support for the plaintiffs' claims, but noting that "an overwhelming amount of case reports of a temporal proximity between a very specific drug and a very specific adverse event might be enough to make a general causation conclusion sufficiently reliable."); *see also Ervin v. Johnson & Johnson, Inc.*, 2006 WL 1529582 at **6–7 (S.D. Ind. May 30, 2006), *aff'd*, 492 F.3d 901 (7th Cir. 2007).