IADC COMMITTEE NEWSLETTER

PRODUCT LIABILITY

NOVEMBER 2016

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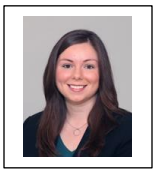
Jaime E. Davis and Lauren R. McClurg analyze when the receipt of adverse event reports may trigger a pharmaceutical manufacturer's duty to warn of an adverse effect with use of a medication.

Reaching Critical Mass: Adverse Event Reports and the Duty to Warn in Pharmaceutical Product Liability Litigation

ABOUT THE AUTHORS



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Failure to warn claims are among the most common allegations asserted by plaintiffs in pharmaceutical product liability litigation. The basic premise of a negligent failure to warn claim is that a manufacturer breached a duty to warn of some danger associated with the foreseeable use of its product. But determining when a pharmaceutical manufacturer's duty to warn of a particular risk is triggered can be a challenge, particularly with regard to the receipt of adverse event reports ("AERs"). The question of when a manufacturer's duty to warn of a particular risk is triggered is frequently in dispute, and often involves (whether rightly or wrongly) an analysis of the receipt of AERs.

I. Adverse Event Reports and Their Limitations

Reporting of adverse events is voluntary in the United States. Healthcare professionals and consumers can voluntarily report adverse events directly to FDA. Alternatively, they may also report adverse events to the products' manufacturer. Once a pharmaceutical manufacturer receives an AER, it is required to submit to the United States Food and Drug Administration ("FDA") information about AERs of which they become aware. *See* 21 C.F.R. § 314.80(c) (reporting requirements for AERs for drug manufacturers).

There are several important limitations with this system. First, as noted above, the submission of AERs to pharmaceutical manufacturers is voluntary and unregulated. Anyone – a patient, family member of a patient, or even a plaintiff's lawyer – can submit an AER, either to the manufacturer or directly to FDA. But whereas FDA regulations regarding medical devices require device user facilities to report AERs to device manufacturers when they have information that reasonably suggests that a device has or may have caused or contributed to the serious illness of, or serious injury to, a patient of the facility, there are no comparable regulations for the reporting of adverse events with pharmaceutical products. For example, a prescribing physician is not required to report any adverse events that happen with his or her patients while taking a medication to the manufacturer or to FDA. Second, because the system is voluntary, not every adverse event necessarily will be reported. Third, and most important, the receipt of an AER does not mean that the event itself was actually caused by the product in question. FDA does not require that a causal relationship between a product and an adverse event be proven to be reported. *See* 21 C.F.R. § 314.80(l) (stating that submitting an AER is not an admission that the drug caused or contributed to the adverse event). Finally, it is not unusual for reports to lack enough detail for a manufacturer to evaluate meaningfully the adverse event.

FDA provides some parameters for when a pharmaceutical manufacturer should warn of a specific risk: they must revise the Warnings and Precautions section of the labeling "to include a warning about a clinically significant hazard as soon as there is reasonable evidence of a causal association." 21 C.F.R. § 201.57(c)(6). Changes to the Adverse

Reactions section should be made when "there is some basis to believe there is a causal relationship between an adverse event and the use of the drug." *See* FDA Guidance for Industry, Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products – Content and Format (Jan. 2006) at 8.

Plaintiffs often still latch on to AERs as "evidence" that the manufacturer knew or should have known of some risk associated with its product and should have warned of this risk (or should have warned sooner than it did). Because AERs can be unreliable and cannot be used to assess causation, some courts properly exclude such evidence at trial. *See, e.g.*, *Wendell v. Johnson & Johnson*, No. C 09-4124 CW, 2014 WL 2943572, *5-6 (N.D. Cal. June 30, 2014) (excluding testimony premised upon "a handful of studies and case reports" for failing to present reliable evidence of causation); *Hollander v. Sandoz Pharms. Corp.*, 95 F. Supp. 2d 1230, 1237 (W.D. Okla. 2000) ("Because of their limitations, case reports have been repeatedly rejected as a scientific basis for a conclusion regarding causation."). Courts that do admit evidence of AERs are divided on how to interpret the receipt of AERs given their limitations. Although evaluating absolute numbers of AERs is just one piece of that analysis, it is instructive to examine the different approaches courts have taken.

II. How Many AERs Does It Take to Trigger the Duty to Warn?

Generally, manufacturers must warn of dangers or potential dangers of using the product of which they are aware or should be aware. *See, e.g.*, *LaBarre v. Bristol-Myers-Squibb Co.*, 544 Fed. App'x 120, 124 (3d Cir. 2013) ("Under Florida law, drug manufacturers have a duty to provide adequate warnings of the drug's dangerous side effects."); *Sterling Drug, Inc. v. Yarrow*, 408 F.2d 978, 992 (8th Cir. 1969) (holding that manufacturer had duty to warn prescribing physicians "when the dangers of the prolonged use of this drug, mass produced and sold in large quantities, became reasonably apparent").

When does receiving one or multiple reports of an adverse event rise to the level of a "danger" or "potential danger"? Some courts have recognized explicitly that receipt of an AER does not automatically trigger the duty to warn. For example, the New Jersey Supreme Court opined that "FDA has legitimate concerns about information overload may lead physicians to ignore drug labels or package inserts or read them without any intention of modifying their prescription practices" because of useless or constantly changing information. *Feldman v. Lederle Labs.*, 592 A.2d 1176, 1200 (N.J. 1991). FDA regulations do not require changing product labeling for every possible side effect because "statements of conflicting opinion would destroy" the usefulness of the product labeling and warnings. *Id.* at 1201.

It may seem common sense that a pharmaceutical manufacturer should not have a duty to warn about every possible adverse event that it may receive for its products. But courts are divided on the question of what creates a genuine issue of material fact as to whether a manufacturer should have known of and warned of a risk associated with use of its product. In some instances, minimal evidence of risk, even if inconclusive, has been deemed sufficient to create an issue of fact as to the duty to warn.

A. One AER

Is one AER enough to trigger the duty to warn? Probably not. For example, in *Finn v. G.D. Seale & Co.*, the California Supreme Court found no duty to warn of the risks of optic nerve atrophy with the use of diodoquin based on a single AER, specifically noting that "[k]nowledge of a potential side effect which is based on a single isolated report of a possible link between a [product] and an injury may not require a warning." 677 P.2d at 1153.

But FDA recognizes that it is possible for a single well-documented AER to be a safety signal. FDA Guidance for Industry, Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment (Mar. 2005) at 4. Although FDA also recognizes that it is nearly impossible to conclude causality based on a single AER (*id.* at 7), that does not preclude a court from finding that the receipt of one AER triggered the manufacturer's duty to warn. For example, if an adverse event is extremely rare and unlikely to be seen in the absence of the medication, receipt of one AER could be viewed as a signal and potentially trigger the duty to warn. *Id*; *In re Tylenol (Acetaminophen) Marketing Sales Practices and Prods. Liab. Litig.*, No. 2:13-md-02436, 2016 WL 4039271, at *7 (E.D. Pa. July 28, 2016) ("A single well-documented adverse event report (AER) may be a safety signal, depending on the circumstances of the adverse event (i.e., the only explanation for the event would be the drug itself.").

B. Multiple AERs Reporting the Same or Similar Adverse Event

Courts also are split on whether receipt of more than one AER triggers the duty to warn, although they are more likely to find a duty to warn is triggered by multiple AERs. *See, e.g.*, *Hermes v. Pfizer, Inc.*, 848 F.2d 66, 68 (5th Cir. 1988) (finding that an FDA computer printout of adverse reaction reports dating back as early as 1970 was sufficient for the jury to find that the duty to warn was triggered); *Newman v. McNeil Consumer Healthcare*, 2012 WL 39793, at *1-3 (N.D. Ill. Jan. 9, 2012) (denying summary judgment for defendant manufacturers where there had been 87 AERs of rare skin conditions Stevens-Johnson Syndrome ("SJS") and Toxic Epidermal Necrolysis ("TEN") with the use of ibuprofen before the plaintiff allegedly contracted SJS as a result of Motrin use).

Even when a manufacturer has received multiple AERs, courts appear more reluctant to impose a duty to warn when the adverse event at issue is one that has a background rate in the general population and/or when

the numbers are relatively small compared to the number of total uses. For example, in *Stupak v. Hoffman-La Roche*, the plaintiff argued Roche failed to warn about the risk of suicide without premonitory (warning) symptoms with Accutane use. 326 F. App'x 553, 554 (11th Cir. 2009). In affirming summary judgment for Roche, the Eleventh Circuit discounted the fact that the company had received "at least 17" AERs of accomplished suicides in Accutane patients with no signs of depression. *Id.* at 560. The court found the 17 AERs to be anecdotal and inconclusive, especially when compared to the millions of Accutane prescriptions. *Id.* The court found that the AERs "provide[d] no more than a 'scintilla of evidence'" to support the plaintiff's claim that Roche knew or should have known of the risk of suicide without premonitory symptoms. *Id.*

No matter how many AERs a manufacturer may have received about its product, that number should not be viewed in a vacuum. It also needs to be put in context with all available safety information, including preclinical/animal studies, any studies conducted by the manufacturer, and the medical literature by someone qualified to evaluate post-marketing safety data. *See, e.g.*, *In re Gadolinium-Based Contrast Agents Prods. Liab. Litig.*, No. 1:08 GD 50000, 2010 WL 5173568, **6-8 (N.D. Ohio June 18, 2010) (declining to reconsider its exclusion of defendant's expert's testimony that four AERs of nephrogenic systemic fibrosis, a rare syndrome, did not constitute a safety signal because, unlike plaintiffs' experts, the defense expert did not consider other available safety information).

Ultimately, there is no "magic number" of AERs that triggers the duty to warn. Courts frequently engage in a fact-intensive analysis. Even one AER may be enough depending on the circumstances, especially if the event is a relatively rare condition. Some courts may hold a manufacturer to a duty to warn as soon as there is a "hint" of a possible association between its drug and an adverse effect. Accordingly, pharmaceutical manufacturers must bear in mind how a court in potential future litigation might view the receipt of AERs when monitoring and evaluating AERs.

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