New FDA Safety Reporting Requirements and the Impact on Litigation

Evaluating Adverse Event Causation in Clinical Trials

By Randall L. Christian and Jason H. Casell

The final rule aims to reduce extraneous reporting of events as adverse reactions that could obscure true safety signals, but it remains to be seen how this will play out.

In an effort to harmonize FDA standards with international standards, on September 28, 2010, the Food and Drug Administration (FDA) issued a final rule codifying the agency's expectations for timely review, evaluation, and submission of safety information of drug and biologic products subject to an investigational new drug (IND) application. The new rule, called "Investigational New Drug Safety Reporting Requirements for Human Drug and Biological Products and Safety Reporting Requirements for Bioavailability and Bioequivalence Studies in Humans," amends parts 312 and 320 of the FDA regulations by revising the requirements for IND safety reporting and for bioavailability and bioequivalence studies in connection with FDA approval of a generic drug. One of the rule's chief aims is to improve patient safety by reducing the number of adverse event reports that the FDA receives mainly to make those that the FDA does receive more useful in detecting danger signals. The rule specifically will harmonize FDA standards with the existing standards of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, the World Health Organization Council for International Organizations of Medical Sciences, and the European Union.

The effective date for the final rule has been extended from March 28, 2011, to September 28, 2011, to give sponsors time to implement the significant internal processing changes necessary to comply with it. This article addresses the changes effectuated by the final rule and how those changes may impact companies involved in litigation, specifically, how defense counsel can deal with causality assessments offered as evidence by plaintiffs' attorneys.

Consider a standard jury question in a standard pharmaceutical case concerning alleged injuries related to a drug: "Did the plaintiff prove by a preponderance of the evidence that he or she had a heart attack because he or she used drug X?" When attempting to answer this seemingly simple question, a jury would consider all of the evidence presented during the trial. The jury would also attempt to piece together

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the evidence to decide if the plaintiff's attorney had offered sufficient evidence of medical causation, and company causality assessments have become a favorite piece of that evidence that plaintiffs' counsel offer.

Internal company causality assessments generally use a "check-the-box" rating-scale format with a list of several predefined answers: "definitely related," "probably related," "possibly related," "probably not related," and "definitely not related." Sometimes a form that a company uses may also require a "yes" or "no" answer to a question along the lines of "is there a reasonable possibility of a causal relationship between the test article and the adverse event?"

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Depending on the responses to the above questions, some companies attempt to summarize their internal causality assessments and may conclude something similar to the following: "Important safety information is available from the safety database. A total of X cases of adverse event Y have been reported from clinical trials, which were rated as 'possibly' or 'probably' related to the administration of the drug. It is reasonable to conclude from this data that the drug may induce or aggravate pre-existing adverse event Y."

A testifying expert for a plaintiff would attempt to rely on the information from a company causality assessment to form his or her opinion on causation. To testify, the expert must be qualified to address scientific issues competently, the testimony must assist the jury to decide a fact in issue, and the expert must use a reliable scientific methodology to generate conclusions.

But there is a significant problem here. A causality assessment is *not* a scientific or a legal assessment of "more likely than not" causation. Rather, it is a regulatory tool for categorizing events for safety monitoring and detecting danger signals. A causality assessment is biased toward finding a positive relationship between a drug and an adverse event associated with that drug. It is based on incomplete clinical information. For instance, it is not based on complete medical records. When used in contexts other than regulatory safety monitoring, a causality assessment does not have objective scientific reliability. And causality assessments inherently lack consistency. Different reporters could report the same case differently.

So how does the FDA final rule address all of this?

Reporting a Suspected Adverse Reaction That Is Both Serious and Unexpected

The former regulations, 21 C.F.R. §312.32, used the term "adverse drug experience" to describe adverse events observed during a clinical trial for an IND. Previously sponsors filed IND safety reports for adverse drug experiences that were "serious" and "unexpected" and "associated with the use of the drug." The FDA did not provide much guidance about which adverse drug experiences observed during a clinical trial required an IND safety report. Therefore, sponsors frequently reported all serious adverse events, even if they had little to no reason to believe that a serious adverse event was associated with the clinical trial drug.

For instance, sponsors reported (1) serious adverse experiences such as mortality or major morbidity that were likely manifestations of an underlying disease; (2) serious adverse experiences that commonly occurred in the study population independent of drug exposure, such as strokes or acute myocardial infarction in an elderly population; and (3) serious adverse experiences that were "study endpoints," meaning that the study was evaluating whether the drug reduced the rate of these events. These three types of events generally are uninformative when reported as single events without comparing the incidence of them in treated to untreated subjects. The FDA found that reviewing these reports without the necessary context drained the resources of the agency, its investigators, and institutional review boards.

The draft guidance document on the new final rule indicates that sponsors tended to report uninformative individual cases because they misapplied the standard of "reasonable possibility" within the definition of "associated with the use of the drug." In the past, when sponsors submitted individual cases of adverse drug experiences as IND safety reports, the sponsors had insufficient evidence to suggest that a reasonable possibility existed that the drugs caused the adverse events, and the sponsors probably should not have submitted those adverse events as IND safety reports.

The new final rule tries to clarify which serious adverse events sponsors *should* report to the FDA as individual cases and circumstances in which they should aggregate cases and compare them to a control group. The new rule has eliminated the term "adverse drug experience" in the new regulation and has replaced it with the phrases "adverse event" and "suspected adverse reaction." The final rule now requires sponsors to file IND safety reports for suspected adverse reactions that are both "serious" and "unexpected."

The new definitions establish a three-tier hierarchy for categorizing an event's relationship to a clinical trial drug. "Adverse event" is defined as "any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related." 21 C.F.R. §312.32(a). A "suspected adverse reaction" is "any adverse event for which there is a reasonable possibility that the drug caused the adverse event," with "reasonable possibility," meaning that the reporter has "evidence to suggest a causal relationship between the drug and the adverse event," but with less certainty about causality than with a suspected adverse reaction. *Id.*

"Serious" means that, in the view of either the investigator or the sponsor, the adverse event results in death, a life-threatening adverse event, meaning it places a patient at immediate risk of death, in-patient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly or birth defect. An "unexpected" adverse event

is one that is not cited in the investigator brochure and is not listed as matching the specificity or severity that previously has been observed. *Id.* "Unexpected" also means an adverse event that is anticipated within the class of drugs but not specifically mentioned as occurring with the new drug under investigation. *Id.*

The revised regulations provide three examples of adverse events that could suggest a causal relationship between the event and the clinical trial drug, and as a result, reporters could classify them as suspected adverse reactions requiring IND safety reports:

- An individual occurrence of an event that is uncommon and known to be strongly associated with drug exposure, for example, angioedema, blood dyscrasias, rhabdomyolysis, hepatic injury, anaphylaxis, or Stevens-Johnson Syndrome, 21 C.F.R. 312.32 §(c)(1)(i)(A);
- One or more occurrences of an event that is not commonly associated with drug exposure but is otherwise uncommon in the population exposed to the drug, such as tendon rupture, heart valve lesions in young adults, or intussusceptions in healthy infants. Often, an event of this type would need to occur more than once in one or more studies before a sponsor could determine that a reasonable possibility existed that the drug caused the adverse event, 21 C.F.R. 312.32 §(c)(1)(i)(B);
- An aggregate analysis of specific events observed in a clinical trial indicating that the adverse event occurs more frequently in the drug treatment group than in the control group, 21 C.F.R. 312.32 §(c)(1)(i)(C).

The draft guidance document notes that a sponsor should "evaluate the available evidence and make a judgment about the likelihood that the drug actually caused the adverse event." And "[a]ppropriately deciding whether the adverse event meets the definition of a suspected adverse reaction is usually the most difficult determination [for a reporter], but it is critical to avoiding the submission of uninformative IND safety reports."

Sponsors Will Report Fewer Cases as Individual Adverse Drug Events

According to 21 C.F.R. §312.32(c)(1)(i), sponsors "should have processes in place to periodically review and analyze their entire safety database, not only for IND safety reporting purposes, but also to update investigator brochures with new safety information."

Under the new rule, as mentioned, not all adverse events would fit the "suspected adverse reaction" definition, but a single adverse event occurrence or small number of uncommon occurrences not commonly associated with drug exposure may satisfy the definition of "suspected adverse reaction" in association with other factors. Those factors might include a strong temporal association between an individual adverse event and drug use or "rechallenge," which means re-administration of a drug suspected of possibly causing an adverse reaction. Sponsors must ensure that they have in place a "systematic approach for safety surveillance," which could include a process for reviewing, evaluating, accumulating, and managing safety data from the entire clinical trial database at appropriate intervals. A sponsor may form a specific committee to perform this function, or the sponsor may choose to create a safety team to oversee the evolving safety profile of the IND and evaluate the accumulating data from individual and multiple clinical trials.

Even if considered part of a study endpoint, sponsors must report serious and unexpected suspected adverse reactions if a reasonable possibility exists that the drug caused the adverse reaction, such as death from anaphylactic reaction. Serious and expected adverse reactions that are study endpoints need only be reported as described in the study protocol when clearly not drug related.

Expected serious events, that is, known consequences of underlying disease, should be compared at appropriate intervals and reported if an imbalance between patients in the treatment arm and control group suggests a reasonable possibility of causation.

Reporting Serious Adverse Events That Occur at a Rate Higher than Expected

The new final rule requires that sponsors report serious adverse reactions that are expected but occur at a rate higher than that listed in investigation protocols or investigator brochures. The specific language mandates that a sponsor file an IND safety report when it discovers "any clinically important increase in the rate of a serious suspected adverse reaction over that listed in the protocol or investigator brochure." 21 C.F.R. 312.32(c)(1)(iv). Sponsors must submit reports within 15 calendar days after initial receipt of the information, but they must submit reports about unexpected fatal or life-threatening suspected adverse reactions within seven calendar days of receiving the information.

Reporting Findings from Other Studies That Suggest a Significant Risk to Study Participants

Under the final rule, a sponsor must now file IND safety reports for findings from "other studies" when the findings suggest a significant risk in humans exposed to the clinical trial drug, irrespective of whether the sponsor conducted the studies or if they were conducted under the sponsor's IND. Other studies include epidemiological studies, pooled analyses of multiple studies, and other clinical studies. The FDA advises that information from "other studies" that warrant filing IND safety reports typically would lead to safety-related changes in the IND sponsor's study protocol, informed consent, changing the investigator brochure, and modifying other aspects of the clinical investigation. C.F.R. §313.32 (c)(1)(ii).

Reporting Findings from In Vitro Testing and Findings from Animal Testing

The final rule expands upon the previous requirement that sponsors must file IND safety reports for findings from animal testing that suggest a significant risk to humans from a clinical trial drug, now requiring sponsors to submit safety reports for in vitro testing that suggests a significant risk for individuals exposed to a clinical trial drug. These findings include reports of mutagenicity, teratogenicity, carcinogenicity, and organ toxicity. Such a finding could suggest a significant risk, but before reporting to the FDA, a sponsor should use judgment to determine whether the finding suggests a significant risk in humans or is too preliminary to interpret without further investigation.

Reporting Serious Adverse Events from Bioavailability and Bioequivalence Studies

The final rule requires that anyone conducting a bioequivalence or bioavailability study, including a contract research organization, must notify the FDA and all participating investigators about any serious adverse event, whether or not the event is considered drug related. 21 C.F.R. §320.31(d)(3).

Reporting Timelines

The final rule does not change the timing of safety reports, which must be filed no later than 15 days after an individual sponsor becomes aware of an event. 21 C.F.R. §312.32(c)(1). If the FDA requests additional data, the sponsor must submit it no later than 15 days after receiving the request. 21 C.F.R. §312.32(c)(1)(v). A sponsor must submit reports of fatal or life-threatening, suspected adverse reactions no later than seven calendar days after learning of the event. 21 C.F.R. §312.32(c)(2). The FDA's draft guidance document recommends that sponsors notify the FDA by telephone, facsimile transmission, or e-mail, if, prior to the transmission, the sponsor contacts the project manager in the FDA review division responsible for reviewing the IND, and determines that other means of communication are acceptable.

How the Changes Will Affect How Companies Will Conduct Causality Assessments

According to the FDA guidance document, although an investigator's view of the causal relationship between an adverse event and an IND clinical trial drug is important, the agency believes that the sponsor is better positioned than an individual investigator to assess the overall safety of a clinical trial drug because the sponsor has access to serious adverse event reports from multiple study sites and can aggregate and analyze these reports. Therefore, an investigator must immediately report any serious adverse event to the sponsor, whether or not considered drug related. 21 C.F.R. §312.64(b).

But it is also important that a sponsor consider the investigator's view when assessing the safety of a study drug and determining whether to report expeditiously to FDA because the investigator has knowledge about the human subject, knowing about his or her medical history or concomitant medications, administers the investigational drug, monitors the subject's response to the drug, understands the subject's clinical state, and thus may make sensitive distinctions between an event due to an underlying disease and an event that possibly may be drug-related, An investigator also may have observed the event. Therefore, an investigator must include an assessment of causality—whether there is a reasonable possibility that the drug caused the event—in the report to the sponsor. 21 C.F.R. §312.64(b). And a sponsor should decide how to capture an investigator's causality assessment, for instance, through a rating scale, or a yes/no response to a question such as, "was there a reasonable possibility that the drug caused the adverse event?"

Conclusion

The FDA draft guidance on the final rule offers help to defense counsel in attacking plaintiffs' attorneys' arguments that causality assessments constitute competent proof of causation in courts. But by requiring sponsors to conduct more in-depth analyses of causality than in the past and to classify some events as "suspected adverse reactions," the new rule will likely buttress plaintiffs' attorneys' arguments that they have proved causation with causality assessments reporting suspected adverse reactions. On the other hand, even under the new regulations, the evaluation required for assessing the possibility of a causal link between drug use and suspected adverse drug reactions does not meet a rigorous scientific review standard. In particular, comparing the incidence of an adverse event in two arms of a study does not meet that standard, although plaintiffs' counsel will represent that comparison as a proper, controlled epidemiologic study generating truly valid, scientific information.

The FDA final rule aims to reduce extraneous reporting of events as adverse reactions that could obscure true safety signals, but it remains to be seen how this will play out. And it does not require any more scientific rigor in a company's assessment of causality. Companies must continue to fight the plaintiffs' bar, which will likely continue to press its erroneous assertion that causality assessments, despite their uncontrolled, anecdotal nature, offer legal proof of causation.