



# Perspective

## New FDA Regulation to Improve Safety Reporting in Clinical Trials

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As part of an initiative designed to modernize the clinical trial enterprise, the Food and Drug Administration (FDA) recently published a regulation establishing a new safety-reporting paradigm for drugs

being studied under investigational new drug applications (INDs).<sup>1</sup> This rule — published last September and effective as of March 28, 2011 — is one in a series of steps the FDA is taking to enhance the protection of human subjects and improve trial conduct by streamlining the regulatory procedures for clinical trials.

Monitoring patient safety during clinical trials is a critical component of the drug-development process. Such monitoring is a dynamic process intended to protect trial volunteers from preventable harm. It depends on observant investigators, responsible analysis by trial sponsors, and prompt reporting to the FDA, all investigators, and institutional review boards

(IRBs) of serious new adverse reactions. Although safety databases are scrutinized when applications for marketing approval are submitted, ongoing safety analyses during trials are critical in ensuring that serious adverse events are discovered as soon as possible. Safety data from ongoing clinical trials influence the clinical care of patients enrolled in those and other trials of a given drug; if the drug is already on the market, these data may affect its clinical use. Safety reports derived from ongoing clinical trials must be meaningful, relevant, and amenable to timely analysis.

The new regulation clarifies the responsibilities of clinical investigators and IND sponsors with

respect to the reporting and analysis of serious, unexpected events that are suspected to be caused by the drug. Because the FDA's previous safety-reporting requirements were not specific regarding the threshold for deeming an adverse event reportable, IND sponsors were often reporting to the agency and clinical investigators, in an expedited manner (typically within 15 days), substantial numbers of serious adverse events, without enough context to permit evaluation of any relationship to drug therapy. Typically, these events were common in the study population or in the disease under investigation, independent of drug therapy. For example, an investigator might report a single case of myocardial infarction or stroke in a trial enrolling an elderly population. Under these circumstances, it is impossible to determine whether drug exposure is causally related to the event. Large numbers of such

**Criteria for Drug Sponsors for Reporting Serious and Unexpected Suspected Adverse Reactions within 15 Days.**

1. The event must be unexpected (not listed in the investigator brochure).
2. The event must be serious — that is, resulting in death, a threat to life, hospitalization or prolongation of hospitalization, persistent or clinically significant incapacity, substantial disruption of the ability to conduct normal life functions, or a congenital anomaly or birth defect.
3. The event must be a suspected adverse reaction, meaning that there must be a “reasonable possibility” (i.e., evidence to suggest) that the drug caused it.

uninterpretable single case reports can distract clinical investigators, the FDA, and IRBs from recognizing genuine drug-safety problems.

Under the new reporting requirements, IND sponsors must still promptly report to the FDA and investigators serious, unexpected suspected adverse reactions occurring during clinical trials (see box). However, the regulation now provides guidance on the causality assessment needed to determine that an adverse event may be caused by the drug.<sup>1</sup> A serious, unexpected suspected adverse reaction is an adverse event not previously observed with the drug and that has a reasonable possibility of having been caused by it. The IND sponsor must report such an event within 15 days if it was serious and within 7 days if it was fatal. Unlike a myocardial infarction in an elderly subject, a single occurrence of Stevens–Johnson syndrome (SJS) would reach this threshold. Not only is SJS unexpected and serious, it is known to be strongly associated with drug exposure. A report of SJS would clearly be informative about the safety of the investigational drug and could have important effects on patient monitoring and care.

To further enhance patient protection, the new regulation states that the sponsor must analyze in the aggregate events that are not interpretable as single cases and report them only if there is an ob-

served imbalance between the drug-treatment group and a control group suggesting that the event is caused by the drug. The regulation also stipulates that IND sponsors should not report events that are study end points (e.g., death or major illnesses) except in unusual cases. Information on these events should be collected and analyzed as specified in the study protocol, usually by an independent data monitoring committee.

Under the new regulation, clinical investigators are now required to report all serious adverse events to the sponsor, whether or not they are considered drug-related. Previously, investigators were directed to make a judgment and report only events that they considered to be probably drug-related. It’s difficult, however, for an investigator to attribute a serious adverse event to a drug on the basis of an isolated incident, and individual investigators often do not have timely access to the entire safety database. Therefore, causality of adverse events is best evaluated in the aggregate by the sponsor.

These changes are intended to ensure that the IND sponsor maintains as complete a view as possible of a drug’s evolving safety profile: the sponsor will be provided with reports of all serious events and will be expected to review, monitor, and analyze, in real time, all accumulating safety data from

investigators from all clinical trials and sites. Access to complete data are critical in establishing a reasonable likelihood of a causal relationship between an adverse event and a drug. The FDA expects that this new approach will reduce reporting-data noise that may mask true signals of significant adverse events, so that what is reported to the FDA, clinical investigators, and IRBs will be more meaningful and relevant to patients’ safety.

We believe that the new regulation will improve the quality of safety reporting and strengthen the FDA’s ability to monitor the safety of drug and biologic products. It will minimize reports that do not contribute to the understanding of a drug’s developing safety profile and decrease the number of uninterpretable reports. In addition, to the extent possible, it harmonizes with international definitions, using the International Conference on Harmonization (ICH) terminology.<sup>2</sup> However, because the new regulation requires the sponsor to make the causality determination on the basis of information from investigators, it differs from the ICH guidance, which recommends that causality assessments be based on the judgment of either the investigator or the sponsor. Again, we believe that such assessments require consideration of the entire safety database, to which any individual investigator would lack access. The FDA is working with international regulators to develop strategies to harmonize safety-reporting requirements.

To implement this regulation, IND sponsors will need to adopt systematic approaches to safety surveillance and monitoring. Published reports and public presentations have indicated that many such systems already exist or are

under development.<sup>3</sup> These systems should provide the capacity to review and evaluate accumulating data on serious adverse events from all trials of an investigational drug. A draft FDA guidance document accompanying the new rule describes the use of data monitoring committees, or similarly constituted sponsor safety groups, to perform this function.<sup>4</sup>

Although the new rule focuses on serious, unexpected suspected adverse reactions, IND sponsors are expected to monitor all adverse events, including nonserious ones, during drug development.

Ultimately, this new rule will increase the interpretability and usefulness of safety data available to the clinical investigators, IRBs, and the FDA. These groups will receive fewer individual reports,

and the reports should be more complete and meaningful. Thus, the rule will enhance patient protection, ensure regular and thorough evaluation of serious adverse events, and therefore generate better data to support clinical decision making. The FDA recognizes that implementing this new approach will be challenging. However, this effort is critical to the FDA's public health mission, which includes promoting effective and efficient development of novel drug therapies while ensuring the highest level of patient protection.

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