

studies. Current regulations at §§ 310.305(c)(1)(ii), 312.32(c)(1), 314.80(e)(1), and 600.80(e)(1) require that serious, unexpected adverse experiences from a study be reported to FDA only if there is a reasonable possibility that the drug caused the adverse experience. The phrase "reasonable possibility" is typically interpreted by sponsors, manufacturers and applicants to mean that there is a possible causal relationship between an adverse experience and a drug or biological product. It would not include adverse experiences considered to be unlikely or remotely related to the product. The proposed definition of SADR maintains the phrase "reasonable possibility" as part of the definition, but defines the phrase to mean that the relationship between a product and a response to the product cannot be ruled out. In some cases, this proposed change would result in submission of more safety reports to FDA. For example, under the current regulations if a sponsor or applicant concludes that the existence of a causal relationship between a drug and an adverse event is unlikely or remote, but not impossible, (e.g., because the event is a recognized consequence of the patient's underlying disease) it would not submit a safety report to FDA. In contrast, under the proposed rule, the sponsor or applicant would be required to submit a safety report to the agency for this SADR, because, although the relationship of the adverse event to the drug is unlikely or remote because of the patient's underlying disease, a causal relationship cannot, nonetheless, be ruled out. FDA is proposing the new definition for SADR to minimize situations in which an adverse event that proves ultimately to be due to a drug or biological product is not reported as soon as possible to the agency because the etiology of the adverse event is attributed to the patient's underlying disease by the sponsor, manufacturer or applicant (e.g., a patient's hepatic deterioration is judged to be related to the patient's viral hepatitis and not to the hepatotoxicity of the drug the patient received.)

FDA recognizes, however, that particularly for those patients who have certain diseases (e.g., fatal diseases such as cancer), the proposed definition of SADR may result in submission of numerous safety reports to the agency for which the reported SADR is not informative as a single report because it is very likely to have been a consequence of the patient's disease. This would be true, for example, for most non-acute deaths in a clinical trial

evaluating a drug in cancer patients. These deaths would have to be reported to FDA as SADRs because a relationship between the drug and the deaths could not be ruled out with certainty. Because such "over-reporting" may make it more difficult for FDA and the sponsor, manufacturer or applicant to recognize adverse events that are really caused by a drug or biological product, the agency wants to minimize receipt of this type of safety report, but in a way that does not compromise receipt of useful safety reports that are perceived as remotely related to an administered drug or biological product but that occur, in fact, as a result of the product. If sponsors, manufacturers or applicants believe that, in a specific situation, there is an alternative way(s) to handle adverse events occurring during clinical studies that would minimize "over-reporting" while assuring that reporting of SADRs would not be compromised, they are invited to propose any such alternative(s) reporting method to the agency. In such situations, if FDA does not oppose the proposed alternative reporting method, the sponsor, manufacturer or applicant would be permitted to report SADRs to the agency according to the alternative method. For example, one such alternative would be to include in study protocols or other documentation a list of known consequences of the disease that would not be submitted to FDA in an expedited manner as individual case safety reports (e.g., events that are the endpoints of the study). These adverse events would, however, be monitored by the sponsor, manufacturer, or applicant and, if they indicated in the aggregate by comparison to a control group or historical experience, that the product in the clinical study may be causing these events, the information would be submitted to FDA in an expedited manner as an information sufficient to consider product administration changes report (see sections III.B.2.c and III.D.2 of this document for discussion of this type of report). FDA invites comment from the public on this alternative and requests suggestions for other alternatives as well that would minimize "over-reporting" of uninformative events and assure submission of meaningful reports of unexpected events. FDA also invites comment on reporting of these types of clinical events that occur in studies not being conducted under an IND (e.g., drug or biological product is marketed in the United States for a particular indication and being investigated in a clinical trial abroad for the same or other indication).

The proposed definition of SADR may result in submission to FDA of some reports from clinical studies and the scientific literature in which the reported SADR is suspected to be associated with the product, but, in fact, it is ultimately demonstrated not to be due to the product. This is also true for reports from spontaneous sources in which manufacturers and applicants must always assume, for safety reporting purposes, that there is at least a reasonable possibility that the drug or biological product caused the spontaneously reported event and submit the report to FDA. Thus, SADR reports are required to be submitted to FDA based on a suspected, not established, causal relationship between an adverse event and a drug. This type of reporting program allows the agency to determine more quickly which SADRs warrant regulatory action by FDA to protect public health (e.g., change in product labeling, withdrawal of product from the market). FDA receives hundreds of thousands of such reports each year, most of which do not result in any regulatory action. But for those reports that do represent a significant change in the benefit-to-risk profile of a product, this system is critical for developing a signal necessitating further evaluation of an SADR.

Some members of the public have maintained that submission of voluntary SADR reports by health care professionals or consumers to manufacturers or to FDA might be discouraged because of concern that a person or entity might be implicated in a product liability action. In addition, industry has expressed its concern that these reports, taken out of context and used in a manner for which they were never intended, can create a product liability vulnerability. FDA is concerned that such liability misuse of these reports could imperil the credibility and functionality of this critical public health reporting system.

Our current safety reporting regulations at §§ 310.305(g), 312.32(e), 314.80(k), and 600.80(l) provide manufacturers, applicants, and sponsors with a disclaimer that permits them to deny that the safety report or other information required to be submitted to FDA under these regulatory provisions constitutes an admission that the drug or biological product caused or contributed to an adverse effect. For example, § 314.80(k) currently reads in pertinent part:

*Disclaimer.* A report or information submitted by an applicant under this section (and any release by FDA of that report or information) does not necessarily reflect a