

III. Description of the Proposed Rule

III.A. Definitions

III.A.1. Suspected Adverse Drug Reaction (SADR)

FDA's existing premarketing safety reporting regulations in § 312.32(a) define "associated with the use of the drug" to mean: "There is a reasonable possibility that the experience may have been caused by the drug."

FDA's existing postmarketing safety reporting regulations in §§ 310.305(b), 314.80(a), and 600.80(a) define "adverse drug experience" ("adverse experience" for § 600.80(a)) to mean:

Any adverse event associated with the use of a drug ("biological product" for § 600.80(a) in humans, whether or not considered drug ("product" for § 600.80(a)) related, including the following: An adverse event occurring in the course of the use of a drug ("biological" for § 600.80(a)) product in professional practice; an adverse event occurring from drug overdose ("from overdose of the product" for § 600.80(a)) whether accidental or intentional; an adverse event occurring from drug abuse ("from abuse of the product" for § 600.80(a)), an adverse event occurring from drug withdrawal ("from withdrawal of the product" for § 600.80(a)); and any failure of expected pharmacological action.

Proposed § 312.32(a) would replace the term "associated with the use of the drug" with the term "suspected adverse drug reaction (SADR)." Proposed §§ 310.305(a) and 314.80(a) would replace the term "adverse drug experience" with the term "suspected adverse drug reaction (SADR)" (see section III.C.1 of this document regarding reorganization of § 310.305). Proposed § 600.80(a) would replace the term "adverse experience" with the term "suspected adverse reaction (SAR)." In this document the term "adverse drug experience" is synonymous with the term "adverse experience" and the abbreviation "SADR" will be used for both "SADR" and "SAR," except when reference is only being made to an "SAR," in which case the abbreviation "SAR" will be used. Proposed §§ 310.305(a), 312.32(a), 314.80(a), and 600.80(a) would also replace the definitions for "associated with the use of the drug," "adverse drug experience" and "adverse experience" with the following definition for "SADR":

A noxious and unintended response to any dose of a drug ("biological" for proposed § 600.80(a)) product for which there is a reasonable possibility that the product caused the response. In this definition, the phrase "a reasonable possibility" means that the relationship cannot be ruled out.

The phrase "the relationship cannot be ruled out" clarifies which individual cases would be reported to FDA. Classifying a case as "probably related," "possibly related," "remotely related," or "unlikely related" to the drug or biological product would signify that a causal relationship between the product and an adverse event could not be ruled out and, thus, the adverse event would be considered an SADR. For example, in some cases an adverse event may most probably have occurred as a result of a patient's underlying disease and not as a result of a drug or biological product the patient was taking, but it cannot usually be said with certainty that the product did not cause the adverse event. Therefore, such an adverse event would be classified as an SADR because there would be at least a "reasonable possibility" that the drug or biological product may have caused the adverse event. Of course, this classification would not establish causality (attributability) by itself, it would only indicate that causality could not be ruled out with certainty.

These proposed changes are consistent with the ICH E2A guidance (60 FR 11284 at 11285), which defines "adverse drug reaction" as:

All noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions. The phrase "response to medicinal products" means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, *i.e.*, the relationship cannot be ruled out.

These proposed amendments would harmonize the agency's premarketing and postmarketing safety reporting definition for SADR, as well as safety reporting worldwide.

Even though FDA has harmonized its proposed definition of SADR with the definition of adverse drug reaction recommended by ICH, the agency would like comment on an alternative definition for SADR: "A noxious and unintended response to any dose of a drug product for which a relationship between the product and the response to the product cannot be ruled out". The alternative and proposed definitions for SADR have the same meaning (*i.e.*, a response to a product is an SADR unless one is sure that the product did not cause the response). The difference between these definitions is that the alternative definition of SADR does not include the phrase "a reasonable possibility." This is because use of this phrase is potentially confusing. The phrase "a reasonable possibility" might be interpreted differently than the phrase "the relationship cannot be ruled out." The agency defines "a reasonable

possibility" as "the relationship cannot be ruled out" to be consistent with ICH. FDA seeks comment as to whether the agency should use the alternative definition of SADR instead of the proposed definition of SADR. The agency also requests comment from sponsors, manufacturers and applicants if their interpretation of these definitions is different than FDA's interpretation.

As explained in the following paragraphs, FDA believes that the proposed definition of SADR would not affect the number of safety reports that are currently submitted to FDA from spontaneous sources, but it could increase the number of safety reports that would be submitted from clinical studies. FDA seeks comment as to whether use of the proposed or alternative definition of SADR would lead to significant increases in reporting to the agency beyond what FDA has identified in the following paragraphs. FDA is particularly interested in learning of examples of events beyond those identified by the agency that are not currently reported to FDA but would be required to be reported under these definitions.

Although FDA is proposing to remove the definition for "adverse drug experience" from its postmarketing safety reporting regulations and replace it with the proposed definition for "SADR," this change would not affect the number of safety reports from spontaneous sources that would be submitted to the agency because every spontaneous report currently must be submitted to FDA, irrespective of whether the manufacturer or applicant considers it to be drug related (see current definition of adverse drug experience at §§ 310.305(c), 314.80(c), and 600.80(c)). Under this proposed rule, every spontaneous report would continue to be submitted to FDA, because, for spontaneous reports, manufacturers and applicants would always be required to assume, for safety reporting purposes only, that there was at least a reasonable possibility in the opinion of the initial reporter that the drug or biological product caused the spontaneously reported event (see sections III.A.7 and III.C.6 of this document for the proposed definition of spontaneous report and for discussion of the proposed reporting requirement for SADRs from spontaneous sources).

On the other hand, with regard to clinical studies of investigational and marketed drugs and biological products, the proposed definition of SADR is likely to result in an increase in the number of safety reports that are currently submitted to FDA from some