

*Serious SADR* means any SADR that results in any of the following outcomes: Death, a life-threatening SADR, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious SADR when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

*Spontaneous report* means a communication from an individual (e.g., health care professional, consumer) to a company or regulatory authority that describes an SADR or medication error. It does not include cases identified from information solicited by the applicant or contractor, such as individual case safety reports or findings derived from a study, company-sponsored patient support program, disease management program, patient registry, including pregnancy registries, or any organized data collection scheme. It also does not include information compiled in support of class action lawsuits.

*Suspected adverse drug reaction (SADR)* means a noxious and unintended response to any dose of a drug 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.

*Unexpected SADR* means any SADR that is not included in the current U.S. labeling for the drug product. Reactions that may be symptomatically and pathophysiologically related to a reaction included in the U.S. labeling, but differ from the labeled reaction because of greater severity or specificity, would be unexpected. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the U.S. labeling only referred to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the U.S. labeling only included cerebral vascular accidents. "Unexpected," as used in this definition, refers to an SADR that has

not been previously observed (i.e., included in the U.S. labeling); it does not refer to an SADR that might be anticipated from the pharmacological properties of the drug product. SADRs that are mentioned in the U.S. labeling as occurring with a class of drugs but not specifically mentioned as occurring with the particular drug are considered unexpected.

*Unlisted SADR* means an SADR whose nature, specificity, severity, or outcome is not consistent with the information included in the CCSI.

(b) *Review of safety information.* (1) Each applicant having an approved application for a drug product under section 505(c) of the act must promptly review all safety information pertaining to its product obtained or otherwise received by the applicant from any source, foreign or domestic, including information derived from commercial marketing experience, postmarketing clinical investigations, postmarketing epidemiology/surveillance studies, animal or in vitro studies, electronic communications with applicants via the Internet (e.g., e-mail), reports in the scientific literature, and unpublished scientific papers, as well as reports from foreign regulatory authorities that have not been previously reported to FDA by the applicant.

(2) Individual case safety reports that are forwarded to the applicant by FDA must not be resubmitted to the agency by the applicant; however, applicants must include information from these individual case safety reports in any comprehensive safety analysis subsequently submitted to FDA. In addition, applicants must submit to FDA all followup information for these individual case safety reports.

(c) *Reporting requirements.* The applicant must submit to FDA two copies of each postmarketing expedited report (described under paragraphs (c)(2)(i) through (c)(2)(vii) of this section) and one copy of each postmarketing periodic safety report of an individual case safety reports—semiannual submission (described under paragraph (c)(3)(v) of this section) pertaining to its drug product. The applicant must also submit to FDA one copy of a PSUR, IPSR, or traditional periodic safety report (TPSR) along with one copy for each approved application for a human drug product covered by the report. FDA may waive the requirement for multiple copies in appropriate instances. Upon written notice, FDA may require, when appropriate, that the applicant submit reports under this section to FDA at times other than those stated. An applicant that wishes to submit reports

under this section at different intervals must submit to FDA a request for a waiver under § 314.90.

(1) *Determination of outcome, minimum data set, and full data set—*(i)(A) *Initial determinations.* Upon initial receipt of an SADR report, the applicant must immediately determine the outcome for the SADR (whether the SADR is serious or nonserious) and at least the minimum data set for the individual case safety report. For reports of actual medication errors that do not result in an SADR and potential medication errors the applicant must immediately determine the minimum information for the individual case safety report (minimum information described under paragraphs (c)(1)(iii)(B) and (c)(1)(iii)(C) of this section). If the applicant is not able to immediately determine the information in this paragraph, active query must be used to obtain it as soon as possible.

(B) *Spontaneous reports.* For spontaneous reports, the applicant must always assume, for safety reporting purposes under this section, that there is at least a reasonable possibility, in the opinion of the initial reporter, that the drug product caused the spontaneously reported event.

(C) *Clinical trials.* For a clinical trial, the possibility that the drug product caused the SADR or that a medication error has occurred must be assumed if either the investigator or the applicant believes that such a reasonable possibility exists.

(ii) *SADRs with unknown outcome.* For an SADR with unknown outcome that cannot be immediately determined, the applicant must continue to use active query to attempt to determine the outcome of the SADR within 30 calendar days after initial receipt of the SADR report by the applicant. The applicant must maintain a record of its efforts to determine the outcome for an SADR with unknown outcome.

(iii)(A) *Minimum data set for SADR reports.* The applicant must not submit an individual case safety report for an SADR to FDA if the report does not contain a minimum data set; instead, the applicant must maintain records of any information received or otherwise obtained for the SADR along with a record of its efforts to obtain a minimum data set.

(B) *Minimum information for reports of actual medication errors that do not result in an SADR.* For reports of actual medication errors that do not result in an SADR, an individual case safety report must be submitted to FDA even though the report does not contain a minimum data set (i.e., does not have an SADR). These reports must contain at