

active query, as either serious or nonserious.

**Serious SAR** means any SAR that results in any of the following outcomes: Death, a life-threatening SAR, 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 SAR 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 SAR or medication error. It does not include cases identified from information solicited by the applicant, shared manufacturer, 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 reaction (SAR)** means a noxious and unintended response to any dose of a biological 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 SAR** means any SAR that is not included in the current U.S. labeling for the licensed biological 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 SAR that has not been previously observed (i.e., included in the U.S. labeling); it does not refer to an SAR that might be anticipated from the pharmacological properties of the licensed biological product. SARs that are mentioned in the U.S. labeling as occurring with a class of products but not specifically mentioned as occurring with the particular product are considered unexpected.

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

(b) *Review of safety information.* (1) Any person having a biologics license under § 601.20 of this chapter 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 the Food and Drug Administration (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.* For nonvaccine biological products, 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 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 product. For nonvaccine biological products, 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 licensed biological product covered by the report. For vaccines, the applicant must submit to VAERS two copies of

each safety report pertaining to its product and required under this section. 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 the agency 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 § 600.90.

(1) *Determination of outcome, minimum data set, and full data set—*(i)(A) *Initial determinations.* Upon initial receipt of an SAR report, the applicant must immediately determine the outcome for the SAR (whether the SAR 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 SAR 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 biological product caused the spontaneously reported event.

(C) *Clinical trials.* For a clinical trial, the possibility that the biological product caused the SAR 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) *SARs with unknown outcome.* For an SAR with unknown outcome that cannot be immediately determined, the applicant must continue to use active query to attempt to determine the outcome of the SAR within 30 calendar days after initial receipt of the SAR report by the applicant. The applicant must maintain a record of its efforts to determine the outcome for an SAR with unknown outcome.

(iii) (A) *Minimum data set for SAR reports.* The applicant must not submit an individual case safety report for an SAR 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 SAR along with a record of its efforts to obtain a minimum data set.