

(4) *SARs with unknown outcome.* Provide a brief discussion of the impact on the overall safety evaluation of any spontaneously reported unlisted and listed SARs with unknown outcome obtained or otherwise received during the reporting period by the applicant from health care professionals and other individuals.

(5) *Class action lawsuits.* Provide a brief discussion of the impact on the overall safety evaluation of any safety information obtained or otherwise received during the reporting period by the applicant from class action lawsuits.

(6) *Lack of efficacy reports.* Provide an assessment of whether it is believed that the frequency of any lack of efficacy reports, obtained or otherwise received during the reporting period, is greater than would be predicted by the premarketing clinical trials for the biological product.

(7) *Medication errors.* Provide a brief discussion of the impact on the overall safety evaluation of all domestic reports of medication errors submitted during the reporting period under paragraph (c)(2)(v) of this section.

(8) *U.S. patient exposure.* Provide, for the reporting period, an estimate of the U.S. patient exposure to the biological product(s) covered by the IPSR (*i.e.*, number of patients, average or median dose received, and average or median length of treatment). The method used to estimate patient exposure must always be described. If the patient exposure is impossible to estimate or is meaningless, an explanation of and justification for such conclusions must be provided. If patient exposure is impossible to estimate, other measures of exposure, such as patient-days, number of prescriptions, or number of dosage units, may be used. If these or other more precise measures are not available and an adequate explanation for the lack of such information is provided, bulk sales may be used.

(9) *Location of safety records.* Provide a list of the current address(es) where all safety reports and other safety-related records for the licensed biological product(s) are maintained.

(10) *Contact person.* Provide the name and telephone number for the licensed physician(s) responsible for the content and medical interpretation of the information contained within the IPSR. Include, if available, the fax number and e-mail address for the licensed physician(s).

(iv) *Pediatric use supplements.* After approval of a pediatric use supplement to an approved application (*i.e.*, a supplement for use of the human biological product in the pediatric population), the applicant must submit

PSURs to FDA as prescribed under paragraph (c)(3)(ii) of this section according to the following schedule: Semiannually for 2 years after U.S. approval of the supplement, annually for the next 3 years, and then every 5 years thereafter. These applicants must also submit IPSRs to FDA as prescribed under paragraph (c)(3)(iii) of this section at 7.5 years and 12.5 years after U.S. approval of the supplement. The data lock point for the PSUR and IPSR is the month and day of the international birth date of the licensed biological product or any other month and day agreed on by the applicant and FDA.

(v) *Semiannual submission of individual case safety reports.* (A) An applicant holding a biologics license under § 601.20 of this chapter for a human biological product must submit to FDA semiannually (*i.e.*, every 6 months) after U.S. approval of the application a separate report that consists of individual case safety reports for certain spontaneously reported SARs for the biological product. The individual case safety reports must be submitted on the form designated by the agency under paragraph (c)(4) of this section. The data lock point for the report is the month and day of the international birth date of the licensed biological product or any other month and day agreed on by the applicant and FDA. This report must be identified as “individual case safety reports—semiannual submission.”

(B) Applicants that submit TPSRs to FDA for the licensed biological product must submit an individual case safety report for each serious, expected SAR, whether domestic or foreign, and each nonserious, unexpected SAR occurring in the United States that is submitted to the applicant during the reporting period from all spontaneous sources (*i.e.*, health care professionals and other individuals). Reports for vaccines must include an individual case safety report for each nonserious, expected SAR and each expected SAR with unknown outcome occurring in the United States that is submitted to the applicant during the reporting period from all spontaneous sources. Applicants that submit PSURs to FDA for the licensed biological product must submit an individual case safety report for each serious, listed SAR, whether domestic or foreign, and each nonserious, unlisted SAR occurring in the United States that is submitted to the applicant during the reporting period from all spontaneous sources. Reports for vaccines must include an individual case safety report for each nonserious, listed SAR and each listed SAR with unknown outcome occurring in the

United States that is submitted to the applicant during the reporting period from all spontaneous sources. If a full data set is not available for a report of a serious SAR, the applicant must submit the information required under paragraph (c)(1)(iv) of this section.

(C) Followup information to SARs submitted in an individual case safety report—semiannual submission may be submitted in the next individual case safety report—semiannual submission unless such information changes the classification of the SAR to a serious, unexpected SAR. In these cases, the followup information must be submitted to FDA as a 15-day followup report (see paragraph (c)(2)(vii) of this section).

(4) *Reporting format.* (i)(A) Except as provided in paragraphs (c)(4)(i)(B), (c)(4)(i)(D), and (c)(4)(v) of this section, the applicant must complete the reporting form designated by FDA for each individual case safety report of an SAR (FDA Form 3500A or, for vaccines, a VAERS form). Reports based on information about individual cases or case series in the scientific literature must be submitted on an FDA Form 3500A(s) or, for vaccines, on a VAERS form(s).

(B) Foreign SARs may be submitted either on an FDA Form 3500A or, if preferred, on a CIOMS I form; foreign SARs for vaccines may be submitted either on a VAERS form or, if preferred, on a CIOMS I form.

(C) Each domestic report of an actual or potential medication error must be submitted on an FDA Form 3500A, or, for vaccines, on a VAERS form.

(D) Reports of overall findings or data in the aggregate from published and unpublished *in vitro*, animal, epidemiological, or clinical studies must be submitted in a narrative format.

(ii) Each SAR in an individual case safety report must be coded on the FDA Form 3500A, VAERS form, or CIOMS I form using the appropriate “preferred term” in the latest version of MedDRA (the medical dictionary for regulatory activities) in use at the time the applicant becomes aware of the individual case safety report. For individual case safety reports of medication errors, the report must be coded both as a medication error and, if applicable, with the preferred term for any SARs associated with the medication error.

(iii) Each completed FDA Form 3500A, VAERS form, or CIOMS I form should refer only to an individual case.

(iv) Each completed FDA Form 3500A, VAERS form or CIOMS I form must include the name and telephone number (and fax number and e-mail address, if available) for the licensed