

approval of the application. In addition, these applicants must submit either an IPSR as described under paragraph (c)(3)(iii) of this section or a TPSR as described under this paragraph 7.5 years and 12.5 years after U.S. approval of the application. The data lock point for the TPSR, PSUR, or 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. Each TPSR must contain:

(A) *Summary*. This section of the TPSR includes:

(1) A narrative summary and analysis of serious, expected SARs and nonserious, unexpected SARs occurring in the United States that were submitted to the applicant during the reporting period from all spontaneous sources (*i.e.*, health care professionals and other individuals) (with an index consisting of a line listing of the applicant's manufacturer report number and SAR term(s));

(2) An analysis of the expedited reports submitted during the reporting period under paragraphs (c)(2)(i) through (c)(2)(vii) of this section (all expedited reports must be appropriately referenced by the applicant's manufacturer report number, SAR term(s), if appropriate, and date of submission to FDA);

(3) A discussion of any increased reporting frequency of serious, expected SARs, including comments on whether it is believed that the data reflect a meaningful change in SAR occurrence, and an assessment of whether it is believed that the frequency of lack of efficacy reports is greater than would be predicted by the premarketing clinical trials for the biological product; and

(4) The applicant's conclusion as to what, if any, safety-related actions should be taken based on the analysis of the safety data in the TPSR (*e.g.*, labeling changes, studies initiated).

(B) *Summary tabulations*. This section of the TPSR includes summary tabulations (*i.e.*, lists of all SAR terms and counts of occurrences) presented by body system or by standard organ system classification scheme for:

(1) All serious expected SARs, nonserious unexpected SARs, nonserious expected SARs, and expected SARs with unknown outcome occurring in the United States that are submitted to the applicant during the reporting period from all spontaneous sources (*i.e.*, health care professionals and other individuals);

(2) All serious unexpected SARs, unexpected SARs with unknown outcome, and always expedited reports that were previously submitted to FDA

in an expedited report under paragraphs (c)(2)(i), (c)(2)(iii), and (c)(2)(iv) of this section (include cumulative data for serious unexpected SARs, *i.e.*, all cases reported to date);

(3) All reports of SARs not previously submitted to FDA by the applicant (*e.g.*, reports submitted to applicants by FDA, reports obtained from FDA from freedom of information requests at the discretion of the applicant, reports from class action lawsuits); and

(4) All domestic reports of medication errors previously submitted to FDA under paragraph (c)(2)(v) of this section. For actual medication errors, provide summary tabulations of serious SARs, nonserious SARs, and no SARs. For potential medication errors, provide the number of reports for specific errors;

(C) *History of safety-related actions taken*. This section of the TPSR includes a history of safety-related actions taken since the last periodic safety report (*e.g.*, labeling changes, studies initiated);

(D) *Location of safety records*. This section of the TPSR includes a list of the current address(es) where all safety reports and other safety-related records for the licensed biological product(s) are maintained; and

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

(ii) *Periodic safety update report (PSUR)*. An applicant holding a biologics license under § 601.20 of this chapter for a human biological product approved on or after January 1, 1998, must submit a PSUR to FDA according to the following schedule: Semiannually (*i.e.*, every 6 months) for 2 years after U.S. approval of the application, annually for the next 3 years, and then every 5 years thereafter. The data lock point for the PSUR 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. Each PSUR must contain:

(A) *Title page, table of contents, and introduction*. (1) The title page includes, at a minimum, the following information:

(i) Name and international birth date of the licensed biological product(s) that is the subject of the PSUR,

(ii) Various dosage forms and formulations of the biological product(s) covered by the PSUR,

(iii) Name and address of the applicant,

(iv) Reporting period covered by the PSUR, and

(v) Date of the PSUR.

(2) The introduction:

(i) Provides a brief description of how the PSUR relates to previous reports and circumstances;

(ii) References relevant biological products reported in other periodic safety reports (*e.g.*, a combination product reported in a separate PSUR); and

(iii) Indicates any data duplication with other PSURs.

(B) *Worldwide marketing status*. This section of the PSUR contains a table of the chronological history of the worldwide marketing status of the biological product(s) covered by the PSUR from the date the product(s) was first approved (*i.e.*, the international birth date) through its current status (*i.e.*, cumulative information). This table consists of:

(1) Dates of biological product approval and renewal;

(2) Safety-related restrictions on product use;

(3) Indications for use and special populations covered by the biological product approval;

(4) Lack of approval of the biological product in any dosage form or for any indication for use by any regulatory authority(ies);

(5) Withdrawal of a pending marketing application for the biological product by the applicant for safety- or efficacy-related reasons;

(6) Dates of market launches; and

(7) Trade name(s).

(C) *Actions taken for safety reasons*.

(1) This section of the PSUR includes details on the following types of regulatory authority-initiated (*e.g.*, by FDA) and/or applicant-initiated actions related to safety that were taken during the period covered by the PSUR and between the data lock point and PSUR submission (*i.e.*, "late-breaking" safety concerns):

(i) Withdrawal or suspension of biological product approval or indication for use approval;

(ii) Failure to obtain a marketing authorization renewal or to obtain an approval for a new indication for use;

(iii) Restrictions on distribution (products recalled for safety reasons);

(iv) Clinical trial suspension;

(v) Dosage modification;

(vi) Changes in target population or indications; and

(vii) Formulation changes.

(2) This section of the PSUR also contains a narrative identifying the safety-related reasons that led to these actions with relevant documentation appended when appropriate.