

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 SADR 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, SADR term(s), if appropriate, and date of submission to FDA);

(3) A discussion of any increased reporting frequency of serious, expected SADRs, including comments on whether it is believed that the data reflect a meaningful change in SADR occurrence, and an assessment of whether it is believed that the frequency of 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 drug product; and

(4) The applicants' 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 SADR terms and counts of occurrences) presented by body system or by standard organ system classification scheme for:

(1) All serious expected SADRs, nonserious unexpected SADRs, nonserious expected SADRs, and expected SADRs 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 SADRs, unexpected SADRs 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 SADRs, *i.e.*, all cases reported to date);

(3) All reports of SADRs 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 SADRs, nonserious SADRs, and no SADRs. 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 drug product 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 an application for a human drug product approved under section 505(c) of the act 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 drug substance 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 drug substance that is the subject of the PSUR,

(ii) Various dosage forms and formulations of the drug substance 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 drug products or substances 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 drug 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). The table consists of:

(1) Dates of drug approval and renewal;

(2) Safety-related restrictions on product use;

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

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

(5) Withdrawal of a pending marketing application for the drug 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 drug 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 (*e.g.*, 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.

(3) Any communication with health care professionals (*e.g.*, Dear Healthcare Professional letters) resulting from such actions must also be described with copies appended.

(D) *Changes to CCSI.* This section of the PSUR describes changes to the CCSI (*e.g.*, new contraindications, precautions, warnings, SADRs, or interactions) made during the period covered by the PSUR. A copy of any modified section of the CCSI must be included. The applicant must use the CCSI in effect at the beginning of the reporting period for the PSUR. The revised CCSI is to be used as the reference document for the next reporting period.