

(E) *Worldwide patient exposure.* (1) This section of the PSUR includes, for the reporting period, an estimate of the worldwide patient exposure to the drug product(s) covered by the PSUR (*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.

(2) When possible, data broken down by gender and age (especially pediatric versus adult) must be provided. For the pediatric population, data must be reported, if possible, by age group (*e.g.*, neonates, infants, children, adolescents). If these data are not available, an explanation must be included.

(3) When a pattern of reports indicates a potential problem, details by country (with locally recommended dosage regimens) or other segmentation (*e.g.*, indication, dosage form) must be presented.

(F) *Individual case safety reports.* (1) This section of the PSUR includes summary tabulations of individual case safety reports (*e.g.*, serious unlisted SADRs, serious listed SADRs, nonserious unlisted SADRs, nonserious listed SADRs) for the following SADRs obtained or otherwise received during the reporting period:

(i) All serious and nonserious SADRs from spontaneous sources that were submitted to applicants by a health care professional;

(ii) All serious SADRs from studies, individual patient INDs, or, in foreign countries, from named-patient "compassionate" use;

(iii) All serious SADRs and nonserious unlisted SADRs from the scientific literature;

(iv) All serious SADRs from regulatory authorities; and

(v) Serious SADRs from other sources such as reports created by poison control centers and epidemiological data bases.

(2) The summary tabulations must be made up of lists by body system or by standard organ system classification scheme of all SADR terms and counts of occurrences. For SADRs that are determined to be both serious and

unlisted, include cumulative data (*i.e.*, all cases reported to date).

(3) The applicant must conclude this section with a brief discussion of the data concerning the individual case safety reports in the PSUR (*e.g.*, discussion of medical significance or mechanism).

(G) *Safety studies.* This section of the PSUR contains a discussion of nonclinical, clinical, and epidemiological studies that contain important safety information, as follows:

(1) All applicant-sponsored studies newly analyzed during the reporting period (copies of full reports should be appended only if new safety issues are raised or confirmed; FDA may request copies of other studies, if necessary);

(2) New studies specifically planned, initiated, or continuing during the reporting period that examine a safety issue, whether actual or hypothetical; and

(3) Published safety studies in the scientific and medical literature, including relevant published abstracts from meetings (provide literature citation).

(H) *Other information.* This section of the PSUR includes:

(1) A discussion of medically relevant lack of efficacy reports (*e.g.*, might represent a significant hazard to the treated population) for a product(s) used to treat serious or life-threatening diseases; and

(2) Any important new information received after the data lock point (*e.g.*, significant new cases).

(I) *Overall safety evaluation.* This section of the PSUR contains a concise, yet comprehensive, analysis of all of the safety information provided in the PSUR, including new information provided under paragraph (c)(3)(ii)(H)(2) of this section. In addition, this section of the PSUR includes an assessment by the applicant of the significance of the data collected during the reporting period, as well as from the perspective of cumulative experience.

(1) The applicant must highlight any new information on:

(i) Serious, unlisted SADRs;

(ii) Increased reporting frequencies of listed SADRs, including comments on whether it is believed that the data reflect a meaningful change in SADR occurrence;

(iii) A change in characteristics of listed SADRs (*e.g.*, severity, outcome, target population); and

(iv) Nonserious, unlisted SADRs.

(2) As part of the overall safety evaluation, the applicant must also explicitly address any new safety issue including but not limited to the

following (lack of significant new information for each of the following must be mentioned):

(i) Drug interactions;

(ii) Experience with overdose, whether deliberate or accidental, and its treatment;

(iii) Drug abuse or intentional misuse;

(iv) Positive or negative experiences during pregnancy or lactation;

(v) Effects with long-term treatment; and

(vi) Experience in special patient groups (*e.g.*, pediatric, geriatric, organ impaired). For the pediatric population, data must be evaluated, if possible, by age group (*e.g.*, neonates, infants, children, adolescents).

(J) *Conclusion.* This section of the PSUR:

(1) Indicates new safety information that is not in accord with previous cumulative experience and with the CCSI in use at the beginning of the reporting period (*e.g.*, new evidence that strengthens a possible causal relationship between the drug product and an SADR such as positive rechallenge, an epidemiological association, or new laboratory studies); and

(2) Specifies and justifies any action recommended or initiated, including changes in the CCSI.

(K) *Appendices.* This section of the PSUR includes:

(1) *Company core data sheet.* Provide a copy of the company core data sheet covered by this PSUR (*i.e.*, in effect at the beginning of the period covered by the PSUR) as well as the company core data sheet for the next reporting period. Company core data sheets must be numbered and dated and include the date of last revision.

(2) *U.S. labeling.* Provide a copy of the current approved U.S. labeling. Specify any safety information that is included in the CCSI but not in the U.S. labeling and provide an explanation for the discrepancy. Describe any safety-related changes or proposed changes to the U.S. labeling made during the reporting period (include the supplement number(s) and date(s) of submission for the supplement(s)) and any suggested change(s) that should be considered based on the safety analysis in the PSUR.

(3) *Spontaneous reports submitted to the applicant by an individual other than a health care professional.* Provide summary tabulations (*e.g.*, serious unlisted SADRs, serious listed SADRs, nonserious unlisted SADRs, nonserious listed SADRs) for all spontaneously reported serious SADRs, whether domestic or foreign, and all spontaneously reported nonserious