

semiannual submission of certain individual case safety reports on FDA Form 3500A (VAERS form for vaccines, CIOMS I form, if desired, for foreign SADRs) (*see* section III.E.4 of this document). However, FDA is willing to accept line listings in PSURs as described in the ICH E2C guidance if applicants wish to include them. FDA believes that such an approach will help further the goal of harmonizing PSUR generation, formatting, and submission globally.

III.E.2.f.ii. *Summary tabulations.* This section of the PSUR would consist of 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:

- All serious and nonserious SADRs from spontaneous sources that were submitted to applicants by a health care professional,
- All serious SADRs from studies, individual patient INDs, or, in foreign countries, from named-patient "compassionate" use,
- All serious SADRs and nonserious unlisted SADRs from the scientific literature,
- All serious SADRs from regulatory authorities, and
- Serious SADRs from other sources such as reports created by poison control centers and epidemiological data bases.

These summary tabulations would be made up of lists by body system or standard organ system classification scheme (*e.g.*, cardiovascular, central nervous system, endocrine, renal) of all SADR terms and counts of occurrences. For SADRs that are determined to be both serious and unlisted, cumulative data would also be provided (*i.e.*, all cases reported to date). Applicants may provide information for this section of the PSUR in a narrative rather than a summary tabulation if the number of cases is small or the information is inadequate for any of the tabulations.

As noted previously, FDA would consider "study" information to include the following: safety information from company-sponsored patient support programs, disease management programs, patient registries, including pregnancy registries, or any organized data collection scheme (*see* section III.A.7 of this document). FDA is proposing to include summary tabulations for serious listed SADRs from study information in PSURs to be consistent with the ICH E2C guidance (62 FR 27470 at 27474), even though the

agency indicated in the clarification guidance of 1997 that only serious and unexpected adverse drug experiences for which there is a reasonable possibility that the drug or biological product caused the adverse drug experience should be reported to FDA from studies.

This section of the PSUR would also contain a brief discussion of the individual case data in the summary tabulations (*e.g.*, discussion of medical significance or mechanism). This section of the PSUR should be used to comment on specific cases rather than to provide an overall assessment of the cases.

III.E.2.g. *Safety studies.* This section of the PSUR would contain a discussion (not just a listing of the studies) of nonclinical, clinical, and epidemiological studies concerning important safety information including:

- All applicant-sponsored studies newly analyzed during the reporting period;
- New studies specifically planned, initiated, or continuing during the reporting period that examine a safety issue, whether actual or hypothetical; and
- Published safety studies in the scientific and medical literature, including relevant published abstracts from meetings (provide citations for all reports from the literature).

As noted previously, FDA would consider "study" information to include the following: safety information from company-sponsored patient support programs, disease management programs, patient registries, including pregnancy registries, or any organized data collection scheme (*see* section III.A.7 of this document).

The study design and results of newly analyzed studies should be clearly and concisely presented with attention to the usual standards of data analysis and description that are applied to nonclinical and clinical study reports. Copies of full reports for these studies should be appended only if new safety issues are raised or confirmed. FDA may request copies of other studies, if necessary.

For new or ongoing studies, the objective, starting date, projected completion date, number of subjects (planned and enrolled), and protocol abstract for each study should be provided. When possible and relevant, interim results of ongoing studies should be presented.

III.E.2.h. *Other information.* This section of the PSUR would contain 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, or any important new information received after the data lock point (*e.g.*, significant new cases).

III.E.2.i. *Overall safety evaluation.*

This section of the PSUR would contain a concise, yet comprehensive, analysis of all of the safety information provided in the PSUR, including new information provided under the section entitled "Other Information." In addition, the section would include an assessment by applicants of the significance of the data collected during the reporting period, as well as from the perspective of cumulative experience. Applicants would highlight any new information on:

- Serious, unlisted SADRs;
- Increased reporting frequencies of listed SADRs, including comments on whether it is believed that the data reflect a meaningful change in SADR occurrence;
- A change in characteristics of listed SADRs (*e.g.*, severity, outcome, target population); and
- Nonserious, unlisted SADRs.

As part of the overall safety evaluation, applicants would also explicitly address any new safety issue including but not limited to the following:

- Drug interactions;
- Experience with overdose, whether deliberate or accidental, and its treatment;
- Drug abuse or intentional misuse;
- Positive or negative experiences during pregnancy or lactation;
- Effects with long-term treatment; and
- Experience in special patient groups (*e.g.*, pediatric population evaluated, if possible, by age group; geriatric; organ impaired).

Applicants would note a lack of significant new information for any of these categories.

III.E.2.j. *Conclusion.* This section of the PSUR would indicate 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 or biological product and an SADR, such as positive rechallenge, an epidemiological association, or new laboratory studies). This section of the PSUR would also specify and justify any action recommended or initiated, including changes in the CCSI.

III.E.2.k. *Appendices.* This section of the PSUR would include the following information as appendices: