

III.E.2. Periodic Safety Update Reports (PSURs)

Proposed §§ 314.80(c)(3)(ii) and 600.80(c)(3)(ii) would amend FDA's postmarketing periodic safety reporting regulations by adding a new type of postmarketing periodic safety report. This new report would be identified as a "periodic safety update report (PSUR)." The proposed content and format for the PSUR, as described below, are consistent with the ICH E2C guidance (62 FR 27470) and would enable applicants to submit a single core document (PSUR excluding appendices) to regulatory authorities worldwide. All dosage forms, formulations, and indications for which applicants hold an approved application (*i.e.*, NDA, ANDA, BLA) for a given drug substance or licensed biological product should usually be covered in one PSUR. The PSUR may include separate presentations of these data as well as other data (*e.g.*, populations) if such presentations would facilitate review of the PSUR. FDA is proposing that a PSUR contain the following information:

III.E.2.a. *Title page, table of contents, and introduction.* The title page would include, at a minimum, the following information:

- Name and international birth date of the drug substance or licensed biological product that is the subject of the PSUR,
- Various dosage forms and formulations of the drug substance or biological product covered by the PSUR,
- Name and address of the applicant,
- Reporting period covered by the PSUR, and
- Date of the PSUR.

The introduction would provide a brief description of how this PSUR relates to previous reports and circumstances, would reference relevant drug products, drug substances, or biological products reported in other periodic safety reports (*e.g.*, a combination product reported in a separate PSUR), and would indicate any data duplication with other PSURs. If two or more companies co-market the same drug substance or licensed biological product, the safety reporting responsibilities of each of the companies should be specified clearly in the introduction.

III.E.2.b. *Worldwide marketing status.* This section of the PSUR would contain a table of the chronological history of the worldwide marketing status of the drug or biological product(s) covered by the PSUR from the date the product was first approved (*i.e.*, the international birth date) through its current status

(*i.e.*, cumulative information). The table would include:

- Dates of drug or biological product approval and renewal,
- Safety-related restrictions on product use,
- Indications for use and special populations covered by the drug or biological product approval,
- Lack of approval of the drug substance or biological product in any dosage form or for any indication for use by any regulatory authority(ies),
- Withdrawal of a pending drug or biological product marketing application by the applicant for safety- or efficacy-related reasons,
- Dates of market launches, and
- Trade name(s).

Drug or biological products that are approved in a country for a particular indication, population, or dosage form that may result in different types of patient exposure in that country should be identified, particularly if there are meaningful differences in the safety information reported in the PSUR due to the difference in patient exposures.

III.E.2.c. *Actions taken for safety reasons.* This section of the PSUR would contain details on regulatory authority-initiated (*e.g.*, 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) including:

- Withdrawal or suspension of product approval or indication for use approval,
- Failure to obtain a marketing authorization renewal or to obtain an approval for a new indication for use,
- Restrictions on distribution (*e.g.*, products recalled for safety reasons),
- Clinical trial suspension,
- Dosage modification,
- Changes in target population or indications, and
- Formulation changes.

This section of the PSUR would also contain a narrative identifying the safety-related reasons that led to these actions with relevant documentation appended when appropriate. Any communication with health care professionals (*e.g.*, Dear Healthcare Professional letters) resulting from such actions would also be described with copies appended.

III.E.2.d. *Changes to CCSI.* This section of the PSUR would describe changes to the CCSI (*e.g.*, new contraindications, precautions, warnings, SADR, or interactions) made during the period covered by the PSUR. A copy of any modified section of the

CCSI would be included. Applicants would use the CCSI in effect at the beginning of the reporting period for the PSUR. The revised CCSI would be used as the reference document for the next reporting period.

III.E.2.e. *Worldwide patient exposure.* This section of the PSUR would include, for the reporting period, an estimate of the worldwide patient exposure to the drug or biological product(s) covered by the PSUR (*i.e.*, number of patients, average or median dose received, and average or median length of treatment). In many cases, accurate patient exposure data for a reporting period may be difficult to obtain. However, applicants should exercise due diligence to obtain an estimate of this exposure. The method used to estimate patient exposure would always be described. If the patient exposure is impossible to estimate or is meaningless, an explanation of and justification for such conclusions would 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, could 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 could be used with estimates of what such numbers may mean in terms of patient exposure.

When possible, data broken down by gender and age (especially pediatric versus adult) would be provided. Data for the pediatric population would be reported, if possible, by age group (*e.g.*, neonates, infants, children, adolescents). If these data are not available, an explanation for the lack of such information would be included. In addition, 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) would also be presented.

Patient exposure for clinical studies should also be provided when SADR data from these types of studies are included in the PSUR. For ongoing or blinded clinical studies, an estimate of patient exposure should be provided.

III.E.2.f. *Individual case safety reports.*

III.E.2.f.i. *Line listings.* Individual line listings of various data points from individual case safety reports are included as part of the format for international PSURs agreed to by ICH (ICH E2C guidance, 62 FR 27470 at 27473 and 27474). FDA will not require submission of such line listings in PSURs because, instead, the agency is proposing to require a separate