

related to safety that were taken during the period covered by the IPSR and between the data lock point and IPSR 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 IPSR 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 IPSR describes changes to the CCSI (*e.g.*, new contraindications, precautions, warnings, SARs, or interactions) made during the period covered by the IPSR. 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 IPSR. The revised CCSI is to be used as the reference document for the next reporting period.

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

(G) *Other information*. This section of the IPSR includes 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.

(H) *Overall safety evaluation*. This section of the IPSR contains a concise, yet comprehensive, analysis of all of the safety information provided in the IPSR. In addition, this section of the IPSR 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 SARs;

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

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

(iv) Nonserious, unlisted SARs.

(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).

(I) *Conclusion*. This section of the IPSR:

(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 biological product and an SAR, 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.

(J) *Appendices*. This section of the IPSR includes:

(1) *Company core data sheet*. Provide a copy of the company core data sheet covered by this IPSR (*i.e.*, in effect at the beginning of the period covered by the IPSR), 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 this IPSR.

(3) *Spontaneous reports submitted to the applicant by an individual other than a health care professional*. Provide a brief discussion of the impact on the overall safety evaluation of any spontaneously reported serious SARs, whether domestic or foreign, and any spontaneously reported nonserious SARs occurring in the United States, obtained or otherwise received during the reporting period by the applicant from an individual other than a health care professional (*e.g.*, reports from consumers).