

for individuals taking the product because, if one of these SADR occurs, the individual might suspect that it was due to the product and not due to the onset of a new disorder. These reports may also serve to signal the emergence of a serious, unexpected/unlisted SADR (e.g., an aggregate of reports of decreased white blood cell counts may be an early indicator of a serious condition such as bone marrow suppressive disorder).

The reports (*i.e.*, individual case safety reports for vaccines or summary tabulations for drugs and licensed biological products that are not vaccines) of nonserious, expected/listed SADRs are used to monitor changes in the frequency of occurrence or severity of a nonserious, expected/listed SADR. Such information could indicate a potential safety problem that is worthy of further investigation (e.g., a new drug or food interaction not previously associated with use of the product).

Proposed changes to FDA's current reporting requirements for these types of SADRs include: (1) Different reporting frequencies for the SADRs, (2) receipt of spontaneously reported serious, expected/listed SADRs from foreign sources and (3) submission of nonserious, expected/listed SADRs in a summary tabulation instead of as individual case safety reports for drugs and licensed biological products that are not vaccines. With regard to different reporting frequencies, some SADRs would be reported less frequently (e.g., semiannually rather than every 3 months) and others would be reported more frequently (e.g., semiannually rather than annually). FDA seeks comment on these proposed changes.

The current approved U.S. labeling would be used as the reference document to determine whether an SADR is unexpected or expected, and the CCSI would be used to determine whether an SADR is unlisted or listed.

As described previously, a minimum data set would be required for all individual case safety reports of an SADR (*see* section III.C.5 of this document). In addition, a full data set would be required for reports of serious, expected SADRs and serious, listed SADRs. If a full data set is not available for these SADR reports, the information required under proposed §§ 314.80(c)(1)(iv) and 600.80(c)(1)(iv) would be provided. For nonserious SADRs with a minimum data set, the proposal would require that all safety information received or otherwise obtained be submitted. The proposal would not require that information in addition to the minimum data set be acquired. Thus, followup would not be

required for nonserious SADRs that contain a minimum data set.

Followup information on SADRs submitted in an individual case safety report—semiannual submission may be submitted in the next individual case safety report—semiannual submission, unless such information changes the classification of the SADR to a serious, unexpected SADR. In these cases, the followup information would be submitted to FDA as an expedited 15-day followup report (*see* section III.D.6 of this document).

Applicants should not submit any reports of lack of efficacy in an individual case safety report—semiannual submission. As noted previously, applicants would be required to submit to FDA in an expedited manner information regarding certain lack of efficacy reports for the product (*i.e.*, expedited reports of information sufficient to consider product administration changes) and also to provide in postmarketing periodic safety reports an assessment of all lack of efficacy reports for the product as compared to premarketing clinical trials for the product (*see* section III.C.7 of this document).

Applicants should not submit SADRs from class action lawsuits to FDA in an individual case safety report—semiannual submission. The agency believes, as noted previously, that SADRs from class action lawsuits would be submitted to FDA from other sources (e.g., spontaneous report) prior to initiation of the class action lawsuit (*see* section III.D.11 of this document). Summary tabulations of these SADRs would be required to be included in postmarketing periodic safety reports (*see* sections III.E.1.e and III.E.2.k.v of this document).

Applicants should not submit reports of medication errors in an individual case safety report—semiannual submission. These reports would be submitted, as previously noted, as an expedited report (*see* section III.D.5 of this document).

III.E.5. Reporting Requirements

III.E.5.a. *Reporting intervals.* Current regulations (§§ 314.80(c)(2)(i) and 600.80(c)(2)(i)) require the submission of postmarketing periodic safety reports at quarterly intervals for 3 years from the date of approval of the application in the United States and then annually thereafter. Quarterly safety reports must be submitted within 30 days of the close of the quarter (the first quarter beginning on the date of U.S. approval of the application); annual safety reports must be submitted within 60 days of the anniversary date of U.S. approval of the

application. FDA is proposing revisions to these reporting requirements. The proposals are consistent with the recommendations of ICH (62 FR 27470 at 27472): "Therefore, it is recommended that the preparation of PSUR's for all regulatory authorities should be based on data sets of 6 months or multiples thereof."

Products approved before January 1, 1998. Proposed §§ 314.80(c)(3)(i) and 600.80(c)(3)(i) would require applicants holding an NDA, ANDA, or BLA that was approved for initial marketing of a drug product containing a drug substance or licensed biological product before January 1, 1998, to submit either a TPSR or a PSUR every 5 years after U.S. approval of the application. The proposed rule would also require these applicants to submit a TPSR or an IPSR 7.5 years and 12.5 years after U.S. approval of the application. Under proposed §§ 314.80(c)(3)(iii) and 600.80(c)(3)(iii), the reporting period for an IPSR would cover the period between the last PSUR or TPSR and the data lock point for the IPSR (e.g., between years 5 and 7.5 for an IPSR with a data lock point at 7.5 years after U.S. approval of the application).

Products approved on or after January 1, 1998. Under proposed §§ 314.80(c)(3)(ii) and 600.80(c)(3)(ii), applicants holding an NDA, ANDA, or BLA that was approved for initial marketing of a drug product containing a drug substance or licensed biological product on or after January 1, 1998, would be required to submit a PSUR to FDA with 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 proposed rule would also require applicants to submit an IPSR 7.5 years and 12.5 years after U.S. approval of the application.

Products with approved pediatric use supplements. Proposed §§ 314.80(c)(3)(iv) and 600.80(c)(3)(iv) would require applicants holding an approved pediatric use supplement to an approved application (*i.e.*, a supplement for use of the human drug or biological product in the pediatric population) to submit a PSUR to FDA with the following schedule:

- Semiannually (*i.e.*, every 6 months) for 2 years after U.S. approval of the supplement,
- Annually for the next 3 years, and
- Then every 5 years thereafter.

The proposed rule would also require these applicants to submit an IPSR 7.5