

one reporting the serious SAR and the other reporting the fatality. However, if the fatality occurs after the report of the serious SAR is submitted to the agency, the blood establishment should update the initial report to report the fatality.

III.E. Postmarketing Periodic Safety Reporting

The proposed rule would require all applicants to submit to FDA semiannually on an FDA Form 3500A (VAERS form for vaccines, CIOMS I Form, if desired, for foreign SADR)s certain spontaneously reported SADR)s (see tables 7 and 9 and section III.E.4 of this document regarding individual case safety reports—semiannual submissions). Applicants would also be required to submit other postmarketing periodic safety reports (*i.e.*, traditional periodic safety reports (TPSR)s, periodic safety update reports (PSUR)s, or interim periodic safety reports (IPSR)s) to FDA with a frequency as described in section III.E.5.a of this document (see tables 7 and 9). PSUR)s, IPSR)s, and TPSR)s would provide FDA with an overview or summary of the safety profile of a drug or licensed biological product (excluding individual case safety reports). A TPSR would essentially contain the same format and content as the periodic safety report currently required by the agency's postmarketing periodic safety reporting regulations (see table 10 and section III.E.1 of this document). A PSUR would essentially be consistent with the format and content of the periodic safety report described in the ICH E2C guidance (see section III.E.2 of this document), and an IPSR would represent an abbreviated form of a PSUR (see section III.E.3 of this document). Applicants with drugs and licensed biological products approved prior to January 1, 1998, would have the option to submit either a TPSR or PSUR to FDA, whereas applicants with products approved on or after January 1, 1998, would be required to submit a PSUR (see tables 7 and 9 and section III.E.5.a of this document). FDA is proposing to require submission of periodic safety reports in a PSUR format for products approved on or after January 1, 1998, to be consistent with the ICH E2C guidance. FDA is not proposing to require submission of PSUR)s for products approved prior to January 1, 1998, because the agency recognizes that the most significant new safety information on a product is usually acquired in the first few years after it has been on the market. It is not necessary for applicants to reformat periodic safety reports for products approved prior to January 1, 1998. In addition, in some cases, it will be

sufficient for FDA to review an abbreviated form of the PSUR (*i.e.*, at 7.5 and 12.5 years after U.S. approval of a product). For these cases, the agency is proposing to require submission of an IPSR instead of a PSUR (see tables 7 and 9 and sections III.E.3 and III.E.5.a of this document).

III.E.1. Traditional Periodic Safety Reports (TPSR)s

Current regulations (§§ 314.80(c)(2)(ii)(a) through (c)(2)(ii)(c) and 600.80(c)(2)(ii)(A) through (c)(2)(ii)(C)) require the submission of postmarketing periodic adverse drug experience reports that contain:

- A narrative summary and analysis of the information in the report and an analysis of the 15-day postmarketing Alert reports submitted during the reporting period (all 15-day Alert reports being appropriately referenced by the applicant's patient identification number, adverse reaction term(s), and date of submission to FDA);
- An FDA Form 3500A describing each adverse drug experience not previously reported (with an index consisting of a line listing of the applicant's patient identification number and adverse reaction term(s)); and
- A history of actions taken since the last periodic report.

Proposed §§ 314.80(c)(3)(i) and 600.80(c)(3)(i) would amend these regulations by replacing the term "periodic adverse drug experience report" with the term "traditional periodic safety report (TPSR)." FDA is proposing this revision to differentiate the existing postmarketing periodic safety report from the proposed new postmarketing periodic safety reports (*i.e.*, PSUR)s and IPSR)s, see sections III.E.2 and III.E.3 of this document).

III.E.1.a. *Narrative summary and analysis of individual case safety reports.* Proposed §§ 314.80(c)(3)(i)(A) and 600.80(c)(3)(i)(A) would amend §§ 314.80(c)(2)(ii)(a) and 600.80(c)(2)(ii)(A) by providing paragraph headings and reorganizing and revising these paragraphs. Proposed §§ 314.80(c)(3)(i)(A)(1) and 600.80(c)(3)(i)(A)(1) would amend §§ 314.80(c)(2)(ii)(a) and 600.80(c)(2)(ii)(A) by replacing the phrase "the information in the report" with the following:

serious, expected SADR)s and nonserious, unexpected SADR)s occurring in the United States that were submitted to the applicant during the reporting period from all spontaneous sources (*i.e.*, health care professionals and other individuals) (with an index consisting of a line listing of the applicant's manufacturer report number and

SADR term(s)). The narrative summary and analysis would include spontaneous reports submitted to the applicant by health care professionals and other individuals (*e.g.*, consumers).

Proposed §§ 314.80(c)(3)(i)(A)(2) and 600.80(c)(3)(i)(A)(2) would amend §§ 314.80(c)(2)(ii)(a) and 600.80(c)(2)(ii)(A) by replacing the phrase "an analysis of the 15-day Alert reports * * * date of submission to FDA)" with the phrase:

An analysis of the expedited reports submitted during the reporting period under paragraphs (c)(2)(i) through (c)(2)(vii) of this section (all expedited reports must be appropriately referenced by the applicant's manufacturer report number, SADR term(s), if appropriate, and date of submission to FDA).

Current regulations at §§ 314.80(c)(2)(iii) and 600.80(c)(2)(iii) state that periodic reporting, except for information regarding 15-day Alert reports, does not apply to adverse drug experience information obtained from postmarketing studies (whether or not conducted under an IND), from reports in the scientific literature, and from foreign marketing experience. FDA is proposing to remove this statement because proposed §§ 314.80(c)(3)(i)(A)(1) and 600.80(c)(3)(i)(A)(1) specifies the type of information that FDA would require in a TPSR.

III.E.1.b. *Individual case safety reports.* FDA is also proposing to remove §§ 314.80(c)(2)(ii)(b) and 600.80(c)(2)(ii)(B) from these regulations. FDA is proposing this change because the requirement to submit individual case safety reports to FDA on FDA Form 3500A (VAERS form for vaccines) would be required in a separate submission on a semiannual basis (see section III.E.4 of this document).

III.E.1.c. *Increased frequency reports.* Proposed §§ 314.80(c)(3)(i)(A)(3) and 600.80(c)(3)(i)(A)(3) would amend §§ 314.80(c)(2)(ii)(a) and 600.80(c)(2)(ii)(A) to require applicants to include in TPSR)s a discussion of any increased reporting frequency of serious, expected SADR)s, including comments on whether it is believed that the data reflect a meaningful change in SADR occurrence. Even though the agency has revoked the requirement to submit increased frequency reports in an expedited manner (62 FR 34166), FDA is interested in reviewing periodically information on increased frequencies of serious, expected SADR)s and is proposing that this type of information be submitted to the agency in TPSR)s.