

years and 12.5 years after U.S. approval of the supplement. These applicants would be required to submit PSURs and IPSRs to FDA even if the pediatric use supplement or original application was approved prior to January 1, 1998. FDA is proposing this action to harmonize acquisition of new safety information regarding pediatric populations for timely review by the agency.

All products. Under proposed §§ 314.80(c)(3)(v) and 600.80(c)(3)(v), applicants holding an NDA, ANDA, or BLA would be required to submit an individual case safety reports—semiannual submission to FDA every 6 months after U.S. approval of an application. The 6-month interval for these reports would coincide with the reporting interval (6-month or multiples of 6 months) for TPSRs, PSURs or IPSRs.

Alternative reporting frequency. Proposed §§ 314.80(c) and 600.80(c) would provide that, when appropriate, FDA may require in writing that applicants submit postmarketing periodic safety reports at time intervals other than prescribed by the regulations (see section III.C.4 of this document). Usually such variations would occur if new safety concerns arose requiring more timely reporting (e.g., approval of a new indication or dosage form for the product, approval for use of the product in a new population, new safety issues in individual case safety reports submitted to FDA for the product). When anticipated, FDA would state the revised reporting interval in the approval letter for the new indication, new population, or new dosage form. In other cases, such revisions to the reporting interval would be conveyed to applicants in a written letter from the director of the responsible review division in FDA with an explanation of why such a new reporting time interval is required.

III.E.5.b. *Submission date.* Proposed §§ 314.80(c)(3) and 600.80(c)(3) would require that the data lock point for postmarketing periodic safety reports be the month and day of the international birth date of the drug product (proposed §§ 314.80(c)(3)(i) and 314.80(c)(3)(v)), drug substance (proposed §§ 314.80(c)(3)(ii), 314.80(c)(3)(iii), and 314.80(c)(3)(iv)) or licensed biological product (proposed §§ 600.80(c)(3)(i) through 600.80(c)(3)(v)) or any other month and day agreed on by the applicant and FDA. For example, applicants that are submitting PSURs on an every 5 year basis may, in agreement with FDA, change the data lock point to facilitate international reporting so long as there is never a time period of greater than 5 years in which FDA has not

received a PSUR. Or, the applicant and FDA may agree to change the data lock point to the month and day of U.S. approval of the application if this date would result in better use of the applicant's resources.

Proposed §§ 314.80(c)(3) and 600.80(c)(3) would require that all postmarketing periodic safety reports be submitted to FDA within 60 calendar days after the data lock point for the report. As noted previously, the data lock point (i.e., month and day) for postmarketing periodic safety reports would be based on the month and day of the international birth date for the product and the frequency for submission of these reports would be based on the product's date (i.e., year) of U.S. approval (see section III.A.10 of this document).

III.E.5.c. *Cover letter.* Proposed §§ 314.80(c)(3) and 600.80(c)(3) would require that applicants include a cover letter with all postmarketing periodic safety reports (i.e., TPSRs, PSURs, IPSRs, individual case safety reports—semiannual submissions). This cover letter would contain a list of the NDA and/or ANDA numbers for the human drug products or BLA numbers for the human biological products covered by the report.

III.E.5.d. *International birth date for combination products.* Proposed §§ 314.80(c)(3) and 600.80(c)(3) would also state that the international birth date for combination products would be the international birth date of the human drug product containing the drug substance or licensed biological product that was most recently approved for marketing. For combination products that are also marketed individually, applicants may submit either a separate PSUR for the combination product or include information for the combination product as a separate presentation in the PSUR for one of the individual components.

III.F. Reporting Format

Current postmarketing safety reporting regulations at §§ 310.305(d)(1), 314.80(f)(1), and 600.80(f)(1) require persons subject to these requirements to submit an FDA Form 3500A (VAERS form for vaccines) for each report of an adverse drug experience. Foreign SADR, including those associated with the use of vaccines, may be submitted on an FDA Form 3500A or, if preferred, on a CIOMS I form.

III.F.1. Forms Versus Narrative Format

Proposed §§ 310.305(d)(1), 314.80(c)(4)(i), and 600.80(c)(4)(i) would amend the current postmarketing safety reporting format regulations by

reorganizing these regulations and by adding new information. Proposed §§ 310.305(d)(1)(i) would prescribe, except as provided in the regulations, that:

* * * the manufacturer must complete an FDA Form 3500A for each individual case safety report of an SADR. Reports based on information about individual cases or case series in the scientific literature must be submitted on an FDA Form 3500A(s).

Proposed §§ 314.80(c)(4)(i)(A) and 600.80(c)(4)(i)(A) would prescribe the same requirements for submission of postmarketing individual case safety reports by applicants. Proposed § 600.80(c)(4)(i)(A) would also describe requirements for use of the VAERS form for vaccines. Proposed §§ 310.305(d)(1)(ii), 314.80(c)(4)(i)(B) and 600.80(c)(4)(i)(B) would prescribe that:

Foreign SADRs may be submitted either on an FDA Form 3500A or, if preferred, on a CIOMS I form (foreign SARs for vaccines, may be submitted either on a VAERS form, or, if preferred, on a CIOMS I form, for proposed § 600.80(c)(4)(i)(B)).

Proposed §§ 310.305(d)(1)(iii), 314.80(c)(4)(i)(C) and 600.80(c)(4)(i)(C) would prescribe that:

Each domestic report of an actual or potential medication error must be submitted on an FDA Form 3500A (or, for vaccines, on a VAERS form for proposed § 600.80(c)(4)(i)(C)).

Proposed §§ 310.305(d)(1)(iv), 314.80(c)(4)(i)(D) and 600.80(c)(4)(i)(D) would prescribe that:

Reports of overall findings or data in the aggregate from published and unpublished in vitro, animal, epidemiological, or clinical studies must be submitted in a narrative format.

These proposed amendments would clarify the reporting format that would be required for individual case safety reports or other safety information (i.e., overall findings or data in the aggregate). Reports of actual and potential medication errors would be required to be submitted on an FDA Form 3500A (or VAERS form, as appropriate) because these reports describe an individual case even if an SADR does not occur or a patient is not identifiable. Reports of overall findings or data in the aggregate would be submitted in a narrative format rather than on FDA Form 3500A because FDA Form 3500A has been designed for reporting of data from an individual case.

III.F.2. Medical Dictionary for Regulatory Activities (MedDRA)

ICH has developed an international medical terminology, MedDRA (the