

“unexpected.” Proposed §§ 310.305(a), 314.80(a), and 600.80(a) would include in the definition of “unexpected SADR” the abbreviation “U.S.” before the word “labeling” to clarify that the approved U.S. labeling would be used to determine whether or not an SADR is “unexpected.” FDA would also amend this definition by replacing the word “event” with the word “reaction” and

by clarifying that the phrase “differ from the event because of greater severity or specificity” refers to a “labeled reaction.” Under proposed §§ 310.305(a), 312.32(a), 314.80(a), and 600.80(a), the agency would also replace the word “listed” with the word “included” in the definition of “unexpected SADR” to minimize confusion with “listed SADRs” in the

CCSI. FDA would also revise the sentence “Unexpected, as used in this definition, refers to an SADR that has not been previously observed * * * rather than from the perspective of such reaction not being anticipated from the pharmacological properties of the drug product” in this definition for clarity.

TABLE 5.—PROPOSED REFERENCE DOCUMENTS FOR SAFETY REPORTS

Marketing status	Safety report	Reference document
Premarketing	IND safety report	Investigator's brochure. If not available, risk information in general investigational plan or elsewhere in the current application.
Postmarketing	Expedited reports	U.S. labeling.
	TPSRs	U.S. labeling.
	PSURs and IPSRs	CCSI.
	Individual case safety reports—semiannual submission:	
	If TPSR is submitted for the product	U.S. labeling.
	If PSUR is submitted for the product	CCSI.

These proposed amendments are consistent with the ICH E2C guidance (62 FR 27470 at 27472):

For purposes of periodic safety reporting, CCSI forms the basis for determining whether an ADR is already Listed or is still Unlisted, terms that are introduced to distinguish them from the usual terminology of “expectedness” or “labeledness” that is used in association with official labeling. Thus, the local approved product information continues to be the reference document upon which labeledness/expectedness is based for the purpose of local expedited postmarketing safety reporting.

Under proposed §§ 310.305(a), 312.32(a), 314.80(a), and 600.80(a), FDA would include the following sentence in the definition of “unexpected SADR:”

SADRs that are mentioned in the U.S. labeling (investigator's brochure for proposed § 312.32(a)) as occurring with a class of drugs (products for proposed § 600.80(a)) but not specifically mentioned as occurring with the particular drug (product for proposed § 600.80(a)) are considered unexpected.

This information is currently included in the draft guidance of 2001. FDA is now proposing to codify this information to clarify which SADRs would be considered “unexpected.”

III.A.10. Data Lock Point and International Birth Date

Proposed §§ 314.80(a) and 600.80(a) would amend FDA's postmarketing safety reporting requirements to define the terms “data lock point” and “international birth date.” The “data lock point” would be defined as:

The date designated as the cut-off date for data to be included in a postmarketing periodic safety report.

The “international birth date” would be defined as:

The date the first regulatory authority in the world approved the first marketing application for a human drug product containing the drug substance (human biological product for proposed § 600.80(a)).

The agency would define these terms to help standardize the submission date (*i.e.*, month and day of submission) for postmarketing periodic safety reports (*i.e.*, PSURs, IPSRs, TPSRs, individual case safety reports—semiannual submissions). The data lock point would signify the end of a reporting period for data to be included in a specific postmarketing periodic safety report. The month and day of the international birth date would serve as a reference point for determining the data lock point. On the date of the data lock point, safety information that is available to applicants would be reviewed and evaluated prior to being submitted to FDA. Postmarketing periodic safety reports would be submitted to FDA within 60 days of the data lock point (see section III.E.5.b of this document). For example, for a drug or biological product approved by FDA on June 15 with a 6-month periodic reporting period and an international birth date of April 1, the first data lock point would be October 1, which is less than 6 months after FDA approval, but is the 6-month anniversary of the international birth date. Therefore, the first postmarketing periodic safety report would cover the period from April 1 through October 1 even though the product had only been approved in the United States on June 15. The

second periodic report would cover the period from October 2 through April 1.

An international birth date would be determined and declared by applicants. Applicants would determine an international birth date for a product based on the date of approval of the first marketing application in the world for a human drug product containing the drug substance or a biological product. A single international birth date would encompass all different dosage forms, formulations, or uses (*e.g.*, indications, routes of administration, populations) of a drug substance or licensed biological product. Thus, postmarketing periodic safety reports for different drug products containing the same drug substance would be submitted to FDA at the same time.

The month and day of the international birth date would be used, as noted previously, to determine the data lock point (*i.e.*, month and day) for postmarketing periodic safety reports. It would not, except as noted below, be used to determine the frequency for submission of these reports (*i.e.*, 6-month intervals or multiples of 6 months). Instead, the date (*i.e.*, year) of U.S. approval of the application for the drug or biological product (*e.g.*, NDA, ANDA, BLA) would be used to determine the frequency for submission of postmarketing periodic safety reports to FDA (see section III.E.5.a of this document). The international birth date would be used to determine both the data lock point and reporting frequency for postmarketing periodic safety reports only when the U.S. approval date is used to determine the international birth date (*e.g.*, FDA is the first