

blood collection or transfusion (see table 2). The report must be submitted to FDA by the collecting facility in the event of a donor reaction and by the facility that performed the compatibility tests in the event of a transfusion reaction.

Current safety reporting regulations under §§ 310.305, 314.80, 314.98, 600.80 and 606.170, as well as the provisions of this proposed rule, do not apply to voluntary reporting of adverse drug experiences to companies or regulatory authorities (e.g., FDA) by an individual (e.g., health care professional, consumer).

II.A.3. Terms Used in This Document

The terms “sponsors,” “manufacturers,” and “applicants” are used in this proposed rule to describe, as appropriate, persons with safety reporting responsibilities. “Sponsors” is used to describe persons subject to the premarketing safety reporting regulations. “Manufacturers” is used, unless otherwise specified, to describe persons subject to the postmarketing safety reporting regulations under § 310.305 for prescription drug products marketed without an approved NDA or ANDA. “Applicants” is used to describe persons subject to the postmarketing safety reporting regulations under §§ 314.80, 314.98, and 600.80 for products with an approved NDA, ANDA, or BLA; for § 600.80, “applicants” includes participants involved in divided manufacturing.

II.B. Rationale for This Proposal

II.B.1. International Standards

Many of the amendments that are being proposed in this rulemaking are intended to harmonize our safety reporting requirements with international standards developed by CIOMS and ICH (see table 4 of this document). These organizations were formed to facilitate international consideration of issues, particularly safety issues, concerning the use of global data in the development and use of drugs and biological products.

The CIOMS working groups have been comprised of representatives from regulatory authorities, including FDA, and the pharmaceutical industry. These groups have worked to develop recommendations for standardization of international reporting of postmarketing adverse reactions by the pharmaceutical industry to regulatory authorities.

ICH was organized to provide an opportunity for tripartite harmonization initiatives to be developed with input from regulatory and industry representatives. ICH has worked to promote the harmonization of technical

requirements for the registration of pharmaceutical products among three regions: The European Union, Japan, and the United States. The six ICH sponsors are the European Commission; the European Federation of Pharmaceutical Industry Associations; the Japanese Ministry of Health and Welfare; the Japanese Pharmaceutical Manufacturers Association; FDA; and the Pharmaceutical Research and Manufacturers of America.

One ICH initiative is to harmonize certain safety reporting requirements of the three regions. Through the ICH process, recommendations have been developed regarding the content, format, and reporting frequency for expedited and periodic safety reports for human drugs and biological products (the ICH E2A and E2C guidances). In addition, a standard medical terminology for regulatory purposes, MedDRA, has been developed (ICH M1). Worldwide implementation of this initiative is in process. FDA, which has been actively involved in the development of these recommendations, has implemented some of them (the October 1997 final rule) and is proposing to implement others in this rulemaking.

FDA believes the changes recommended by ICH and CIOMS will result in more effective and efficient safety reporting to regulatory authorities worldwide. For example, postmarketing periodic safety reports are, for the most part, currently submitted to regulatory authorities in the three regions at different times with different formats and content. International harmonization efforts are beginning to decrease some of these differences, but harmonization of the format and content, as well as the reporting frequency, of these reports by all countries in the three regions is essential to eliminate unnecessary reporting burdens on industry so that companies can focus on the safety profiles of their products and not on the different reporting requirements of different regions. The PSUR recommended for postmarketing periodic safety reporting in the ICH E2C guidance provides regulatory authorities with a comprehensive overview of the safety profile of a product along with other relevant information such as estimates of worldwide patient exposure and worldwide marketing status of the product. In this rulemaking, FDA is proposing to require submission of PSURs for certain products (see sections III.E.2 and III.E.5.a of this document). FDA is also interested in receipt of additional information and is proposing to require that such information be submitted with these reports as

appendices (e.g., copy of current U.S. approved labeling, information on medication errors, resistance to antimicrobial drug products and class action lawsuits) (see section III.E.2.k of this document). Thus, companies can prepare the same core document for all three regions and any additional information required by FDA would simply be attached to this document.

Another international harmonization effort is standardization of medical terminology used for regulatory purposes. As noted previously, ICH has developed MedDRA for this purpose. Currently, companies use various medical terminologies for safety reporting purposes (e.g., WHO's Adverse Reaction Terminology (WHOART), Coding Symbols for a Thesaurus of Adverse Reaction Terms (COSTART), Japan's Adverse Reaction Terminology (J-ART)). The established terminologies have been criticized for a number of reasons, including: Lack of specificity, limited data retrieval options, and an inability to effectively handle complex combinations of signs and symptoms (syndromes). In addition, use of different terminologies at different stages in the development and use of products complicates data retrieval and analysis of information and makes it difficult to effectively cross-reference data through the lifetime of a product. Internationally, communication is impaired between regulatory authorities because of the delays and distortions caused by the translation of data from one terminology to another.

Use of different terminologies also has significant consequences for pharmaceutical firms. Companies operating in more than one jurisdiction have had to adjust to subsidiaries or clinical research organizations that use different terminologies because of variations in data submission requirements. The difficulty of analyzing data comprehensively may be compounded by use of incompatible terminologies and could lead to delays in recognizing potential public health problems.

For these reasons, it is critical that a single medical terminology be used internationally for coding postmarketing safety reports. FDA is proposing to use MedDRA for this purpose (see section III.F.2 of this document). MedDRA is the best choice because it was developed with input from regulatory authorities and industry and the problems associated with the other terminologies were taken into consideration during development of MedDRA. Some companies have begun to voluntarily