

In the **Federal Register** of October 27, 1994 (59 FR 54046), FDA published a proposed rule to amend its expedited and periodic pre- and postmarketing safety reporting regulations for human drug and biological products (the October 1994 proposal). In the **Federal Register** of October 7, 1997 (62 FR 52237), FDA published a final rule amending its expedited pre- and postmarketing safety reporting regulations for human drug and biological products (the October 1997 final rule). The October 1997 final rule implemented certain international standards recommended in an ICH guidance entitled "Clinical Safety Data Management: Definitions and Standards for Expedited Reporting" (60 FR 11284, March 1, 1995) (the ICH E2A guidance). FDA is now proposing additional amendments to its expedited pre- and postmarketing safety reporting regulations based on recommendations in the ICH E2A guidance that were not included in the October 1994 proposal. Although the ICH E2A guidance pertains to expedited safety reporting during the premarketing phase of drug development, the agency has determined that many of the definitions and standards also should apply to FDA's expedited postmarketing safety reporting requirements.

The proposed amendments to the postmarketing periodic safety reporting requirements in the October 1994 proposal were based on recommendations in a CIOMS II report issued in 1992 ("International Reporting of Periodic Drug-Safety Update Summaries") (Ref. 28). As explained in the October 1997 final rule, the agency decided not to finalize these proposed amendments (62 FR 52237 and 52238) until FDA considered ICH's recommendations on this topic. These recommendations were published in an ICH final guidance entitled "Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs" (PSURs) (the ICH E2C guidance) (62 FR 27470, May 19, 1997). After review of the ICH E2C guidance, FDA decided to repropose the postmarketing periodic safety reporting amendments in the October 1994 proposal. These amendments are being repropose in this rulemaking based on recommendations in the ICH E2C guidance and comments submitted in response to the October 1994 proposal.

An addendum to the ICH E2C guidance has been prepared by ICH based on experience gained over the past 5 years in preparation of PSUR reports by companies and review of them by regulators (the ICH V1 draft guidance) (67 FR 79939; December 31, 2002). FDA is interested in harmonizing, to the extent possible, its

postmarketing periodic safety reporting regulations with the recommendations in the ICH V1 draft guidance. In this regard, FDA is interested in comment from the public on whether the agency should implement these recommendations (e.g., permit use of summary bridging reports, include an executive summary in PSURs, permit use of different versions of reference safety information within a reporting interval or use of the version in effect at the end of the reporting interval).

Some of the comments submitted in response to the October 1994 proposal noted that several of the proposed amendments to the postmarketing periodic safety reporting regulations would result in duplicative reporting of information currently required in postmarketing approved new drug application (NDA) annual reports. The comments questioned the value of submitting similar information to FDA in two different reports and requested that the agency require inclusion of this information in either one report or the other, but not in both of them. In light of these comments, FDA is proposing to revoke the requirement for safety-related information in postmarketing approved NDA annual reports.

In the **Federal Register** of December 2, 1998 (63 FR 66632), FDA issued a final rule amending its postmarketing approved NDA annual reports regulations to require reporting of specific information regarding studies in pediatric populations (the 1998 pediatric final rule). The 1998 pediatric final rule also required a new annual report for biological products with approved biologics license applications (BLAs) that contains the same type of information on studies of licensed biological products in pediatric populations. FDA is proposing to amend the annual reporting requirements for licensed biological products to revoke the requirement to submit safety-related information in these reports. This proposal is consistent with the proposed amendments to the postmarketing approved NDA annual reporting requirements.

In the **Federal Register** of June 25, 1997 (62 FR 34166), FDA published a final rule revoking the postmarketing safety reporting requirement for submission of increased frequency reports in an expedited manner (the increased frequency reports final rule). These reports contained information regarding a significant increase in frequency of an adverse drug experience (synonymous with adverse experience) that is both serious and expected for marketed human drug and licensed biological products. FDA is now proposing to amend its regulations to require submission of increased

frequency type information for marketed human drugs and licensed biological products in postmarketing periodic safety reports.

In the **Federal Register** of August 27, 1997 (62 FR 45425), FDA published a notice of availability of a guidance for industry entitled "Postmarketing Adverse Experience Reporting for Human Drug and Licensed Biological Products; Clarification of What to Report" (the clarification guidance of 1997). This guidance clarifies the agency's policy concerning certain postmarketing safety reporting requirements for human drugs and licensed biological products. The guidance: (1) Describes the information that should be obtained before an individual case safety report (*i.e.*, FDA Form 3500A, CIOMS I Form, Vaccine Adverse Event Reporting System (VAERS) Form) of an adverse experience should be considered for submission to FDA; (2) clarifies how solicited safety information from planned contacts with patients should be handled; and (3) informs applicants that FDA will entertain waiver requests for periodic submission of individual case safety reports for adverse experiences that are determined to be nonserious and expected.

FDA received 28 comments from medical centers, physicians, and consumers regarding the clarification guidance of 1997. All of these comments pertained to the item regarding waiver requests for periodic submission of individual case safety reports for adverse experiences that are determined to be nonserious and expected. The agency considered these comments in developing this proposed rule. All of the comments requested that FDA postpone granting these waivers until this new policy receives more complete public scrutiny and debate. The comments stated that the new waiver policy would deprive the public of access to important safety information about adverse reactions to approved drugs and biological products. The comments noted that, in some cases, adverse reactions classified as "nonserious" may, in fact, be related to very serious reactions. The comments also indicated that the new waiver policy provides industry with an incentive to classify serious reactions as "nonserious" so that the reactions would not have to be reported to FDA.

Even though applicants may currently request waivers for submission of individual case safety reports for nonserious, expected adverse experiences, the agency should continue to receive information regarding these experiences. The clarification guidance