

effect immediately. FDA is proposing to revise this requirement as follows:

An investigator must report to the sponsor any serious SADR (as defined in § 312.32(a)) immediately and any other SADR (as defined in § 312.32(a)) promptly unless the protocol or investigator's brochure specifies a different timetable for reporting the SADR.

FDA is proposing this revision to be consistent with the proposed definition for SADR and to clarify what information investigators must submit to sponsors expeditiously.

III.C. Postmarketing Safety Reporting

III.C.1. Prescription Drugs Marketed for Human Use Without an Approved Application

Current regulations (§ 310.305) require manufacturers, packers, and distributors of marketed prescription drug products that are not the subject of an approved NDA or ANDA to establish and maintain records of and report to FDA all serious, unexpected adverse drug experiences associated with the use of their drug products. The proposed rule would amend these regulations by revising the language in this section to be consistent with the language for the postmarketing expedited safety reporting requirements under § 314.80. FDA is also proposing to reorganize and renumber § 310.305 to be consistent with § 314.80. FDA is proposing these revisions to harmonize, to the extent possible, the postmarketing expedited safety reporting requirements for human marketed drugs with approved applications (*i.e.*, NDAs, ANDAs) and prescription drugs marketed for human use without an approved application.

III.C.2. Review of Safety Information

Current postmarketing safety reporting regulations under §§ 314.80(b) and 600.80(b) require applicants to promptly review all safety information obtained or otherwise received from any source, foreign or domestic, including information derived from commercial marketing experience, postmarketing clinical investigations, postmarketing epidemiological/surveillance studies, reports in the scientific literature, and unpublished scientific papers. FDA is proposing to amend these regulations by adding "animal and in vitro studies," "electronic communications with applicants via the Internet (*e.g.*, e-mail)," and "reports from foreign regulatory authorities that have not been previously reported to FDA by the applicant" to the list of examples. FDA is proposing to add animal and in vitro studies to the list of examples because many of these studies report relevant

safety-related information (*e.g.*, carcinogenicity, mutagenicity, teratogenicity).

FDA is proposing to add electronic communications with applicants via the Internet (*e.g.*, e-mail) to the list of examples to clarify for applicants what safety information on the Internet would be required to be reviewed. An applicant would be required to review information received on an Internet site(s) that it sponsors, but would not be required to review Internet sites that it does not sponsor. However, if an applicant becomes aware of safety information on an Internet site that it does not sponsor, the applicant would be responsible for reviewing the information.

FDA would not expect applicants to review safety data bases generated by foreign regulatory authorities. However, proposed §§ 314.80(b)(1) and 600.80(b)(1) would require that any safety information acquired or received from a foreign regulatory authority be reviewed to determine whether the information must be reported to FDA. The agency is proposing these amendments to further clarify some of the types of safety information that must be examined to determine whether the information must be submitted in postmarketing safety reports.

Proposed § 310.305(b)(1) would amend FDA's postmarketing safety reporting regulations for prescription drugs marketed for human use without an approved application by adding the following sentence:

Each manufacturer of a prescription drug product marketed for human use without an approved application must promptly review all safety information pertaining to its product obtained or otherwise received by the manufacturer from any source, foreign or domestic, including information derived from commercial marketing experience, postmarketing clinical investigations, postmarketing epidemiology/surveillance studies, animal or in vitro studies, electronic communications with manufacturers via the Internet (*e.g.*, e-mail), reports in the scientific literature, and unpublished scientific papers, as well as reports from foreign regulatory authorities that have not been previously reported to FDA by the manufacturer.

This proposed amendment would further clarify some of the types of safety information that must be examined to determine whether the information must be submitted in postmarketing expedited safety reports (see section III.D of this document). This proposed revision would provide uniformity between FDA's safety reporting requirements for human marketed drugs with approved applications (*i.e.*, NDAs, ANDAs) and prescription drugs marketed for human

use without an approved application (*i.e.*, without an approved NDA or ANDA).

Current postmarketing safety reporting regulations in §§ 314.80(b) and 600.80(b) state that applicants are not required to resubmit to FDA safety reports forwarded to the applicant by FDA; however, applicants must submit all followup information on such reports. Proposed §§ 314.80(b)(2) and 600.80(b)(2) would amend these regulations to state that individual case safety reports forwarded to the applicant by FDA must not be resubmitted to the agency by applicants. FDA is proposing this revision to prevent duplicate reports from being entered into the agency's safety reporting database. Applicants that inadvertently resubmit such reports to FDA will be informed not to do so in the future.

Proposed §§ 314.80(b)(2) and 600.80(b)(2) would also amend these regulations to require that applicants include information from individual case safety reports forwarded to the applicant by FDA in any comprehensive safety analysis subsequently submitted to the agency. This proposed amendment, which was discussed in the preamble but inadvertently omitted from the codified section of the October 1994 proposal (59 FR 54046 at 54053), would clarify how safety information received from FDA must be handled.

Current postmarketing safety reporting regulations at §§ 314.80(b) and 600.80(b) state that applicants must develop written procedures for the surveillance, receipt, evaluation, and reporting of postmarketing adverse drug experiences to FDA. FDA is proposing to amend this provision by adding the phrase "and maintain" after the phrase "must develop." This proposed amendment would clarify that applicants must maintain records of the written procedures for review by FDA. FDA would review the written procedures either upon request by the agency (proposed §§ 314.80(f) and 600.80(f)) or during inspections by the agency. FDA is also proposing to replace the phrase "adverse drug experiences" with the phrase "postmarketing safety information." For organizational purposes, FDA is proposing to move the written procedures provision to proposed §§ 314.80(g) and 600.80(g). FDA is proposing the same type of amendments to § 310.305.

Current § 314.80(b) applies to applicants having an approved application under § 314.50 or, in the case of a 505(b)(2) application, an effective approved application. FDA is proposing to amend this provision by replacing the phrase "under § 314.50 or,