

in no event later than 15 calendar days after the sponsor's initial receipt of the information." The agency is proposing this revision because the information in this sentence is redundant with a provision of proposed § 312.32(c)(1)(i).

III.B.2.c. *Information sufficient to consider product administration changes.* Under proposed § 312.32(c)(1)(ii), FDA would amend § 312.32(c)(1)(i) by replacing the phrase "Any finding from tests in laboratory animals that suggests a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity" with the sentence:

The sponsor must also notify FDA and all participating investigators in a written IND safety report of information that, based upon appropriate medical judgment, might materially influence the benefit-risk assessment of an investigational drug or that would be sufficient to consider changes in either product administration or in the overall conduct of a clinical investigation. The sponsor must submit this information to FDA and all participating investigators as soon as possible, but in no case later than 15 calendar days after determination by the sponsor that the information qualifies for reporting under this paragraph. Examples of such information include any significant unanticipated safety finding or data in the aggregate from an in vitro, animal, epidemiological, or clinical study, whether or not conducted under an IND, that suggests a significant human risk, such as reports of mutagenicity, teratogenicity, or carcinogenicity or reports of a lack of efficacy with a drug product used in treating a life-threatening or serious disease.

This proposed amendment is consistent with the ICH E2A guidance (60 FR 11284 at 11286):

There are situations in addition to single case reports of "serious" adverse events or reactions that may necessitate rapid communication to regulatory authorities; appropriate medical and scientific judgment should be applied for each situation. In general, information that might materially influence the benefit-risk assessment of a medicinal product or that would be sufficient to consider changes in medicinal product administration or in the overall conduct of a clinical investigation represents such situations. Examples include:

- a. For an "expected, serious ADR, ["] an increase in the rate of occurrence which is judged to be clinically important.
- b. A significant hazard to the patient population, such as lack of efficacy with a medical product used in treating life-threatening disease.
- c. A major safety finding from a newly completed animal study (such as carcinogenicity).

In contrast to the ICH recommendations, the proposed rule would not require reports of an increase in the rate of occurrence of expected, serious SADRs to be submitted to the

agency in an expedited manner. However, sponsors should report this information to FDA in their IND annual reports under § 312.33(b)(1). Proposed § 312.32(c)(1)(ii) would be consistent with the increased frequency reports final rule that revoked the postmarketing safety reporting requirement for submission of increased frequency reports in an expedited manner. Although the increased frequency reports final rule pertains to postmarketing expedited safety reporting, FDA has decided to apply this rule to its requirements for premarketing expedited safety reports because of the limited reliability of increased frequency reports. See the increased frequency reports final rule (62 FR 34166) for a discussion of the limited reliability of increased frequency reports. With regard to premarketing clinical trials in progress, FDA does not believe that baseline incidence rates would be available for serious expected SADRs which would make it difficult for sponsors to predict an increase in the rate of occurrence of these SADRs.

III.B.2.d. *Reporting format.* Current IND safety reporting regulations at § 312.32(c)(1)(i) require sponsors to submit written IND safety reports from animal or epidemiological studies in a narrative format. Proposed § 312.32(c)(1)(iii) would amend these regulations by replacing the phrase "reports from animal or epidemiological studies" with the phrase "reports of overall findings or data in the aggregate from published and unpublished in vitro, animal, epidemiological, or clinical studies." The proposed rule would require sponsors to submit reports of overall findings or data in the aggregate in a narrative format rather than on FDA Form 3500A because the form is designed for reporting safety information for an individual case.

III.B.3. Telephone Safety Reports

Current IND safety reporting regulations at § 312.32(c)(2) require sponsors to notify FDA by telephone or by facsimile transmission of any unexpected fatal or life-threatening experience associated with the use of an investigational drug as soon as possible but in no event later than 7 calendar days after the sponsor's initial receipt of the information. FDA is proposing to amend this requirement to read:

The sponsor must also notify FDA by telephone or by facsimile transmission of any unexpected fatal or life-threatening SADR based on the opinion of the investigator or sponsor as soon as possible but in no case later than 7 calendar days after receipt by the

sponsor of the minimum data set for the unexpected fatal or life-threatening SADR.

These proposed revisions are consistent, as described previously, with the proposed amendments to § 312.32(c)(1)(i) for written IND safety reports and the ICH E2A guidance (60 FR 11284 at 11286).

III.B.4. IND Safety Reporting for Drugs Marketed in the United States

Current IND safety reporting regulations at § 312.32(c)(4) state that a sponsor of a clinical study of a marketed drug is not required to make a safety report for any adverse experience associated with the use of the drug that is not from the clinical study itself. FDA is proposing to amend this regulation by making the following revisions:

A sponsor of a clinical study under an IND for a drug marketed in the United States is only required to submit IND safety reports to FDA (review division that has responsibility for the IND) for SADRs from the clinical study itself, whether from domestic or foreign study sites of the IND. The sponsor must also submit to FDA safety information from these clinical studies as prescribed by the postmarketing safety reporting requirements under §§ 310.305, 314.80, and 600.80 of this chapter.

FDA is proposing this change to clarify, for sponsors investigating under an IND drugs and biological products that are already marketed in the United States, what SADRs must be reported in IND safety reports under § 312.32. The agency notes that sponsors investigating under an IND drug and biological products that are not marketed in the United States are required, under § 312.32, to report to FDA safety information obtained or otherwise received for the product from any source, domestic or foreign, including safety information from foreign commercial marketing experience (see section III.B.1 of this document). Proposed § 312.32(c)(4) also clarifies that sponsors investigating under an IND drugs and biological products that are already marketed in the United States must submit safety information for these clinical studies as prescribed by the postmarketing safety reporting requirements in §§ 310.305, 314.80, and 600.80.

III.B.5. Investigator Reporting

Current investigator safety reporting regulations at § 312.64(b) state that the investigator shall promptly report to the sponsor any adverse effect that may reasonably be regarded as caused by, or probably caused by, the drug. If the adverse effect is alarming, the investigator shall report the adverse