

regulatory authority in the world to approve the human drug product containing the drug substance or biological product for marketing).

The use of a standardized submission date (*i.e.*, month and day), which is consistent with the ICH E2C guidance (62 FR 27470 at 27472), would enable applicants to submit a single core report (PSUR excluding appendices) to regulatory authorities worldwide. Currently, different regulatory authorities require submission of postmarketing periodic safety reports on varying time schedules. The submission of a single core report to multiple regulatory authorities would significantly reduce the time spent preparing these reports, thereby permitting more time for the evaluation of the medical significance of any safety information reported.

III.B. IND Safety Reports

III.B.1. Review of Safety Information

Current IND safety reporting regulations in § 312.32(b) require that sponsors promptly review all information relevant to the safety of the drug under investigation obtained or otherwise received by the sponsor from any source, foreign or domestic. Sources of information include any clinical or epidemiological investigations, animal investigations, commercial marketing experience, reports in the scientific literature, and unpublished scientific papers, and reports from foreign regulatory authorities that have not already been previously reported to FDA by the sponsor. FDA is proposing to amend this requirement by adding “in vitro studies” to the list of examples because some in vitro studies report relevant safety-related information (*e.g.*, carcinogenicity studies performed in cell lines). FDA is also proposing to move the phrase “commercial marketing experience” to the end of the list and to revise it to read “and reports of foreign commercial marketing experience for drugs that are not marketed in the United States” to clarify that sponsors are not required to review safety information from commercial marketing experience for drugs that are marketed in the United States and are being further studied under an IND. Safety reports from commercial marketing experience for these drugs would be reviewed for safety information as prescribed by FDA’s postmarketing safety reporting regulations (see section III.C.2 of this document). This proposed revision is consistent with existing regulations at § 312.32(c)(4) and proposed amendments to § 312.32(c)(4) described below (see section III.B.4 of

this document). The proposed amendments would further clarify some of the types of safety information that must be examined to determine whether the information must be submitted in an IND safety report.

III.B.2. Written IND Safety Reports

Current IND safety reporting regulations at § 312.32(c)(1)(i) require sponsors to notify FDA and all participating investigators in a written IND safety report of any adverse experience associated with the use of the drug that is both serious and unexpected or any finding from tests in laboratory animals that suggests a significant risk for human subjects, including reports of mutagenicity, teratogenicity, or carcinogenicity. These written IND safety reports must be made as soon as possible and in no event later than 15 calendar days after the sponsor’s initial receipt of the information. For clarity, FDA is proposing to amend § 312.32(c)(1) by reorganizing and renumbering this paragraph.

III.B.2.a. *Minimum data set.* FDA is proposing to amend § 312.32(c) to state that sponsors must not submit an IND safety report for an SADR to the agency if the report does not contain a minimum data set (*i.e.*, identifiable patient, identifiable reporter, suspect drug or biological product, and SADR). If a minimum data set is not available, a sponsor would be required to maintain records of any information received or otherwise obtained for the SADR along with a record of its efforts to obtain a minimum data set for the IND safety report. This proposed amendment would clarify for sponsors that, at a minimum, certain information must be submitted to FDA for each IND safety report of an SADR to allow an initial evaluation of the significance of the SADR. This proposed revision is consistent with the ICH E2A guidance (60 FR 11284 at 11287):

The minimum information required for expedited reporting purposes is: an identifiable patient; the name of a suspect medicinal product; an identifiable reporting source; and an event or outcome * * *.

III.B.2.b. *Serious and unexpected SADRs.* FDA is also proposing to amend § 312.32(c)(1)(i) by replacing the phrase “any adverse experience associated with the use of the drug that is both serious and unexpected” with the phrase “any SADR that, based on the opinion of the investigator or sponsor, is both serious and unexpected, as soon as possible, but in no case later than 15 calendar days after receipt by the sponsor of the minimum data set for the serious,

unexpected SADR.” This proposed amendment would require that the determination of the possibility of causality (attributability) of an SADR to an investigational drug be based on the opinion of either the investigator or sponsor, which is consistent with the ICH E2A guidance (60 FR 11284 at 11286):

Causality assessment is required for clinical investigation cases. All cases judged by either the reporting health care professional or the sponsor as having a reasonable suspected causal relationship to the medicinal product qualify as ADR’s.

In situations in which a sponsor does not believe that there is a reasonable possibility that an investigational drug caused a response, but an investigator believes that such a possibility exists, the proposed rule would require that the sponsor submit a written IND safety report to FDA for the SADR. In the opposite situation, the same would also be true.

The proposed rule would also require that written IND safety reports be submitted to FDA no later than 15 calendar days after receipt by the sponsor of the minimum data set for the serious, unexpected SADR. This proposed revision would clarify when the 15 calendar day timeframe would begin. FDA expects sponsors to use due diligence to acquire immediately the minimum data set for a report and to determine the outcome (whether the SADR is serious or nonserious) and expectedness of an SADR upon initial receipt of the SADR. Sponsors should include in any written IND safety reports subsequently filed with FDA a chronological history of their efforts to acquire this information if there is a delay in obtaining the information (it is not necessary to include the chronological history in IND safety reports sent to investigators). This proposed amendment is consistent with the ICH E2A guidance (60 FR 11284 at 11286):

Information for final description and evaluation of a case report may not be available within the required timeframes for reporting * * *. Nevertheless, for regulatory purposes, initial reports should be submitted within the prescribed time as long as the following minimum criteria are met: An identifiable patient; a suspect medicinal product; an identifiable reporting source; and an event or outcome that can be identified as serious and unexpected, and for which, in clinical investigation cases, there is a reasonable suspected causal relationship. * * *

FDA is also proposing to amend § 312.32(c)(1)(i) by removing the following sentence: “Each notification shall be made as soon as possible and