

biological product caused the spontaneously reported event. Proposed §§ 310.305(c)(1)(i)(C), 314.80(c)(1)(i)(C), and 600.80(c)(1)(i)(C) state that, for a clinical trial, the possibility that the drug or biological product caused the SADR or that a medication error has occurred would be assumed if either the investigator or the applicant/manufacturer believes that such a reasonable possibility exists.

These proposed changes would clarify that all spontaneous reports received by manufacturers and applicants that contain a minimum data set (minimum information for a report of a medication error that does not result in SADR) would be reported to FDA (*i.e.*, as an individual case safety report and/or in a summary tabulation). These changes are consistent with the premarketing safety reporting requirements described in section III.B.2.b of this document (*i.e.*, determination of the possibility of causality (attributability) of an SADR to the drug or biological product in a clinical investigation would be based on the opinion of either the applicant/sponsor or investigator). These proposed amendments are also 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. For purposes of reporting, adverse event reports associated with marketed drugs (spontaneous reports) usually imply causality.

III.C.7. Lack of Efficacy Reports

With regard to reports of a lack of efficacy for an approved drug or biological product, the guidance of 1992 and guidance of 1993 advise applicants to submit all individual cases of such reports that occur in the United States in postmarketing periodic safety reports. In this proposed rule, FDA would not require submission of individual case safety reports for reports of a lack of efficacy. Instead, applicants would be required to submit to FDA expedited reports of information sufficient to consider a product administration change, based upon appropriate medical judgement, for any significant unanticipated safety finding or data in the aggregate from a study that suggests a significant human risk. For example, applicants would be required to submit information concerning reports of a lack of efficacy with a drug or biological product used in treating a life-threatening or serious disease (see section III.D.2 of this document). In addition, applicants would be required

to include in postmarketing periodic safety reports (*i.e.*, TPSRs, PSURs, IPSRs) an assessment of whether it is believed that the frequency of lack of efficacy reports is greater than would be predicted by the premarketing clinical trials for the drug or biological product (see sections III.E.1.c, III.E.2.k.vi, and III.E.3 of this document). This assessment would be provided for reports of a lack of efficacy whether a serious SADR, nonserious SADR, or no SADR occurs. Applicants that submit PSURs and IPSRs to FDA would also include in these reports a discussion of medically relevant lack of efficacy reports (*e.g.*, might represent a significant hazard to the treated population) for a product(s) used to treat serious or life-threatening diseases (see sections III.E.2.h and III.E.3 of this document).

III.D. Postmarketing Expedited Reports

Current postmarketing expedited safety reporting regulations at §§ 310.305(c), 314.80(c), and 600.80(c) require submission of "15-day Alert reports" to FDA. FDA is proposing to amend these regulations by removing the term "15-day Alert report" and replacing it with the term "expedited report" to be consistent with terminology used in the ICH E2A guidance. FDA is also proposing the following revisions to its postmarketing expedited safety reporting regulations.

III.D.1. Serious and Unexpected SADRs

Under the existing postmarketing expedited safety reporting regulations at § 310.305(c)(1)(i), persons subject to this requirement must report to FDA each adverse drug experience received or otherwise obtained that is both serious and unexpected as soon as possible, but in no case later than 15 calendar days of initial receipt of the information by the person. Under the existing postmarketing expedited safety reporting regulations at §§ 314.80(c)(1)(i) and 600.80(c)(1)(i), persons subject to these requirements must report each adverse drug experience that is both serious and unexpected, whether foreign or domestic, as soon as possible, but in no case later than 15 calendar days of initial receipt of the information by the person.

FDA is proposing minor revisions to these regulations for consistency. Proposed § 310.305(c)(2)(i) would amend § 310.305(c)(1)(i) by adding the phrase "whether foreign or domestic" after the phrase "that is both serious and unexpected." Proposed §§ 314.80(c)(2)(i) and 600.80(c)(2)(i) would amend §§ 314.80(c)(1)(i) and

600.80(c)(1)(i) by adding the phrase "to FDA" after the word "report" and by adding the phrase "received or otherwise obtained" before the phrase "that is both serious and unexpected."

Proposed §§ 310.305(c)(2)(i), 314.80(c)(2)(i), and 600.80(c)(2)(i) would amend §§ 310.305(c)(1)(i), 314.80(c)(1)(i), and 600.80(c)(1)(i) by removing the phrase "of initial receipt of the information by the person whose name appears on the label ("by the applicant" for § 314.80(c)(1)(i), and "by the licensed manufacturer" for § 600.80(c)(1)(i)) and replacing it with the phrase "after receipt by the manufacturer ("applicant" for proposed §§ 314.80(c)(2)(i), and 600.80(c)(2)(i)) of the minimum data set for the serious, unexpected SADR." This proposed amendment is consistent with proposed revisions to the premarketing expedited safety reporting regulations at proposed § 312.32(c)(1)(i) (see section III.B.2.b of this document). The amendment would clarify that the 15 calendar day timeframe would begin as soon as manufacturers and applicants have knowledge of the minimum data set for an SADR that is serious and unexpected. Manufacturers and applicants must use due diligence to acquire this information. For this purpose, they would be required, as described in section III.C.5 of this document, to use active query to determine the outcome for the SADR (whether the SADR is serious or nonserious) and acquire at least the minimum data set for the individual case safety report if they are not able to immediately obtain this information. Manufacturers and applicants should include in postmarketing expedited safety reports a chronological history of their efforts to acquire a minimum data set and to determine the seriousness and expectedness of an SADR if there is a delay in obtaining such information.

Proposed §§ 310.305(c)(2)(i), 314.80(c)(2)(i) and 600.80(c)(2)(i) state that if a full data set is not available for a serious and unexpected SADR report at the time of initial submission of the report to FDA, manufacturers and applicants must submit the information required under proposed §§ 310.305(c)(1)(iv), 314.80(c)(1)(iv) and 600.80(c)(1)(iv) as described in section III.C.5 of this document and also submit a 30-day followup report as described in section III.D.6 of this document. FDA is proposing this action to clarify the importance of acquiring complete information for serious SADRs.