

manufacturer, joint manufacturer, packer, or distributor whether or not its name appears on the label of the product; licensee; contract research organization) that have entered into a contract with the applicant (includes participants involved in divided manufacturing). FDA would define this term to specify which contractors would be subject to the agency's postmarketing safety reporting requirements under proposed §§ 310.305(c)(2)(xi), 314.80(c)(2)(x), and 600.80(c)(2)(x) (see section III.D.9 of this document). Persons under contract to manufacture, pack, sell, distribute, or develop the drug or licensed biological product, or to maintain, create, or submit records regarding SADRs or medication errors (whether or not the medication error results in an SADR; see section III.A.8 of this document) would have postmarketing safety reporting responsibilities.

III.A.5. Minimum Data Set and Full Data Set for an Individual Case Safety Report

Proposed §§ 310.305(a), 312.32(a), 314.80(a), and 600.80(a), would amend FDA's premarketing and postmarketing safety reporting regulations to define the term "minimum data set." A "minimum data set" for an individual case safety report of an SADR would include: an identifiable patient, an identifiable reporter, a suspect drug (biological for proposed § 600.80(a)) product, and an SADR.

Proposed §§ 310.305(a), 314.80(a), and 600.80(a), would also amend FDA's postmarketing safety reporting regulations to define the term "full data set." A "full data set" for a postmarketing individual case safety report would include:

Completion of all the applicable elements on FDA Form 3500A (or the Vaccine Adverse Event Reporting System (VAERS) form for proposed § 600.80(a)) (or on a Council for International Organizations of Medical Sciences (CIOMS) I form for reports of foreign SADRs) including a concise medical narrative of the case (*i.e.*, an accurate summary of the relevant data and information pertaining to an SADR or medication error).

The proposed rule would define these terms to clarify the type of information that manufacturers and applicants would be required to submit to FDA for SADRs and medication errors. The proposed rule would, as described below, require at least a minimum data set for all individual case safety reports, except for certain reports of medication errors (see sections III.B.2.a and III.C.5 of this document). In addition, a full data set would be required for postmarketing individual case safety

reports of serious SADRs, always expedited reports, and medication error reports (see sections III.C.5, III.D.1, III.D.4, III.D.5, and III.E.4 of this document). Reports of nonserious SADRs with a minimum data set would include all safety information received or otherwise obtained by the manufacturer or applicant for the SADR. However, except for reports of nonserious SADRs resulting from a medication error, information in addition to the minimum data set would not be required to be acquired by the manufacturer or applicant (see sections III.C.5 and III.E.4 of this document). Manufacturers and applicants would be required to submit a full data set for reports of nonserious SADRs resulting from a medication error (see sections III.C.5 and III.D.5 of this document).

As noted previously, for each individual case safety report, a suspect product would be required to be identified. Reports from blinded clinical studies (*i.e.*, the sponsor and investigator are blinded to individual patient treatment) should be submitted to FDA only after the code is broken for the patient or subject that experiences an SADR. The blind should be broken for each patient or subject who experiences a serious, unexpected SADR unless arrangements have been made otherwise with the FDA review division that has responsibility for review of the IND (*e.g.*, the protocol or other documentation clearly defines specific alternative arrangements for maintaining the blind). Exceptions to breaking the blind for a study usually involve situations in which mortality or certain serious morbidities are indeed the clinical endpoint of the study. This is consistent with the discussion of managing blinded therapy cases in the ICH E2A guidance (60 FR 11266):

* * * Although it is advantageous to retain the blind for all patients prior to final study analysis, when a serious adverse reaction is judged reportable on an expedited basis, it is recommended that the blind be broken only for the specific patient by the sponsor even if the investigator has not broken the blind. * * * However, when a fatal or other "serious" outcome is the primary efficacy endpoint in a clinical investigation, the integrity of the clinical investigation may be compromised if the blind is broken. Under these and similar circumstances, it may be appropriate to reach agreement with regulatory authorities in advance concerning serious events that would be treated as disease-related and not subject to routine expedited reporting.

In addition to the exception for breaking the blind mentioned above, FDA is also interested in considering whether the blind should be broken for other serious SADRs that are not the clinical endpoint

of the study, but occur at a rate high enough that the overall study blind would be threatened if each such case were individually unblinded. FDA invites comment from the public on how reporting of these SADRs should be handled.

III.A.6. Active Query

Under proposed §§ 310.305(a), 314.80(a), and 600.80(a), FDA would amend its postmarketing safety reporting regulations to define the term "active query" to mean:

Direct verbal contact (*i.e.*, in person or by telephone or other interactive means such as a videoconference) with the initial reporter of a suspected adverse drug reaction (SADR) or medication error by a health care professional (*e.g.*, physician, physician assistant, pharmacist, dentist, nurse, any individual with some form of health care training) representing the manufacturer (applicant for proposed §§ 314.80(a) and 600.80(a)). For SADRs, active query entails, at a minimum, a focused line of questioning designed to capture clinically relevant information associated with the drug product (licensed biological product for proposed § 600.80(a)) and the SADR, including, but not limited to, information such as baseline data, patient history, physical exam, diagnostic results, and supportive lab results.

The agency would define this term to describe the process that manufacturers and applicants would be required to use to acquire safety information expeditiously. Active query would be used to:

- Determine whether an SADR is serious or nonserious if the manufacturer or applicant is not able to immediately make this determination (see section III.C.5 of this document),
- Obtain at least the minimum data set for all SADRs and the minimum information for medication errors that do not result in an SADR if the manufacturer or applicant is not able to immediately obtain this information (see section III.C.5 of this document),
- Obtain a full data set for individual case safety reports of serious SADRs, always expedited reports, and medication error reports if a full data set is not available for the report (see section III.C.5 of this document), and
- Obtain supporting documentation for a report of a death or hospitalization (*e.g.*, autopsy report, hospital discharge summary) (see section III.D.7 of this document).

Active query would entail direct verbal contact either in person or by telephone or other interactive means (*e.g.*, a videoconference) with the initial reporter of an SADR or medication error. FDA believes that, in many cases, use of active query during initial contact with these reporters would provide