

reasonable times, to have access to and copy and verify the records established and maintained under this section.

(g) *Written procedures.* Each manufacturer must develop and maintain written procedures for the surveillance, receipt, evaluation, and reporting of postmarketing safety information to FDA.

(h) *Disclaimer.* A report or information submitted by a manufacturer under this section (and any release by FDA of that report or information) does not necessarily reflect a conclusion by the manufacturer or by FDA, that the report or information constitutes an admission that the drug caused or contributed to an SADR. The manufacturer need not admit, and may deny, that the report or information submitted under this section constitutes an admission that the drug caused or contributed to an SADR.

PART 312—INVESTIGATIONAL NEW DRUG APPLICATION

3. The authority citation for 21 CFR part 312 continues to read as follows:

Authority: 21 U.S.C. 321, 331, 351, 352, 353, 355, 371; 42 U.S.C. 262.

4. Section 312.32 is amended by revising paragraphs (a), (b), the introductory text of paragraph (c), paragraphs (c)(1) and (c)(4), and the first sentence of paragraph (c)(2); in paragraph (d)(3) by removing the phrase “adverse drug experience” and by adding in its place the abbreviation “SADR” and by removing the phrase “such experience” and by adding in its place the phrase “such reaction”; and in paragraph (e) by removing the phrase “adverse experience” both times it appears and by adding in its place the abbreviation “SADR” to read as follows:

§ 312.32 IND safety reports.

(a) *Definitions.* The following definitions of terms apply to this section:

Disability means a substantial disruption of a person’s ability to conduct normal life functions.

Life-threatening suspected adverse drug reaction (SADR) means any SADR that, in the view of the investigator or sponsor, places the patient or subject at immediate risk of death from the SADR as it occurred. It does not include an SADR that, had it occurred in a more severe form, might have caused death.

Minimum data set means the report includes an identifiable patient, an identifiable reporter, a suspect drug product, and an SADR.

Serious SADR means any SADR that results in any of the following outcomes: Death, a life-threatening

SADR, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious SADR when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Suspected adverse drug reaction (SADR) means a noxious and unintended response to any dose of a drug product for which there is a reasonable possibility that the product caused the response. In this definition, the phrase “a reasonable possibility” means that the relationship cannot be ruled out.

Unexpected SADR means any SADR, the specificity or severity of which is not consistent with the current investigator brochure; or, if an investigator brochure is not required or available, the specificity or severity of which is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the investigator brochure only referred to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the investigator brochure only included cerebral vascular accidents. “Unexpected,” as used in this definition, refers to an SADR that has not been previously observed (e.g., included in the investigator brochure); it does not refer to an SADR that might be anticipated from the pharmacological properties of the drug product. SADRs that are mentioned in the investigator’s brochure as occurring with a class of drugs but not specifically mentioned as occurring with the particular drug are considered unexpected.

(b) *Review of safety information.* The sponsor must promptly review all information relevant to the safety of the drug obtained or otherwise received by the sponsor from any source, foreign or domestic, including information derived from any clinical or epidemiological

investigations, animal or in vitro studies, 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 sponsor and reports of foreign commercial marketing experience for drugs that are not marketed in the United States.

(c) *IND safety reports.* The sponsor must not submit an individual case safety report for an SADR to FDA if the report does not contain a minimum data set; instead, the sponsor must 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.

(1) *Written reports—(i) Serious and unexpected SADR.* The sponsor must notify FDA and all participating investigators in a written IND safety report of 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. The sponsor must identify all safety reports previously filed with the IND concerning a similar SADR, and must analyze the significance of the SADR in light of previous, similar reports.

(ii) *Information sufficient to consider product administration changes.* 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 the 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.

(iii) *Submission of written reports.* Each written report may be submitted on an FDA Form 3500A or in a narrative format. Foreign SADRs may be