

(iii) Either a statement that the new owner has a complete copy of the approved application, including supplements and records that are required to be kept under § 314.81, or a request for a copy of the application from FDA's files. FDA will provide a copy of the application to the new owner under the fee schedule in § 20.45 of FDA's public information regulations.

(b) The new owner shall advise FDA about any change in the conditions in the approved application under § 314.70, except the new owner may advise FDA in the next annual report about a change in the drug product's label or labeling to change the product's brand or the name of its manufacturer, packer, or distributor.

[50 FR 7493, Feb. 22, 1985; 50 FR 14212, Apr. 11, 1985, as amended at 50 FR 21238, May 23, 1985; 67 FR 9586, Mar. 4, 2002; 68 FR 25287, May 12, 2003]

#### § 314.80 Postmarketing reporting of adverse drug experiences.

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

*Adverse drug experience.* Any adverse event associated with the use of a drug in humans, whether or not considered drug related, including the following: An adverse event occurring in the course of the use of a drug product in professional practice; an adverse event occurring from drug overdose whether accidental or intentional; an adverse event occurring from drug abuse; an adverse event occurring from drug withdrawal; and any failure of expected pharmacological action.

*Individual case safety report (ICSR).* A description of an adverse drug experience related to an individual patient or subject.

*ICSR attachments.* Documents related to the adverse drug experience described in an ICSR, such as medical records, hospital discharge summaries, or other documentation.

*Disability.* A substantial disruption of a person's ability to conduct normal life functions.

*Life-threatening adverse drug experience.* Any adverse drug experience that places the patient, in the view of the initial reporter, at *immediate* risk of death from the adverse drug experience as it occurred, *i.e.*, it does not include

an adverse drug experience that, had it occurred in a more severe form, might have caused death.

*Serious adverse drug experience.* Any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, 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 adverse drug experience 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.

*Unexpected adverse drug experience.* Any adverse drug experience that is not listed in the current labeling for the drug product. This includes events that may be symptomatically and pathophysiologically related to an event listed in the labeling, but differ from the event because of greater severity or specificity. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the labeling only referred to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the labeling only listed cerebral vascular accidents. "Unexpected," as used in this definition, refers to an adverse drug experience that has not been previously observed (*i.e.*, included in the labeling) rather than from the perspective of such experience not being anticipated from the pharmacological properties of the pharmaceutical product.

(b) *Review of adverse drug experiences.* Each applicant having an approved application under § 314.50 or, in the case of a 505(b)(2) application, an effective

approved application, must promptly review all adverse drug experience information obtained or otherwise received by the applicant from any source, foreign or domestic, including information derived from commercial marketing experience, postmarketing clinical investigations, postmarketing epidemiological/surveillance studies, reports in the scientific literature, and unpublished scientific papers. Applicants are not required to resubmit to FDA adverse drug experience reports forwarded to the applicant by FDA; however, applicants must submit all followup information on such reports to FDA. Any person subject to the reporting requirements under paragraph (c) of this section must also develop written procedures for the surveillance, receipt, evaluation, and reporting of postmarketing adverse drug experiences to FDA.

(c) *Reporting requirements.* The applicant must submit to FDA adverse drug experience information as described in this section. Except as provided in paragraph (g)(2) of this section, these reports must be submitted to the Agency in electronic format as described in paragraph (g)(1) of this section.

(1)(i) *Postmarketing 15-day “Alert reports”.* The applicant must report each adverse drug experience that is both serious and unexpected, whether foreign or domestic, as soon as possible but no later than 15 calendar days from initial receipt of the information by the applicant.

(ii) *Postmarketing 15-day “Alert reports”—followup.* The applicant must promptly investigate all adverse drug experiences that are the subject of these postmarketing 15-day Alert reports and must submit followup reports within 15 calendar days of receipt of new information or as requested by FDA. If additional information is not obtainable, records should be maintained of the unsuccessful steps taken to seek additional information.

(iii) *Submission of reports.* The requirements of paragraphs (c)(1)(i) and (c)(1)(ii) of this section, concerning the submission of postmarketing 15-day Alert reports, also apply to any person other than the applicant whose name appears on the label of an approved drug product as a manufacturer, pack-

er, or distributor (nonapplicant). To avoid unnecessary duplication in the submission to FDA of reports required by paragraphs (c)(1)(i) and (c)(1)(ii) of this section, obligations of a nonapplicant may be met by submission of all reports of serious adverse drug experiences to the applicant. If a nonapplicant elects to submit adverse drug experience reports to the applicant rather than to FDA, the nonapplicant must submit, by any appropriate means, each report to the applicant within 5 calendar days of initial receipt of the information by the nonapplicant, and the applicant must then comply with the requirements of this section. Under this circumstance, the nonapplicant must maintain a record of this action which must include:

(A) A copy of each adverse drug experience report;

(B) The date the report was received by the nonapplicant;

(C) The date the report was submitted to the applicant; and

(D) The name and address of the applicant.

(2) *Periodic adverse drug experience reports.* (i) The applicant must report each adverse drug experience not reported under paragraph (c)(1)(i) of this section at quarterly intervals, for 3 years from the date of approval of the application, and then at annual intervals. The applicant must submit each quarterly report within 30 days of the close of the quarter (the first quarter beginning on the date of approval of the application) and each annual report within 60 days of the anniversary date of approval of the application. Upon written notice, FDA may extend or reestablish the requirement that an applicant submit quarterly reports, or require that the applicant submit reports under this section at different times than those stated. For example, the agency may reestablish a quarterly reporting requirement following the approval of a major supplement. Followup information to adverse drug experiences submitted in a periodic report may be submitted in the next periodic report.

(ii) Each periodic report is required to contain:

(A) *Descriptive information.* (1) A narrative summary and analysis of the information in the report;

(2) An analysis of the 15-day Alert reports submitted during the reporting interval (all 15-day Alert reports being appropriately referenced by the applicant's patient identification code, adverse reaction term(s), and date of submission to FDA);

(3) A history of actions taken since the last report because of adverse drug experiences (for example, labeling changes or studies initiated); and

(4) An index consisting of a line listing of the applicant's patient identification code, and adverse reaction term(s) for all ICSRs submitted under paragraph (c)(2)(ii)(B) of this section.

(B) *ICSRs for serious, expected, and nonserious adverse drug experiences.* An ICSR for each adverse drug experience not reported under paragraph (c)(1)(i) of this section (all serious, expected and nonserious adverse drug experiences). All such ICSRs must be submitted to FDA (either individually or in one or more batches) within the timeframe specified in paragraph (c)(2)(i) of this section. ICSRs must only be submitted to FDA once.

(iii) Periodic reporting, except for information regarding 15-day Alert reports, does not apply to adverse drug experience information obtained from postmarketing studies (whether or not conducted under an investigational new drug application), from reports in the scientific literature, and from foreign marketing experience.

(d) *Scientific literature.* A 15-day Alert report based on information in the scientific literature must be accompanied by a copy of the published article. The 15-day reporting requirements in paragraph (c)(1)(i) of this section (*i.e.*, serious, unexpected adverse drug experiences) apply only to reports found in scientific and medical journals either as case reports or as the result of a formal clinical trial.

(e) *Postmarketing studies.* An applicant is not required to submit a 15-day Alert report under paragraph (c) of this section for an adverse drug experience obtained from a postmarketing study (whether or not conducted under an investigational new drug application) unless the applicant concludes that there

is a reasonable possibility that the drug caused the adverse experience.

(f) *Information reported on ICSRs.* ICSRs include the following information:

(1) *Patient information.*

(i) Patient identification code;

(ii) Patient age at the time of adverse drug experience, or date of birth;

(iii) Patient gender; and

(iv) Patient weight.

(2) *Adverse drug experience.*

(i) Outcome attributed to adverse drug experience;

(ii) Date of adverse drug experience;

(iii) Date of ICSR submission;

(iv) Description of adverse drug experience (including a concise medical narrative);

(v) Adverse drug experience term(s);

(vi) Description of relevant tests, including dates and laboratory data; and

(vii) Other relevant patient history, including preexisting medical conditions.

(3) *Suspect medical product(s).*

(i) Name;

(ii) Dose, frequency, and route of administration used;

(iii) Therapy dates;

(iv) Diagnosis for use (indication);

(v) Whether the product is a prescription or nonprescription product;

(vi) Whether the product is a combination product as defined in §3.2(e) of this chapter;

(vii) Whether adverse drug experience abated after drug use stopped or dose reduced;

(viii) Whether adverse drug experience reappeared after reintroduction of drug;

(ix) Lot number;

(x) Expiration date;

(xi) National Drug Code (NDC) number; and

(xii) Concomitant medical products and therapy dates.

(4) *Initial reporter information.*

(i) Name, address, and telephone number;

(ii) Whether the initial reporter is a health care professional; and

(iii) Occupation, if a health care professional.

(5) *Applicant information.*

(i) Applicant name and contact office address;

(ii) Telephone number;

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(iii) Report source, such as spontaneous, literature, or study;

(iv) Date the report was received by applicant;

(v) Application number and type;

(vi) Whether the ICSR is a 15-day “Alert report”;

(vii) Whether the ICSR is an initial report or followup report; and

(viii) Unique case identification number, which must be the same in the initial report and any subsequent followup report(s).

(g) *Electronic format for submissions.*

(1) Safety report submissions, including ICSRs, ICSR attachments, and the descriptive information in periodic reports, must be in an electronic format that FDA can process, review, and archive. FDA will issue guidance on how to provide the electronic submission (e.g., method of transmission, media, file formats, preparation and organization of files).

(2) An applicant or nonapplicant may request, in writing, a temporary waiver of the requirements in paragraph (g)(1) of this section. These waivers will be granted on a limited basis for good cause shown. FDA will issue guidance on requesting a waiver of the requirements in paragraph (g)(1) of this section.

(h) *Multiple reports.* An applicant should not include in reports under this section any adverse drug experiences that occurred in clinical trials if they were previously submitted as part of the approved application. If a report applies to a drug for which an applicant holds more than one approved application, the applicant should submit the report to the application that was first approved. If a report refers to more than one drug marketed by an applicant, the applicant should submit the report to the application for the drug listed first in the report.

(i) *Patient privacy.* An applicant should not include in reports under this section the names and addresses of individual patients; instead, the applicant should assign a unique code for identification of the patient. The applicant should include the name of the reporter from whom the information was received as part of the initial reporter information, even when the reporter is the patient. The names of patients,

health care professionals, hospitals, and geographical identifiers in adverse drug experience reports are not releasable to the public under FDA’s public information regulations in part 20 of this chapter.

(j) *Recordkeeping.* The applicant must maintain for a period of 10 years records of all adverse drug experiences known to the applicant, including raw data and any correspondence relating to adverse drug experiences.

(k) *Withdrawal of approval.* If an applicant fails to establish and maintain records and make reports required under this section, FDA may withdraw approval of the application and, thus, prohibit continued marketing of the drug product that is the subject of the application.

(l) *Disclaimer.* A report or information submitted by an applicant under this section (and any release by FDA of that report or information) does not necessarily reflect a conclusion by the applicant or FDA that the report or information constitutes an admission that the drug caused or contributed to an adverse effect. An applicant 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 adverse effect. For purposes of this provision, the term “applicant” also includes any person reporting under paragraph (c)(1)(iii) of this section.

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§314.81 Other postmarketing reports.

(a) *Applicability.* Each applicant shall make the reports for each of its approved applications and abbreviated applications required under this section and section 505(k) of the act.

(b) *Reporting requirements.* The applicant shall submit to the Food and Drug Administration at the specified times two copies of the following reports:

(1) *NDA—Field alert report.* The applicant shall submit information of the following kinds about distributed drug