CHAPTER 53 - POSTMARKETING SURVEILLANCE AND EPIDEMIOLOGY: HUMAN DRUGS

UPON RECEIPT

ENFORCEMENT OF THE POSTMARKETING ADVERSE DRUG EXPERIENCE REPORTING REGULATIONS

SEPTEMBER 30, 1999

INDUSTRY CODES: 53 (Rx only) 53001A CDER INITIATED WORK

56 53001B DISTRICT INITIATED WORK

60-64 53R806 FOREIGN ADE INSPECTIONS

FIELD REPORTING REQUIREMENTS:

Copies of all Establishment Inspection Reports with exhibits and endorsement/recommendation, investigational reports, and follow-up correspondence will be forwarded to HFD-332.

PART I - BACKGROUND

This compliance program provides guidance to the FDA field staff for the enforcement of the Postmarketing Adverse Drug Experience (ADE) Reporting Regulations (21 CFR 310.305, 314.80 and 314.98).

NOTE: Bold type reflects updated information for this program since June 1997. A final rule revoking the requirement for increased frequency reports was published on June 25, 1997, and is now in effect. Another rule finalizing the expedited safety reporting provisions in the October 27, 1994 proposed rule was published on October 7, 1997, and its provisions become effective on April 6, 1998. All persons affected by the final rule of
October 7, 1997 may comply with the provisions of the final rule prior to its effective date. FDA also issued a new guidance document to industry on August 27, 1997 that clarifies certain postmarketing safety reporting requirements.

A. THE ADVERSE DRUG EXPERIENCE REGULATION

Prescription drug manufacturers, both applicant and non-applicant holders, prescription drug packers, and own label distributors of prescription drugs are required to submit to the Agency Postmarketing Adverse Drug Experience reports. This revised compliance program provides guidance for a new inspectional strategy. The primary focus of this program is to determine if the regulated industry is submitting all adverse drug experience reports to the Agency in accordance with regulatory time frames. The secondary focus of this program is to provide greater emphasis on verifying completeness and accuracy of ADE data submitted to the FDA. Congress has required that adverse drug experience information relating to all prescription drugs be made available to FDA so that the Agency can take appropriate action to protect the public health when necessary.

B. BACKGROUND

The postmarketing adverse drug experience (ADE) regulations (21 CFR 310.305, 314.80 and 314.98) became effective on August 22, 1985, September 2, 1986, and June 29, 1992, and cover prescription drugs. The regulations also apply to OTC drugs that have approved applications, including those initially marketed as prescription drugs under approved applications (i.e., Rx-to-OTC switched drugs).

The purpose of postmarketing ADE surveillance is to obtain information on rare, latent or long term drug effects not identified during premarket testing. Sponsors, manufacturers, packers and distributors are required to report all serious, unexpected (not listed in the drug product’s current labeling) ADEs to FDA within 15 working days. This requirement becomes 15 calendar days as of April 6, 1998. A serious ADE is one that is fatal or life-threatening, or is permanently disabling, or requires inpatient hospitalization, or is a congenital anomaly, cancer, or overdose. As of April 6, 1998, the terms "cancer" and "overdose" will not be part of the definition of a serious ADE, but if a patient experiences cancer it is still reportable as a serious ADE. In addition, as of April 6, 1998 "serious" includes prolongation of existing hospitalization, and important medical events based upon appropriate medical judgement.
The term "permanently disabling" will be changed to "persistent or significant disability/incapacity."

For ADEs not meeting the criteria in the previous paragraph, periodic reports must be submitted to FDA quarterly during the first three years following approval of the drug and annually thereafter. This does not apply to drugs under 21 CFR 310.305. Applicants may request a waiver under 21 CFR 314.90 for submission of individual cases of nonserious labeled ADEs.

PART II - IMPLEMENTATION

A. OBJECTIVES

The guidance in this program will ensure that the agency is informed of all required adverse drug experience reports. Receipt of these reports is critical for the agency to monitor the safety and effectiveness of marketed drugs.

B. PROGRAM MANAGEMENT INSTRUCTIONS

CDER may issue assignments to cover specific manufacturers and drugs when review of ADE information determines that additional data or inspectional coverage is needed.

Districts may initiate coverage of establishments and/or manufacturers that maintain postmarketing ADE reports either on a surveillance or compliance basis. Other sites may be inspected to investigate specific ADE incidents. Districts are encouraged to contact HFD-332 prior to initiating inspections to obtain ADE information that could assist in selecting establishments and specific drug products for inspectional coverage.

PART III - INSPECTIONS

A. PURPOSE

Inspections are conducted to determine whether drug applicants, drug manufacturers, packers and own label distributors submit all required postmarketing ADE reports to the agency, and whether ADE reports are complete, accurate and submitted in accordance with reporting time frames.

B. SITE SELECTION
The regulations do not specify where applicants must maintain postmarketing ADE reports. It is acceptable that applicants who have more than one business location maintain ADE reports at either their corporate office or other sites. Site locations will be noted in Center-initiated assignments. HFD-332 should be contacted for this information prior to conducting district-initiated assignments.

C. STANDARD OPERATING PROCEDURES AND PERSONNEL QUALIFICATIONS

The regulations (21 CFR 211.198) require that drug finished dosage form manufacturers and repackers, without approved applications, have written procedures for complaint files including provisions for determining whether a complaint represents a serious and unexpected ADE. The regulations (21 CFR 211.25) also require that qualified personnel investigate and evaluate ADEs. If serious deficiencies are found during the inspection, obtain copies of the procedures and determine personnel qualifications and staffing, especially if the firm utilizes computerized reporting. **Effective April 6, 1998, any person subject to the ADE Reporting regulations, including those that do not have approved applications, shall develop written procedures for the surveillance, receipt, evaluation, and reporting of postmarketing adverse drug experiences to FDA (21 CFR 314.80(b) and 21 CFR 310.305(a)).** (See Attachment A for additional information on written procedure requirements.)

D. SELECTION OF DRUG PRODUCTS

When the number of ADE reports is extensive, focus resources on:

1. Drugs most likely to have unexpected serious adverse experiences, or
   - Drugs that could cause serious medical problems if they fail to produce their expected pharmacological actions.

Drugs most likely to have unexpected adverse experiences are those meeting the following criteria:

1. Approved within the last three years, focusing on lack of effect reports.
   - New molecular entities.
   - Known or suspected bioavailability or bioequivalence problems.
Center-initiated assignments will identify priority drugs based on the above criteria or other available information.

E. ADVERSE DRUG EXPERIENCE (ADE) REPORT FORMS

Current regulations refer to form FDA-1639 for reporting ADEs. Applicants may also use FDA Form 3500A or their own computer-generated forms designed to contain information identical to MedWatch FDA Form 3500A, if prior approval is received from the Division of Pharmacovigilance and Epidemiology (HFD-730). Effective April 6, 1998, the form FDA-1639 may not be used and the FDA Form 3500A or preapproved computer-generated forms must be used after that date. Until that time, any of the following forms may be used:

1. Form FDA-1639 can be used by anyone.

2. MedWatch FDA Form 3500A used by applicants, manufacturers, packers or distributors for mandatory reporting of domestic ADEs.

3. MedWatch FDA Form 3500 used by health care professionals or consumers for voluntary reporting of ADEs.

4. Preapproved computer-generated FDA Form 3500As used by drug firms.

Manufacturers may report 15-day adverse events occurring in foreign countries on a CIOMS I form, with prior approval from FDA. The form was designed by the World Health Organization's Council for International Organizations of Medical Sciences. Effective April 6, 1998 the CIOMS I form may be used for foreign events without prior approval. (See Attachment B for examples of ADE reporting forms.)

F. SELECTION OF ADE REPORTS

When selecting ADEs to determine adherence to required reporting practices, completeness, and accuracy, look for:

1. Serious unlabeled ADEs, particularly those involving death or hospitalization.

2. Incomplete serious, unexpected ADE reports or reports with unlabeled ADEs and no outcome reported.
3. Periodic reports which include serious unexpected ADEs that should have been submitted as 15-day reports.

G. VERIFICATION OF ADE REPORTS

IT IS ESSENTIAL THAT DISTRICTS FOCUS ON DETERMINING WHETHER THE MANUFACTURER SUBMITTED ALL REPORTABLE ADEs, PARTICULARLY SERIOUS UNLABELED ADEs, TO THE AGENCY. Check the firm’s written procedures describing how ADEs are investigated, evaluated, and submitted to the agency and determine whether they are followed. Check the complaint files to see whether there are any ADE complaints not submitted on a postmarket ADE form to FDA. If any significant ADE violations are identified during the inspection, select and copy up to twenty-five (25) serious unexpected ADE reports of one or more selected products and submit them with the establishment inspection report to HFD-332. These reports will be used to verify the information submitted to the agency.

Verify the completeness and accuracy of the selected reports against other information in the firm’s files as follows:

1. Was information on the form available at the time of submission?
2. Was all relevant information included on the form?
3. Was the initial receiving date supplied to the agency (FDA Form 3500A Section G Item 4) the same date as the initial receipt of information by the manufacturer?
4. Was new information obtained by the firm during their follow-up investigation and was this information submitted to the agency?
5. Where feasible, particularly when hospitalization, permanent (becomes persistent or significant as of April 6, 1998) disability or death occurred, did the firm obtain important follow-up information to enable complete evaluation of the report?

Determine the timely submission of reports as follows:

15-Day Reports

Serious, unexpected ADEs must be submitted to the agency within 15 working days. This requirement becomes 15 calendar days as of April 6, 1998.
The 15-working day time frame begins on the date the manufacturer or any of its affiliates (including foreign) received the information. Sometimes an ADE report initially not classified as a 15-day report is reclassified as "serious and unexpected" after the firm’s follow-up investigation. In this case the 15-day time frame begins on the date the firm received the information that caused the report to be reclassified. If the applicant receives new follow-up information on a 15-day report, then the G4 date is the date of this new information. A follow-up 15-day report has to be submitted within 15 working days after receipt of the information. This requirement becomes 15 calendar days as of April 6, 1998.

An establishment’s report may include a causality assessment of whether the ADE was related to the drug. The regulations do not permit submission delays for 15-day reports pending completion of a causality assessment.

Periodic Reports

Spontaneous (not derived from a study nor literature), domestic ADEs that do not meet the criteria of a 15-day report are required to be submitted to the agency in periodic reports under 21 CFR 314.80 only. Periodic reports must be submitted quarterly for the first three years after application approval and annually thereafter. The periodic report submission date is usually based on the date the NDA/ANDA was approved. If a date other than the approval date is used to calculate the due date, determine if the firm received the required written FDA approval.

H. FDA-483, INSPECTIONAL OBSERVATIONS

Document deviations from the ADE regulations. Clear deviations such as, failure to submit ADE reports, failure to promptly investigate an ADE event, inaccurate information, incomplete disclosure of available information, lack of written procedures or failing to adhere to reporting requirements, should be cited on the FDA-483 issued to management. Questions on medical judgement or evaluation on the part of the firm’s management should be discussed with the firm and included in the narrative report but should not be cited on the FDA-483.

I. SAMPLE COLLECTION

Physical or documentary samples are not required to support Warning Letters and should be collected only to support injunction or prosecution. Serious violations of regulations should always be documented in the establishment inspection report and exhibits including copies of drug labeling, as appropriate.
J. ESTABLISHMENT INSPECTION REPORT

Even if no significant deviations are found, the report should list all drug products covered during the inspection. It may be limited to a Summary of Findings or use minimal headings, as appropriate.

For significant deviations warranting a Warning Letter or more serious regulatory action, the report must include information for each drug product covered as follows:

1. The drug product identification and its NDA/ANDA number.
2. NDA/ANDA approval date from the firm’s files.
3. The date the firm introduced the drug into the market.
4. The date used by the firm as the basis for determining reporting cycles under the periodic reporting requirements, if other than the NDA/ANDA approval date.
5. The time periods during which the ADE reports covered by the inspection were received by the firm, and the dates they submitted the reports to the agency.
6. Labeling (including package inserts) in use for the drug product covered during the inspection.
7. An explanation of the manufacturer’s report number assigned to each ADE report.

PART IV - ANALYTICAL

No analytical activities are planned under this program.

PART V - REGULATORY/ADMINISTRATIVE STRATEGY

Recommendations for regulatory action, including Warning Letter drafts, shall be forwarded to the Division of Prescription Drug Compliance and Surveillance (HFD-330).
Issuance of a Warning Letter should be considered when significant deviations or violations exist and corrections may reasonably be expected by the firm’s management.

The following violations are considered significant to warrant issuance of a Warning Letter:

1. Failure to submit ADE reports for serious and unexpected adverse drug experience events (21 CFR 314.80(c)(1) and 310.305(c)).

2. 15-day alert reports that are submitted as part of a periodic report and which were not otherwise submitted under separate cover as 15-day alert reports. This applies to foreign and domestic ADE information from scientific literature and postmarketing studies as well as spontaneous reports (21 CFR 314.80(c)(1) and 310.305(c)).

3. 15-day alert reports that are inaccurate and/or not complete.

4. 15-day alert reports that are not submitted on time.

5. The repeated or deliberate failure to maintain or submit periodic reports in accordance with the reporting requirements (21 CFR 314.80(c)(2)).

6. Failure to conduct a prompt and adequate follow-up investigation of the outcome of ADEs that are serious and unexpected (21 CFR 314.80(c)(1) and 310.305(c)(3)).

7. Failure to maintain ADE records for marketed prescription drugs or to have written procedures for investigating ADEs for marketed prescription drugs without approved applications (21 CFR 314.80(i) and 211.198). Written procedures for the surveillance, receipt, evaluation, and reporting of postmarketing adverse drug experiences to FDA for marketed prescription drugs subject to approved applications, becomes a requirement under 21 CFR 314.80 (b), effective April 6, 1998. These written procedures also become a requirement for drugs without approved applications under 21 CFR 310.305(a), effective April 6, 1998.

8. Failure to submit 15-day reports derived from a postmarketing study where there is a reasonable possibility that the drug caused the adverse drug experience.

Districts should consider holding compliance meetings with firms in situations where incomplete corrections were made by the firm following a Warning Letter and the existing violations do not warrant any of the following enforcement actions.
Withdrawal of NDA/ANDA approval is warranted only when agency evaluation of ADEs show that the drug is no longer safe and should be removed from the market, or the drug product requires labeling changes that the applicant is unwilling to make (FD&C Act, Section 505(e)).

Seizure will, generally, not be a readily available remedy under this program. That is, seizure for failure to comply with Postmarketing Adverse Drug Experience Reporting Regulations would only be possible if the approval of the application for the product has first been withdrawn under the conditions cited in the preceding paragraph (FD&C Act, Section 304(a)(1). Seizure would then be based on failure to hold an approved new drug application.

Injunction should be considered when appropriate follow-up inspection/investigation shows the firm has a continued pattern of significant and substantial deviations despite previous attempts by the agency to obtain compliance. Repeated failures on the part of the firm to submit required serious ADEs or failure to take steps to ensure that required serious ADE reports are complete and accurate may warrant injunctive action.

Evidence that a firm is not submitting reports for required serious ADEs, or is withholding important information, or submitting false information (the submission of which might have resulted in the agency requiring labeling changes or withdrawal of an application), should be considered under the agency’s Application Integrity Policy. Such evidence should be discussed with HFD-332 to determine the need for additional investigation. Evidence of this kind of activity warrants consideration for citation/prosecution.

PART VI - REFERENCES, ATTACHMENTS AND PROGRAM CONTACTS

A. REFERENCES

1. FD&C Act - Sections 301(e), 505(e) and 505(k)

2. 21 CFR 310.305, 314.80, 314.98, 314.150, 211.198 and 314.81


4. Compliance Program 7356.021 - Drug Quality Reporting System (DQRS)/NDA-Field Alert Reporting


7. International Conference on Harmonization: Guideline on Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (ICH E2A Guideline); March 1, 1995


B. ATTACHMENTS

1. Attachment A - Additional information on requirements for written procedures

2. Attachment B - ADE Reporting Forms

   FDA Form 1639

   FDA Form 3500

   FDA Form 3500A

   CIOMS I form

3. Attachment C - Comparison of current regulations versus requirements of new Final Rules

C. PROGRAM CONTACT

1. CDER

Questions regarding CDER inspectional assignments, compliance problems and technical matters:

Nancy Haggard, ADE Manager/Compliance Officer or Denis Mackey, Compliance Officer Adverse Drug Reaction and Compounding Team (HFD-332)
Division of Prescription Drug Compliance and Surveillance
Office of Compliance
7520 Standish Place
Rockville, Maryland 20855
Telephone (301) 594-0101

2. ORA

Jon W. Hunt, SCSO,
Drug Group,
Division of Emergency and Investigational Operations (HFC-130)
Investigation Branch (HFD-132)
Telephone: (301) 827-5658

PART VII - CENTER RESPONSIBILITIES

A. Division of Pharmacovigilance and Epidemiology (HFD-730)

1. Monitors postmarketing adverse drug experience reports, including periodic reports.

2. Notifies the Division of Prescription Drug Compliance and Surveillance (HFD-330) of discovered significant violations of postmarketing adverse drug experience reporting requirements.

3. Reviews and evaluates the medical/epidemiological aspects of field inspectional findings and advises the Division of Prescription Drug Compliance and Surveillance.

4. Provides technical guidance and support.

B. Division of Prescription Drug Compliance and Surveillance, Office of Compliance (HFD-330)

1. Assesses compliance issues related to possible violations by applicants, manufacturers, packers and distributors.

2. Identifies, prepares and issues all CDER-initiated assignments to the field.

3. Monitors all CDER-initiated assignments.
4. Serves as the CDER contact point for field inquiries on assignments and compliance issues.

5. Provides guidance and support to the field during all phases of inspections, investigations, and litigation.

6. Reviews reports and regulatory recommendations from district offices and serves as CDER compliance office for postmarketing ADE program areas.

Attachment A

Manufacturers and packers, marketing prescription drugs not subject of approved new drug or abbreviated new drug applications, are required to have written procedures for ADE (21 CFR 211.198). Effective April 6, 1998, any person subject to the Postmarketing ADE reporting requirements, including those who have approved applications, shall develop written procedures for the surveillance, receipt, evaluation, and reporting of postmarketing adverse drug experiences to FDA. However, the regulations for written procedures do not specify what is required. Written procedures should be adequate to ensure that ADEs are properly evaluated and are reported to the agency as required by regulations. If a manufacturer of marketed prescription drugs that are not the subject of approved new drug or abbreviated new drug applications does not have written procedures or the procedures are inadequate, the investigator should cite the observations on the FDA-483. Failure of applicants and manufacturers of approved drugs to have written procedures should not be cited on the FDA-483 until April 6, 1998. The failure to have such procedures can be noted on the FDA-483 after April 6, 1998.

Guidance recommendations to determine the adequacy of the written procedures are listed below. However, the list is not all-inclusive and should not be used as the basis for an FDA-483 observation:

1. A designated office with final authority and responsibility for performing the duties required by the ADE regulations including minimum qualifications of person(s) who investigate and evaluate ADE reports,
2. the firm’s internal procedures describe how to track, investigate and evaluate ADE reports, including the system used to assign tracking codes. If problems appear to be connected to a firm’s computerized reporting system, contact HFD-332,

3. all control activities used by the manufacturer to ensure that all ADE reports are properly investigated (including specific follow-up procedures), evaluated and submitted to FDA as required are described,

4. written procedures are dated and signed by a responsible official of the firm.

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**Attachment B**

Copies of the various ADE reporting forms.

1. [FDA-1639](#)
2. [FDA-3500](#)
3. [FDA-3500A](#)
4. [CIOMS](#)

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**Attachment C**

The following is a comparison of the regulations prior to July 25, 1997 and the changes since the issuance of the Final Rules on Increased Frequency Reports on June 25, 1997 and the Expedited Safety Reporting Requirements for Human Drug and Biological Products published on October 7, 1997. Persons may comply with the provisions of the final rule of October 7 prior to its effective date.

**INCREASED FREQUENCY FINAL RULE**

<table>
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<tr>
<th>PRIOR TO JULY 25, 1997</th>
<th>FINAL RULE EFFECTIVE ON JULY 25, 1997</th>
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The applicant shall review periodically the frequency of reports of adverse drug experiences that are both serious and expected and reports of therapeutic failure (lack of effect) and report any significant increase in frequency as soon as possible but in any case within 15 working days.

The final rule removed the increase frequency reporting requirement. Now the firms don't have to submit the 15 day reports for increased frequency nor do they need to calculate increased frequency.

### DEFINITION - DISABILITY

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<tr>
<th>CURRENT REGULATION</th>
<th>FINAL RULE EFFECTIVE APRIL 6, 1998</th>
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<tbody>
<tr>
<td>The term disability is not defined in the current regulations.</td>
<td>21 CFR 314.80(a) and 310.305(b)</td>
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<tr>
<td>A substantial disruption of a person’s ability to conduct normal life functions.</td>
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### DEFINITION - LIFE THREATENING

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<th>CURRENT REGULATION</th>
<th>FINAL RULE EFFECTIVE APRIL 6, 1998</th>
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<tr>
<td>21 CFR 314.80(a) and 310.305(b)</td>
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The term life threatening is not defined in the current regulations. Life threatening adverse drug experience is 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.

### DEFINITION - SERIOUS ADVERSE DRUG EXPERIENCE

<table>
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<tr>
<th>CURRENT REGULATION</th>
<th>FINAL RULE EFFECTIVE</th>
<th>APRIL 6, 1998</th>
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<tbody>
<tr>
<td><strong>21 CFR 314.80(a) and 310.305(b)(4)</strong></td>
<td>21 CFR 314.80(a) and 310.305(b)</td>
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<tr>
<td>Serious means an adverse drug experience that is fatal or life-threatening, is permanently disabling, requires inpatient hospitalization, or is a congenital anomaly, cancer, or overdose.</td>
<td>Serious adverse drug experience is 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.</td>
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experience when, based upon appropriate medical judgement, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in the definition.

REPORT SUBMISSION TIME FRAMES OF 15-DAY REPORTS AND FOLLOW-UP REPORTS

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<th>CURRENT REGULATION</th>
<th>FINAL RULE EFFECTIVE APRIL 6, 1998</th>
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<tbody>
<tr>
<td>21 CFR 314.80(c)(1)(i) and 310.305(c)</td>
<td>21 CFR 314.80(c)(1) and 310.305(c)</td>
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<tr>
<td>The applicant shall report each adverse drug experience that is both serious and unexpected, regardless of source, as soon as possible but in any case within 15 working days of initial receipt of the information. The applicant shall submit follow up reports within 15 working days of receipt of new information.</td>
<td>The applicant should 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 applicant. The applicant shall submit follow up reports within 15 calendar days of receipt of new information.</td>
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<tr>
<td>21 CFR 314.80(1)(i) and 310.305(c)(3)</td>
<td>21 CFR 314.80(1)(ii) and 310.305</td>
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<tr>
<td>If additional information is not obtainable, a follow up report may</td>
<td>If additional information is not obtainable, records should be maintained of the unsuccessful</td>
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be required that describes briefly the steps taken to seek additional information and the reasons why it could not be obtained.

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<tr>
<th>21 CFR 314.80(c)(1)(iii) and 310.305(c)(5)</th>
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<tr>
<td>If a nonapplicant (e.g., packer or distributor) elects to submit adverse drug experience reports to the applicant rather than to FDA, it shall submit each report to the applicant within 3 working days of its receipt by the nonapplicant.</td>
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<tr>
<th>21 CFR 314.80(c)(1)(iii) and 310.305(c)(3)</th>
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<tr>
<td>The nonapplicant shall submit each report to the applicant within 5 calendar days of receipt of the report by the nonapplicant.</td>
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FDA REPORTING FORMS

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<th>CURRENT REQUIREMENT</th>
<th>FINAL RULE EFFECTIVE</th>
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<tr>
<td>21 CFR 314.80(f) and 310.305(d)</td>
<td>APRIL 6, 1998</td>
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<tr>
<td>The applicant shall complete a Form FDA-1639 (Adverse Reaction Report) for each report of an adverse drug experience.</td>
<td>The applicant shall complete FDA Form 3500A for each report of adverse drug experience (foreign events may be submitted either on an FDA form 3500A or, if preferred, on a CIOMS I form)</td>
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| Firms are allowed to submit foreign events on a CIOMS I form with prior FDA approval. The CIOMS I form is not specifically | Foreign events may be submitted either on an FDA Form 3500A or if preferred, on a CIOMS I form. |
mentioned in the current regulations.

Instead of using the form FDA-1639, firms may use a computer-generated FDA-1639 or other alternative format provided that the format is approved by the Division of Epidemiology and Surveillance (HFD-730).

An alternative format must be agreed to in advance by Medwatch: The FDA Medical Products Reporting Program.

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### MISCELLANEOUS REQUIREMENTS

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<th>CURRENT REQUIREMENT</th>
<th>FINAL RULE EFFECTIVE</th>
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<tr>
<td>Standard Written Procedures are not addressed in the Postmarketing Adverse Drug Experience Regulations.</td>
<td>APRIL 6, 1998</td>
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<tr>
<td>Standard Written Procedures 21 CFR 314.80(b) and 21 CFR 310.305(a).</td>
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<tr>
<td>Any person subject to the reporting requirements under paragraph (c) of this section shall also develop written procedures for the surveillance, receipt, evaluation and reporting of postmarketing adverse drug experiences to FDA.</td>
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<tr>
<td>21 CFR 314.80 (b) and 310.305(c)(5)</td>
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<tr>
<td>Applicants are not required to resubmit to FDA adverse drug experience reports forwarded to</td>
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<tr>
<td>Not addressed</td>
<td>the applicant by FDA; however applicants must submit all follow up information on such reports to FDA.</td>
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