
CENTER FOR DRUG EVALUATION AND RESEARCH

Guidance for Industry

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES, FOOD AND DRUG ADMINISTRATION



**GUIDELINE FOR POSTMARKETING REPORTING OF
ADVERSE DRUG EXPERIENCES**

**U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION**

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration
Center for Drug Evaluation and Research

GUIDELINE FOR POSTMARKETING REPORTING OF
ADVERSE DRUG EXPERIENCES
[Docket No. 85D-0249]

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For further information regarding the guideline, please contact:

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I. Introduction

Adverse drug experiences (ADE's) must be reported in accordance with the requirements of 21 CFR 310.305 and 314.80.

Those regulations require three types of ADE reports: (1) 15-day reports of serious, unlabeled events; (2) 15-day narrative increased frequency reports of serious, labeled events; and (3) periodic reports. This guideline has been developed to assist applicants in meeting their reporting requirements.

The agency advises that this guideline represents its current position on the requirements for reporting of ADE's. This guideline does not bind the agency, and it does not create or confer any rights, privileges, or benefits for or on any persons.

II. Scope

This guideline is intended to assist applicants and other persons with ADE reporting responsibilities in meeting the adverse experience reporting requirements in 21 CFR 310.305 and 314.80. This guideline applies to each applicant having an approved abbreviated or full application under 21 CFR Part 314. In addition, this guideline applies to the reporting of ADE's under 21 CFR 310.305 for prescription drugs not subject to premarket approval.

This guideline does not apply to the following reports: (1) Investigational new drug application safety reports (21 CFR 312.32), (2) safety update reports for drugs covered by a pending marketing application (21 CFR 314.50(d)(5)(vi)), and product defect reports (21 CFR 314.81(b)). This guideline also does not provide guidance on the annual report requirements of 21 CFR 314.81(b)(2).

III. Who Must Report

The "manufacturer" or "applicant" is required to report. In addition, any person whose name appears on the label of a marketed drug as its manufacturer, packer, or distributor has reporting responsibilities, as does the individual or corporate entity that holds an approved new drug application (NDA), abbreviated new drug application (ANDA), or antibiotic application. For purposes of this guideline, "applicant" includes all persons with reporting responsibility under 21 CFR 310.305 and 314.80.

IV. What to Report

To summarize, the following must be reported:

- (a) All reports of spontaneous adverse events occurring within the United States (domestic reports).
- (b) Foreign, literature, and study reports involving:
 - (1) Serious, unlabeled events;
 - (2) Increased frequency of serious, labeled events.

(Study reports must only be submitted if there is "a reasonable possibility that the drug caused the adverse experience" (21 CFR 310.305(c)(1)(ii) and 21 CFR 314.80(e)(1)).)

15-Day Reports of Serious, Unlabeled Events

Reports of serious, unlabeled events must be reported to FDA on Form FDA 1639 as soon as possible but in any case within 15 working days of the time of initial receipt of the information by the applicant.

Submit 15-day reports in duplicate under separate cover with "15-Day Alert Report" marked on the outside envelope. Multiple 15-day reports and followup 15-day reports may be submitted in the same envelope, though they should not be stapled together. For marketed prescription drugs without approved NDA's, ANDA's, or antibiotic applications, 15-day reports should be marked "15-Day Alert Report - 310.305" and a single copy sent.

Note that outcome (Form FDA 1639, Items 8-12, and/or life-threatening, congenital anomaly, overdose, and cancer) must be determined before a report can be identified as "serious."

When an applicant receives information that should be submitted in a 15-day report, but it is not possible to provide all the desired information within 15 working days, a preliminary report must be submitted. Additional followup information must be sought and submitted within 15 working days after obtaining the new information. (See "Followup Reports" section.)

We encourage attachment of discharge summaries, autopsy reports, relevant laboratory data, and other concise critical clinical data.

DO NOT submit a copy of the initial or followup 15-day report (Form FDA 1639) in the next periodic report.

15-Day Narrative Increased Frequency Report of Serious, Labeled Events

Reports of an increased frequency of serious, labeled events must be reported to FDA in a narrative format as soon as possible, but in any case within 15 working days of determining that a significant increase in frequency exists.

For each adverse event reported in a 15-day narrative increased frequency report, a Form FDA 1639 should be completed. Note that only Form FDA 1639's reporting spontaneous domestic events should be included in the periodic report.

For foreign, literature, and study reports, Form FDA 1639's should be completed but they should not be included in the periodic report. They should only be attached to the narrative increased frequency report as described below.

The Form FDA 1639 (including spontaneous domestic, foreign, literature, study, etc.) for increased frequency cases should be attached to the end of the narrative increased frequency report and be clearly marked "Duplicate for Increased Frequency Report."

An increased frequency can be determined using a formula (coupled with a table). Using the formula below, an increased frequency exists if the number of reports for the "report interval" is greater than or equal to the critical number of reports "C" which is determined from the numbers of reports for the two report intervals and the estimated drug use for the two intervals using the following formula:

$$C = (R * X_c) + (1.645 * \sqrt{(X_c + X_r) * R})$$

Where X_c is the number of reports for the "comparison interval"
 X_r is the number of reports for the "report interval"
R is the marketing ratio of the "report interval" to the "comparison interval"
* multiplication sign

The marketing ratio is defined as:

$$R = \frac{\text{Estimated drug use (e.g., number of prescriptions, unit volumes, sales, etc.) for the "report interval"}}{\text{Estimated drug use (same units and scope as in the numerator) for the "comparison interval"}}$$

Appendix C describes in more detail how to identify an increase in frequency. It provides a sample format for the narrative report and examples on how to identify an increase in frequency using the formula and a reference table.

Further, note that no increased frequency report is required if the number of reports received during the "report interval" is less than four.

Determination of 15-Day Reporting Period

Fifteen-day reports must be submitted within 15 working days of the time (1) of initial receipt by the applicant of the serious, unlabeled status of the event or (2) of determining that an increase in frequency of a serious, labeled event has occurred. (Refer to the definition of "serious" in Appendix A.)

Followup information for 15-day reports must also be submitted within 15 working days of its receipt. The date of receipt should be entered into Item 24c. of Form FDA 1639.

For foreign reports, the 15-day time clock begins when the applicant or its foreign affiliate has received sufficient data to suggest that 15-day criteria have been met (based on U.S. labeling and definitions of serious experience). Applicants must therefore establish effective mechanisms to ensure rapid information transfer from their foreign affiliates.

Periodic Reports

Periodic reports are required for each approved NDA, ANDA, and antibiotic application. Periodic reports are due quarterly for the first 3 years after approval, and annually thereafter. If marketing is delayed, these reports should also be submitted quarterly for the first 3 years of marketing.

Periodic reports due quarterly must be submitted within 30 days of the last day of the reporting quarter. Reports due annually must be submitted each year within 60 days of the anniversary date of approval of the drug.

Upon written notice, FDA may extend or reestablish the requirement that an applicant submit quarterly reports or require that the applicant submit reports under 21 CFR 314.80(c)(2) at different times.

A periodic report must contain the following four components described below. Each should be clearly separated by an identifying tab and arranged in the following order:

1. Form FDA 1639's for serious, labeled and nonserious (labeled and unlabeled) ADE's from spontaneous, domestic sources. (Form FDA 1639's for serious, unlabeled experiences should not be included in the periodic report since they should have been previously submitted as 15-day reports.)

A separate Form FDA 1639 must be completed for followup as well as for initial reports for each individual person experiencing an adverse event.

It may not be necessary to include attachments with the submitted Form FDA 1639's. However, discharge summaries and other concise critical data are encouraged if they help to explain the adverse experience.

Initial Form FDA 1639's should be separated from followup Form FDA 1639 reports.

The applicant should not submit initial and followup Form FDA 1639's on the same case in the same periodic report. All initial and followup information should be combined and submitted as one initial Form FDA 1639.

Note that adverse experiences include reports of failure to produce the expected pharmacologic action, i.e., "lack of effect."

2. Index line listing of Form FDA 1639's included in "1" above. A line listing for each Form FDA 1639 submitted should include:

- a. Manufacturer control number.
- b. Adverse event(s).
- c. Page number of the individual Form FDA 1639 as located in the periodic report.

Also, for any "drug interaction" listed as an adverse event, the interacting drugs should be identified in the periodic report line listing.

3. Narrative summary and analysis of the information in the periodic report and an analysis of the 15-day reports submitted during the reporting period.

This section should include:

- a. Listing of the 15-day reports of serious, unlabeled experiences submitted during the period. This listing should include manufacturer control number, adverse event(s), and date sent to FDA.

b. Listing of the 15-day increased frequency narrative reports of serious, labeled events submitted during the period. This listing should include the adverse event(s) and date sent to FDA.

c. Listing by body system of all ADE terms and counts of occurrences submitted during the period (taken from the 15-day reports of serious, unlabeled experiences and the Form FDA 1639's submitted in the periodic report).

For the ADE term "drug interaction," the interacting drugs should be identified in the tabulation.

d. Summary of the ADE reports in which the drug was listed as one of the suspect drugs, but the report was filed to another NDA or ANDA held by the applicant.

e. Narrative discussion of the clinical significance of the 15-day reports (reports of serious, unlabeled events and increase in frequency of serious, labeled events). This narrative should assess clinical significance by type of event, body system, and overall drug safety relating the new information received during this period to what was already known about the drug.

4. Narrative discussion of action taken, including labeling changes and studies initiated since the last periodic report.

The "narrative of action taken" section should include the following:

a. A copy of current product labeling.

b. A listing of any labeling changes made during the period.

c. Studies initiated.

d. Summary of important foreign actions; e.g., new warnings, limitations in the indications and use of the product.

e. Communication of new safety information; e.g., a "Dear Doctor" letter.

If information for one of these tabs is not included, an explanatory note must accompany that section of the report.

Each page of the periodic report should be numbered and include the name and NDA number of the drug.

Each copy of the periodic report should be covered by a transmittal letter, which includes the drug name, NDA number, time period covered, number of initial periodic ADE reports (Form FDA 1639)

contained in the submission, and number of followup periodic ADE reports (Form FDA 1639) contained in the submission. Data from the Form FDA 1639's should not be included in the transmittal letter. (See Appendix D for a sample transmittal letter.)

If no adverse experiences were identified for the period involved and no actions taken, a transmittal letter stating this must be submitted along with a copy of the current labeling.

Periodic submissions must be clearly marked "Periodic ADE Submission" on the front cover of each volume.

Followup Reports

A followup report provides information about an event that has been reported previously as an initial report with a unique manufacturer control number (Item 24b, Form FDA 1639).

A followup report should provide a complete picture of the current understanding of the adverse experience. Information in the initial report should be combined with the followup information to present a true and comprehensive description of the adverse experience as it is understood at the time of the followup. Information from the initial report later found to be inaccurate should not be repeated in the followup. Thus, it should not be necessary to send the initial Form FDA 1639 with the followup Form FDA 1639.

The followup report should include:

Correct information contained in the initial report plus the new data. The new data should be marked (e.g., with an asterisk, highlighted, underlined, etc.). Any attachments submitted in the initial report (e.g., journal articles, discharge summaries) should not be resubmitted.

Item 24b - The same unique manufacturer control number used on the initial report; this is essential to prevent duplicate counting of reports.

Item 24c - The date the followup information was received by the applicant.

Item 25a - Clearly marked "followup."

To summarize, the followup report (and attachments, if any) must contain the applicant's same unique internal recordkeeping number (control number, Item 24b on Form FDA 1639) as the initial report.

If the initial report was submitted as a 15-day report, the followup report should be submitted as a 15-day followup report even if the followup information shows that the event was labeled or not

serious. Conversely, a 15-day followup report should be submitted if the event is found to be serious and unlabeled, even if the original report was not submitted as a 15-day report.

DO NOT submit a followup report if additional relevant information is not obtained. However, the documentation of the procedure followed in seeking to obtain the additional information should be maintained. FDA may request this documentation.

Fifteen-day followup reports should not be submitted in the same envelope with periodic reports. "15-Day Alert Report" should be marked on the outside envelope of the 15-day followup reports.

DO NOT submit a followup report when reporting a different experience in a patient for whom a previous experience was reported and submitted. Submit an initial report with a new control number (Item 24b) on a Form FDA-1639 for a new, subsequent experience. Thus, a followup report follows an experience, not a patient.

V. How and Where to Report

What and Where to Report

For prescription drugs without approved NDA's, ANDA's, or antibiotic applications, adverse experience reports should be sent as single copies to:

Division of Epidemiology and Surveillance (HFD-730)
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

For drugs with approved NDA's, ANDA's, or antibiotic applications, all 15-day Form FDA 1639 reports of serious, unlabeled events; 15-day narrative increased frequency reports of serious, labeled events; periodic reports; followup reports, and letters stating no reports were received during the reporting period should be sent in duplicate to:

Central Document Room
Food and Drug Administration
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20857

All submissions must be legible, preferably typewritten. Legible photostatic copies are acceptable. However, visual contrast must be adequate to assure clear readable microfilm copies.

If the applicant becomes aware of a reportable adverse event, the applicant is responsible for transferring the information to a Form FDA 1639 (and narrative increased frequency report if indicated) and submitting it to FDA. If it is a serious, unlabeled event, the Form FDA 1639 should be submitted within 15 days. The applicant should not assume the reporting requirements are fulfilled by asking the initial reporter to return a Form FDA 1639 to the applicant or FDA. The applicant should not wait for the reporter to complete a Form FDA 1639 before submitting a report of a serious, unlabeled event to FDA. A 15-day report can and should be submitted based only on verbal information.

All ADE reports, except 15-day narrative increased frequency reports, should be reported on a Form FDA 1639. (Detailed guidelines for narrative increased frequency reports are in Appendix C.)

How To Obtain Copies of Form FDA 1639

To obtain up to 10 copies of Form FDA 1639 write to:

Division of Epidemiology and Surveillance (HFD-730)
Food and Drug Administration
5600 Fishers Lane, Room 15B-31
Rockville, MD 20857

Additional copies can be obtained from:

PHS Forms and Publications Distribution Center (HFA-268)
12100 Parklawn Drive
Rockville, MD 20852

Copies of blank Form FDA 1639 can also be duplicated by the applicant.

Computerized Forms

In lieu of using the preprinted Form FDA 1639, a computer-generated report may be submitted if it contains all of the elements of information in the identical enumerated sequence of Form FDA 1639, is completed in accordance with this guideline, and is forwarded with the appropriate number of copies. The typeset must be large and clear enough to assure readable microfilm copies.

Each applicant's use of a modified form must be preapproved by FDA in writing.

Electronic Submissions

Electronically produced adverse drug experience reports may be submitted; however, each applicant must obtain prior written approval.

At this time, only periodic reports may be submitted electronically. Fifteen-day reports (serious, unlabeled events and an increase in frequency of serious, labeled events) may not be submitted electronically. Also, followup reports (to both 15-day and non-15-day reports) may not be submitted electronically.

CIOMS Forms for Foreign Reports

The Council for International Organizations for Medical Sciences (CIOMS), working with several member nations and industry, has developed a format (resembling Form FDA 1639) for international ADE reporting. With prior written approval, this format can be used for reporting foreign adverse experiences to the U.S. Food and Drug Administration.

Questions or Comments about Reporting Formats

Requests for approval of reporting formats (computerized forms, electronic submissions, CIOMS formats, etc.) should be addressed to:

Surveillance and Data Processing Branch (HFD-737)
Division of Epidemiology and Surveillance
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857
Phone: 301-443-6414

Questions about Determining and Reporting Increased Frequencies

Questions about determining increased frequencies should be addressed to:

Epidemiology Branch (HFD-733)
Division of Epidemiology and Surveillance
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857
Phone: 301-443-2306

Other Questions and Comments

General questions or comments about this guideline or ADE reporting should be addressed to:

Reports Evaluation Branch
Division of Epidemiology and Surveillance (HFD-735)
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857
Phone: 301-443-4580

VI. Special Situations

A number of special situations occur that may seemingly complicate reporting requirements. Following are several:

a. Scientific Literature Reports

Serious, unlabeled adverse events that are reported in the literature (or as an unpublished manuscript) must be submitted as 15-day reports on Form FDA 1639.

A copy of the article or manuscript must be attached to the completed Form FDA 1639.

A separate Form FDA 1639 must be completed for each identifiable patient (with an identifiable adverse event). Thus, if an article describes six patients with a given adverse experience, six Form FDA 1639's should be completed.

When an ADE is based on a foreign language article or manuscript, the applicant is expected to translate the publication into English promptly. The original article or manuscript and translation should be attached to the submitted Form FDA 1639.

All literature reports and manuscript reports should be marked "Literature" in Item 24d.

If multiple drug products are mentioned in the article, Form FDA 1639 should be submitted only by the manufacturer whose drug is the suspect drug.

The suspect drug is that identified by the article's author, and is usually mentioned in the article's title.

b. Postmarketing, Clinical Trial, or Surveillance Study of Drugs Involving ADE Monitoring

For the purposes of this section, a study refers to a formal research effort including a protocol with specific objectives and a scientific methodology for collecting and analyzing ADE data. Anything less rigorous should be treated as a spontaneous report.

The only experiences from studies that should be considered for submission to FDA under 21 CFR 310.305 or 314.80 are those that would be reported as (1) 15-day reports of serious, unlabeled events and (2) 15-day narrative increased frequency reports of serious, labeled events. These should be reported only if there is a "reasonable possibility" that the event is causally related to the drug exposure.

Events reportable from investigational new drug (IND) trials (with marketed drugs) also must be submitted to the IND as described in 21 CFR 312.32.

For each ADE, a suspect drug must be identified. Thus, for blinded studies, reports shall be completed only after the code is broken.

Postmarketing, clinical trial, and surveillance studies as described in this section and under 21 CFR 310.305 or 314.80(e) refer to studies specifically monitoring adverse effects of the drug. Adverse events incidental to other types of studies should be treated as spontaneous reports.

c. Foreign Reports

Only 15-day reports of serious, unlabeled events and 15-day narrative increased frequency reports of serious, labeled events are required to be submitted with respect to foreign reports. Other foreign reports, including serious, labeled events and all nonserious events, are not required to be submitted. However, reports of serious, labeled events should be available and submitted to FDA if requested.

Reports are also to be submitted if the foreign ADE is for a product that has the same active moiety as the product marketed in the United States. This is true even if the excipients, dosage forms, strengths, routes of administration, and indications vary.

When a foreign report is submitted on a product that is not identical to the product marketed in the United States, Item 24a should contain the foreign trade name, the generic name of the same active moiety as marketed in the United States, and should read, "similar to NDA number ____."

When determining whether there has been an increased frequency of an ADE using foreign reports, the denominator should be the foreign drug use data.

d. "Death" Reports

Because death is always a serious outcome, if death is associated with an unlabeled event, or if death is associated with a labeled event and the labeling does not specify that the event may be associated with a fatal outcome, a 15-day report should be submitted on a Form FDA 1639.

Each report involving death is analyzed for an increase in frequency in two distinct ways.

For one analysis, death reports associated with a given labeled event should be combined with other serious reports of that particular event, and are analyzed periodically (at least quarterly for the first 3 years of marketing and annually thereafter) for an increase in frequency.

For the other analysis, unlabeled death reports, labeled death reports, and reports of "death only" are combined and analyzed for an increase in frequency. ("Death only" reports are those reporting death with no other specific adverse event.)

For an increase in frequency assessment, analyze together only reports from a single source type (e.g., compare spontaneous reports with spontaneous reports; compare study reports with reports from comparable studies; do not combine spontaneous reports with study reports; do not combine foreign reports with domestic reports). If an increase in frequency is detected, a 15-day narrative increased frequency report should be submitted.

Spontaneous domestic reports of "death only" should be included in the periodic report.

e. "Overdose" Reports

Reports of overdose should be submitted only when the overdose was associated with an adverse event. The adverse experiences associated with the overdose should be reported as are other serious reactions. If the event is unlabeled, a 15-day Form FDA 1639 should be completed; if the event is labeled, a Form FDA 1639 should be submitted in the periodic report for spontaneous domestic cases.

Overdose reports associated with a given labeled event should be combined with other serious reports of that particular event and should be analyzed periodically (at least quarterly for the first 3

years of marketing and annually thereafter) for an increase in frequency.

For an increase in frequency assessment, only analyze reports for that event from a single source type (e.g., compare spontaneous reports with spontaneous reports; compare study reports with reports from comparable studies; do not combine spontaneous reports with study reports; do not combine foreign reports with domestic reports). If an increase in frequency is detected, a 15-day increased frequency narrative report should be submitted. (Note that an increased frequency analysis is not required for all overdose reports, combining events.)

f. "Lack of Effect" Reports

"Failure to produce the expected pharmacologic action" is synonymous with "lack of effect."

All spontaneous domestic reports of "lack of effect" should be reported on Form FDA 1639 and submitted in the periodic report with other ADE's. The lot number of the suspect drug should be included in Item 14.

These reports should be analyzed (at least quarterly for the first 3 years of marketing; annually thereafter) for an increase in frequency. For drugs with multiple indications, "lack of effect" should also be analyzed separately for each indication. If an increase in frequency is detected, a narrative report should be submitted within 15 days of detection.

Spontaneous reports of "lack of effect" should be analyzed separately from study reports for an increase in frequency. Foreign "lack of effect" reports should be neither reported nor analyzed for an increase in frequency.

If the report of "lack of effect" is for an unapproved indication, the event is not reportable. However, this information may be included in the narrative summary section of the periodic report.

g. Pediatric Patients

For children under 5 years of age:

Item 1: Include the child's date of birth.

Item 2: Write age as days, weeks, or months, e.g., "15 weeks;" make certain that "days," "weeks," or "months" is clearly written.

15). For all pediatric patients, include body weight and dose (Item 15).

For reports of congenital anomaly:

Give age and sex of the infant.

Followup reports for the infant should be considered followup to the initial report.

Followup for the mother will be considered a new initial case report on a separate Form FDA 1639.

The birth date or date pregnancy is terminated should be the event onset date.

h. Reporting for Prescription Drugs Marketed Without an Approved NDA, ANDA, or Antibiotic Application (21 CFR 310.305)

For marketed prescription drugs without an approved NDA, ANDA, or antibiotic application, all serious, unlabeled ADE's must be reported on Form FDA 1639 within 15 working days; narrative increased frequency reports of serious, labeled events must also be submitted within 15 working days.

These reports should be submitted in SINGLE copy under separate cover with the outside envelope labeled, "15-Day Alert Report" and "310.305."

A copy of product labeling should accompany each report.

i. Another Applicant's Drug

Reports of ADE's in which the initial reporter identifies the suspect drug as one marketed by another applicant should be promptly forwarded to that applicant. Such reports should NOT be reported to the agency by the applicant to whom the ADE was originally reported.

An applicant who receives such a report about its drug from another applicant is required to submit the report to FDA with the time constraints applicable to any other report received from a third party.

An exception to this is when serious, unlabeled experiences are found for another applicant's drug during the conduct of an IND study of a marketed drug. In this instance, such reports may be submitted directly to FDA by the applicant conducting the study.

j. Multiple Suspect Drugs from the Same Applicant

If a reportable event involves two or more drugs from the same manufacturer, only one Form FDA 1639 should be completed. It should be submitted to the NDA, ANDA, or antibiotic application considered "most suspect" by the initial reporter. If they are ranked equally, the report should be submitted to the drug first in alphabetical order.

The adverse event is also reported in the narrative summary portion of the periodic report of the other drug(s).

k. Suspect Drugs with Multiple NDA's, ANDA's, or Antibiotic Applications by the Same Applicant

A drug product may be the subject of more than one approved NDA, ANDA, or antibiotic application. This section applies to this situation.

If an applicant receives a report for a drug and the specific application is identifiable, the report should be submitted to that application.

If a drug has more than one application, and it cannot be determined which of the approved applications is involved, the report should be submitted to the application that was approved first (usually the one with the lowest application number).

For drugs having more than one application due to different dosages, reports should be analyzed for an increase in frequency for each individual dosage as well as all dosages combined.

l. Unlabeled Indications

An adverse experience associated with the use of a drug for an unapproved indication should be reported as any other adverse event: 15-day report of a serious, unlabeled event on Form FDA 1639; 15-day narrative increased frequency report; or the periodic report.

"Lack of effect" for an unlabeled indication, however, should not be reported on a Form FDA 1639 nor used in increased frequency calculations; such information may be included in the narrative summary section of the periodic report.

m. Drug Interactions

If an applicant receives a report classified as a drug interaction, each of the drugs must be identified in Item 14 as a suspect drug.

n. Product Defects

If a product defect results in an adverse experience, the adverse event should be reported as described in this guideline.

o. Internal System for Monitoring, Identifying, and Reporting Adverse Events

Each applicant should develop standardized, formal procedures for the surveillance, receipt, evaluation, and reporting of ADE's to FDA. As a general rule, FDA will consider an applicant responsible for information known to its employees and agents. All applicants should develop procedures that allow expedited report handling, and the applicant should keep on file documentation of due diligence. This applies to both domestic and international surveillance for, and processing of, ADE's.

p. Labeling Ambiguities

In some cases, it may be difficult to decide whether or not the reported experience is labeled. In these situations, the event should be considered unlabeled.

APPENDIX A

GLOSSARY

AFFILIATE - Any corporate entity related to the applicant, including all subsidiaries, licensees, licensors, etc.

APPLICANT - Entity who holds the new drug application (NDA), abbreviated new drug application (ANDA), or antibiotic application, and is thus required to report adverse drug experiences. For purposes of this guideline, this term includes manufacturers, packers, and distributors of the drug product.

CAUSALITY ASSESSMENT - Determination of whether there is reasonable possibility that the drug is etiologically related to the adverse event. Causality assessment includes, for example, assessment of temporal relationships, dechallenge/rechallenge information, association with (or lack of association with) underlying disease, presence (or absence) of a more likely cause, plausibility, etc.

CHALLENGE - Administration of a suspect drug by any route.

DECHALLENGE - Withdrawal of a drug from the patient's therapeutic regimen.

NEGATIVE DECHALLENGE - Continued presence of an adverse experience after withdrawal of the drug.

POSITIVE DECHALLENGE - Partial or complete disappearance of an adverse event after withdrawal of the drug.

RECHALLENGE - Reintroduction of a drug suspected of having caused an adverse event following a positive dechallenge.

NEGATIVE RECHALLENGE - Failure of the drug, when reintroduced, to produce signs or symptoms similar to those observed when the drug was previously introduced.

POSITIVE RECHALLENGE - Reoccurrence of similar signs and symptoms upon reintroduction of the drug.

EXPERIENCE - Synonymous with adverse drug experience, adverse experience, adverse drug event, adverse event.

ADVERSE DRUG EXPERIENCE (ADE) - Any undesirable event that is associated with the use of a drug in humans, whether or not considered drug-related by the applicant. Reporting an adverse experience does not necessarily reflect a conclusion

APPENDIX A--CONTINUED

by the applicant or FDA that the event is causally related to the drug.

EXPECTED (LABELED) EXPERIENCE - Event is listed in the current FDA-approved labeling for the drug as a possible complication of drug use.

UNEXPECTED (UNLABELED) EXPERIENCE - Event is not listed in the current FDA-approved labeling for the drug. This includes an event that may differ from a labeled reaction because of greater severity or specificity (e.g., abnormal liver function versus hepatic necrosis). Events listed as occurring with a class of drugs but not specifically mentioned with a particular drug are considered unlabeled. (For example, rash with antibiotic X would be unlabeled even if the labeling said "rash may be associated with antibiotics." This is because the labeling does not specifically state "rash is associated with antibiotic X.") Reports of death from an adverse event are considered unlabeled unless the possibility of a fatal outcome from that adverse event is stated in the labeling.

INCREASED FREQUENCY - Increase in the rate of reporting for an adverse drug experience or related events during a specified time period (after adjustment for drug marketing data or number of patients exposed) when compared to the adjusted rate for similar reports during a previous period.

INITIAL REPORTER - The original source of the information submitted by the applicant on Form FDA 1639.

REPORT - A submission to FDA as described in this guideline.

ANNUAL REPORT - Contains information described in 21 CFR 314.81 and is NOT addressed in this guideline.

FIFTEEN-DAY REPORT - Fifteen-day reports must be submitted within 15 working days of the time (1) of initial receipt by the applicant of the serious, unlabeled status of the event or (2) of determining that an increase in frequency of a serious, labeled event has occurred.

PERIODIC REPORT - The four-part report described in the text of this guideline and in the regulations.

SERIOUS - An adverse drug experience that is associated with:

Death;

APPENDIX A--CONTINUED

Initial inpatient hospitalization;

Prolongation of hospitalization;

Permanent or severe disability - permanent or severe disruption in one's ability to carry out normal life functions;

A life-threatening situation - the initial reporter believed the patient was at immediate risk of death from the event as it occurred;

Congenital anomaly;

Cancer;

Overdose.

STUDY - Systematic collection of ADE's resulting from a protocol designed specifically to investigate drug(s) and adverse event(s).

SUSPECT DRUG - Drug associated with the ADE as determined by the initial reporter, regardless of the opinion of the applicant.

APPENDIX B

HOW TO COMPLETE FORM FDA 1639

In addition to the specific instructions on the back of Form FDA 1639, the following may be helpful:

Item 1--For children under 5 years of age, date of birth should be indicated in Item 1.

Item 2--For a child less than 5 years of age, the age can be stated in months, e.g., "18 months." However, make certain that the words "days," "weeks," or "months" are legibly written.

Items 4-6--For congenital anomalies, the date of birth or the date pregnancy is terminated should be used for the reaction date.

Item 7--The reaction should be described in detail using the reporter's own words. All relevant clinical information about the reaction should be summarized (signs, symptoms, diagnoses, clinical course, etc.). An additional sheet may be attached.

If serious, explain why.

Specify if reaction is life-threatening, cancer, overdose, congenital anomaly, or resulted in severe or permanent disability.

Use initial reporter's own words; FDA COSTART or other coding may also be added.

Items 8-12--The box for hospitalization should be checked only if the adverse event resulted in hospitalization or prolonged the hospitalization. For other hospitalized patients (i.e., those whose length of stay was not increased by the ADE), the hospitalization box should be left blank.

Item 13--Include available relevant baseline laboratory data (prior to drug administration) and all laboratory data used in diagnosing the reaction. This section should also include any available drug levels.

Item 14--Include the product the initial reporter suspected caused the adverse event (regardless of the applicant's opinion about causality).

The report should be filed to the first approved NDA if a product has several NDA's and the specific one cannot be determined.

APPENDIX B--CONTINUED

If the report lists two products by the same applicant as suspect, the report should be filed to the most suspect product as determined by the initial reporter. If they are equally ranked, the report should be filed to the drug that is first alphabetically.

Use trade name as marketed in the United States, if known. If unknown, use the generic name and manufacturer or distributor.

For foreign reports, use the foreign trade name, generic name as used in the United States, and include "similar to NDA ____."

Item 15--The daily dose should be clearly expressed. For pediatric patients, body weight should always be included.

For reports involving overdose, the amount of drug ingested as an overdose should be listed, not the usual dose.

Section IV. Only for Reports Submitted by Manufacturer

For manufacturer reports, each of the items in this section must be completed for the report to be in compliance with 21 CFR 310.305 and 21 CFR 314.80.

Item 24c--Use date applicant first became aware of the adverse event. For followup reports, use date followup information was received.

Item 24d--A report may be received from any of several sources, and each applicable source should be checked.

A report may be received from any of the following:

- (1) Health professional.
- (2) Postmarketing, clinical trial, or surveillance study.
- (3) Scientific literature and unpublished manuscripts.

A copy of the article or manuscript must be included. Foreign language articles should be translated.

A separate Form FDA 1639 must be completed for each identifiable patient.

- (4) Foreign sources include foreign governments, foreign affiliates of the application holder, foreign licensors and licensees, etc. The country of origin should be included.

APPENDIX B--CONTINUED

(5) Consumer (including attorneys).

Generally, additional information should be sought from the treating health care provider. A determined effort should be made to obtain additional detailed information from health professionals for all serious reactions initially reported by consumers. When this additional information is obtained, Item 24d should be checked "health professional" rather than "consumer."

Item 25--Fifteen-day reports should be clearly identified by checking the "yes" block. (For periodic reports, the "no" block should be checked.)

Item 25a--Initial and followup reports should be clearly identified by checking the appropriate block.

Item 26a--Reports that originate from the Centers for Disease Control (CDC) surveillance systems should be entered as "CDC" in Item 26a and "health professional" in Item 24d.

Attachments

Attachments may include:

Copies of hospital discharge summaries, autopsy/biopsy reports, or relevant office visit notes.

Summaries of relevant laboratory tests and other diagnostic procedures, particularly pre- and post-drug values.

In general, attachments should not include:

Lengthy legal records.

Complete medical records.

Each page of the attachment must have the applicant's unique internal control number for that case (Item 24b).

APPENDIX C

SAMPLE

FIFTEEN-DAY NARRATIVE INCREASED FREQUENCY REPORT
OF SERIOUS, LABELED EVENTS

PRODUCT: (Brand name and nonproprietary name)
MANUFACTURER AND NDA: (Name and number)
ADVERSE EVENT(S): (Describe event; list COSTART term)
**DATE INCREASED
FREQUENCY RECOGNIZED:** (Date)
SUBMISSION DATE: (For this report)
REPORT INTERVAL: (Dates of marketing period during which
increased frequency is detected. Note
that these intervals are determined
differently for drugs during the first 3
years of marketing and for older drugs.)

For drugs marketed 3 years or less,
During the first 3 years of
marketing, the usual report
interval is a quarter (3 months).

Drugs marketed longer than 3 years,
the usual report interval is a
year.

COMPARISON INTERVAL: (Dates of marketing period used for
comparison. Note that these intervals
are determined differently for drugs
during the first 3 years of marketing
and for older drugs.)

For drugs marketed 3 years or less,
dates for interval from initial
marketing to end of quarter before
"report interval."

Drugs marketed longer than 3 years,
dates for year preceding "report
interval."

APPENDIX C--CONTINUED

**ADVERSE EVENTS
REPORTED**

(Numbers of events by type of event or COSTART term. For events in "report interval," attach copies of Form FDA 1639 clearly labeled DUPLICATE FOR INCREASED FREQUENCY REPORT. For events in comparison interval, attach list of manufacturer control numbers.)

**DRUG USE
ESTIMATES**

(Estimated prescriptions, sales, volume, or other appropriate measure.)

EVENT RATES:

(Number of events during report interval divided by drug use for report interval; number of events during comparison interval divided by drug use for comparison interval.)

**INTERPRETATION
OF DATA**

This section should present the applicant's interpretation of the increased frequency, including possible explanations for the increased frequency. The applicant should make a judgment about the meaning of the signal. This should include an assessment of the plausibility of the increased frequency, changes in reporting rates, changes in the patient population receiving the drug (age, sex, race, concomitant drugs, other relevant medical history), etc.

Inclusion of cases in "report" and "comparison" intervals is based upon the dates reports were received by the applicant.

Dates for drug use may not correspond exactly to dates for "report" and "comparison" intervals because of limitations of available data.

APPENDIX C--CONTINUED

DETERMINATION OF REPORT INTERVAL FOR NARRATIVE INCREASED FREQUENCY REPORTS

The report interval is determined differently for drugs marketed 3 years or less than for older drugs. Determination of these report intervals follows:

Drugs Marketed 3 years or Less

For drugs marketed 3 years or less, "increased frequency" can be determined by comparing the number of reports for the most recent quarter of marketing (the "report interval") to the number of reports for the interval from initial marketing until the close of the quarter preceding the most recent one. The numbers of reports for the "report interval" and the "comparison interval" are first adjusted for drug use by dividing the number of reports in each interval by the estimated drug use for that interval.

For Drugs Marketed Longer Than 3 Years

For drugs marketed longer than 3 years, "increased frequency" can be determined by comparing the number of reports for the most recent year of marketing ("report interval") to the number of reports for the preceding year ("comparison interval"). The numbers of reports for the "report interval" and the "comparison interval" are first adjusted for drug use by dividing the number of reports in each interval by the estimated drug use for that interval.

Reporting of Increased Frequency

An "increased frequency" exists if the adjusted reporting for the "report interval" is at least two times greater than the adjusted reporting for the "comparison interval." An exception is that no increased frequency report is required if the number of reports received during the "report interval" is less than four.

IDENTIFYING AND REPORTING AN INCREASED FREQUENCY

An increased frequency can be determined using a formula (coupled with a table). Using the formula below, an increased frequency exists if the number of reports of adverse drug experiences that are both serious and expected for the "report interval" is greater than or equal to the critical number of reports C which is determined from the numbers of reports for the two report intervals and the estimated drug use for the two intervals using the following formula:

$$C = (R * X_c) + (1.645 * \sqrt{(X_c + X_r) * R})$$

Where X_c is the number of reports for the "comparison interval"
 X_r is the number of reports for the "report interval"
 R is the marketing ratio of the "report interval" to the "comparison interval"
 * multiplication sign

The marketing ratio is defined as

Estimated drug use (e.g., number of prescriptions, unit volumes, sales, etc.) for the "report interval"

R =

Estimated drug use (same units and scope as in the numerator) for the "comparison interval"

Note, additionally, that there must be at least four reports in the "report interval" for the increased frequency to be submittable.

A reference table (Table C.1) for the reporting of no more than 10 ADE's for the "comparison interval" is attached for routine decisionmaking.

To use the table, one should first calculate the marketing ratio. Second, one should determine the number of reports for the "comparison interval." One can then readily identify the number of reports for the "report interval" that are necessary to identify an increased frequency. The minimum number of reports necessary for an increased frequency is thus the intersection of the marketing ratio and comparison interval (the x and y axes of the table).

Table C.1. Increased Frequency Identification

Minimum Numbers of Reports for the "Report Interval"
 which Constitute Increased Frequency for Given Numbers of Reports
 for "Comparison Interval" Adjusting for Marketing Ratios

Row #	Marketing Ratio*	Number of Reports for the "Comparison Interval"										
		0	1	2	3	4	5	6	7	8	9	10
1	0.25	1	2	3	3**	4	4	5	5	5	6	6
2	0.50	2	3	4	5	6	7	8	9	9	11	12
3	0.75	3	4	6	7	8	10	11	12	13	14	15
4	1.00	3	6	7	9	11	12	14	15	17	18	19
5	1.25	4	7	9	11	13	15	17	18	20	21	24
6	1.50	5	8	10	13	15	17	20	22	24	26	28
7	1.75	5	9	12	15	17	20	23	25	27	30	32
8	2.00	6	10	14	17	20	23	25	28	31	34	36
9	2.25	7	11	12	19	22	25	28	31	34	37	40
10	2.50	7	12	17	20	24	28	31	35	38	41	45
11	2.75	8	13	18	22	26	30	34	38	42	45	49
12	3.00	9	15	20	24	29	33	37	41	45	49	53
13	3.50	10	17	23	28	33	38	43	48	52	57	61
14	4.00	11	19	26	32	38	46	49	54	59	65	70
15	4.50	13	21	29	36	42	48	55	61	67	72	78
16	5.00	14	24	32	39	47	54	60	67	74	80	87
17	5.50	15	26	35	43	51	59	66	74	81	88	95
18	6.00	17	27	38	47	55	64	72	80	88	96	103
19	6.50	18	30	41	51	60	69	78	86	95	103	112
20	7.00	19	32	44	54	64	74	84	93	102	111	120

* Estimated drug use (e.g., prescriptions, volumes, sales) for the "report interval"
Estimated drug use (same units and scope) for the "comparison interval"

** No reporting is required when the number of reports in the "Report Interval" is less than 4.

APPENDIX ~~B~~

SAMPLE OF TRANSMITTAL LETTER FOR PERIODIC REPORT

DATE

Food and Drug Administration
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20852

Dear Sir or Madam:

Pursuant to 21 CFR 314.80, enclosed is the periodic ADE report for (drug product name).

NDA 99999 (NDA or ANDA number)

The time period covered by this report is June 1, 1990, to August 31, 1990.

There are 197 initial Form FDA 1639's and 5 followup Form FDA 1639's in this report.

Sincerely,

Jane P. Doe, Director
Drug Product Regulatory Affairs
Pharmaceuticals, Inc.
Happiness, New York

APPENDIX E

REPORT CHECKLIST

Before mailing your reports to FDA, the following should be reviewed:

A. For All Form FDA-1639 Reports

1. Have you completed a separate Form FDA 1639 for each patient?
2. Have you included your firm's internal recordkeeping number in Item 24b?
3. Have you clearly marked the report "Periodic" or "15-Day" as appropriate in Item 25?
4. Have you clearly marked the report "Initial" or "Followup" as appropriate in Item 25a? Do not package and send a 15-day followup report with a periodic followup report.
5. Have you included the name, address, and telephone number of the initial reporter in Items 26-26b?
6. Have you eliminated unnecessary attachments? All information should be submitted on Form FDA-1639. Attachments should be included, only when relevant, for 15-day reports.
7. If two or more products produced by your firm were suspected by the initial reporter:
 - (a) Have you completed only one Form FDA-1639? (Do not prepare more than one Form FDA-1639 even if more than one of the suspect products was produced by your company.)
 - (b) Have you identified all the suspect products in Item 14?
 - (c) Have you indicated on Form FDA-1639 the drug considered most suspect by the initial reporter and directed the report accordingly? (If the initial reporter ranked them equally, submit Form FDA-1639 to the file of the first

APPENDIX E--CONTINUED

suspect product in alphabetical order. List the reaction in the narrative summary of the periodic report of the other suspected product(s).)

8. Have you completed a Form FDA-1639 for another applicant's drug? (If you did, send it to the applicant holder of the suspect drug and not to FDA.)

B. For 15-Day Reports

1. Have you clearly marked Form FDA-1639 "15-Day Report" in Item 25?
2. Have you packaged the 15-day report (Form FDA-1639 or narrative, initial, or followup) separately? (Do not package and send a 15-day report with a periodic report. Do not submit copies of 15-day reports with a periodic report.)
3. Have you submitted the report in duplicate? (An exception: for drugs without approved NDA's, ANDA's, or antibiotic applications, only a single copy should be sent.)
4. Have you clearly marked the outside mailing envelope "15-Day Alert Report?"

C. For Periodic Reports

1. Have you included the four types of information required in the periodic report (including a copy of the current product labeling) and have you clearly separated the four sections by marked tabs?
2. Have you completed and attached a transmittal letter to each duplicate copy of the periodic report?
3. Have you submitted the report in duplicate?
4. Have you eliminated all unnecessary attachments to Form FDA 1639's submitted with the periodic report?

D. For Followup Reports

1. Have you included your firm's internal recordkeeping number in Item 24b? (Note: this number must be identical to the manufacturer control number on the initial report.
2. Have you marked Form FDA-1639 "Followup" in Item 25a?
3. For drugs with an approved application, have you submitted the report in duplicate?

Federal Register

**Thursday
June 3, 1993**

Part II

**Department of
Health and Human
Services**

Food and Drug Administration

**Form for Reporting Serious Adverse
Events and Product Problems With
Human Drug and Biological Products and
Devices; Availability; Notice**

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 93N-0072]

Form for Reporting Serious Adverse Events and Product Problems With Human Drug and Biological Products and Devices; Availability

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing the availability of a new form for reporting adverse events and product problems with human drug products, biologic products, medical devices (including in-vitro diagnostics), special nutritional products (dietary supplements, medical foods, infant formulas), and other products regulated by FDA. There are two versions of the form. One version of the form (FDA Form 3500) is available for use by health professionals for voluntary reporting; the other version of the form (FDA Form 3500A) is to be used by user facilities, distributors, and manufacturers for reporting that is required by statute or FDA regulations. The new form will simplify and consolidate the reporting of adverse events and product problems and will enhance agency-wide consistency in the collection of postmarketing data. This notice also responds to written comments the agency received on proposed versions of this form. Copies of both versions of the new form appear at the end of this document.

DATES: Version FDA 3500 (for voluntary reporting) is effective immediately; version FDA 3500A (for mandatory reporting) will become effective on November 30, 1993. Manufacturers, medical device distributors, and user facilities are encouraged to begin using FDA 3500A now.

ADDRESSES: Copies of version 3500 (for voluntary reporting) and/or instructions for completing the form may be obtained by calling 1-800-FDA-1088 or writing MEDWATCH, 5600 Fishers Lane, Rockville, MD 20857-9787. Ten copies or less of version 3500A (for mandatory reporting) and/or a copy of the instructions for completing the form may be obtained from either: Division of Epidemiology and Surveillance (HFD-730), Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857; Adverse Experience Branch (HFM-220), Center for Biologics Evaluation and Research,

Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852-1448; or Division of Small Manufacturers Assistance (HFZ-220), Center for Devices and Radiological Health, 5600 Fishers Lane, Rockville, MD 20857. Bulk copies of both version 3500 and version 3500A may be obtained by writing to the Consolidated Forms and Publications Distribution Center, Washington Commerce Center, 3222 Hubbard Rd., Landover, MD 20785. The guideline for postmarketing reporting of adverse drug experiences is available from the CDER Executive Secretariat Staff (HFD-8), Center for Drug Evaluation and Research, 7500 Standish Pl., Rockville, MD 20855.

FOR FURTHER INFORMATION CONTACT: Dianne L. Kennedy, Office of the Commissioner (HF-2), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-443-0117.

SUPPLEMENTARY INFORMATION:

I. Background

In the Federal Register of February 26, 1993 (58 FR 11768), FDA announced the availability of two proposed versions of a form for reporting adverse events and product problems with human drug products, medical devices, and other FDA-regulated products excluding vaccines. The draft form requested information concerning the patient, the adverse event or product problem, the suspect human drug product or medical device, and other information concerning the manufacturer, user facility, or distributor. FDA developed the new form to simplify and consolidate the mandatory reporting of adverse events and product problems for human drugs, biologics (excluding vaccines), and medical devices, as well as to facilitate the voluntary reporting of adverse events for these and other FDA-regulated products. FDA found that there was confusion about what to report to the agency, and the existing patchwork of reporting forms and systems sometimes made it difficult to report problems quickly and easily.

The new form is part of MEDWATCH—FDA's new Medical Products Reporting Program, which is intended to facilitate the reporting of adverse events and product problems for all FDA-regulated products by the entire health care community (manufacturers, distributors, user facilities, and health professionals). The main focus of the MEDWATCH program is to inform and encourage health professionals (physicians, physician assistants, pharmacists, nurses, and others) about reporting serious adverse

events and product problems. Currently, FDA relies, for the most part, on manufacturers, distributors, and user facilities (hospitals, ambulatory surgical facilities, nursing homes, or outpatient treatment facilities) for reports of adverse events and product problems. These parties usually obtain such information from health professionals. Adverse event reporting by health professionals is an efficient means for monitoring the safety of marketed drug products and medical devices.

Health professionals should use FDA version 3500 to report adverse events or product problems to manufacturers or to FDA. FDA encourages health professionals to use version 3500 if they suspect that a drug or biological product, medical device, or other FDA-regulated product may have been associated with a serious outcome, such as death, a life-threatening condition, initial or prolonged hospitalization, disability, congenital anomaly, or may have resulted in a condition that required surgical or medical intervention to prevent permanent impairment or damage. FDA also encourages health professionals to report product quality problems such as defective devices, inaccurate or unreadable product labeling, packaging or product mix-up, contamination or stability problems, and particulate matter in injectable products.

Manufacturers, distributors, and user facilities should use FDA version 3500A to report adverse events and product problems to FDA as required in the applicable statutes and regulations.

The new form is intended to replace the following adverse event and product problem reporting forms:

FDA Form 1639 (all versions):

Adverse Drug and Biologic Experience Reporting;

FDA Form 3318: Drug Quality Reporting System;

FDA Form 2519f: Medical Device and Laboratory Product Problem Reporting Program;

FDA test Form 3375: Medical Device Reporting;

FDA Form 3322: Medical Device Report.

FDA is preparing a proposal to amend the adverse drug experience reporting regulations to revise the definition of "serious" and to require, among other things, that version 3500A be used instead of Form 1639. In addition, FDA is also preparing a final rule for adverse experience reporting for licensed biological products, and a final rule on medical device user facility, distributor, and manufacturer reporting, certification, and registration. These rules will provide consistency with the

provisions of the new form. Biologics manufacturers and medical device manufacturers, distributors, and user facilities will be required to use Form 3500A when the agency has finalized the respective adverse event reporting regulations for these entities. Drug manufacturers will be required to use Form 3500A by November 30, 1993. All manufacturers, medical device distributors, and user facilities, however, are encouraged to begin using Form 3500A now.

Adverse events associated with vaccines should continue to be reported on a Vaccine Adverse Event Reporting System (VAERS) form and not on the new form.

As stated in the February 26, 1993, notice, FDA is committed to working with health professionals and user facilities, distributors, and manufacturers to identify rapidly serious adverse events and product problems. For the past year, FDA has consulted with industry and health professional organizations representing physicians, dentists, nurses, and pharmacists regarding the development of the new form and an education program. On May 4, 1993, FDA held a premeeting with organizations representing health care professionals to discuss ways in which these organizations can work with FDA to inform their members about FDA's MEDWATCH program. FDA is also planning to conduct a conference with organizations representing health professionals and industry to announce and explain the MEDWATCH program. In June 1993, FDA intends to publish articles about the MEDWATCH program in the *Journal of the American Medical Association* and the *American Journal of Hospital Pharmacy*. In addition, the agency is planning conferences, exhibits, speeches, and articles to inform health professionals about MEDWATCH. The agency is also making available to health professionals the "FDA Desk Guide For Adverse Event and Product Problem Reporting." Health professionals may obtain a copy by calling 1-800-FDA-1088.

II. Provisions of the Final Form and Other Reporting Information

Both versions of the form contain identical reporting provisions for the following sections:

A. Patient Information: Patient identifier, age or date of birth, sex, and weight.

B. Adverse Event or Product Problem: Outcome attributed to event (e.g., death, disability, etc.), date of event, date of report, description of event or problem,

relevant tests or laboratory data and other relevant history.

C. Suspect Medication(s) (all products except medical devices): Name, dose, frequency and route used, therapy dates, diagnosis for use, lot number, expiration date, national drug code (NDC) number, and other information.

D. Suspect Medical Device: Brand name, type of device, manufacturer name and address, operator of device, expiration date, product identification number, date implanted and explanted, and other information.

E. Reporter: For version 3500, the reporter is the person who makes the report; for version 3500A, the reporter is the person who made the initial report of the adverse event or product problem to the user facility; distributor, or manufacturer.

Both versions of the form also request certain information that is specific to health professionals, user facilities, distributors, and manufacturers. For example, version 3500 includes "Advice About Voluntary Reporting," and describes "serious adverse events" and "product problems." FDA encourages health professionals to report even if they are not certain the product caused the event or if they lack all the details. The "Advice" also instructs health professionals to use additional blank pages if needed, and to use a separate form for each patient. It also advises health professionals to notify the responsible person in the facility where a medical device adverse event occurred, and provides telephone numbers by which reports may be submitted to FDA by FAX or modem, and telephone numbers to request additional information, to report product quality problems, or to request a VAERS form to report adverse events associated with vaccines.

In version 3500A, section F asks medical device user facilities and distributors to provide information about themselves and the report. Section G in version 3500A requests information from all manufacturers concerning adverse event or product problem reports. Section H in version 3500A requests information from device manufacturers concerning adverse events or product problem reports. Sections F, G, and H appear on the reverse side of version 3500A. If a human drug or biologic product manufacturer is reporting an adverse event in which no suspect medical device is involved, the manufacturers section (section G) on the reverse side of version 3500A may be completed and reproduced in place of the suspect medical device section (section D) on the front side of the form. This makes

it possible for human drug product and biologics manufacturers to submit all necessary information on one side of the form. Version 3500A does not have to be submitted as a one page front-and-back form. If desired, the user facility, distributor, or manufacturer may submit their reports on two pages.

The specific provisions of these sections are explained in more detail in section III. of this document.

III. Comments on the Proposed Form

The February 26, 1993, notice requested comments on the proposed form. FDA received 79 comments from representatives of the pharmaceutical, biotechnology, and medical device industries, as well as from hospitals, academic institutions, and health profession associations. Although the comments generally supported the use of a consolidated reporting form, many comments offered useful suggestions on revising the proposed form.

A. General Comments

1. Confidentiality

Many comments were concerned with the issue of patient/reporter confidentiality and the confidentiality statement on the proposed version 3500. That statement read as follows:

Confidentiality: The identity of the patient is held in strictest confidence by the FDA. The identity of the reporter will be shared with the manufacturer unless you request otherwise. However, the FDA will not disclose the reporter's identity in response to a request from the public.

Some comments questioned whether FDA and/or manufacturers are permitted by statute or regulation to protect the confidentiality of patients and/or reporters. Other comments questioned whether FDA and/or manufacturers would actually take steps to ensure confidentiality if so permitted. Several comments asked about State regulation of confidentiality and Federal preemption.

The Department of Health and Human Services (HHS) has a longstanding policy of providing strict protection to the confidentiality of patient information. This policy is based on a recognition of the extreme sensitivity of this information and the personal harm that can result from the disclosure of such information found in HHS' records.

FDA, a component of HHS, has long shared the same belief in the importance of personal privacy and has implemented this confidentiality policy in its public information regulations (see part 20 (21 CFR part 20)). Under the authority of Exemption 6 of the

Freedom of Information Act (FOIA), these regulations have for many years protected patient names and other identifying information from disclosure in response to requests filed under the FOIA.

The agency also recognizes the importance of protecting the identity of individuals who voluntarily report information to the agency, specifically including those who report adverse reactions or product experiences. Thus, the regulations also protect from public disclosure the identity of the individual voluntarily reporting, whether that individual is the patient or a health professional, as well as the identity of the hospital or other institution associated with the report (see § 20.111).

The agency has maintained its protection of the identity of voluntary reporters because of its belief that confidentiality is a key to encouraging health professionals to report serious adverse experiences. Such reporting is essential to the agency's postmarketing surveillance program, which is designed to help ensure the continued safety of marketed health products in the United States.

FDA has been informed of a number of lawsuits pending in State courts in which manufacturers have been requested and, in some cases, ordered to provide the names of those reporting adverse reactions to particular products and, rarely, the names of the patients involved. Because of the agency's concern about these confidentiality issues, the agency, through the Department of Justice, has filed a statement of interest in a number of these cases. The statement informed the courts of the potential damage the agency believes would be done to its postmarketing surveillance program if the identities of patients and reporters are released to plaintiffs in these cases. The agency believes that the confidentiality of this information has been maintained in all of the cases in which it has participated. Because such cases are of continuing concern, FDA is currently exploring ways in which it might further strengthen its regulations to protect patient and reporter confidentiality.

In order to emphasize some of these precautions, the confidentiality statement on version 3500A has been revised to read as follows:

Confidentiality: The patient's identity is held in strict confidence by FDA and protected to the fullest extent of the law. The reporter's identity may be shared with the manufacturer unless requested otherwise. However, FDA will not disclose the reporter's identity in response to a request

from the public, pursuant to the Freedom of Information Act.

2. Consistency With Other Forms

Several comments asked how and whether the agency's efforts to issue a consolidated form were consistent with recent initiatives on clinical safety data management by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and the international reporting of drug safety by the Council for International Organizations of Medical Sciences (CIOMS).

The agency believes the form is consistent with adverse reaction reports created or proposed by international organizations. For example, ICH is working on a draft guideline that would consider a serious adverse event, experience, or reaction to be an incident that results in death, requires inpatient hospitalization or prolongs existing hospitalization, results in persistent or significant disability/incapacity, or is life-threatening. The companies may continue to use the CIOMS form for reporting foreign events with prior approval.

3. Development of Guidelines

Several comments requested additional information about the following statement made in the February 26, 1993, notice: "Specific user facility, distributor, and manufacturer reporting guidelines will be developed to provide guidance in the use of the new form." The comments asked whether the guidelines being developed are specific to the new form and when will they be made available. In addition, the comments asked about the availability of guidelines for the existing adverse event and product problem reporting regulations for human drugs, biologics, and medical devices.

To explain more thoroughly the voluntary reporting program for health professionals, FDA has prepared the "FDA Desk Guide for Adverse Event and Product Problem Reporting" which includes the instructions for completing the voluntary Form 3500. FDA also has prepared instructions for completing the mandatory reporting Form 3500A. Both versions of the form and their respective instructions are available now and may be obtained from the Center for Drug Evaluation and Research (CDER), the Center for Biologics Evaluation and Research (CBER), and the Center for Devices and Radiological Health (CDRH) (addresses identified above). Copies of both sets of instructions are also

available on the FDA electronic bulletin board system at 1-800-222-0185.

To explain more thoroughly the mandatory reporting requirements for manufacturers, distributors, and user facilities, CBER and CDRH are preparing specific reporting guidelines to accompany each Center's adverse event reporting regulations. When these regulations become final and the guidelines are completed, FDA will announce their availability in a future issue of the **Federal Register**.

Concerning adverse event reporting for human drug products, FDA has made available the "Guideline for Postmarketing Reporting of Adverse Drug Experiences." These guidelines will be updated to be consistent with the changes made in the regulations for the reporting of adverse drug experiences and the new Form 3500A.

4. Space on the Form

Several comments asked what should be done if more space is needed to complete the sections of the form.

FDA advises reporters to use additional blank sheets of paper, referenced to the section of the form being described, to complete any narrative sections of the form. Reporters should use additional copies of the form to complete all other sections. FDA reminds reporters to number all extra pages and the form with "page ___ of ___."

Several comments stated that the space permitted for the requested information on the form as reproduced in the February 26, 1993, **Federal Register** was insufficient.

FDA advises that the actual size of the form is 8 1/2" by 11" and that its size had been reduced to accommodate publication in the **Federal Register**. Copies of two versions of the form in their actual size may be obtained by request as stated at the beginning of this notice.

5. Recommendations for Additional Information on the Form

One comment recommended that reporters should be able to indicate "ethnicity" on the form.

The agency notes that section B.7 on both versions requests "Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)." A reporter may indicate ethnic origin in this section.

One comment asked where on version 3500 reporters should indicate whether the report is an initial report or an update.

For the initial reporter, the information should be included in section B.5 of version 3500. For user facilities, distributors, and manufacturers, this information should be included in section G.7 of version 3500A.

Several comments suggested that the disclaimer at the bottom of the front side of proposed version 3500 page should be broadened to say: "Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event." One comment suggested that the language for the disclaimer should be the same as the language in § 803.24(f) (21 CFR 803.24(f)), which provides more specifically that medical device reports do not in themselves constitute admissions of causality or liability.

FDA has amended the form to add the language "or contributed" to the disclaimer. The agency has not, however, adopted the language of § 803.24(f) for the form because that degree of specificity would be inappropriate for purposes of this form.

6. Reports from Consumers and to Manufacturers

Several comments asked whether there will be a form that consumers can use to report adverse events and product problems to FDA, or whether consumers should use the form for health professionals.

Although FDA expects that most reports will come from health professionals, consumers are encouraged to work with their health professionals to submit version 3500.

One comment stated that the submission of version 3500 to FDA would impede the ability of manufacturers to take corrective action concerning adverse events or product problems.

FDA disagrees with the comment. The agency intends to inform expeditiously manufacturers of any product problem reports it receives as well as reports of serious adverse experiences. The agency will expedite the transmission of these reports to enable manufacturers to conduct rapid and effective followup. In addition, the agency notes that health professionals may report to FDA or the manufacturer.

7. Use of the Form on a Test Basis

One comment recommended that the form should be used on a test-basis first before it is finalized.

The agency advises that in developing the draft form, it consulted health professional organizations representing physicians, dentists, nurses,

pharmacists, and industry regarding the design and content of the form. FDA modified the draft form in response to many of the suggestions made by these groups. In addition, FDA has made a number of revisions to the final form based on comments made by health professionals and industry representatives who will be using this form. Finally, during the initial period of its use, FDA will continue to closely monitor comments and suggestions it receives from interested parties on the form, and will consider making further modifications to clarify and simplify the form as the need arises.

B. Section A (Versions 3500 and 3500A)—Patient Information

Section A.1 of the proposed form requested "patient initials" and stated that the initials would be "in confidence." FDA received numerous comments expressing concern about asking for the patient's initials, claiming that providing a patient's initials would compromise patient confidentiality. Some comments also noted that other identifiers, such as an identifying number in a clinical trial, might be more available and more useful. One comment suggested adding or substituting the pharmacy prescription number of the suspect medication as the identifier.

FDA has modified section A.1 to request a "patient identifier." The form does not specify the type of identifier that may be used. The reporter may use any number or other identifier that will allow the reporter to identify the patient if contacted for followup. This change will allow different reporters to use the identifier they believe is most appropriate, and will provide additional protection to the patient involved.

Section A.2 in the proposed form requested the patient's "age at time of event." Several comments suggested that FDA include the date of birth in addition to, or instead of, the age of the patient. One comment asked how to record the age at the time of event when multiple experiences are being reported, and one noted that there was no reference to age in hours when an adverse event affecting a neonate is being reported.

FDA has revised the form to enable the reporter to supply the patient's date of birth or age at the time of the event. As for recording the age at the time of the event when multiple experiences are being reported, the age reported should be the age at event onset. The form does not specify years or months, so hours can be used if a neonate is involved.

Section A.3 in the proposed form requested information on the patient's

gender. One comment observed that there was no place to designate that the gender is not known.

FDA believes that health professionals will generally know the patient's gender, and FDA encourages whoever has the first direct contact with the patient or knowledge of the event to provide as much information as possible. As with all the fields in the report, if information is not known, the field can be marked as unknown.

Section A.4 in the proposed form requested the patient's weight in pounds or kilograms. Several comments said that weight data are difficult to obtain and are meaningless unless height data are also provided. One comment noted that there was no place for pediatric body weight.

FDA has decided to retain the space on the form for weight for those instances in which it can be provided. Some dosages are prescribed in terms of a patient's weight without regard to height, and so there may be instances where the weight is useful by itself. FDA can determine from the age of the patient whether the weight is pediatric weight.

C. Section B (Versions 3500 & 3500A)—Adverse Event or Product Problem

Section B in the proposed form was titled, "Adverse event or product problem." One comment suggested changing the title to "product related event" rather than "product related problem." The comment asserted that health professionals might be less likely to report an adverse event if the language suggests that the product has already been determined to be the cause of the problem.

The agency disagrees with this comment. The term "product problem" might be better understood by more people than the term "event" and may therefore lead to more comprehensive reporting of possible problems.

Another comment suggested that the term "product problem" be reserved for devices only.

Although the term "adverse drug experience" is associated with the regulations pertaining to adverse drug experience reporting, the more general "product problem" may be applicable to other FDA-regulated products, including drugs and biological products, as well as devices. A general term that is applicable to all classes and types of products is more appropriate for a single form that is used for the reporting of problems associated with each of the types of products. FDA has retained the headings and terminology referring to adverse events and product problems. The agency does not believe that the

language is misleading. The outcomes attributed to the adverse event will be described and the description of the event or problem will clarify whether the product being reported is a drug or a device. This will facilitate the agency's direction of the form to the proper program for attention.

Section B.1 of the proposed form asked whether the report pertained to an "adverse event and/or product problem (defect or malfunction)." Several comments supported drawing a distinction between defect and malfunction of medical devices. The proposed form did not define these terms, but listed them separately, i.e., "defects or malfunctions." However, some comments suggested deleting the terms "defect" and "defective," stating that such terms could have an impact on product liability action.

The final form has replaced "defect or malfunction" with "defect/malfunction." Defects may be related to product design or manufacture whereas malfunctions may be related to a device not operating as intended. For purposes of reporting, however, the agency does not believe these distinctions need to be set out on the form itself, because the agency is not asking the reporter to make such distinctions on the form. Although the underlying information may be relevant to product liability issues, submitting the form itself, as is clearly stated on the form, does not constitute an admission that the product caused the adverse event. FDA needs information on defects and malfunctions to protect the public health.

Section B.2 in the proposed form pertained to "Reasons for reporting adverse event" and listed seven reasons: "death," "life-threatening," "hospitalization—initial or prolonged due to event," "disability," "congenital anomaly," "required intervention to prevent permanent damage," and "other;" for reporting an adverse event. The proposed form directed the person completing the form to "check all that apply." FDA received many comments stating that some listed reasons for reporting apply only to certain classes of products and the categories are, therefore, too broad, and suggested that these specific limitations to classes of products be described in the section of the form listing outcomes.

FDA acknowledges that not all reasons listed are applicable to all classes of products and reporters. Some relate primarily to drugs (e.g., congenital anomalies, as included in §§ 310.305, 312.32, and 314.80 (21 CFR 310.305, 312.32, and 314.80)), and some relate primarily to medical devices (e.g.,

required intervention to prevent permanent impairment/damage, as derived from § 803.3 (21 CFR 803.3)). This section is for the general reporting and description of the event. FDA does not want to limit the choices of reasons for reporting in this general section, but would rather leave the reporter all the options that might be applicable. Further specificity may be provided in later sections of the form.

In addition, the purpose of the new form is to consolidate the reporting of adverse events and product problems for all FDA-regulated products in order to enhance agency-wide consistency in the collection of postmarketing data.

Several comments asked FDA to define "disability."

As noted above, FDA is asking that only serious adverse events be reported. An event is serious if it results in a disability that is significant, persistent, or permanent, as described on the reverse side of version 3500.

Several comments asked FDA to explain the phrase "required intervention to prevent permanent damage." Other comments said that this pertains only to devices and should be so described.

FDA has replaced "required intervention to prevent permanent damage" with "required intervention to prevent permanent impairment/damage" to be consistent with statutory and regulatory language. The agency is proposing to add this element to the regulatory definition of "serious" as that term is applied to adverse experiences with drugs and biologics. This proposed change makes the definition of "serious" consistent for drugs, biologics, and devices and also reflects the definition of "serious" proposed by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). The agency believes it is desirable, where possible, to have a consistent definition of what constitutes a serious adverse event for all regulated products. FDA hopes that such consistency will eliminate confusion about what events should be reported. Further guidance will be provided in adverse event regulations in the near future.

One comment asked whether treatment with a drug is an intervention.

The agency advises that drug treatment necessary to preclude permanent impairment of a body function or permanent damage to a body structure would constitute intervention.

Another comment sought clarification of the term "permanent damage."

"Permanent damage" means damage that is not reversible.

FDA received one comment concerning the "other" listed reason for reporting an adverse event. One comment suggested that FDA could increase the number of reports received by broadening the "other" category to include such reasons as loss of work, physician visit required, pharmacist intervention required, product not working properly, product defect, and unexpected effect.

The reporter may indicate the "other" category for any serious event that does not fit into the other categories provided. The reporter may explain the reason in the space provided immediately after the word "other" and in the narrative in section B.5.

FDA received several comments questioning the purpose of and support for reporting congenital anomalies. One comment suggested that it might involve drawing conclusions that could be legally damaging to a provider and beyond the capacity of the risk manager in a particular hospital.

FDA has retained the category of congenital anomalies because these events are relevant to the evaluation of the safety and efficacy of products. Experience has shown that these abnormalities can occur through the use of certain drug products. For example, the drug thalidomide, used in Europe as a sedative in the 1960's, caused serious congenital anomalies in the fetus, including dysmelia, or malformation of the limbs, when taken early in pregnancy.

The form is intended to help FDA identify possible serious adverse events and product problems in order to protect the public health. Version 3500A bears specific disclaimers stating that submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer, or product caused or contributed to the event. Version 3500 bears a similar disclaimer that submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

One comment suggested that FDA delete "Reasons for reporting adverse event," but retain "check all that apply" because the outcomes listed are pertinent outcomes but may not be the reason the event is being reported.

To address this concern, FDA has modified the title of this field to "Outcomes attributed to adverse event." This will clarify the agency's intent that pertinent outcomes thought to be attributable to the adverse event are the ones that reporters should identify.

On a related issue, one comment stated that if the date of death were

being included with the reasons for reporting adverse events, it would be important to leave space to clarify whether the reported adverse event was the cause of death. Another comment said that the form should indicate whether "death" should be checked if it is not related to the adverse event.

The revised form does include a space for the date of death. Since the reporter is told that section B.2 is for "Outcomes attributed to adverse event," if the patient died while using the product, but the reporter does not think the death was related to the event, the reporter should not check the box for "death" on the form.

Sections B.3 and B.4 of the proposed form pertained to the "date of event" and "date of this report," respectively. FDA received several comments suggesting that these dates are ambiguous or unnecessary.

One comment asked how the date of the report in section B.4 differs from the date the manufacturer receives the report, which is requested in section G.

FDA has not changed these sections of the form. FDA believes that both of the dates are necessary because they provide important information for both identification and regulatory purposes.

To provide clarification for the terms "date of event" and "date of this report," the "date of event" is the date of first onset of the adverse event. The "date of this report" is the date that the report is filled out by the individual submitting the report. The date the report is filled out may or may not differ from the date that the manufacturer receives the report. The date of the report in section B is not redundant with the date the manufacturer receives the report because these two dates also may differ.

One comment said that section B should include an entry for the date of completion of an investigation of an adverse event so that FDA can verify that the report has been submitted within 10 days of the investigation. Another comment stated that a date indicating the date it is determined that an event is reportable should be added.

FDA does not believe that it needs information in this section that describes the length of the investigation, the date the reporter determines that an event is reportable, or the date of completion of the investigation. Pursuant to revisions in section F.6 that are described more fully below, the revised form will now provide information from which FDA can determine the lengths of investigations or the date that a reporter determines that an event is reportable, to the extent

that such information is relevant for regulatory purposes.

Section B.5 of the proposed form requested a reporter to "describe event or problem," and to "attach hospital discharge summary, if available." One comment suggested adopting the language from the FDA test Form 3375 (Medical Device Reporting) that requires a narrative description of relevant information.

FDA believes that any information that is relevant to help FDA determine the causation of an adverse event should be included in the narrative if it is not already provided by other sections of the form. However, "Attach hospital discharge summary, if available" has been deleted from the final form to dispell the impression that the hospital discharge summary is required. FDA encourages the reporter, however, to attach the discharge summary if available.

Section B.7 of the proposed form pertained to a listing of "preexisting medical conditions and other relevant history." In the proposed form for user facilities, manufacturers, and distributors, this section contained four lines for entering information. Several comments opposed the inclusion of the preprinted lines.

The preprinted lines were originally included to allow for the option of optical scanning, but the lines are not necessary for the technology that FDA currently uses and have been deleted from the final versions of the form. For submission of adverse events related to the use of biologics, optical scanning remains a useful tool for FDA to enhance the speed and accuracy of data entry, and FDA urges biologics manufacturers to submit forms that can be optically scanned. The agency recognizes that for the successful application of optical scanning technology, replication of version 3500A will require a high level of precision. Manufacturers will be required to submit their computer-generated version of the form for approval by the agency.

One comment indicated that preexisting medical conditions are part of the confidential medical record and should not be required on either version of the form.

The knowledge of preexisting medical conditions is often crucial to an adequate evaluation of an event. If a confidential patient identifier is used, it is not likely that simply indicating a patient's medical history would identify the patient.

One comment suggested including allergies in the list of preexisting medical conditions.

FDA agrees that it would be useful to include allergies in the list of conditions and has revised the form accordingly.

One comment asked whether ICD-9 codes (an International Classification of Diseases code) and verbatim terms should be included in this section.

Including ICD-9 codes and descriptors of the codes is optional for manufacturers.

D. Section C (Versions 3500 and 3500A)—Suspect Medication(s)

Section C in the proposed form would require information on "suspect medication(s)," such as the dose, frequency, and route of administration, therapy dates, diagnosis for use or indication, and expiration date.

One comment preferred the use of "associated medication(s)" rather than "suspect medication(s)," saying that the term "suspect" implies causality that, ostensibly, has not been proven.

FDA has retained the use of the term "suspect" because the report is intended to alert manufacturers and FDA to suspected links between particular products and adverse events. The agency does not believe that this term "suspect" implies that causality has been proven. In addition, the term "associated medications" might be construed as "related" or "concomitant" medications. The form is intended to collect information about drug products connected with particular adverse events and problems. The concomitant medications are requested separately on the form.

Two comments suggested adding "manufacturers only" to "Suspect medication(s)" because user facilities are not required to report medication problems. One comment noted that user facilities who choose to report medication problems can use version 3500.

Not all elements of version 3500A are required by regulation for each type of reporter. The agency believes that asking user facilities to report on two different versions of the form would be confusing and will not facilitate the ability of a user facility to receive a report from a health professional and relay it to FDA. In addition, FDA wants to know about suspect drug products that may have contributed to an adverse event associated with a medical device.

Section C.1 of the proposed form requested information on the "Name & strength (give mfr/labeler if known)" for the "Suspect medication(s)." The proposed form provided lines for two separate suspect medications and designated them as "a" and "b." Several comments suggested replacing the

letters "a" and "b" with numbers ("1" and "2").

FDA has revised the form as suggested by the comments.

One comment suggested removing the preprinted lines to facilitate more efficient use of available space by computer systems.

The final form retains one line for each of two possible listed suspect medications. FDA believes that providing the lines will make the submission of information clearer and easier to read.

Regarding the section requesting the name and strength of suspect medications, one comment said that drugs are not addressed in the tentative final rule entitled *Medical Devices; Medical Device, User Facility, Distributor, and Manufacturer Reporting, Certification, and Registration* published in the *Federal Register* of November 26, 1991 (56 FR 60024) and are not subject to the rules applicable to medical device reporting.

As noted earlier, the reporting form is not for devices only. FDA regulations at §§ 310.305, 312.32, and 314.80 require adverse event or safety reports for human drug products. CBER is also preparing final regulations that adopt similar reporting requirements for biologics. Adverse experience information is used to further FDA's objectives of effectively monitoring the safety and efficacy of human drug and biological products.

Section C.2 of the proposed form requested information on the "dose, frequency & route" for the suspect medication(s). One comment suggested that these items pertain to the drug product "as used" rather than "as labeled."

Although the proposed form did not specify either "as used" or "as labeled," FDA has adopted the suggestion. Consequently, section C.2 of the final form pertains to the suspect medication's dose, frequency, and route "used."

One comment suggested that providing total daily dose would be clearer than providing the dose, frequency, and route as prescribed.

FDA believes that total daily dose will not provide important information about dosing intervals and dosage strength that might distinguish between multiple preparations of the same chemical substance. In addition, total daily dose can be calculated from dose and frequency.

Section C.3 of the proposed form pertained to "Therapy dates (or give duration)."

Several comments expressed concern that duration of therapy does not

provide sufficient information to evaluate the relationship between the suspect medication and the adverse event. The comments suggested that FDA revise the section to indicate the temporal relationship between the starting and stopping dates of the administration of the drug and the onset of the adverse event.

FDA agrees that, when available, starting and stopping dates of drug therapy are very important pieces of information. However, when these dates are not known, it is preferable to have information on duration of therapy than to have no timing information at all. The agency, therefore, declines to revise this section except to encourage the reporter to estimate the dates and duration if exact dates are not known.

Section C.4 in the proposed form concerned the "Diagnosis for use (indication)." FDA received one comment suggesting that the words "if known" should be added to the heading of "Diagnosis for use (indication)" because community pharmacists may not know the underlying diagnosis for a prescription.

FDA declines to accept the suggestion. In most cases, FDA expects that the reporter will know the diagnosis for use because the reporter either will be the physician who made the diagnosis or the manufacturer who can obtain the information from the initial reporter. The reporter may also state on the form that the diagnosis is unknown if the information is not available.

Section C.5 in the proposed form asked whether the adverse event "abated after use stopped or dose reduced." The form contained "yes/no" boxes for two products, designated as "a" and "b." Several comments suggested that a space be added for "not applicable" for drugs, such as insulin, that are generally not discontinued after an adverse event, or "unknown," for cases in which the information is not available. FDA received several similar comments for section C.8 in the proposed form, which asked whether the event reappeared after reintroduction of the drug product.

In each instance, FDA has added a box to check for "doesn't apply" but, because of space limitations, has declined to add an entry for "unknown." Generally, FDA expects that the reporter will know whether the event abated after reduction or elimination of the drug treatment and whether it reappeared after reintroduction. The field may be left blank or "unknown" may be written in if the information requested is not available.

Section C.9 in the proposed form requested the suspect medication(s) NDC number, if known. FDA received several comments stating that the NDC number is often not available and is of little value.

FDA has revised the form to specify providing the NDC number when reporting "product problems only (if known)." Knowledge of the NDC number is critical when evaluating a reported drug quality problem. However, if the reporter does not know the NDC number, it can be omitted.

Section C.10 in the proposed form required information on "other medications/devices used prior to event" and "therapy dates." The form also contained three lines, marked "a," "b," and "c" for listing information. Several comments said that this language was misleading and suggested that "concomitant medical products" would more clearly indicate that the information sought pertains to products used immediately prior to or at the same time that the event occurred. Some comments asked that the preprinted lines be deleted.

FDA agrees that the word "concomitant" provides a clearer description of the information sought and has revised the form accordingly. The agency has also removed the preprinted lines from the form to provide more flexibility in entering information.

One comment suggested that this section and its counterpart in D.10, "other medications/devices used prior to event," be combined and moved to section B (Adverse event or product problem).

The agency declines to make this change. FDA wants to separate the specific data concerning drugs or devices so that each may be addressed separately. Section B of the form is for describing the adverse event itself, while sections C.10 and D.10 respectively request a description of concomitant medical products in use at the time of the adverse event but not used to treat the event. FDA believes that reporting the information in this way will be clearer and less likely to cause confusion.

E. Section D (Versions 3500 and 3500A)—Suspect Medical Device

Section D of the proposed form, "Suspect medical device," requested 10 items of information: (1) The product name of the device; (2) the type of device; (3) the device manufacturer's name and address; (4) whether the person operating the device was a health professional, lay user/patient, or "assistive personnel;" (5) the expiration

date of the device (if known); (6) information specifically identifying the device, such as the model, catalog, serial, lot, or other number; (7) if implanted, the date of implantation; (8) if removed, the date of removal; (9) whether the device had been returned and was available for evaluation; and (10) other medications or devices used prior to the event and the therapy dates.

FDA received a number of general comments on this section. Several comments proposed reversing the locations of Sections G ("All manufacturers") and D so that all information regarding suspect medications could be presented on one side of the MEDWATCH form.

As stated above and in the February 26, 1993, notice, if a medication manufacturer is reporting an adverse event in which no suspect medical device is involved, the manufacturers section (section G) on the reverse side of version 3500A may be completed and identically reproduced in place of the suspect medical device section (section D) on the front of the form. This makes it possible for medication manufacturers to submit all necessary information on one side of the form.

One comment suggested that manufacturers be permitted to submit and refer to the user facility report rather than repeating the information in section D.

FDA agrees with this comment. The manufacturer does not have to recopy the information supplied by the user facility and may refer to the answer in the user facility/distributor section (section F in version 3500A) if the manufacturer, after conducting an appropriate investigation, verifies the information.

One comment suggested replacing the heading, "Suspect Medical Device" with "Subject Medical Device."

FDA declines to accept this suggestion. The form is intended to provide information on "serious adverse events" and deaths that are suspected of being related to a device. The term "Suspect medical device" quite appropriately focuses the reporter's attention to a possible association between a serious injury or death and a medical device.

FDA, on its own initiative, has changed the caption of section D.1 from "product name" to "brand name." "Brand name" is more commonly used in the device industry and will identify products with a greater degree of specificity.

Section D.3 of the proposed form asked for the manufacturer's name and address. Several comments asked

whether this referred to the manufacturing site or the reporting site.

FDA advises that the name and address refers to the reporting or headquarters site. The agency urges voluntary reporters to provide whatever information is available to them regarding the manufacturer. In the final form, section G.1, mandatory for all manufacturers, now specifies that the name and address for the contact office and the site of manufacturing for a device be provided.

Section D.4 of the proposed form asked whether a health professional, lay person, patient, or "assistive personnel" operated the suspect medical device. Several comments questioned the term "assistive personnel," noting that health professionals rarely use this term.

FDA agrees with these comments and has replaced the term with an "other" designation which can be used by individuals, such as nurse's aides, orderlies, or engineers who are in a position to detect an adverse event involving a medical device.

One comment requested that FDA provide a way of designating devices that do not require an operator.

FDA recognizes that there are a significant number of devices that do not require operators. In such cases, the subsection would not apply.

Section D.5 of the proposed form asked for the device's "exp. date." Several comments noted that the term "exp. date" could be understood as an abbreviation of "explant date."

To avoid any possible confusion, FDA has replaced "exp. date" with "expiration date."

Section D.8 of the proposed form requested the date on which the suspect medical device was "removed." Several comments stated that the word "explant" more accurately described the information sought under this subsection than remove.

FDA agrees with these comments and has changed the form to provide a space to indicate the date implanted devices may have been "explanted."

Section D.9 of the proposed form asked whether the device was "available for evaluation" and whether the device had been returned to the manufacturer. Several comments suggested that the agency should advise user facilities to return allegedly faulty devices to manufacturers.

FDA advises that requiring user facilities to return devices is beyond the scope of the user facility reporting authority under section 519 of the act (21 U.S.C. 360i) and accordingly beyond the scope of this report form. User facilities should be aware that the failure to return a device to the

manufacturer generally reduces the manufacturer's ability to identify the cause of the problem. It may not be practicable, however, to return all devices as, for example, when a patient who owns a device will not relinquish it or where shipping the device might pose possible public health problems.

The agency, on its own initiative, has amended section D.9 of the form to state that the suspect medical device should not be sent to FDA. The agency has made this change because manufacturers, not the agency, have the primary responsibility for performing an evaluation of the device and are best equipped to provide instructions on the shipping and handling of a device.

One comment asked FDA to include a space "for the current possessor of the device."

FDA declines to amend the form as suggested by the comment. FDA notes that the form, at section D.9, asks whether the device is available for evaluation or is in the manufacturer's possession. Based on the responses to this section, as well as information in other sections of the form, FDA believes that the agency and manufacturers will be able to determine where a suspect medical device is located, if necessary.

One comment stated that FDA should provide "instruction in the proper handling of 'explanted' materials."

FDA believes that such instruction could vary, depending on the medical device involved, and so it would be impractical, given the limited space on the form, to amend the form to provide instructions for every possible type of explanted device. FDA acknowledges, however, that the issue raised by the comment is important and intends to address these issues in the future.

Section D.10 in the proposed form requested information on "other medications/devices used prior to event" and also requested "therapy dates." Several comments claimed this request was too broad or would yield little value. Other comments stated that the requested information might not be pertinent, and that FDA should limit the requested information to drugs or devices that might have had a bearing on the adverse event being reported. One comment suggested that FDA amend the form to specify other medications or devices that might have had an impact on the event. Another comment suggested the listing of other medications and devices in use at the time of the event.

The agency agrees that the proposed form's request for "Other medications/devices used prior to event—give therapy dates," was overly broad and might yield information that is not

pertinent. FDA also agrees with the comments suggesting listing other medications and devices in use at the time of the event and specifying other medications or devices that may have had an impact on an event. Accordingly, FDA has deleted the request for "Other medications/devices used prior to event," and replaced it with "Concomitant medical products and therapy dates (exclude treatment of event)." FDA believes that this revision will provide the key information necessary to determine whether the cause of an adverse event is related to possible drug or device interactions.

Other comments suggested that the agency amend the form to permit reporters to determine whether concomitant treatments were related to the adverse event.

The agency declines to accept this suggestion. The emphasis on adverse event reporting is to identify events and possible interactions which are not already known or, if known, occur at a greater frequency than expected. Thus, restricting concomitant products to those which the reporter believes "may have had an impact" may result in incomplete information or delay the discovery of previously unknown interactions.

F. Section E (Version 3500 Only for Voluntary Reporting)—Reporter

Section E in the proposed version for health professionals requested information about the reporter (name, address, and telephone number), whether the reporter was a health professional, the reporter's occupation, whether the information had been reported to the manufacturer, user facility, or distributor, and whether the reporter did not want his or her identity disclosed to the manufacturer.

Several comments asked FDA to explain who the "reporter" is.

The "reporter" on version 3500 is the health professional or consumer, who may submit the form to manufacturers, user facilities, and distributors, as well as to FDA. If one health professional is completing the form for another, the reporter on the form should be the health professional who can be contacted in the event that followup is necessary. FDA recognizes that the hospital pharmacist may serve as the facilitator for reporting by physicians.

Several comments asked for clarification of the entry of the reporter's name, address, and telephone number. Two comments asked for specific data entry lines for identification of the doctor, university, or other relevant information in addition to name, address, and telephone number.

FDA declines to amend the form as suggested by the comment. There is sufficient space to provide any additional identifying information that the reporter may believe is useful.

Several comments said section E.2, which asked whether the reporter is a health professional, is unnecessary on version 3500, which is created expressly for health professionals. One comment suggested that the form provide space for a specific health profession.

Asking whether the reporter is a health professional is not redundant because version 3500 may be completed by consumers as well as by health professionals.

The form includes a space, designated section E.3, for the reporter to indicate his or her occupation; if the reporter is a health professional, this is the place to indicate a specific profession and specialty.

Section E.3 in the proposed form for health professionals pertained to "Occupation." FDA received two comments seeking clarification as to whose occupation was being requested.

The initial reporter's occupation should be provided.

G. Section E (Version 3500A Only for Mandatory Reporting)—Initial Reporter

Section E in the proposed form for user facilities, distributors, and manufacturers also requested information about the reporter (name, address, and telephone number), whether the reporter was a health professional, the reporter's occupation, and whether the information had been reported to the manufacturer, user facility, or distributor.

Several comments asked FDA to clarify who the "reporter" is.

FDA has modified the title of section E of version 3500A to read "Initial Reporter." This will allow the user facility, distributor, or manufacturer to indicate who reported the adverse event to it.

Section E.4 in the proposed form asked whether the information had been reported to the manufacturer, user facility, or distributor. One comment suggested that FDA add a space to indicate whether the initial reporter also sent the report to FDA.

FDA has revised section E.4 to ask whether the initial reporter also sent a report to FDA. This will allow FDA to know whether the initial reporter has also sent the agency a voluntary report of the same event. The agency has deleted the references to a manufacturer, user facility, or distributor in section E.4 of version 3500A because version 3500A is submitted by those parties.

One comment asked FDA to define "user facility" when an adverse event is being reported by a manufacturer.

FDA has deleted this portion on version 3500A. Only the health professional's form (version 3500) continues to ask whether the event was also reported to a manufacturer, user facility, or distributor. As for the definition of "user facility," FDA has defined the term in the next section.

H. Section F (Version 3500A Only)—For Use by User Facility/Distributor—Devices Only

Section F of proposed version 3500A requested device data from user facilities or distributors. The proposed section requested 14 items of information: (1) Designation of the reporter as either a user facility or distributor; (2) a report number; (3) the user facility's or distributor's name and address; (4) the contact person's name; (5) the phone number where the contact person can be reached; (6) the date the event was reported to the user facility or distributor; (7) the type of report (initial or followup); (8) the report's date; (9) the device purchase date; (10) event (patient and device) problem codes; (11) whether a report has been sent to FDA; (12) the location where the event occurred; (13) whether a report was sent to the manufacturer; and (14) the manufacturer's name and address.

Section F.1 in proposed version 3500A asked whether the reporter was a user facility or distributor. One comment asked FDA to define "user facility." Section 519(b)(5) of the act defines "Device User Facility" as a "hospital, ambulatory surgical facility, nursing home, or outpatient treatment facility which is not a physician's office."

Under section 519(e)(5) of the act, the Secretary of HHS may, by regulation, include an outpatient diagnostic facility which is not a physician's office within the definition "device user facility." FDA, in its tentative final rule published in the *Federal Register* of November 26, 1991 (56 FR 60024), proposed to include such outpatient diagnostic facilities within the definition of device user facilities. Unless and until FDA issues a final regulation requiring outpatient diagnostic facilities that are not physician's offices to submit adverse event reports, such entities are not required to report. In the interim, however, FDA encourages the submission of voluntary reports from such entities.

Proposed section F.2 requested information on the "report number." Seven comments asked FDA to clarify the term "report number."

In response to these requests for clarification, FDA has revised the wording so that the entry in the final form requests the "UF/Dist Report Number" which is an abbreviation of User Facility/Distributor Report Number. The number consists of the facility's Health Care Financing Administration (HCFA) number, the calendar year, and a consecutive 4-digit number for each report filed that year by the facility, e.g., xxxxxxx-1991-0001, xxxxxxx-1991-0002. If a facility does not have a HCFA number, the first report should be submitted with all zeros in the HCFA space, and FDA will assign a number to be used on future reports. If a facility has more than one HCFA number, the facility may choose any one of those numbers, but must use the same number for subsequent submissions. These numbers, which will be unique to each form, will facilitate tracking and auditing by FDA. Device distributors follow the same format but use their FDA registration number with the calendar year and sequence number.

Proposed section F.4 of the form requested that user facilities or distributors list a contact person. One comment sought clarification as to who the contact person should be.

User facility submissions should be made by an individual who is designated by the facility's most responsible person as the device user facility contact for this requirement. FDA will conduct its medical device reporting (MDR) correspondence with this individual. The contact person may or may not be an employee of the facility. However, the facility and its responsible officials will remain the parties ultimately responsible for compliance with the requirements.

Proposed section F.6 of the form requested the date the adverse event was reported to the user facility or distributor. Four comments said this date should be the date on which the user facility or distributor determined that the event was reportable. One comment noted that without requesting this information, FDA would be unable to determine if the user facility complied with the provision in the Safe Medical Devices Act of 1990 (the SMDA) (Pub. L. 101-629), which requires user facilities to report an event within 10 days after the user facility becomes "aware" of a reportable event (21 U.S.C. 360i(b)(1)).

FDA has revised section F.6 to read, "Date user facility or distributor became aware of event." The agency believes that this language is the most relevant to the distributor and user facility reporting requirements because it is

derived directly from the statutory language relating to user facilities in section 519(b)(1) of the act, and from the distributor reporting regulations, part 803 (21 CFR part 803), which became final by operation of law on May 28, 1992. This statutory and regulatory language triggers a reporting requirement for those entities within 10 days after they are deemed to "become aware" of the event. FDA, in its November 26, 1991, tentative final rule requiring user facility reporting, stated that the user facilities are deemed to "become aware" of information that triggers the reporting requirements only when they have sufficient information to make a determination that a report is required. Distributors, however, only serve as a conduit of information submitted to them, and are deemed to become "aware" of information that triggers reporting requirements when they receive a report.

Proposed section F.7 requested that user facilities and distributors specify whether the report is an initial or followup report. FDA received four comments on this section. One comment suggested mandatory resubmission of the entire form with each addendum.

FDA disagrees with the comment suggesting mandatory resubmission of the entire form for each addendum. Resubmission of the entire form would hinder FDA's ability to determine whether an initial or followup form was being submitted and also make it difficult to identify new information. Such resubmissions would also place additional paperwork burdens on user facilities or distributors without any apparent benefit to the user facility, distributor, or FDA. Consequently, FDA declines to require resubmissions of an entire form with each addendum.

Another comment suggested that FDA amend the form so the designation of an initial report or a followup report would appear in a section requesting "general information."

FDA has taken this comment under advisement and will consider it after the agency acquires some experience with the final form.

One comment asserted that the proposed section F.7 did not adequately distinguish between initial and followup reports.

The agency disagrees with the comment. Section F.7 in version 3500A permits the user facility or distributor to check simply whether the report is an initial report or a followup report. By permitting these parties to check an appropriate box, FDA believes that a user facility or distributor can readily determine and indicate which type of

form it is completing and that agency personnel will be able to determine quickly whether they are receiving an initial or followup report.

Proposed section F.8 of the form asked for the "date of this report."

Three comments asked FDA to explain how this date differed from the entry in proposed section B.4 of the form for the "date of this report."

The date of the report in section B.4 of the form is the date that the report is filled out by the reporter, who may or may not be a user facility or distributor. The date of the report in section F.8 refers to the date the user facility or distributor forwards the report to FDA or the manufacturer. This information is relevant because it indicates the date that statutory and regulatory timeframes for reporting are triggered. (See the discussion to comments for section F.6.)

Proposed section F.9 of the form asked for the "device purchase date." FDA received eight comments on this section. Some comments noted that the device purchase date was often not accessible to a distributor. Other comments suggested that it would be more realistic to request the approximate age of the device.

The agency agrees that purchase dates may often not be accessible and that approximate age of the device is more appropriate. Therefore "device purchase date" has been revised to read, "Approximate age of device."

Section F.10 in the proposed form requests "Event problem codes" and refers to a "coding manual." FDA received many comments expressing confusion over these codes as well as the coding manual to be used in section F.10.

The agency intends to make the Coding Manual available at the time version 3500A is effective.

Proposed section F.11 asked whether a report had been sent to FDA and, if so, the date the report was sent.

One comment said that the information requested in this entry is redundant to section F.7 ("Type of report").

The agency disagrees with the comment. Section F.7 asks whether the information being provided is part of an initial or followup report; it does not ask whether the report was sent to FDA, nor does it ask when the report was sent. In contrast, section F.11 will inform manufacturers and others analyzing the report whether FDA has also been informed of possible problems with the device.

One comment stated that the question whether a report had been sent to FDA could make user facilities and

distributors believe that they should send a report to FDA.

FDA advises that distributors and user facilities must submit reports of certain adverse events to FDA. Under section 519(b) of the act, a user facility must submit reports of deaths that are suspected of being device related to FDA and to the manufacturer, if known. User facilities must also submit reports of serious injuries that are suspected of being device related to the manufacturer or, if the manufacturer of the device is unknown, to FDA. Similarly, distributors are required by regulation to submit all reportable adverse events to FDA and to the manufacturer. Thus, the statute and regulations do require user facilities and distributors to report to FDA.

Proposed section F.12 listed seven possible choices—"hospital," "home," "nursing home," "outpatient treatment facility," "outpatient diagnostic facility," "ambulatory/surgical facility," and "other"—for the location at which the adverse event occurred.

One comment questioned whether the request for "location" referred to the location of the adverse event or the user facility.

The "location" request in the form means the location where the adverse event occurred.

Thirteen comments asked FDA to delete "home" from the form. Several comments stated that reporting home events is not required under the SMDA. One comment suggested putting "(voluntary)" after the entry for "home."

FDA does not agree that the reporting of certain events that occur in the home is not required under the SMDA. For example, a distributor that becomes aware that one of the devices it distributed is suspected of causing a death or serious injury while being used in someone's home must report this event to FDA. Accordingly, inclusion of the choice "home" in F.12 is appropriate and should not be followed by the word "voluntary."

Another comment suggested adding "home" as a possible location of the adverse event to version 3500, the voluntary form used by health professionals.

FDA does not believe it is necessary to include this information on the voluntary form. The agency will have this information for all deaths and other serious adverse events on the report form submitted by the distributor and/or user facility.

One comment suggested changing "nursing home" to "residential care facility" in order to encompass a broader range of institutions.

FDA declines to amend the form as requested. The category of "nursing home" is specified in the SMDA, and the "other" option will allow reporters to indicate different kinds of facilities that are not specifically indicated on the form.

One comment suggested changing "ambulatory/surgical facility" to "ambulatory surgical facility."

FDA agrees with comment and has changed the form accordingly.

Proposed section F.13 of the form asked whether the user facility or distributor had sent a report to the manufacturer, and the date of such a report. One comment expressed concern over the accuracy of the information provided to the manufacturer.

The agency is aware that information provided to manufacturers may be anecdotal or incomplete, but notes that it is the manufacturer's obligation to investigate reports of adverse events related to their devices.

Proposed section F.14 of the form asked user facilities or distributors to provide the manufacturer's name and address. Three comments claimed that this provision duplicated information requested in section D.3 ("Manufacturer name & address") and section G.1 ("Manufacturer name/address & phone # (site of mfr for device)") (now "Contact Office name/address (& mfring. site for devices)").

The agency disagrees with the comments. The three sections cited by the comment can result in different manufacturing names and addresses from different parties. Section D.3, for example, which requests the manufacturer's name and address for the suspect medical device, may be completed by a voluntary reporter. This individual will probably only have access to the device itself and will therefore supply the name or address of the manufacturer that is imprinted or attached to the device. In contrast, section F.14, which is completed by the user facilities or distributors, will provide the manufacturer's name and the address these reporting entities use for the purpose of communicating adverse event information to the manufacturer. The name and address may be different from the manufacturer name and address present on the device itself. FDA has revised the request for information in section G.1 of the final form, which is completed by manufacturers, to clarify that the manufacturer must identify both a contact office and include the name and address of the manufacturing site for the device. The contact office and manufacturing site information provided by the manufacturer may be

different from the information filled out in section D.3 or F.14.

I. Section G (Version 3500A Only)—All Manufacturers

Section G in the proposed form for user facilities, distributors, and manufacturers requested information from all manufacturers, including the manufacturer's name, address, and telephone number, the report source (such as literature, health professional, user facility, etc.), the date the manufacturer received the report, the application number if the report involved a human drug product, the type of report, the adverse event term(s) (for a biological product), and the report/control number.

Section G.1 in the proposed form requested the manufacturer's name, address, and telephone number.

FDA has, on its own initiative, changed the description of the information sought in section G.1 to identify a "Contact office—name/address (& mfring. site for devices)." In addition, FDA has created a new section G.2 for the contact office's telephone number.

Section G.2 in the proposed form (now renumbered as G.3) requested information on the report source. The section lists several possible sources, such as "foreign," "study," "literature," "consumer," "health professional," "user facility," "company representative," "distributor," and "other." Several comments said that "company representative" should be deleted because the report source should be the original reporter.

FDA disagrees with the comment. FDA recognizes that certain segments of the industry frequently receive reports from company representatives. The agency wants to track reports received in this manner.

One comment suggested designating the last four items in the list of report sources (user facility, company representative, distributor, and other) as being relevant to devices only, and another suggested adding "foreign health authorities." One comment objected to the use of the term "literature."

The proposed form did include, and the final version retains, the choice of a "foreign" source. However, FDA has not revised the form to make the other suggested changes. FDA realizes that "user facility," for example, may only be relevant to device-related adverse events. The purpose of this form, however, is to provide one form that can be used to report adverse events that are related to several FDA-regulated products. It is therefore necessary to

include some choices in this section that may not be relevant to a specific FDA-regulated product. FDA also does not agree with the comment which objects to the request for "literature" as a report source. FDA regulations at § 314.80(b) provide that each applicant having an approved application under 21 CFR 314.50 or 314.94 shall 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, scientific literature, and unpublished scientific papers. Current regulations for device manufacturers and distributors also require submission of reports from any source, including literature (see part 803). Thus, the form appropriately lists possible sources of reports.

Section G.3 in the proposed form (now renumbered as G.4) requested information on the "date received by manufacturer." FDA received several comments requesting clarification of this date. Two comments wanted to ensure that the date meant the date the manufacturer received enough information to make a report, and one asked whether the date meant receipt of information by the corporation anywhere in the world or in the United States.

The date received by manufacturer means the date the manufacturer initially received information to determine that an adverse event occurred. This would apply to a report received anywhere in the world.

Section G.4 in the proposed form (now renumbered as G.5) pertained to an NDA number, IND number, PLA number, and asked whether the drug product was a "pre-1938" product. One comment suggested that the form either specify that the acronyms (NDA, ANDA, etc.) pertain only to pharmaceutical manufacturers or spell out the terms.

The acronyms pertain to human drug products. "ANDA" stands for "abbreviated new drug application;" "NDA" stands for "new drug application;" "IND" refers to an investigational new drug application, and "PLA" refers to a "product license application." The agency has not, however, revised the form as the comment suggests because it believes medical device and drug and biological product manufacturers know what abbreviations are applicable to their products.

Several comments asked why the form did not request the application numbers for applications submitted

under section 510(k) of the act (21 U.S.C. 360(k)) or the premarket approval application (PMA) number for medical devices. One comment suggested they be included.

FDA has not required the 510(k) number or the PMA number on version 3500A because this information would duplicate other information FDA may receive in periodic reports from device manufacturers.

Two comments asked whether reports for investigational device exemptions (IDE's) are to be included in this form.

Devices that are subject to IDE's pursuant to 21 CFR parts 812 and 813 are exempt under § 803.36(b) from the adverse event reporting requirements. These devices are instead subject to IDE reporting requirements.

One comment asked whether the form should be used to report adverse events for IND products in development.

Adverse events associated with these products should be reported. FDA Form 3500A is not required but may be used to report 10-day IND safety alerts. One comment asked whether, for marketed biologic products, both the IND and the PLA numbers should be provided for spontaneous postmarketing reports and asked about products with multiple IND's but only one PLA.

For a marketed biologic product, the PLA number should be provided for spontaneous postmarketing reports. The IND number should only be referenced if the suspect product associated with the adverse event was administered under a specific IND protocol, and the report is being submitted as a 10-day IND Safety Report.

One comment said the form should ask whether the product is an over-the-counter (OTC) product.

FDA agrees and has revised the form to include a box to indicate whether the report concerns an OTC product.

Section G.6 in the proposed form (now renumbered as G.7) concerned the "type of report" and included six possible choices: 5-day, 10-day, 15-day, initial, periodic, or followup. One comment said that the form repeatedly asks whether a report was an initial report or a followup.

FDA disagrees with the comment. The designation of an initial or followup report by manufacturers only appears once on the form.

Section G.7 in the proposed form (now renumbered as G.8) concerned "adverse event term(s)" for biologics and provided three lines for entering information. FDA received many comments noting that the information was requested only for biologics and asked whether FDA intended to limit this section to biologics. Several

comments asked whether this information could be moved to section B ("Adverse event or product problem"). Some comments said that the preprinted lines limited the number of terms that could be provided.

FDA has revised the form to delete the term "Biologics" because the agency did not intend to limit the applicability of this section to biologics. FDA has also deleted the preprinted lines. FDA declines, however, to move this information to section B because the agency believes this information is best linked to other information provided by the manufacturer in section G.

Section G.8 in the proposed form (now renumbered as G.9) requested the "Report/control #." Several comments sought clarification of this section. One comment asked how the report/control number differed from the manufacturer report number. Another comment noted that the manufacturer report number is already required at the top of the form and questioned why manufacturers should provide the number in section G.8 (now renumbered as G.9).

FDA has revised both entries to read "Mfr. report number." The manufacturer report number is required in both places to allow the front and back pages of a particular report to be matched in the event they are submitted as separate pages or if they are copied as separate pages.

J. Section H (Version 3500A Only)— Device Manufacturers Only

Section H in the proposed form for user facilities, distributors, and manufacturers requested device manufacturers to provide 13 items of information: (1) A contact office, including an address and phone number; (2) the device manufacture date; (3) the product code; (4) whether the device is labeled for single use; (5) the report type; whether it concerns a death, serious injury, a malfunction, or some other problem; (6) whether the event being reported involved the initial use or reuse of the device; (7) whether the manufacturer has evaluated the device, and, if so, whether it has conducted a failure analysis; (8) if the report is a followup report, whether it reports a correction, provides additional information, responds to an FDA request, or involves a device evaluation; (9) evaluation codes, including entries for method, results, and conclusions; (10) the type of remedial action initiated, such as recall, repair, or replacement; (11) whether the action was being reported to FDA under FDA regulations; (12) a manufacturer narrative, and (13) corrected data.

FDA, in response to comments and on its own initiative, has significantly reorganized and revised this section. Section H, as revised, assigns greater prominence to certain entries, such as the type of reportable event and whether the manufacturer has evaluated the device, and deleted the entry concerning "product code." The agency will discuss these comments in the order in which they relate to the sections in the final form.

Section H.1 in the final form requests information on the "Type of Reportable Event." This section was at H.5 in the proposed form, and was originally captioned "Type of Report." Several comments stated that the information requested in this section duplicated that requested in section B.2, "Reasons for reporting adverse event."

FDA disagrees with the comments. Section B.2, which is now titled, "Outcomes attributed to adverse event," applies to medications, medical devices, and other FDA-regulated products. Consequently, it identifies possible adverse events or problems, such as congenital anomaly, that may not be applicable to medical devices. In contrast, section H.1 is devoted exclusively to medical device manufacturers and is specific to the categories of adverse events that device manufacturers are required to report. Further, the agency anticipates that section B.2 will contain information provided by the initial reporter, such as a user facility, and forwarded to the manufacturer. After an investigation, the manufacturer's interpretation of the event may differ from that provided by the initial reporter.

Several comments requested that FDA change the phrase "malfunction that might cause death or serious injury if it were to recur" to "malfunction that is likely to cause death" in order to conform to section 519(b)(1)(B) of the act and 21 CFR 803.24.

FDA has amended the language to refer only to a "malfunction." The agency notes that, under the 1992 amendments enacted on June 16, 1992, Congress has changed the standard for determining when adverse events must be reported. This law will be effective 1 year from the date of enactment of these amendments. Moreover, FDA has not yet published a final MDR reporting regulation, based on comments submitted in response to the November 26, 1991, tentative final rule. Accordingly, at the time of publication of this notice, it is impossible to provide the exact standard that will be required for reporting under the new law and future regulations. Regulations or other

guidance will be issued by FDA by the effective date of this form.

One comment objected to including "other" as a type of report, stating that the SMDA only requires reports of death, serious illness, or serious injury. Another comment asked what type of event would fall under this category.

The form's reference to "other" is intended to capture any reports that a manufacturer believes the agency should be aware of that are not covered by "death," "serious injury," and "malfunction," as these terms are defined by statute or regulations. This category can be used to notify FDA of a correction action or removal. Section 519(f)(1) of the act states that no report of corrective action or removal is required if it has been reported per section 519(a) of the act. Moreover, under the Medical Device Amendments of 1992, the category can be used to report "other significant adverse device experience as determined by the Secretary to be necessary to be reported."

Section H.8 of the proposed form (now renumbered as H.2 in the final form) was captioned, "If follow-up, what type?" The form provided four boxes to indicate whether the followup was a correction, additional information, response to FDA request, or device evaluation. Several comments requested clarification. One comment asked whether a manufacturer had to complete a new form whenever new information became available. Another comment requested clarification of the term "correction." A third comment asked whether the agency was trying to determine whether a report was an original or followup report.

Section H.2 is intended to assist agency personnel swiftly determine the purpose behind a followup report. For example, a "correction" would indicate that the manufacturer has already submitted a report and is correcting information provided in the previous report. If the manufacturer indicated that it was responding to an FDA request, this would alert FDA personnel to the possible existence of documents or discussions on the adverse event or product problem. FDA does not expect device manufacturers to submit reports that contain information the agency has received in a previous report. The manufacturer should simply provide the new information to FDA and mark the box indicating what kind of followup report is being submitted.

One comment suggested that FDA place a similar entry regarding the type of followup report in section F for use by user facilities and distributors. The comment said such information could

be "helpful in clarifying the nature of the particular problem."

FDA does not agree that adding these entries under the user facility/distributor reporting section will provide clarifying information. The user facility and distributor reports are forwarded to the manufacturer. The manufacturer must then submit a report based on the distributor or user facility report indicating the kind of followup report. Accordingly, requiring this information from user facilities or distributors would provide duplicative information to FDA.

Section H.7 of the proposed form, "Device evaluated by mfr?" (now renumbered as H.3 in the final form), contained three boxes that device manufacturers could mark: "yes," "failure analysis attached," and "no (if no, attach page to explain why not) or provide code." Two comments said FDA should delete this section or, if retained, change "failure analysis attached" to "evaluation summary attached."

FDA disagrees that this section should be eliminated. It is the manufacturer's primary responsibility to determine whether its devices have caused an adverse event and, in turn, to provide such information to FDA so the agency can determine whether further steps are needed to protect the public health. The agency agrees, however, that the term "failure analysis attached" might be interpreted to preclude any other evaluation outcomes and has replaced it with "evaluation summary attached."

Another comment suggested that a manufacturer may be unable to conduct an evaluation for all types of devices, notably devices that are disposable.

The agency advises manufacturers who believe that they cannot conduct an evaluation for a medical device to use the "no" option and attach an explanation or provide the appropriate code. If the manufacturer believes that direct evaluation is not applicable, the manufacturer, in some circumstances, could perform a surrogate method of evaluation.

One comment suggested that FDA create an additional box to indicate "not returned."

FDA agrees and has added a modified version of this suggestion, "not returned to mfr." to the final form.

Several comments said FDA should delete section H.2 in the proposed form, "Device manufacture date," (now renumbered as section H.4 in the final form) because it duplicated information requested in section D.6, which asks for the suspect medical device's model number, catalog number, serial number, lot number, and other numbers.

FDA disagrees with the comment. These two sections provide different information to FDA. Section D.6 does not request the manufacturing date; it merely provides information that will help identify a specific medical device. This information may help FDA determine whether a specific device design is a problem. Section H.4 asks when the device was manufactured; this information may be important should the manufacturer or FDA determine that the adverse event may be caused by manufacturing problems during a certain time period.

Another comment noted that the manufacturing date "may not be readily available for large equipment" and asked FDA to delete this item.

FDA does not agree with this comment's suggestion. As discussed above, determining the manufacturing date of a product is extremely important in enabling FDA to trace device defects to flaws in the manufacturing process. Consumers, health professionals, distributors, and others affected may then be informed with some precision of the products posing a risk, and any possible recall can be limited to the period in which the manufacturing flaw appeared.

One comment asked that, in order to reduce the burden on manufacturers, the manufacturing date should be changed from month, day, and year to month and year only.

FDA agrees and has revised the final form to request only the month and year.

Section H.4 in the proposed form (now renumbered as section H.5 in the final form) asks whether a device is "Labeled for single use." FDA received two comments suggesting that the section was not relevant to devices. Another comment requested clarification of this provision.

FDA does not agree with the assertion that the section is not relevant to devices. FDA is aware that adverse events can arise from the reuse of devices that are intended to be used only once.

Another comment stated that this section was not relevant to capital equipment.

If the section is not relevant to the device being reported, such as capital equipment, the "No" box is the appropriate selection.

One comment asserted that this section constituted FDA interference in the practice of medicine.

FDA does not agree with this comment because the requested information is part of section H of the form which only requests information from device manufacturers and

concerns labeling information. Information from this section is not intended to be used to interfere with the practice of medicine; it is intended to provide FDA with information to carry out its statutory obligation to protect the public health. Information from this category may, in turn, be provided to health care professionals to make them aware of unsafe devices for the protection of their patients.

FDA has enlarged and reformatted section H.9, "Evaluation codes; of the proposed form" (now renumbered as section H.6 in the final form). Several comments said FDA should eliminate this section because it was too narrow and called for subjective judgments rather than objective facts.

FDA does not agree with these assertions. Although all codes require a measure of subjective evaluation, they also enable reviewers to ascertain very quickly certain key facts. Manufacturers have, or can obtain, the best initial assessment of the product problem, and this will help FDA and the manufacturer determine the cause of the problem and take any steps necessary to protect the public health.

Section H.10 in the proposed form, "If remedial action initiated, check type," (now renumbered as section H.7 of the final form) provided nine boxes: "recall," "repair," "replace," "relabeling," "notification," "inspection," "patient monitoring," "modifications, adj.," and "other" that device manufacturers could select. FDA received two comments on this section.

One comment noted that some terms had not been defined, could "overlap," and requested clarification.

Most of these terms are defined or further explained in the act or in existing FDA regulations concerning recalls and remedial action (see 21 U.S.C. 360h and 21 CFR parts 7 and 803). FDA believes that the remaining terms are self-explanatory. If a manufacturer believes there is some overlap or that more than one type of remedial action applies, more than one box may be checked.

Another comment suggested that the "recall" option be placed in section H.11 (now renumbered as section H.9 in the final form) which requests that, if action is required under 21 U.S.C. 360i(f), the correction or removal reporting number be listed.

FDA believes the current format more clearly presents the requested information and allows FDA to determine quickly what remedial action has been taken by the manufacturer.

FDA also advises that the proposed form stated an incorrect citation, which has been corrected.

Section H.6 "Usage of Device," in the proposed form, is now renumbered as section H.8 in the final form. The proposed form offered three options: "initial use of device," "reuse," or "unknown." One comment claimed this section was not relevant to medical devices.

For the reasons stated in FDA's response to comments to section H.5, FDA disagrees with this comment. Adverse events can be related to reuse of devices only intended for a single use. Moreover, this information may help FDA to determine whether the adverse event is attributable to the device or to its operation and maintenance.

In section H.12 in the proposed form, "Manufacturer narrative," (now renumbered and renamed as section H.10, "Additional manufacturer narrative," in the final form) two comments questioned how this manufacturer narrative differed from the narrative requested in section B.5, "Describe event or problem."

FDA notes that Section H is to be completed solely by device manufacturers. In contrast, section B, "Adverse event or product problem," may be completed by individuals or entities other than device manufacturers. The accounts of the event by the manufacturer in section H may differ from the accounts presented by others in section B. This is particularly true because a manufacturer is obligated to investigate the causes of the adverse event, and is therefore likely to have additional information. FDA, however, does not wish the manufacturer to duplicate information that has already been provided in section B. In order to clarify that the manufacturer should only include in section H.10 information that is additional to that in section B.5, FDA has renamed section H.10 to request "Additional" manufacturer narrative.

In the proposed form, the manufacturer could indicate in section H.13, "Corrected data," (now renumbered as H.11 in the final form) as an alternative response to the proposed section H.12 request for "Manufacturer narrative." One comment suggested that FDA replace "12. manufacturer narrative or 13. corrected data" with a reference to the manufacturer narrative "and/or" corrected data, to clarify that both sections could be checked or only one section.

FDA agrees that both sections or one section could be checked and that "and/or" language is more appropriate. Device manufacturers could provide "corrected data" in addition to a "manufacturer narrative" or, under

certain circumstances, could provide only corrected data, or only "additional manufacturer narrative." Accordingly, FDA has revised this section to read "10. Additional manufacturer narrative and/or 11. Corrected data."

One comment requested clarification of "corrected data." Another comment asked whether checking the "corrected data" box would require the manufacturer to submit a 510(k) or PMA supplement.

The "correction" option is only to be used to indicate changes to information previously submitted. It refers to corrected information in the form and

not to any corrections the manufacturer may have made to the medical device or to data supporting the safety or effectiveness of the device.

Consequently, this option indicates only the form is being corrected, and a 510(k) or PMA supplement will not be necessary unless otherwise required under FDA regulations.

In addition, the agency, on its own initiative, has deleted draft section H.1, captioned, "Contact office—include address and phone if different from G.1" from section H, and merged the information request with section G.1 ("Contact office—name/address").

FDA received many comments on section H.3, "Product Code," in the proposed form. The comments expressed confusion over what information was being requested.

FDA has deleted this section.

The following versions of the form that appear on the next page are a representation and are not the actual size.

Dated: May 26, 1993.

David A. Kessler,
Commissioner of Food and Drugs.

BILLING CODE 4160-01-F

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

For VOLUNTARY reporting
by health professionals of adverse
events and product problems

Form Approved: OMB No. 0910-0291 Expires: 12/31/94
See OMB statement on reverse

FDA Use Only

Triage unit
sequence #

Page of

A. Patient information			
1. Patient identifier In confidence	2. Age at time of event: or Date of birth:	3. Sex <input type="checkbox"/> female <input type="checkbox"/> male	4. Weight ____ lbs or ____ kgs
B. Adverse event or product problem			
1. <input type="checkbox"/> Adverse event and/or <input type="checkbox"/> Product problem (e.g., defects/malfunctions)			
2. Outcomes attributed to adverse event (check all that apply)			
<input type="checkbox"/> death (mo day yr)	<input type="checkbox"/> disability	<input type="checkbox"/> congenital anomaly	<input type="checkbox"/> required intervention to prevent permanent impairment/damage
<input type="checkbox"/> life-threatening	<input type="checkbox"/> hospitalization - initial or prolonged	<input type="checkbox"/> other:	
3. Date of event (mo day yr)	4. Date of this report (mo day yr)		
5. Describe event or problem			
6. Relevant tests/laboratory data, including dates			
7. Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)			

C. Suspect medication(s)		
1. Name (give labeled strength & mfr/labeler, if known)		
#1 _____		
#2 _____		
2. Dose, frequency & route used		3. Therapy dates (if unknown, give duration) from to (or best estimate)
#1 _____		#1 _____
#2 _____		#2 _____
4. Diagnosis for use (indication)		5. Event abated after use stopped or dose reduced
#1 _____		#1 <input type="checkbox"/> yes <input type="checkbox"/> no <input type="checkbox"/> doesn't apply
#2 _____		#2 <input type="checkbox"/> yes <input type="checkbox"/> no <input type="checkbox"/> doesn't apply
6. Lot # (if known)		7. Exp. date (if known)
#1 _____		#1 _____
#2 _____		#2 _____
8. Event reappeared after reintroduction		
#1 <input type="checkbox"/> yes <input type="checkbox"/> no <input type="checkbox"/> doesn't apply		
#2 <input type="checkbox"/> yes <input type="checkbox"/> no <input type="checkbox"/> doesn't apply		
9. NDC # (for product problems only)		
- - -		
10. Concomitant medical products and therapy dates (exclude treatment of event)		

D. Suspect medical device	
1. Brand name	
2. Type of device	
3. Manufacturer name & address	4. Operator of device
	<input type="checkbox"/> health professional <input type="checkbox"/> lay user/patient <input type="checkbox"/> other:
5. Expiration date (mo day yr)	
6. model #	7. If implanted, give date (mo day yr)
catalog #	
serial #	8. If explanted, give date (mo day yr)
lot #	
other #	
9. Device available for evaluation? (Do not send to FDA)	
<input type="checkbox"/> yes <input type="checkbox"/> no <input type="checkbox"/> returned to manufacturer on (mo day yr)	
10. Concomitant medical products and therapy dates (exclude treatment of event)	

E. Reporter (see confidentiality section on back)			
1. Name, address & phone #			
2. Health professional? <input type="checkbox"/> yes <input type="checkbox"/> no			
3. Occupation		4. Also reported to	
		<input type="checkbox"/> manufacturer <input type="checkbox"/> user facility <input type="checkbox"/> distributor	
5. If you do NOT want your identity disclosed to the manufacturer, place an "X" in this box. <input type="checkbox"/>			



Mail to: MEDWATCH
5600 Fishers Lane
Rockville, MD 20852-9787

or FAX to:
1-800-FDA-0178

ADVICE ABOUT VOLUNTARY REPORTING

Report experiences with:

- medications (drugs or biologics)
- medical devices (including in-vitro diagnostics)
- special nutritional products (dietary supplements, medical foods, infant formulas)
- other products regulated by FDA

Report **SERIOUS** adverse events. An event is serious when the patient outcome is:

- death
- life-threatening (real risk of dying)
- hospitalization (initial or prolonged)
- disability (significant, persistent or permanent)
- congenital anomaly
- required intervention to prevent permanent impairment or damage

Report even if:

- you're not certain the product caused the event
- you don't have all the details

Report product problems – quality, performance or safety concerns such as:

- suspected contamination
- questionable stability
- defective components
- poor packaging or labeling

How to report:

- just fill in the sections that apply to your report
- use section C for all products except medical devices
- attach additional blank pages if needed
- use a separate form for each patient
- report either to FDA or the manufacturer (or both)

Important numbers:

- 1-800-FDA-0178 to FAX report
- 1-800-FDA-7737 to report by modem
- 1-800-FDA-1088 for more information or to report quality problems
- 1-800-822-7967 for a VAERS form for vaccines

If your report involves a serious adverse event with a device and it occurred in a facility outside a doctor's office, that facility may be legally required to report to FDA and/or the manufacturer. Please notify the person in that facility who would handle such reporting.

Confidentiality: The patient's identity is held in strict confidence by FDA and protected to the fullest extent of the law. The reporter's identity may be shared with the manufacturer unless requested otherwise. However, FDA will not disclose the reporter's identity in response to a request from the public, pursuant to the Freedom of Information Act.

The public reporting burden for this collection of information has been estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send your comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Reports Clearance Officer, PHS
Hubert H. Humphrey Building,
Room 721-B
200 Independence Avenue, S.W.
Washington, DC 20201
ATTN: PRA

and to:
Office of Management and
Budget
Paperwork Reduction Project
(0910-0291)
Washington, DC 20503

Please do NOT
return this form
to either of these
addresses.

FDA Form 3500-back

Please Use Address Provided Below – Just Fold In Thirds, Tape and Mail

Department of Health and Human Services

Public Health Service
Food and Drug Administration
Rockville, MD 20857

Official Business
Penalty for Private Use \$300

MEDWATCH

The FDA Medical Products Reporting Program
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20852-9787

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

For use by user-facilities,
distributors and manufacturers for
MANDATORY reporting

Page _____ of _____

Form Approved: OMB No. 0910-0291 Expires: 7/31/94
See OMB statement on reverse

Mfr report #
UFDAI report #
FDA Use Only

A. Patient information

1. Patient Identifier	2. Age at time of event: or Date of birth:	3. Sex <input type="checkbox"/> female <input type="checkbox"/> male	4. Weight ____ lbs or ____ kgs
-----------------------	--	--	---

In confidence

B. Adverse event or product problem

1. <input type="checkbox"/> Adverse event and/or <input type="checkbox"/> Product problem (e.g., defects/malfunctions)	
2. Outcomes attributed to adverse event (check all that apply)	
<input type="checkbox"/> death (mo day yr)	<input type="checkbox"/> disability
<input type="checkbox"/> life threatening	<input type="checkbox"/> congenital anomaly
<input type="checkbox"/> hospitalization - initial or prolonged	<input type="checkbox"/> required intervention to prevent permanent impairment/damage
<input type="checkbox"/> other:	
3. Date of event (mo day yr)	4. Date of this report (mo day yr)

5. Describe event or problem

6. Relevant tests/laboratory data, including dates

7. Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

C. Suspect medication(s)

1. Name (give labeled strength & mfr/labeler, if known)	
#1	
#2	
2. Dose, frequency & route used	3. Therapy dates (if unknown, give duration from to or best estimate)
#1	#1
#2	#2
4. Diagnosis for use (indication)	5. Event abated after use stopped or dose reduced
#1	#1 <input type="checkbox"/> yes <input type="checkbox"/> no <input type="checkbox"/> doesn't apply
#2	#2 <input type="checkbox"/> yes <input type="checkbox"/> no <input type="checkbox"/> doesn't apply
6. Lot # (if known)	7. Exp. date (if known)
#1	#1
#2	#2
8. Event reappeared after reintroduction	
#1 <input type="checkbox"/> yes <input type="checkbox"/> no <input type="checkbox"/> doesn't apply	
#2 <input type="checkbox"/> yes <input type="checkbox"/> no <input type="checkbox"/> doesn't apply	
9. NDC # - for product problems only (if known)	
10. Concomitant medical products and therapy dates (exclude treatment of event)	

D. Suspect medical device

1. Brand name	
2. Type of device	
3. Manufacturer name & address	4. Operator of device
	<input type="checkbox"/> health professional <input type="checkbox"/> lay user/patient <input type="checkbox"/> other
5. Expiration date (mo day yr)	6. If implanted, give date (mo day yr)
7. If explanted, give date (mo day yr)	8. If explanted, give date (mo day yr)
9. Device available for evaluation? (Do not send to FDA)	
<input type="checkbox"/> yes <input type="checkbox"/> no <input type="checkbox"/> returned to manufacturer on (mo day yr)	
10. Concomitant medical products and therapy dates (exclude treatment of event)	

E. Initial reporter

1. Name, address & phone #			
2. Health professional?	3. Occupation	4. Initial reporter also sent report to FDA	
<input type="checkbox"/> yes <input type="checkbox"/> no		<input type="checkbox"/> yes <input type="checkbox"/> no <input type="checkbox"/> unk	



FDA Form 3500A (6/93)

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

Medication and Device Experience Report (continued)

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

Refer to guidelines for specific instructions

Page of

FDA Use Only

F. For use by user facility/distributor—devices only. 1. Check one: user facility, distributor. 2. UF/Dist report number. 3. User facility or distributor name/address. 4. Contact person. 5. Phone Number. 6. Date user facility or distributor became aware of event. 7. Type of report: initial, follow-up #. 8. Date of this report. 9. Approximate age of device. 10. Event problem codes. 11. Report sent to FDA? 12. Location where event occurred. 13. Report sent to manufacturer? 14. Manufacturer name/address.

H. Device manufacturers only. 1. Type of reportable event: death, serious injury, malfunction, other. 2. If follow-up, what type? correction, additional information, response to FDA request, device evaluation. 3. Device evaluated by mfr? not returned to mfr, yes, no. 4. Device manufacture date. 5. Labeled for single use? 6. Evaluation codes (method, results, conclusions). 7. If remedial action initiated, check type: recall, repair, replace, relabeling, other. 8. Usage of device: initial use, reuse, unknown. 9. If action reported to FDA under 21 USC 360(f), list correction/removal reporting number. 10. Additional manufacturer narrative and/or 11. Corrected data.

G. All manufacturers. 1. Contact office - name/address (& mfring site for devices). 2. Phone number. 3. Report source (check all that apply): foreign, study, literature, consumer, health professional, user facility, company representative, distributor, other. 4. Date received by manufacturer. 5. (A)NDA #, IND #, PLA #, pre-1938, OTC product. 6. If IND, protocol #. 7. Type of report (check all that apply): 5-day, 10-day, initial, 15-day, periodic, follow-up #. 8. Adverse event term(s). 9. Mfr. report number.

The public reporting burden for this collection of information has been estimated to average one-hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send your comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to...

Reports Clearance Officer, PHS Hubert H. Humphrey Building, Room 721-B 200 Independence Avenue, S.W. Washington, DC 20201 ATTN: PRA

and to: Office of Management and Budget Paperwork Reduction Project (6010-0291) Washington, DC 20503

Please do NOT return this form to either of these addresses.

FDA Form 3500A - back

[FR Doc. 93-12917 Filed 6-2-93; 8:45 am]

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