DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 20, 310, 312, 314, and 600

[Docket No. 93N–0181]

RIN 0910–AA97

Expedited Safety Reporting Requirements for Human Drug and Biological Products

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is amending its expedited safety reporting regulations for human drug and biological products to provide consistency with the elements of FDA Form 3500A for use in pre- and postmarketing safety reporting;

implement definitions, reporting periods, formats, and standards as recommended by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and by the World Health Organization's Council for International Organizations of Medical Sciences (CIOMS); require applicants, manufacturers, packers, and distributors, as well as licensed manufacturers and other manufacturers of biological products, to develop written procedures for postmarketing safety monitoring and reporting; state that FDA Form 3500A reports that FDA forwards to any person subject to the postmarketing safety reporting requirements are not required to be resubmitted to the agency; and make other revisions to the regulations to provide uniformity with definitions and procedures used in expedited pre- and postmarketing safety reporting for human drug and biological products. These changes simplify and facilitate expedited safety reporting and enhance agencywide consistency in the collection of postmarketing safety data.

DATES: This regulation is effective April 6, 1998. Submit written comments on the information collection provisions of this final rule by December 8, 1997.

ADDRESSES: Submit written comments on the information collection provisions of this final rule to the Dockets Management Branch (HFA-305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1-23, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT:

For information concerning human drug products: Audrey A. Thomas, Center for Drug Evaluation and Research (HFD-7), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-594-5625.

For information concerning human biological products: Valerie A. Butler, Center for Biologics Evaluation and Research (HFM-17), Food and Drug Administration, 1401 Rockville Pike, suite 200N, Rockville, MD 20852-1448, 301-594-3074.

SUPPLEMENTARY INFORMATION:

I. Introduction

In the **Federal Register** of October 27, 1994 (59 FR 54046), FDA published a proposed rule to amend the regulations for expedited and periodic pre- and postmarketing safety reporting for human drug and biological products (hereinafter referred to as the October 1994 proposal). FDA also proposed to amend the requirements for clinical study design and conduct and annual sponsor reporting in the investigational new drug application (IND) regulations.

As explained in the October 1994 proposal, the amendments to the safety reporting regulations are intended to provide consistency with certain standardized definitions, procedures, and formats developed by ICH and CIOMS (59 FR 54046 at 54047). In the **Federal Register** of July 9, 1993 (58 FR 37408), FDA published an ICH draft guideline entitled "Clinical Safety Data Management: Definitions and Standards for Expedited Reporting" (hereinafter referred to as the draft ICH E2A guideline). The public was given an opportunity to comment on the draft ICH E2A guideline. After consideration of the comments received and revisions to the draft guideline, ICH finalized the guideline. In the **Federal Register** of March 1, 1995 (60 FR 11284), FDA published the ICH final guideline (hereinafter referred to as the final ICH E2A guideline). Although the final ICH E2A guideline pertains to expedited safety reporting during the preapproval phase of drug development, for consistency and simplicity many of the definitions, reporting periods, formats, and standards also could apply to FDA's expedited postmarketing safety reporting requirements.

In this final rule, FDA is amending its regulations for expedited safety reporting to implement certain definitions, reporting periods, and formats recommended in the final ICH E2A guideline. FDA is considering other recommendations in the final ICH E2A guideline that were not included in the October 1994 proposal and plans to propose additional amendments to its expedited safety reporting regulations shortly (e.g., pre- and postmarketing reporting of adverse drug reactions rather than adverse drug experiences, submission of expedited safety reports to FDA from clinical investigations based on the opinion of either the sponsor or investigator).

FDA is delaying finalization of the proposed amendments to the periodic postmarketing safety reporting regulations (59 FR 54046). The proposed amendments were based, for the most part, on recommendations developed by the CIOMS Working Group II (Ref. 1). ICH also developed recommendations, based on the CIOMS Working Group II proposals, for periodic postmarketing safety reporting. In the **Federal Register** of May 19, 1997 (62 FR 27470), FDA published an ICH final guideline entitled "Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs" (hereinafter referred to as the ICH E2C guideline). FDA will finalize the proposed amendments to the periodic postmarketing safety reporting regulations after consideration of the provisions of the ICH E2C guideline.

In light of the comments the agency received, FDA has reconsidered the proposed amendments to the requirements for clinical study design and conduct and annual sponsor reporting under the IND (59 FR 54046). In general, the comments opposed the proposed amendments because the current IND regulations protect the safety of the public in all but the most unusual cases. Based on these general comments and others specific to each of the proposed amendments, the agency has decided to withdraw the proposed amendments to the IND requirements for clinical study design and conduct and annual sponsor reporting. The agency will, instead, develop a guidance document providing recommendations on study design and monitoring of investigational drugs used to treat serious and potentially fatal illnesses, with particular attention to detection of adverse events that are similar to those caused by the underlying disease. In developing the draft guidance document, FDA will consider comments submitted in response to the proposed amendments and will provide opportunity for public input on the document prior to its implementation. Thus, in this final rule, FDA is withdrawing the proposed amendments to the IND regulations (part 312 (21 CFR part 312)) at §§ 312.23, the second sentence of 312.32(c)(1)(i), 312.33, 312.37, 312.42, 312.44, 312.56, and 312.64 (59 FR 54046 at 54057 to 54059).

In the **Federal Register** of June 25, 1997 (62 FR 34166), FDA published a final rule to amend its regulations on expedited reporting of postmarketing adverse experiences to revoke the requirement for increased frequency reports as expedited reports for human drug and licensed biological products. Thus, in this final rule, FDA is withdrawing the proposed amendments to the increased frequency reporting requirements published in the October 1994 proposal.

II. Background

In the **Federal Register** of June 3, 1993 (58 FR 31596), FDA announced the availability of a new form for reporting single cases of adverse events and product problems with medications, devices, and other FDA-regulated medical products (hereinafter referred to as the June 1993 notice). This form is available in two versions: FDA Form 3500 is for use by health care professionals and consumers for

voluntary reporting; FDA Form 3500A is for use by any person subject to FDA's mandatory safety reporting regulations. Adverse events associated with vaccines continue to be reported to FDA and the Centers for Disease Control and Prevention using the Vaccine Adverse Event Reporting System (VAERS) form.

Under the existing regulations, manufacturers, packers, and distributors; applicants of approved new and abbreviated marketing applications for drugs and antibiotics; and licensed manufacturers and other manufacturers of biological products must submit expedited reports of postmarketing adverse drug experiences under 21 CFR 310.305, 314.80, 314.98, and 600.80. Sponsors of IND's must also submit expedited reports, under § 312.32, for adverse experiences associated with the use of an investigational human drug or biological product. Currently, there is no standard form for these IND expedited safety reports.

FDA Forms 3500 and 3500A are part of FDA's Medical Products Reporting Program (MedWatch) and are designed to facilitate safety reporting for most FDA-regulated human medical products by the entire health care community, including manufacturers, distributors, user facilities, and health care professionals. FDA issued the new forms to simplify and consolidate safety reporting for human drug products, biologics, and medical devices, as well as other FDA-regulated medical products. The new forms eliminate redundant or nonessential elements from past reporting forms and clarify those areas that have caused confusion.

In developing FDA Forms 3500 and 3500A, and in developing the revisions to the expedited safety reporting regulations that are the subject of this final rule, the agency considered several ICH and CIOMS recommendations. These organizations were formed to facilitate international consideration of issues, particularly safety issues, concerning the use of both foreign and domestic data in the development and use of drugs and biological products. ICH has worked to promote the harmonization of technical requirements for the registration of pharmaceutical products among three regions: The European Union, Japan, and the United States. In addition, several CIOMS working groups have served to coordinate and standardize the international reporting of suspected postmarketing adverse drug reactions by pharmaceutical manufacturers to regulatory authorities. FDA believes the changes recommended by CIOMS and ICH will result in more effective and efficient safety reporting to regulatory authorities worldwide.

III. Description of the Final Rule

This final rule amends parts 20, 310, 312, 314, and 600 (21 CFR parts 20, 310, 312, 314, and 600) to revise definitions, requirements, and procedures for expedited pre- and postmarketing safety reporting. This rulemaking finalizes many of the expedited safety reporting provisions as proposed in the October 1994 proposal. In addition, this final rule reflects amendments to the October 1994 proposal that were made in response to comments (discussed in section IV of this document), including comments recommending greater consistency with the ICH E2A guideline and uniformity between pre- and postmarketing safety reporting definitions. This final rule also incorporates minor revisions for clarity and further consistency. The major provisions of the final rule are summarized as follows:

1. *FDA Forms 3500/3500A.* As proposed, the final rule permits sponsors to submit IND safety reports, under § 312.32(c)(1)(i), on FDA Form 3500A rather than in a narrative format, and replaces, at §§ 310.305 and 314.80, Form FDA–1639 with FDA Form 3500A for use in postmarketing safety reporting for human drug products. The final rule also replaces, at § 20.112, Form FDA–1639 with FDA Form 3500 for voluntary drug experience reporting by physicians and hospitals. The final rule, like the proposed rule, instructs applicants, manufacturers, packers, and distributors to obtain approval from FDA's MedWatch office before using an alternative reporting format for postmarketing safety reporting under §§ 310.305(d)(3)(ii) and 314.80(f)(3)(ii). Pre- and postmarketing safety reporting of foreign events may continue to be reported to FDA on the CIOMS I form (Ref. 2). After consideration of the comments, the final rule, unlike the proposed rule, permits use of the CIOMS I form for this purpose without prior FDA approval.

2. *Definitions.* In response to comments, the proposed definition of "serious" at §§ 310.305(b), 312.32(a), 314.80(a), and 600.80(a) has been revised to make it consistent with the definition of "serious" in the final ICH E2A guideline and with the definition of "serious" used in FDA Form 3500A. To provide uniformity between the pre- and postmarketing definitions of "serious," the following information has been removed from the current definition of "serious adverse experience" at § 312.32(a) and added as a reporting requirement to the IND safety reporting regulations at § 312.32(c)(1)(i):

> With respect to results obtained from tests in laboratory animals, a serious adverse drug experience includes any experience suggesting a significant risk for human subjects, including any finding of mutagenicity, teratogenicity, or carcinogenicity.

This revision represents an organizational change that does not impose a new burden because sponsors are already required to report such information to FDA.

In response to comments, the final rule also amends the proposed definitions of "disability" and "life-threatening" at §§ 310.305(b), 314.80(a), and 600.80(a) for consistency with the final ICH E2A guideline and for clarity. In addition, the definition of "disability" has been added to the "definitions" section of the premarketing safety reporting regulations at § 312.32(a), and the definition of "life-threatening" has been removed from the "telephone safety report" section of the premarketing safety reporting regulations at § 312.32(c)(2) and added to the "definitions" section of these regulations at § 312.32(a). For further clarity and consistency in reporting adverse drug experiences that are life-threatening, FDA has decided to replace, at §§ 310.305(b), 312.32(a), 314.80(a), and 600.80(a), the word "serious" with "severe" so that the first sentence of the definition of "life-threatening" includes the following: "* * *, i.e., [Life-threatening] does not include a reaction that, had it occurred in a more severe form, might have caused death." As explained in the final ICH E2A guideline, "severe" refers to the intensity (severity) of a specific event (e.g., mild, moderate, or severe myocardial infarction); the event itself may be of relatively minor medical significance such as a severe headache. The term "serious," however, is based on patient/event outcome or action criteria usually associated with events that pose a threat to a patient's life or functioning (e.g., an event that results in death or that is life-threatening or requires inpatient hospitalization) (60 FR 11284 at 11285). FDA has also decided to remove the following sentence from this definition: "For example, drug-induced hepatitis that resolved without evidence of hepatic failure would not be considered life-threatening even though drug-induced hepatitis can be fatal." Use of hepatitis as an example for life-threatening may be confusing because viral transmission of certain types of hepatitis through blood products could be life-

threatening. To harmonize pre- and postmarketing safety reporting definitions, FDA has decided to withdraw the examples listed in the proposed postmarketing definition of "life-threatening" at §§ 310.305(b), 314.80(a), and 600.80(a). The agency has decided, instead, to revise the guidances associated with this final rule to include examples of life-threatening adverse drug experiences (CDER's "Guideline for Postmarketing Reporting of Adverse Drug Experiences," March 1992 and CBER's "Guideline for Adverse Experience Reporting for Licensed Biological Products," October 1993).

In this final rule, FDA is incorporating minor changes to the definition of "unexpected" adverse drug experience at §§ 310.305(b), 312.32(a), 314.80(a), and 600.80(a) to provide uniformity between pre- and postmarketing safety reporting definitions and consistency with the ICH E2A guideline.

The definition of "unexpected" adverse drug experience at §§ 310.305(b), 314.80(a), and 600.80(a) currently states:

> * * * an adverse drug experience that is not listed in the current labeling for the drug product and includes an event that may be symptomatically and pathophysiologically related to an event listed in the labeling, but differs from the event because of greater severity or specificity. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the labeling only referred to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the labeling only listed cerebral vascular accidents.

To clarify what must be reported to the agency as an "unexpected adverse drug experience," FDA is amending this definition by adding the following sentence:

> "Unexpected," as used in this definition, refers to an adverse drug experience that has not been previously observed (i.e., included in the labeling) rather than from the perspective of such experience not being anticipated from the pharmacological properties of the pharmaceutical product.

This amendment is consistent with the discussion of "expectedness of an adverse drug reaction" in the final ICH E2A guideline:

> The purpose of expedited reporting is to make regulators, investigators, and other appropriate people aware of new, important information on serious reactions. Therefore, such reporting will generally involve events previously unobserved or undocumented, and a guideline is needed on how to define an event as "unexpected" or "expected" (expected/ unexpected from the perspective of previously observed, not on the basis of what might be anticipated from the pharmacological properties of a medicinal product).

The definition of "unexpected adverse experience" at § 312.32(a) currently states:

> * * * any adverse experience that is not identified in nature, severity, or frequency in the current investigator brochure; or, if an investigator brochure is not required, that is not identified in nature, severity, or freuquency [sic] in the risk information described in the general investigational plan or elsewhere in the current application, as amended.

For clarity and consistency, FDA is amending this definition to conform with the definition of "unexpected" at §§ 310.305(b), 314.80(a), and 600.80(a) by removing the references to frequency, replacing the word "nature" with the word "specificity," adding examples of unexpected adverse drug experiences, and making other minor revisions. The revised definition at § 312.32(a) states:

> *Unexpected adverse drug experience*: Any adverse drug experience, the specificity or severity of which is not consistent with the current investigator brochure; or if an investigator brochure is not required or available, the specificity or severity of which is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the investigator brochure only referred to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the investigator brochure only listed cerebral vascular accidents.
> "Unexpected," as used in this definition, refers to an adverse drug experience that has not been previously observed (e.g., included in the investigator brochure) rather than from the perspective of such experience not being anticipated from the pharmacological properties of the pharmaceutical product.

3. *IND Safety Reports.* As proposed, the final rule revises the time period for submitting written IND safety reports, under § 312.32(c)(1) and (d)(3), from 10 working days to 15 calendar days, and revises the time period for submitting telephone IND safety reports, under § 312.32(c)(2), from 3 working days to 7 calendar days. The final rule also permits telephone safety reports to be made by facsimile transmission under § 312.32(c)(2). The final rule, as proposed with minor revisions for clarity, also states, at § 312.32(c)(1)(i), that FDA may require sponsors to submit additional data.

In response to comments, FDA is making minor revisions to its IND safety reporting regulations to provide greater consistency with the final ICH E2A guideline. Currently, the requirement at § 312.32(b) states:

> The sponsor shall promptly review all information relevant to the safety of the drug obtained or otherwise received by the sponsor from any source, foreign or domestic, including information derived from clinical investigations, animal investigations, commercial marketing experience, reports in the scientific literature, and unpublished scientific papers.

To clarify the phrase "any source," FDA is adding "epidemiological investigations" and "foreign regulatory authorities that have not already been previously reported to the agency by the sponsor" to the list of examples in § 312.32(b). This revision does not impose a new burden because sponsors are already required to review all information relevant to the safety of the drug obtained or otherwise received by the sponsor from any source, foreign or domestic. The amendment clarifies for sponsors the type of safety information that must be examined for determination of whether information should be submitted to the agency in IND safety reports. This revision is consistent with the final ICH E2A guideline (60 FR 11284 at 11285 and 11286):

> [Expedited reporting] applies to reports from spontaneous sources and from any type of clinical or epidemiological investigation, independent of design or purpose.

The agency does not expect sponsors to search adverse drug experience data bases generated by regulatory authorities for safety information or to submit to FDA adverse drug experience reports submitted to them by FDA.

FDA is also amending its IND safety reporting regulations at § 312.32(c)(1)(i), as noted above, by adding, with minor revisions, language that is being moved from the current definition of "serious adverse experience" at § 312.32(a):

> any finding from tests in laboratory animals that suggests a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity.

This revision represents an organizational change that does not impose any new burden because sponsors are currently required to report such information to FDA. For clarity and consistency, FDA is amending § 312.32(c)(1)(i) to state that reports from animal studies and epidemiological studies must be submitted in a narrative format rather than on FDA Form 3500A because FDA Form 3500A has been designed for reporting of adverse experience information from an individual patient.

4. *Postmarketing 15-day Alert and Followup Reports.* As proposed, the final rule revises, at §§ 310.305(c), 314.80(c), and 600.80(c), the time period for submitting postmarketing Alert reports from 15 working days to 15 calendar days. For clarity, the final rule is being amended, at § 310.305(c)(1)(i),

to state that the 15 calendar day timeframe for reporting adverse drug experiences on marketed prescription drugs for human use without approved new drug applications (NDA's) begins upon initial receipt of the information by the person whose name appears on the label. In addition, the final rule at §§ 310.305(c)(2), 314.80(c)(1)(ii), and 600.80(c)(1)(ii), as proposed, advises any person subject to the reporting requirements under §§ 310.305(c), 314.80(c), and 600.80(c), who has been unable to obtain additional information for adverse drug experiences that are the subject of postmarketing 15-day Alert reports, to maintain records of their unsuccessful attempts to seek additional information. For clarity, the final rule is being amended, at § 310.305(c)(2), to state that 15-day Alert reports and followups to them must be submitted under separate cover.

The final rule specifies, like the proposed rule, at §§ 310.305(c)(6), 314.80(b), and 600.80(b), that no one subject to this rule is required to resubmit to the agency reports of adverse drug experiences that the agency has forwarded to them. For clarity, the final rule is being amended, at §§ 310.305(c)(6), 314.80(b), and 600.80(b), to emphasize that followup reports must be submitted for reports received from the agency. The final rule also requires, at §§ 310.305(a), 314.80(b), and 600.80(b), any person subject to the reporting requirements under §§ 310.305(c), 314.80(c), and 600.80(c) to develop written procedures for the postmarketing surveillance, receipt, evaluation, and reporting of adverse drug experiences to FDA. In response to comments, the final rule permits persons subject to the reporting requirements under §§ 310.305(c), 314.80(c), and 600.80(c) to submit reports of serious adverse drug experiences to a manufacturer, applicant, or licensed manufacturer of a final biological product instead of FDA in 5 calendar days, instead of 3 calendar days as proposed.

In this final rule, FDA is also amending the postmarketing expedited reporting regulations, at §§ 314.80(c)(1)(i) and 600.80(c)(1)(i), by replacing, in the first sentence, the phrase "regardless of source" with the phrase "whether foreign or domestic." This amendment is consistent with §§ 314.80(b) and 600.80(b) which describe adverse drug experience information that must be reviewed by applicants and licensed manufacturers:

> Each applicant (Any person having a product license) * * * shall promptly review all adverse drug experience information (pertaining to its product) obtained or otherwise received by the applicant (licensed manufacturer) from any source, foreign or domestic, including * * *.

FDA is making this revision to clarify that 15-day Alert reports are to be submitted for appropriate foreign as well as domestic adverse drug experiences.

5. *Implementation Schedule.* The effective date for this final rule has been extended to 180 days after its publication in the **Federal Register** to allow sufficient time for the agency to comply with the provisions of the Paperwork Reduction Act of 1995. Any person subject to FDA's mandatory safety reporting requirements may comply with the provisions of this final rule prior to its effective date.

6. *Guidances.* In the **Federal Register** of February 27, 1997 (62 FR 8961), FDA published a notice of a guidance document entitled "Good Guidance Practices (GGP's)," in which FDA announced that notices of draft and final guidances will be provided both in the **Federal Register** and on the FDA World Wide Web (WWW) home page (http://www.fda.gov) (62 FR 8961 at 8965). In this final rule, FDA is amending its postmarketing safety reporting regulations at §§ 314.80(j) and 600.80(j) to remove reference to guidelines prepared by the agency for submission of reports of adverse drug experiences and suggested followup investigation of these reports. FDA is also withdrawing its proposed amendments of October 27, 1994, regarding the availability of adverse experience reporting guidelines under §§ 310.305(g), 314.80(j), and 600.80(j). FDA is making these amendments because the guidance document of February 27, 1997, describes processes for timely notification of availability of draft and final guidance documents and it is no longer necessary for the agency to include reference to these documents in its postmarketing safety reporting regulations.

At the present time, FDA is in the process of revising guidances pertaining to this final rule (CDER's "Guideline for Postmarketing Reporting of Adverse Drug Experiences," March 1992 and CBER's "Guideline for Adverse Experience Reporting for Licensed Biological Products," October 1993) to provide persons with the agency's current thinking on reporting of postmarketing adverse drug experiences. The agency will provide notice of availability of any draft or final guidance document pertaining to these regulations in the **Federal Register** and on the FDA WWW home page.

IV. Comments on the Proposed Rule

FDA received 57 comments on the proposed rule from representatives of pharmaceutical companies, health care professional and pharmaceutical associations, academic and government institutions, and individuals. The comments addressed all aspects of the October 1994 proposal, including those areas that are not being finalized in this final rule. In general, the comments endorsed FDA's efforts in the proposal to support global harmonization through the adoption of certain ICH and CIOMS recommendations. However, many comments described areas where the proposed regulations did not conform to the international guidelines, and recommended that the proposal be revised to be more consistent. The agency also received comments recommending uniformity between its pre- and postmarketing safety reporting definitions. In response to these comments, FDA, as described in section III of this document, is amending its regulations to implement additional provisions recommended in the final ICH E2A guideline and to provide uniformity in its safety reporting definitions.

A discussion of the comments pertaining to this final rule and the agency's responses follows.

A. Definition of Disability

FDA proposed to define "disability," in §§ 310.305(b), 314.80(a), and 600.80(a), as "a substantial disruption of a person's ability to carry out normal life functions."

1. Eight comments requested clarification of this definition. One comment asked whether it included missing work because of an adverse experience, quitting a job, an inability to get out of bed, or a decrease in earning capacity. Another comment asked if it included nausea, vomiting, and diarrhea that would keep a person home from work. One questioned whether the proposed definition included events such as migraine headaches, severe influenza, or accidental trauma (e.g., sprained ankle). Another comment contended that if the proposed definition is intended to mean the substantial disruption of normal life functions, then such a condition would require hospitalization or the in-house use of life-support equipment.

FDA proposed to include the definition of "disability" in the regulations to enable reporters to determine when a "serious" adverse drug experience occurs. The extent of a disability required for a serious adverse drug experience is described in the

nition of "serious" by the phrase * * results in *persistent* or *significant* disability/*incapacity* * * *." Thus, only a persistent or significant or incapacitating disability is intended. The type of disability that would constitute a serious adverse drug experience is also described in the final ICH E2A guideline, which states that a serious adverse drug experience is based on events that pose a threat to a patient's life or functioning and not on events of relatively minor medical significance (60 FR 11284 at 11285). Thus, disability is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle).

For clarity, FDA has revised the proposed definition of "disability" by substituting the words "to conduct" for the words "to carry out."

To assure a consistent interpretation of serious adverse drug experience in premarketing and postmarketing safety reporting, FDA has decided to revise the "definitions" section of the IND safety reports regulation, at § 312.32(a), by adding the definition of "disability" that used in the postmarketing safety reporting regulations at §§ 310.305(b), 314.80(a), and 600.80(a).

B. Definition of Life-Threatening

FDA proposed to define "life-threatening," in §§ 310.305(b), 314.80(a), and 600.80(a), as follows:

[T]hat the patient was, in the view of the initial reporter, at immediate risk of death from the adverse experience as it occurred. It does not include an adverse experience that, had it occurred in a more serious form, might have caused death. For example, product-induced hepatitis that resolved without evidence of hepatic failure would not be considered life-threatening even though hepatitis of a more severe nature can be fatal. Similarly, an allergic reaction resulting in angioedema of the face would not be life-threatening, even though angioedema of the larynx, allergic bronchospasm, or anaphylaxis can be fatal.

2. Five comments opposed the use of the phrase "in the view of the initial reporter." The comments stated that the initial reporter could be a lay person whose judgment of what constitutes an "immediate risk of death" may be contrary to an evaluation by a medically knowledgeable source. Several comments suggested alternative language for the definition to minimize inaccurate reporting of events. One comment requested deletion of the word "initial." Another suggested changing the phrase "initial reporter" to "a health care professional directly associated with the care of the patient," while a third recommended changing the word "reporter" to "health care provider who reports the adverse experience."

FDA declines to amend the proposed definition of "life-threatening" by deleting or revising the phrase "in the view of the initial reporter." As explained in the June 1993 notice (58 FR 31596 and 31604), FDA encourages health care professionals and consumers to report adverse drug experiences to manufacturers. FDA Form 3500A includes a section for identifying the "initial reporter" and for indicating the reporter's occupation and whether the person is a health care professional. Thus, the manufacturer and FDA will know whether the adverse drug experience report came from a lay person or a health care professional and can take that information into account when evaluating the report.

Current IND safety reporting regulations for telephone reports define a "life-threatening" experience at § 312.32(c)(2), as:

* * * that the patient was, in the view of the investigator, at *immediate* (emphasis added) risk of death from the reaction as it occurred, i.e., it does not include a reaction that, had it occurred in a more serious form, might have caused death. For example, drug-induced hepatitis that resolved without evidence of hepatic failure would not be considered life-threatening even though drug-induced hepatitis can be fatal.

FDA has decided, on its own initiative, to remove the definition of "life-threatening" from the telephone safety reports section, at § 312.32(c)(2), and add it to the general "definitions" section of § 312.32, at § 312.32(a). This action will clarify that reporting of life-threatening events apply to both written and telephone IND safety reports. FDA has also replaced "serious" with "severe" in the definition of "life-threatening" to make it consistent with the final ICH E2A guideline. FDA has also decided, on its own initiative, to add the words "or subject" after "patient" in this definition to clarify that IND safety reports apply to healthy subjects as well as patients. FDA has also removed the last sentence in the definition of "life-threatening" under § 312.32 (and the last two sentences in the proposed postmarketing definition of "life-threatening" under §§ 310.305(b), 314.80(a), and 600.80(a)), as noted in section III of this document, to minimize confusion. The revised definition of "life-threatening adverse drug experience" in the IND safety reporting regulations at § 312.32(a) reads as follows:

Any adverse drug experience that places the patient or subject, in the view of the investigator, at *immediate* risk of death from the reaction as it occurred, i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death.

C. Definition of Serious

FDA proposed to revise the definition of "serious," in §§ 310.305(b), 312.32(a), 314.80(a), and 600.80(a), to read as follows:

Serious means an adverse drug experience occurring at any dose that is fatal or life-threatening, results in persistent or significant disability/incapacity, requires or prolongs inpatient hospitalization, necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure, or is a congenital anomaly.

3. Twenty-five comments opposed all or parts of the phrase "necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure." Nine comments stated that this phrase makes the U.S. definition of "serious" inconsistent with harmonized safety reporting standards such as the ICH E2A and E6 guidelines and with the CIOMS II report. One comment said that although the phrase was included to provide a consistent definition of what constitutes a serious adverse event for all FDA-regulated products, it causes inconsistency between United States and international reporting requirements. Another comment said that the difference in definitions between the United States and the international community will cause confusion and additional expense for manufacturers who are complying with the reporting requirements of several countries. One comment stated that if the definition is finalized as proposed, preparation and submission of a single postmarketing periodic report worldwide will not be possible. Another comment said that a definition as important as "serious" should be internationally consistent in order to be easy to learn, quote, and recognize in global clinical development and medical safety. One comment noted that it would be especially difficult to implement the proposed criterion of "medical/surgical intervention" during the course of an ongoing clinical study.

Ten comments recommended deletion of the phrase. Eleven comments requested clarification of the phrase because it is too vague and misinterpretation would result in overreporting or underreporting of adverse events. Another comment suggested that the phrase be reworded as an "unusual and potentially serious experience that necessitates any medical or surgical intervention." One comment recommended adopting the approach in the final ICH E2A guideline of including "medical and surgical intervention"

within the area of "other important medical events." The comment indicated that the guideline leaves the determination of whether or not such an event is serious to medical and scientific judgment.

As explained in the June 1993 notice (58 FR 31596), FDA Forms 3500 and 3500A are designed to encourage and facilitate the reporting of adverse events and product problems for most FDA-regulated human medical products by the entire health care community, including manufacturers, distributors, user facilities, and health care professionals. This includes reporting of adverse events and product problems with human drug products, biologics, and medical devices, as well as other FDA-regulated medical products.

FDA adopted several recommendations from ICH and CIOMS in developing the definitions used in the forms and in the proposed amendments to the safety reporting regulations for human drug and biological products. The agency believes that certain standardized definitions, procedures, and formats proposed by ICH and CIOMS will result in more effective and efficient safety reporting to regulatory authorities worldwide. The agency proposed to amend the definition of "serious" to have a consistent definition of what constitutes a serious adverse drug experience for all FDA-regulated products and to avoid confusion about what events should be reported to regulatory authorities worldwide.

FDA agrees with the comments that the differences between the definition of serious, as proposed, and the definition recommended in the final ICH E2A guideline and in the CIOMS II report may create confusion about what events to report as serious. Therefore, the agency has revised the definition of "serious" to be consistent with the final ICH E2A guideline (60 FR 11284 at 11285) and FDA Forms 3500 and 3500A. The revised definition states:

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

The term "serious" is defined similarly in the final ICH E2A guideline (60 FR 11284 at 11285) as:

A serious adverse event (experience) or reaction is any untoward medical occurrence that at any dose:

- Results in death,
- Is life-threatening,

* * *

- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect.

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

The revised definition of "serious" is also consistent with section B.2 of FDA Forms 3500 and 3500A, which directs persons completing the forms to indicate which of the following outcomes is attributed to the adverse event: "death, life-threatening, hospitalization—initial or prolonged, disability, congenital anomaly, required intervention to prevent permanent impairment/damage, or other."

In order to make the definition of "serious" in the premarketing safety reporting regulations at § 312.32(a) uniform with the revised definition of "serious" in the postmarketing safety reporting regulations at §§ 310.305(b), 314.80(a), and 600.80(a), FDA is removing the following sentence from the current definition of "serious" at § 312.32(a), and adding it, with minor revisions, to the IND written safety reporting requirements under § 312.32(c)(1)(i):

With respect to results obtained from tests in laboratory animals, a serious adverse drug experience includes any experience suggesting a significant risk for human subjects, including any finding of mutagenicity, teratogenicity, or carcinogenicity.

4. One comment requested adding the phrase "including overdose and underdose" after the phrase "occurring at any dose" in the definition of "serious" in order to eliminate confusion. Otherwise, the comment claimed, adverse outcomes associated with underdoses may be interpreted as a lack of therapeutic effect rather than an adverse drug experience.

FDA declines to amend the definition of "serious" to include the phrase "including overdose or underdose." Use of the phrase "occurring at any dose" in the revised definition of "serious" will ensure that serious adverse drug experiences occurring at any dose, including an overdose or an underdose, must be reported.

5. Five comments asked for examples of what is considered serious. One comment asked whether intravenous (IV) treatment for dehydration without hospital admission or the use of IV antibiotics, blood products, or dialysis would be considered serious.

FDA advises that use of IV fluids, antibiotics, or blood products, or dialysis may or may not be serious, depending on why they are being used. A decision using medical judgment should be made based on the circumstances surrounding each case. As stated in the revised definition of "serious", other examples include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, and the development of drug dependency or drug abuse.

6. Five comments requested clarification of the following sentence in the preamble to the proposed rule under the discussion of the definition of "serious": "FDA notes that a serious adverse experience would not include the discontinuation of therapy, changes in dosage, or routine treatment with a prescription medication" (59 FR 54046 at 54048). One comment stated that the sentence should also be included in the codified definition of "serious" because the qualifiers are extremely important in limiting the range of events not considered serious. Three comments asked for clarification of the phrase "routine treatment with a prescription medication." One of these comments noted that treatment with any new medication could potentially be considered a medical intervention and therefore could be classified as serious. Another comment requested clarification of the phrase "would not include discontinuation of therapy" because it implies that discontinuation of therapy in response to a clinically significant rise in serum aminotransferases or serum creatinine would not be considered intervention and therefore would not be serious.

FDA declines to revise the definition of "serious" to include examples of events not considered serious. FDA

clarifies that discontinuation of therapy, nges in dosage, and routine tment with a prescription dication are not in themselves serious events but may occur as the result of a serious event.

7. Several comments discussed the use of the words "persistent" and "permanent" in the definition of "serious". One comment requested rewording the phrase "persistent or significant disability" to read "permanent or persistent disability." Another comment suggested that the term "permanent disability" in the current definition of "serious" should be retained because replacing "permanent" with "persistent" does not further define disability. The comment noted that a condition like influenza might be significantly incapacitating but may not qualify as a serious event. Three comments recommended changing the word "permanent" to "persistent" in the phrase "preclude permanent impairment of a body function or permanent damage to a body system." One comment requested that the phrase "persistent or significant disability" be used instead of "permanent or significant disability" in the definition of "serious" in proposed 2.32(a) in order to be consistent proposed §§ 310.305(b), 314.80(a), d 600.80(a).

As explained in the preamble to the October 1994 proposal (59 FR 54046 at 54047), FDA is revising the phrase "is permanently disabling" to "results in a persistent or significant disability/incapacity" in order to clarify that a disability need not be permanent to be considered a serious adverse drug experience. Thus, FDA declines to substitute the phrase "permanent or persistent disability" for "persistent or significant disability" or retain "permanent disability." In addition, FDA has corrected the typographical error in proposed § 312.32(a) by revising "permanent or significant disability" to read "persistent or significant disability."

8. One comment requested the addition of the word "immediately" before "life-threatening" in the definition of "serious". The comment stated that although "immediate" is stated in the definition of "life-threatening", it is not indicated on FDA Form 3500 or 3500A. As a result, reporters may interpret "life-threatening" to mean "potentially" life-threatening rather than "immediately" threatening.

DA declines to revise the definition of "serious" to add the word "immediately" before "life-threatening" because the phrase "at *immediate* risk of death" is part of the definition of "life-threatening adverse drug experience." Although the word "immediately" does not appear before the word "life-threatening" on FDA Forms 3500 and 3500A, the MedWatch "FDA Desk Guide for Adverse Event and Product Problem Reporting" explains that a life-threatening adverse event would be immediate.

D. IND Safety Reports—Written

FDA proposed to revise the requirements for submitting written IND safety reports, under § 312.32(c)(1) and (d)(3), by altering the time period for submitting such reports from 10 working days to 15 calendar days. In addition, FDA proposed to permit sponsors to submit written IND safety reports to the agency by using FDA Form 3500A or in a narrative format. If a sponsor chose to use FDA Form 3500A, additional narrative data might be required if the agency determined that insufficient data were submitted on the form.

9. Three comments expressed support for the 15 calendar days timeframe. One comment commended FDA for requiring the same timeframe for both pre- and postmarketing expedited reporting. Two other comments requested that the timeframe be increased to 20 calendar days, while another comment recommended any period longer than 15 calendar days. The comments stated that 15 calendar days would not provide enough time for the submission of reports or for contacting non-U.S. physicians. One comment noted that a longer timeframe would permit better review and reporting of serious adverse experiences.

As explained in the October 1994 proposal (59 FR 54046 at 54051), FDA believes that the extended timeframe is sufficient for sponsors to gather appropriate data to help initially interpret the reports before submitting them to FDA. This timeframe is also consistent with the 15 calendar day period in the final ICH E2A guideline (60 FR 11284 at 11286).

10. Although one comment expressed support for use of FDA Form 3500A for written IND safety reports because it would provide consistency with the form for postmarketing reports, another comment requested that the form not be required for these reports because of limited space for describing narrative information.

FDA notes that it is not "requiring" use of FDA Form 3500A for written IND safety reports. Reporters may use the form or, alternatively, may submit these reports in a narrative format. In addition, as explained in the June 1993 notice announcing the availability of the form, reporters may use additional blank sheets of paper, referenced to the section of the form being described, to complete any narrative sections of the form.

In the June 1993 notice (58 FR 31596 at 31598), FDA also stated that companies may use the CIOMS I form for reporting foreign events after obtaining FDA approval. FDA has decided, based on comments to its postmarketing safety reporting regulations (see section IV.F of this document), to amend § 312.32(c)(1) to permit use of the CIOMS I form for reporting foreign events without prior approval. FDA has decided to take this action to expedite reporting of foreign events and harmonize its pre- and postmarketing safety reporting regulations.

11. One comment requested clarification about what sponsors must include in a written IND safety report. The comment also requested guidance on how often a report should be submitted and whether one is required every time a new case is reported.

Under § 312.32(b), as amended in this final rule, FDA requires that the sponsor must promptly review all information relevant to the safety of the drug obtained or otherwise received by the sponsor from any source, foreign or domestic, including information derived from any clinical or epidemiological investigations, animal investigations, commercial marketing experience, reports in the scientific literature, and unpublished scientific papers, as well as reports from foreign regulatory authorities that have not already been previously reported to the agency by the sponsor. This requirement qualifies for sponsors the type of safety information that must be examined for determination of whether the information should be included in IND safety reports.

As noted earlier, FDA is amending its IND safety reports regulations, at § 312.32, by moving, for organizational purposes, certain information from the current definition of "serious adverse experience," at § 312.32(a), to the written IND safety reports section, at § 312.32(c)(1)(i). Under § 312.32(c)(1)(i), as revised in this final rule, sponsors must submit written IND safety reports to FDA and all participating investigators within 15 calendar days after the sponsor's receipt of information on any adverse experience associated with the use of the drug that is both serious and unexpected; or any finding from tests in laboratory animals that suggests a significant risk for human subjects including reports of

mutagenicity, teratogenicity, or carcinogenicity.

FDA advises sponsors, as described in greater detail in the final ICH E2A guideline (60 FR 11284 at 11285 and 11286), to submit in written IND safety reports as much information as possible on a case. In some instances, information for final description and evaluation of a case report may not be available within 15 calendar days. Nevertheless, initial reports should be submitted within this timeframe when the following minimum criteria are met: An identifiable patient; a suspected medicinal product; an identifiable reporter; and an adverse event or outcome that can be identified as serious and unexpected, and for which, in clinical investigation cases, there is a reasonable suspected causal relationship between the investigational product and the adverse event (i.e., the causal relationship cannot be ruled out). For reportable events that occur during a "blinded" clinical investigation, sponsors should only break the blind for the subject in question. Sponsors should consult with the FDA review division responsible for their IND in situations in which the sponsor believes that breaking the blind would compromise their study (e.g., when a fatal or other serious outcome is the primary efficacy endpoint in a clinical investigation). Reportable events attributed to a specific dosage form, formulation, or route of administration should be cross-referenced to other IND's for the drug. Reportable events associated with a particular population or for a specific indication should also be cross-referenced to other IND's for the drug.

FDA expects sponsors to submit written IND safety reports every time the sponsor receives or otherwise obtains information about a serious and unexpected adverse experience associated with the use of the drug until the current investigator brochure or, if the investigator brochure is not required, until the risk information described in the general investigational plan or elsewhere in the current application is amended. This is consistent with the final ICH E2A guideline (60 FR 11284 at 11285): "Until source documents are amended, expedited reporting is required for additional occurrences of the reaction."

12. One comment asked when a written safety report would be due if the 15th day occurs on a weekend or holiday.

FDA advises that if the 15th calendar day occurs on a weekend or U.S. Federal holiday, the written safety report would be due the 1st working day after the weekend or U.S. Federal holiday.

E. IND Safety Reports—Telephone

FDA proposed to revise the requirements for submitting IND safety reports by telephone, under § 312.32(c)(2), by altering the time period for submitting such reports from 3 working days to 7 calendar days. FDA also proposed to allow telephone safety reports to be made by facsimile transmission.

13. Two comments expressed support for the 7 calendar day timeframe. Other comments requested longer timeframes because 7 days does not provide a significant difference from the current time period, and because additional time is needed for contacting non-U.S. physicians. One comment asked for a timeframe of 10 calendar days, and another requested any period longer than 7 calendar days.

FDA declines to lengthen the timeframe for IND safety reports by telephone or facsimile transmission. FDA believes it is important that unexpected fatal or life-threatening experiences associated with the use of the drug be reported to the agency as expeditiously as possible. A 7 calendar day timeframe is reasonable for these types of reports. This timeframe is also consistent with recommendations in the final ICH E2A guideline (60 FR 11284 at 11286).

14. Three comments supported FDA's proposal to accept telephone safety reports by "facsimile transmission." The comments also requested that FDA permit transmission of these reports by other electronic mechanisms such as Internet or electronic mail systems.

In the **Federal Register** of March 20, 1997 (62 FR 13430), FDA published a final rule that permits the agency to accept electronic records, electronic signatures, and handwritten signatures executed to electronic records as generally equivalent to paper records and handwritten signatures executed on paper. FDA stated in this final rule that it will announce in the **Federal Register** when it is prepared to accept certain submissions in electronic format only. At the present time, FDA is not prepared to accept electronic submission of IND safety reports, but is developing a system to accept such submissions in the future.

15. One comment requested that FDA restore the phrase "in the clinical studies conducted under the IND" to the language in § 312.32(c)(2) for telephone safety reports of any unexpected fatal or life-threatening experience associated with the use of the drug. The phrase did not appear in the October 27, 1994, proposed revisions to this section.

It is FDA's intention not to restrict telephone safety reports of any unexpected fatal or life-threatening experience associated with the use of the drug to clinical studies conducted under the IND. As stated under § 312.32(b), as revised in this final rule, the sponsor shall promptly review all information relevant to the safety of the drug obtained or otherwise received by the sponsor from any source, foreign or domestic, including information derived from any clinical or epidemiological investigations, animal investigations, commercial marketing experience, reports in the scientific literature, and unpublished scientific papers, as well as reports from foreign regulatory authorities that have not already been previously reported to the agency by the sponsor. Thus, the sponsor is responsible for notifying FDA by telephone or facsimile transmission, as soon as possible, but in no event later than 7 calendar days, of any unexpected fatal or life-threatening experience associated with the use of the drug from any source. This requirement is consistent with the final ICH E2A guideline (60 FR 11284 at 11286):

> Information obtained by a sponsor or manufacturer on serious, unexpected reports from any source should be submitted on an expedited basis to appropriate regulatory authorities if the minimum criteria for expedited reporting can be met.

F. Postmarketing Alert and Followup Reports

FDA proposed to amend §§ 310.305(c), 314.80(c), and 600.80(c) by reorganizing, renumbering, and retitling the paragraphs in these sections to distinguish between postmarketing 15-day Alert reports and followups to these reports. FDA also proposed to distinguish between the reporting intervals for postmarketing 15-day Alert reports and the intervals proposed for postmarketing periodic reports. In addition, FDA proposed to amend §§ 310.305(c)(1) through (c)(4), 314.80(c)(1)(i) through (c)(1)(iv), and 600.80(c)(1)(i) through (c)(1)(iv), to alter the time period for submitting postmarketing 15-day Alert reports and followup reports from 15 working days to 15 calendar days.

16. Twelve comments stated that the 15 calendar day timeframe is overly burdensome. One comment noted that the change from 15 working days to 15 calendar days would result in approximately one-third (6 days) less time for preparation of reports for submission to FDA. Another comment indicated that, although the proposed

timeframe is in accord with the final ICH E2A guideline, it would cause significant disruption in reporting schedules and would probably result in incomplete reports. Another comment stated that the revised timeframe would not provide international companies with sufficient time to receive and translate foreign reports. One comment said that the proposed timeframe incorrectly assumes that reporters are universally accessible anywhere in the world. Six comments offered suggestions for alternative timeframes. Three comments recommended 20 calendar days, one recommended 21 calendar days, and another recommended 22 calendar days. Two of the comments encouraged retention of the 15 working day timeframe currently required by FDA.

FDA declines to revise its proposed 15 calendar day timeframe for postmarketing Alert reports. The agency proposed to revise the reporting period from 15 working days to 15 calendar days to provide consistency in pre- and postmarketing safety reporting timeframes for products and to decrease misunderstandings with reporting requirements by stating all timeframes in terms of calendar days. This timeframe is consistent with the 15 calendar day reporting timeframe in the final ICH E2A guideline (60 FR 11284 at 11286) and consistent with the change in timeframe set forth in this final rule at § 312.32(c)(1) and (d)(3) for IND safety reporting of serious and unexpected experiences. This timeframe is sufficient for persons subject to the postmarketing safety reporting requirements to gather appropriate data and initially interpret reports before submitting them to the agency.

In this final rule, FDA is amending its postmarketing expedited safety reporting regulations, at § 310.305(c)(1)(i), by adding the following phrase to the end of the first sentence: "by the person whose name appears on the label." FDA is making this revision to clarify when the 15 calendar day timeframe begins for marketed prescription drugs for human use without approved new drug applications. This change is consistent with current language under §§ 314.80(c)(1)(i) and 600.80(c)(1)(i) for marketed prescription drugs for human use with approved NDA's and for licensed biological products. Under § 314.80(c)(1)(i), 15-day Alert reports must be submitted no later than 15 calendar days of initial receipt of information by the applicant. Under § 600.80(c)(1)(i), such reports must be submitted within the same timeframe based on initial receipt of information by the licensed manufacturer.

17. Two comments requested that they be permitted to use the CIOMS I form for reporting foreign events as an alternative to FDA Form 3500A without obtaining prior FDA approval. In addition, the comments preferred using the CIOMS I form instead of FDA Form 3500A for all adverse drug experience reporting worldwide.

In the June 1993 notice, the agency stated that reporters may use the CIOMS I form for reporting foreign events with prior FDA approval. FDA has considered the comments and has decided to revise §§ 310.305, 314.80, and 600.80 to permit the use of the CIOMS I form for reports of foreign events without first obtaining prior FDA approval. FDA is taking this action to expedite the reporting of foreign events.

FDA will continue to require use of FDA Form 3500A for reports of domestic events. FDA Form 3500A is more comprehensive than the CIOMS I form and includes elements recommended by the final ICH E2A guideline that are not part of the CIOMS I form (60 FR 11284 at 11287). For example, the following items are included in FDA Form 3500A and requested in the ICH E2A guideline but are not included in the CIOMS I form: Body weight, the terms "congenital anomaly" and "other" (identifiers of adverse event outcomes), the lot number and dosage strength of suspected medicinal product(s), details on the event reporter, and the regulatory code number (e.g., IND/NDA number).

18. One comment requested that FDA accept postmarketing 15-day Alert and followup reports through electronic transmission.

As explained above, FDA has published a final rule to permit the agency to accept electronic records, electronic signatures, and handwritten signatures executed to electronic records as generally equivalent to paper records and handwritten signatures executed on paper (62 FR 13430). At the present time, FDA is not prepared to accept electronic submission of 15-day Alert reports, but is developing a system to accept such submissions in the future.

G. Written Procedures for Monitoring Adverse Drug Experiences

FDA proposed to amend §§ 310.305(a), 314.80(b), and 600.80(b) to require that any person subject to the reporting requirements under §§ 310.305(c), 314.80(c), and 600.80(c) develop written procedures for the surveillance, receipt, evaluation, and reporting of adverse drug experiences to FDA.

19. One comment opposed this amendment. The comment stated that these written procedures are customary and usual in the industry and, if made part of a regulation, could be potentially burdensome to manufacturers and would permit FDA to dictate internal procedures.

FDA declines to withdraw this proposed amendment. As explained in the preamble to the October 1994 proposal (59 FR 54046 at 54053), this requirement would improve postmarketing surveillance by applicants and manufacturers and would enhance an applicant's and a manufacturer's ability to evaluate and report adverse drug experiences to the agency. In addition, because such written procedures are usual and customary, FDA believes that this provision would not impose a new burden on applicants and manufacturers.

20. One comment stated that it is inappropriate to require packers and distributors to develop written procedures for the surveillance, receipt, evaluation, and reporting of adverse drug experiences to FDA if they elect to submit these reports to the manufacturer.

Under §§ 310.305(c)(1)(i), 314.80(c)(1)(iv), and 600.80(c)(1)(iv), packers and distributors are subject to the reporting requirements if their name appears on the label of a marketed prescription drug product or licensed biological product. A packer or distributor who elects to submit adverse drug experience reports to an applicant, manufacturer, or licensed manufacturer of a final biological product under §§ 310.305(c)(4), 314.80(c)(1)(iv), and 600.80(c)(1)(iv) must include information about making such an election in their written procedures, as well as procedures for recordkeeping required to be maintained under these regulations. For the reasons explained in the October 1994 proposal (59 FR 54046 at 54053), it is appropriate to require that these packers and distributors develop written procedures to ensure that they comply with these regulations.

21. One comment requested that FDA specify the minimum requirements for a company's written procedures for reporting adverse drug experiences.

FDA declines to specify minimum requirements for written reporting procedures. As explained in the October 1994 proposal (59 FR 54046 at 54053), written procedures for handling adverse drug experiences are customary and usual in the pharmaceutical industry. In

addition, such procedures have been required for many years by FDA's current good manufacturing practice (CGMP) regulations for finished pharmaceuticals (21 CFR 211.198).

H. Submission of Postmarketing 15-day Alert Reports by Persons Other Than Applicants, Manufacturers, and Licensed Manufacturers of a Final Biological Product

Current postmarketing safety reporting regulations, at § 310.305(c)(5), permit packers and distributors to submit reports of serious adverse drug experiences to the manufacturer instead of FDA. Under § 314.80(c)(1)(iii), manufacturers, packers, and distributors may submit these reports to the applicant. Under § 600.80(c)(1)(iii), packers, distributors, and manufacturers other than licensed manufacturers of the final biological product may submit these reports to the licensed manufacturer of the final product. Currently, these reports must be submitted within 3 working days of their receipt. FDA proposed to revise this timeframe to 3 calendar days. The manufacturer, applicant, and licensed manufacturer of the final biological product would then comply with the requirements described in this section by submitting the report to FDA as soon as possible, but in no case later than 15 calendar days of initial receipt of the information.

22. Five comments opposed changing 3 working days to 3 calendar days because the new timeframe is overly burdensome, especially if the period includes holidays or weekends. One comment said that manufacturers, packers, distributors, and shared and joint manufacturers would probably submit these reports directly to FDA in order to utilize the longer timeframe. This would result in duplicative reporting to the agency. The comments suggested alternative timeframes. Three comments recommended 5 calendar days, one recommended 7 calendar days, and another recommended that the current requirement of 3 working days be maintained.

FDA agrees with the comments and has revised the final rule at §§ 310.305(c)(4), 314.80(c)(1)(iv), and 600.80(c)(1)(iv) to permit manufacturers, packers, and distributors, as well as manufacturers, packers, distributors, shared manufacturers, joint manufacturers, and any other participant involved in divided manufacturing of a biological product, to submit reports of serious adverse drug experiences to the manufacturer, applicant, or licensed manufacturer of the final biological product in 5 calendar days.

23. One comment requested that the regulations state that manufacturers should not submit to FDA reports it receives from a reporter, if the reporter has submitted the report to FDA.

FDA declines to revise its regulations to exempt manufacturers from submitting safety reports to FDA that it receives from a voluntary reporter who has submitted the report to FDA, regardless of whether the reporter is a physician, pharmacist, or other health care professional, or a consumer. The agency requires manufacturers to submit such reports to FDA to ensure that the agency receives all safety reports. However, as now stated at §§ 310.305(c)(6), 314.80(b), and 600.80(b), no one subject to the postmarketing safety reporting regulations at §§ 310.305(c), 314.80(c), and 600.80(c) is required to resubmit to the agency FDA Form 3500A reports that the agency has forwarded to them.

I. General Comments

24. One comment asked whether the **Federal Register** notices announcing the availability of FDA Forms 3500 and 3500A had been withdrawn, revised, or replaced by the October 1994 proposal. The comment indicated that the effective date for FDA Form 3500A was put on hold pending revision of the regulations for safety reporting.

The June 1993 notice (58 FR 31596), announced the availability of FDA Forms 3500 and 3500A. The use of FDA Form 3500 was effective immediately, while the use of FDA Form 3500A was scheduled to be effective on November 30, 1993. Manufacturers, medical device distributors, and user facilities were encouraged to begin using the form immediately. In the **Federal Register** of December 3, 1993 (58 FR 64001), FDA extended the effective date for use of FDA Form 3500A until FDA issues a final rule amending the regulations to require the use of the form. This final rule makes the requirement for use of FDA Form 3500A effective on April 6, 1998.

25. Four comments requested that FDA publish guidelines to explain the proposed regulations. Two of the comments asked whether a draft guideline could be published with an opportunity for public comment before publication of the final rule.

In the **Federal Register** of March 1, 1995 (60 FR 11284), FDA published the final ICH E2A guideline "Clinical Safety Data Management: Definitions and Standards for Expedited Reporting." Concerning the opportunity for comment on guidances, on July 9, 1993 (58 FR 37408), FDA published the draft ICH E2A guideline for public comment.

As described under section III of this document, FDA is in the process of revising guidances pertaining to this final rule and will provide opportunity for public comment and notice of availability of any draft or final guidance documents in the **Federal Register** and on FDA's WWW home page, under the GGP's (62 FR 8961).

26. One comment asked whether information on the United Kingdom Medicines Control Agency's Medical Dictionary for Drug Regulatory Affairs would be incorporated into the final rule.

This terminology was not discussed in the proposed rule and will not be incorporated into this final rule. At the September 1994 CIOMS meeting, it was agreed that this terminology would be the basis for the development of a new international medical terminology to support classification of terms relating to all aspects of drug regulation. In July 1997, ICH developed a final consensus guideline on this topic (ICH M1). At this time, FDA is considering the ICH M1 document.

V. Environmental Impact

The agency has determined under 21 CFR 25.30(h) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

VI. Analysis of Impacts

The agency has considered the potential economic impact of this final rule under Executive Order 12866, the Regulatory Flexibility Act (5 U.S.C. 601–612), as amended by Subtitle D of the Small Business Regulatory Fairness Act of 1996 (Pub. L. 104–721), and the Unfunded Mandates Reform Act of 1995 (Pub. L. 104–4). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). The agency believes that this final rule is consistent with the regulatory philosophy and principles identified in the Executive Order. In addition, the final rule is not a significant regulatory action as defined by the Executive Order and so is not subject to review under the Executive Order.

The Regulatory Flexibility Act ·uires agencies to analyze regulatory .ions that would minimize any ..gnificant impact of a rule on small entities. The agency certifies that the final rule will not have a significant economic impact on a substantial number of small entities. According to the Small Business Administration, manufacturers of medicinals and botanicals or pharmaceutical preparations with 750 or less employees, and manufacturers of diagnostic substances or biological products with 500 or less employees are considered a small business. As discussed in section VII of this document, modifications and additions to the recordkeeping requirements will not result in a change in industry's current recordkeeping burden hours. Therefore, under the Regulatory Flexibility Act, no further analysis is needed.

The final rule will also not impose annual expenditures of $100 million or more on either State, local, and tribal governments in aggregate, or on the private sector. Therefore, a written statement and economic analysis is not required as prescribed under section ~?2(a) of the Unfunded Mandates 'orm Act of 1995.

·ıI. Paperwork Reduction Act of 1995

This final rule contains information collection provisions that are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501–3520). The title, description, and respondent description of the information collection provisions are shown below.

Title: Expedited Safety Reporting Requirements for Human Drug and Biological Products; Final Rule.

Description: FDA is amending its current expedited safety reporting requirements to replace current Form FDA–1639 with new FDA Form 3500A; to revise certain definitions, reporting periods and formats; to require applicants, manufacturers, packers, and distributors, as well as licensed manufacturers and other manufacturers of biological products to develop written procedures for postmarketing safety monitoring and reporting of adverse drug experiences to FDA; and to make other revisions to provide uniformity to the expedited pre- and ~stmarketing safety reporting ılations. These changes will simplify .ı facilitate expedited safety reporting and enhance agencywide consistency in the collection of postmarketing safety data.

Respondent Description: Businesses and other for-profit organizations, State or local governments, Federal agencies, and nonprofit institutions.

FDA believes that this final rule will not result in any increase in paperwork burden as compared to current expedited safety reporting requirements. The new requirement under §§ 310.305(a), 314.80(b), and 600.80(b), that persons subject to the postmarketing safety reporting requirements develop written procedures for the surveillance, receipt, evaluation, and reporting to FDA of adverse drug experiences, does not impose a new burden because it codifies a practice that is already customary and usual in the pharmaceutical industry for handling adverse drug experiences.

The new recordkeeping requirements under §§ 310.305(c)(2), 314.80(c)(1)(ii), and 600.80(c)(1)(ii), that persons subject to the postmarketing safety reporting requirements maintain records of unsuccessful attempts to obtain additional followup information on 15-day Alert reports, do not result in a change in the burden. Current regulations provide for submission of a followup report describing steps taken to seek additional information and the reasons why it could not be obtained; FDA estimates that the effort needed to file this existing information will be, at worst, no more than the effort that would have been required to submit it to FDA.

The new language in § 312.32(b) explicitly requiring that sponsors review: (1) Information derived from any epidemiological investigations, or (2) reports from foreign regulatory authorities that have not already been previously reported to the agency by the sponsor does not impose a new burden because this amendment is only a clarification. Sponsors are already required to review all information relevant to the safety of the drug obtained or otherwise received by the sponsor from any source, foreign or domestic.

Although the October 1994 proposal provided a 90-day comment period under the Paperwork Reduction Act of 1980, FDA is providing an additional opportunity for public comment under the Paperwork Reduction Act of 1995, which was enacted after the expiration of the comment period and applies to this final rule. Therefore, FDA now invites comments on: (1) Whether the proposed collection of information is necessary for the proper performance of FDA's functions, including whether the information will have practical utility; (2) the accuracy of FDA's estimate of the burden of the proposed collection of information, including the validity of the methodology and assumptions used; (3) ways to enhance the quality, utility, and clarity of the information to be collected; and (4) ways to minimize the burden of the collection of information on respondents, including through the use of automated collection techniques, when appropriate, and other forms of information technology. Individuals and organizations may submit comments on the information collection provisions of this final rule by December 8, 1997. Comments should be directed to the Dockets Management Branch (address above).

At the close of the 60-day comment period, FDA will review the comments received, revise the information collection provisions as necessary, and submit these provisions to OMB for review and approval. FDA will publish a notice in the **Federal Register** when the information collection provisions are submitted to OMB, and an opportunity for public comment to OMB will be provided at that time. Prior to the effective date of this final rule, FDA will publish a notice in the **Federal Register** of OMB's decision to approve, modify, or disapprove the information collection provisions. An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

VIII. References

The following references have been placed on display at the Dockets Management Branch (address above) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

1. International Reporting of Periodic Drug-Safety Update Summaries, Final Report of CIOMS Working Group II, 1992.

2. International Reporting of Adverse Drug Reactions, Final Report of CIOMS Working Group I, 1990.

List of Subjects

21 CFR Part 20

Confidential business information, Courts, Freedom of information, Government employees.

21 CFR Part 310

Administrative practice and procedure, Drugs, Labeling, Medical devices, Reporting and recordkeeping requirements.

21 CFR Part 312

Drugs, Exports, Imports, Investigations, Labeling, Medical research, Reporting and recordkeeping requirements, Safety.

21 CFR Part 314

Administrative practice and procedure, Confidential business information, Drugs, Reporting and recordkeeping requirements.

21 CFR Part 600

Biologics, Reporting and recordkeeping requirements.

Therefore, under the Federal Food, Drug, and Cosmetic Act, the Public Health Service Act, and under authority delegated to the Commissioner of Food and Drugs, 21 CFR parts 20, 310, 312, 314, and 600 are amended as follows:

PART 20—PUBLIC INFORMATION

1. The authority citation for 21 CFR part 20 continues to read as follows:

Authority: Secs. 201–903 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321–393); secs. 301, 302, 303, 307, 310, 311, 351, 352, 354–360F, 361, 362, 1701–1706, 2101 of the Public Health Service Act (42 U.S.C. 241, 242, 242a, 242l, 242n, 243, 262, 263, 263b–263n, 264, 265, 300u–300u–5, 300aa–1); 5 U.S.C. 552; 18 U.S.C. 1905; 19 U.S.C. 2531–2582; 21 U.S.C. 1401–1403.

§ 20.112 [Amended]

2. Section 20.112 *Voluntary drug experience reports submitted by physicians and hospitals* is amended in paragraph (a) by removing the words "Form FDA–1639" and adding in their place "FDA Form 3500".

PART 310—NEW DRUGS

3. The authority citation for 21 CFR part 310 continues to read as follows:

Authority: Secs. 201, 301, 501, 502, 503, 505, 506, 507, 512–516, 520, 601(a), 701, 704, 705, 721 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 331, 351, 352, 353, 355, 356, 357, 360b–360f, 360j, 361(a), 371, 374, 375, 379e); secs. 215, 301, 302(a), 351, 354–360F of the Public Health Service Act (42 U.S.C. 216, 241, 242(a), 262, 263b–263n).

4. Section 310.305 is amended by adding a new sentence at the end of paragraph (a); by revising paragraphs (b), (c), (d)(1), (d)(3)(ii), and (d)(4); by removing in paragraph (d)(2), the introductory text of paragraph (d)(3), and paragraph (d)(3)(i) the words "Form FDA–1639" or "FDA–1639" and adding in their place "FDA Form 3500A" to read as follows:

§ 310.305 Records and reports concerning adverse drug experiences on marketed prescription drugs for human use without approved new drug applications.

(a) * * * Any person subject to the reporting requirements of paragraph (c) of this section shall also develop written procedures for the surveillance, receipt, evaluation, and reporting of postmarketing adverse drug experiences to FDA.

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

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

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

Life-threatening adverse drug experience. Any adverse drug experience that places the patient, in the view of the initial reporter, at *immediate* risk of death from the adverse drug experience as it occurred, i.e., it does not include an adverse drug experience that, had it occurred in a more severe form, might have caused death.

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

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

(c) *Reporting requirements.* Each person identified in paragraph (c)(1)(i) of this section shall report to FDA adverse drug experience information as described in this section and shall submit one copy of each report to the Division of Pharmacovigilance and Epidemiology (HFD–730), Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857.

(1) *Postmarketing 15-day "Alert reports".* (i) Any person whose name appears on the label of a marketed prescription drug product as its manufacturer, packer, or distributor shall report to FDA each adverse drug experience received or otherwise obtained that is both serious and unexpected as soon as possible, but in no case later than 15 calendar days of initial receipt of the information by the person whose name appears on the label. Each report shall be accompanied by a copy of the current labeling for the drug product.

(ii) A person identified in paragraph (c)(1)(i) of this section is not required to submit a 15-day "Alert report" for an adverse drug experience obtained from a postmarketing study (whether or not conducted under an investigational new drug application) unless the applicant concludes that there is a reasonable possibility that the drug caused the adverse experience.

(2) *Postmarketing 15-day "Alert reports"—followup.* Each person identified in paragraph (c)(1)(i) of this section shall promptly investigate all serious, unexpected adverse drug experiences that are the subject of these postmarketing 15-day Alert reports and shall submit followup reports within 15 calendar days of receipt of new information or as requested by FDA. If additional information is not obtainable, records should be maintained of the unsuccessful steps taken to seek additional information. Postmarketing 15-day Alert reports and followups to them shall be submitted under separate cover.

(3) *Submission of reports.* To avoid unnecessary duplication in the submission of, and followup to, reports required in this section, a packer's or distributor's obligations may be met by submission of all reports of serious adverse drug experiences to the manufacturer of the drug product. If a packer or distributor elects to submit these adverse drug experience reports to the manufacturer rather than to FDA, it shall submit each report to the manufacturer within 5 calendar days of its receipt by the packer or distributor, and the manufacturer shall then comply with the requirements of this section even if its name does not appear on the label of the drug product. Under this circumstance, the packer or distributor shall maintain a record of this action which shall include:

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

(ii) The date the report was received by the packer or distributor;

(iii) The date the report was submitted to the manufacturer; and

(iv) The name and address of the manufacturer.

(4) Each report submitted to FDA under this section shall bear prominent identification as to its contents, i.e., "15-day Alert report," or "15-day Alert report-followup."

(5) A person identified in paragraph (c)(1)(i) of this section is not required to resubmit to FDA adverse drug experience reports forwarded to that person by FDA; however, the person must submit all *followup* information on such reports to FDA.

(d) * * * (1) Except as provided in paragraph (d)(3) of this section, each person identified in paragraph (c)(1)(i) of this section shall submit each report of a serious and unexpected adverse drug experience on an FDA Form 3500A (foreign events may be submitted either on an FDA Form 3500A or, if preferred, on a CIOMS I form).

* * * * *

(3) * * *

(ii) The format is agreed to in advance by MedWatch: The FDA Medical Products Reporting Program.

(4) Ten copies or fewer of FDA Form 3500A and/or a copy of the instructions for completing the form may be obtained from the Division of Pharmacovigilance and Epidemiology (HFD-730), Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857. More than 10 copies of the form may be obtained by writing to the Consolidated Forms and Publications Distribution Center, Washington Commerce Center, 3222 Hubbard Rd., Landover, MD 20785.

* * * * *

PART 312—INVESTIGATIONAL NEW DRUG APPLICATION

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

Authority: Secs. 201, 301, 501, 502, 503, 505, 506, 507, 701 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 331, 351, 352, 353, 355, 356, 357, 371); sec. 351 of the Public Health Service Act (42 U.S.C. 262).

6. Section 312.32 is amended by revising paragraphs (a), (b), (c)(1)(i), (c)(2), and (d)(3); by adding in the second sentence of paragraph (c)(3) the words "new drug review" before the phrase "division in the Center for Drug Evaluation and Research" and the words "the director of the product review division in" before the phrase "the Center for Biologics Evaluation and Research"; and by removing in paragraph (e) the word "section" and replacing it with the word "part", to read as follows:

§ 312.32 IND safety reports.

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

Associated with the use of the drug. There is a reasonable possibility that the experience may have been caused by the drug.

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

Life-threatening adverse drug experience. Any adverse drug experience that places the patient or subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death.

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

Unexpected adverse drug experience: Any adverse drug experience, the specificity or severity of which is not consistent with the current investigator brochure; or, if an investigator brochure is not required or available, the specificity or severity of which is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the investigator brochure only referred to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the investigator brochure only listed cerebral vascular accidents. "Unexpected," as used in this definition, refers to an adverse drug experience that has not been previously observed (e.g., included in the investigator brochure) rather than from the perspective of such experience not being anticipated from the pharmacological properties of the pharmaceutical product.

(b) *Review of safety information.* The sponsor shall promptly review all information relevant to the safety of the drug obtained or otherwise received by the sponsor from any source, foreign or domestic, including information derived from any clinical or epidemiological investigations, animal investigations, commercial marketing experience, reports in the scientific literature, and unpublished scientific papers, as well as reports from foreign regulatory authorities that have not already been previously reported to the agency by the sponsor.

(c) *IND safety reports.* (1) *Written reports*—(i) The sponsor shall notify FDA and all participating investigators in a written IND safety report of:

(A) Any adverse experience associated with the use of the drug that is both serious and unexpected; or

(B) Any finding from tests in laboratory animals that suggests a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity. Each notification shall be made as soon as possible and in no event later than 15 calendar days after the sponsor's initial receipt of the information. Each written notification may be submitted on FDA

Form 3500A or in a narrative format (foreign events may be submitted either on an FDA Form 3500A or, if preferred, on a CIOMS I form; reports from animal or epidemiological studies shall be submitted in a narrative format) and shall bear prominent identification of its contents, i.e., "IND Safety Report." Each written notification to FDA shall be transmitted to the FDA new drug review division in the Center for Drug Evaluation and Research or the product review division in the Center for Biologics Evaluation and Research that has responsibility for review of the IND. If FDA determines that additional data are needed, the agency may require further data to be submitted.

* * * * *

(2) *Telephone and facsimile transmission safety reports.* The sponsor shall also notify FDA by telephone or by facsimile transmission of any unexpected fatal or life-threatening experience associated with the use of the drug as soon as possible but in no event later than 7 calendar days after the sponsor's initial receipt of the information. Each telephone call or facsimile transmission to FDA shall be transmitted to the FDA new drug review division in the Center for Drug Evaluation and Research or the product review division in the Center for Biologics Evaluation and Research that has responsibility for review of the IND.

* * * * *

(d) * * *

(3) If the results of a sponsor's investigation show that an adverse drug experience not initially determined to be reportable under paragraph (c) of this section is so reportable, the sponsor shall report such experience in a written safety report as soon as possible, but in no event later than 15 calendar days after the determination is made.

* * * * *

PART 314—APPLICATIONS FOR FDA APPROVAL TO MARKET A NEW DRUG OR AN ANTIBIOTIC DRUG

7. The authority citation for 21 CFR part 314 continues to read as follows:

Authority: Secs. 201, 301, 501, 502, 503, 505, 506, 507, 701, 704, 721 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 331, 351, 352, 353, 355, 356, 357, 371, 374, 379e).

8. Section 314.80 is amended by revising paragraphs (a), (c)(1), (f)(1), (f)(3)(ii), and (f)(4) and the introductory text of paragraph (c); by adding two new sentences at the end of paragraph (b); by removing in paragraph (d)(2) the words "Epidemiology and Surveillance" and adding in their place the words "Pharmacovigilance and Epidemiology"; by removing in paragraphs (c)(2)(ii)(b), (d)(2), (f)(2), and (f)(3) and in the heading for paragraph (f) the words "Form FDA-1639" or "FDA-1639" and adding in their place the words "FDA Form 3500A"; and by removing paragraph (j) and redesignating paragraphs (k) and (l) as paragraphs (j) and (k), respectively, to read as follows:

§ 314.80 Postmarketing reporting of adverse drug experiences.

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

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

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

Life-threatening adverse drug experience. Any adverse drug experience that places the patient, in the view of the initial reporter, at *immediate* risk of death from the adverse drug experience as it occurred, i.e., it does not include an adverse drug experience that, had it occurred in a more severe form, might have caused death.

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

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

(b) * * * Applicants are not required to resubmit to FDA adverse drug experience reports forwarded to the applicant by FDA; however, applicants must submit all followup information on such reports to FDA. Any person subject to the reporting requirements under paragraph (c) of this section shall also develop written procedures for the surveillance, receipt, evaluation, and reporting of postmarketing adverse drug experiences to FDA.

(c) *Reporting requirements.* The applicant shall report to FDA adverse drug experience information, as described in this section. The applicant shall submit two copies of each report described in this section to the Central Document Room, 12229 Wilkins Ave., Rockville, MD 20852. FDA may waive the requirement for the second copy in appropriate instances.

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

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

them shall be submitted under separate cover.

(iii) *Submission of reports.* The requirements of paragraphs (c)(1)(i) and (c)(1)(ii) of this section, concerning the submission of postmarketing 15-day Alert reports, shall also apply to any person other than the applicant (nonapplicant) whose name appears on the label of an approved drug product as a manufacturer, packer, or distributor. To avoid unnecessary duplication in the submission to FDA of reports required by paragraphs (c)(1)(i) and (c)(1)(ii) of this section, obligations of a nonapplicant may be met by submission of all reports of serious adverse drug experiences to the applicant. If a nonapplicant elects to submit adverse drug experience reports to the applicant rather than to FDA, the nonapplicant shall submit each report to the applicant within 5 calendar days of receipt of the report by the nonapplicant, and the applicant shall then comply with the requirements of this section. Under this circumstance, the nonapplicant shall maintain a record of this action which shall include:

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

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

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

(D) The name and address of the applicant.

(iv) *Report identification.* Each report submitted under this paragraph shall bear prominent identification as to its contents, i.e., "15-day Alert report," or "15-day Alert report-followup."

* * * * *

(f) * * * (1) Except as provided in paragraph (f)(3) of this section, the applicant shall complete FDA Form 3500A for each report of an adverse drug experience (foreign events may be submitted either on an FDA Form 3500A or, if preferred, on a CIOMS I form).

* * * * *

(3) * * * (ii) the format is agreed to in advance by MedWatch: The FDA Medical Products Reporting Program.

(4) Ten copies or fewer of FDA Form 3500A and/or a copy of the instructions for completing the form may be obtained from the Division of Pharmacovigilance and Epidemiology (HFD-730), Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857. More than 10 copies of the form may be obtained by writing to the Consolidated Forms and Publications Distribution Center, Washington Commerce Center, 3222 Hubbard Rd., Landover, MD 20785.

* * * * *

PART 600—BIOLOGICAL PRODUCTS: GENERAL

9. The authority citation for 21 CFR part 600 continues to read as follows:

Authority: Secs. 201, 501, 502, 503, 505, 510, 519, 701, 704 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 351, 352, 353, 355, 360, 360i, 371, 374); secs. 215, 351, 352, 353, 361, 2125 of the Public Health Service Act (42 U.S.C. 216, 262, 263, 263a, 264, 300aa-25).

10. Section 600.80 is amended by revising paragraphs (a), (c)(1), (f)(1), and the first sentence of paragraph (g); by adding two new sentences at the end of paragraph (b); and by removing paragraph (j) and redesignating paragraphs (k), (l), and (m) as paragraphs (j), (k), and (l), respectively, to read as follows:

§ 600.80 Postmarketing reporting of adverse experiences.

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

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

Blood Component. As defined in § 606.3(c) of this chapter.

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

Life-threatening adverse experience. Any adverse experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse experience as it occurred, i.e., it does not include an adverse experience that, had it occurred in a more severe form, might have caused death.

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

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

(b) * * * Licensed manufacturers are not required to resubmit to FDA adverse product experience reports forwarded to the licensed manufacturer by FDA; licensed manufacturers, however, must submit all followup information on such reports to FDA. Any person subject to the reporting requirements under paragraph (c) of this section shall also develop written procedures for the surveillance, receipt, evaluation, and reporting of postmarketing adverse experiences to FDA.

(c) * * *

(1)(i) *Postmarketing 15-day "Alert reports".* The licensed manufacturer shall report each adverse experience that is both serious and unexpected, whether foreign or domestic, as soon as possible but in no case later than 15 calendar days of initial receipt of the information by the licensed manufacturer.

(ii) *Postmarketing 15-day "Alert reports"—followup.* The licensed manufacturer shall promptly investigate

ll adverse experiences that are the ubject of these postmarketing 15-day Alert reports and shall submit followup reports within 15 calendar days of receipt of new information or as requested by FDA. If additional information is not obtainable, records should be maintained of the unsuccessful steps taken to seek additional information. Postmarketing 15-day Alert reports and followups to them shall be submitted under separate cover.

(iii) *Submission of reports.* The requirements of paragraphs (c)(1)(i) and (c)(1)(ii) of this section, concerning the submission of postmarketing 15-day Alert reports, shall also apply to any person whose name appears on the label of a licensed biological product as a manufacturer, packer, distributor, shared manufacturer, joint manufacturer, or any other participant involved in divided manufacturing. To avoid unnecessary duplication in the submission to FDA of reports required by paragraphs (c)(1)(i) and (c)(1)(ii) of this section, obligations of persons other than the licensed manufacturer of the final biological product may be met by submission of all reports of serious dverse experiences to the licensed nanufacturer of the final product. If a person elects to submit adverse experience reports to the licensed manufacturer of the final product rather than to FDA, the person shall submit each report to the licensed manufacturer of the final product within 5 calendar days of receipt of the report by the person, and the licensed manufacturer of the final product shall then comply with the requirements of this section. Under this circumstance, a person who elects to submit reports to the licensed manufacturer of the final product shall maintain a record of this action which shall include:

(A) A copy of all adverse biological product experience reports submitted to the licensed manufacturer of the final product;

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

(C) The date the report was submitted to the licensed manufacturer of the final product; and

(D) The name and address of the licensed manufacturer of the final product.

(iv) *Report identification.* Each report submitted under this paragraph shall bear prominent identification as to its contents, i.e., "15-day Alert report," or "15-day Alert report-followup."

* * * * *

(f) *Reporting forms.* (1) Except as provided in paragraph (f)(3) of this section, the licensed manufacturer shall complete the reporting form designated by FDA for each report of an adverse experience (FDA Form 3500A, or, for vaccines, a VAERS form; foreign events including those associated with the use of vaccines, may be submitted either on an FDA Form 3500A or, if preferred, on a CIOMS I form).

* * * * *

(g) *Multiple reports.* A licensed manufacturer should not include in reports under this section any adverse experience that occurred in clinical trials if they were previously submitted as part of the license application. * * *

* * * * *

Dated: September 25, 1997.

William K. Hubbard,

Associate Commissioner for Policy Coordination.

[FR Doc. 97-26255 Filed 10-6-97; 8:45 am]

BILLING CODE 4160-01-F