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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 310, 312, 314, 320, 600, 601, and 606

[Docket No. 00N-1484]

RIN 0910-AA97

Safety Reporting Requirements for Human Drug and Biological Products

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is proposing to amend its pre- and postmarketing safety reporting regulations for human drug and biological products to implement definitions and reporting formats and standards 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); codify the agency's expectations for timely acquisition, evaluation, and submission of relevant safety information for marketed drugs and licensed biological products; require that certain information, such as domestic reports of medication errors, be submitted to the agency in an expedited manner; clarify certain requirements; and make other minor revisions. FDA is also proposing to amend its

postmarketing annual reporting regulations for human drug and licensed biological products by revising the content for these reports. FDA is taking this action to strengthen its ability to monitor the safety of human drugs and biological products. The intended effect of these changes is to further worldwide consistency in the collection of safety information and submission of safety reports, increase the quality of safety reports, expedite FDA's review of critical safety information, and enable the agency to protect and promote public health. These proposed changes would be an important step toward global harmonization of safety reporting requirements and additional efforts are underway within the Department of Health and Human Services to harmonize the reporting requirements of U.S. Federal agencies (e.g., FDA and the National Institutes of Health (NIH) are continuing to work together to address the best ways to streamline information sharing and harmonize, to the extent possible, the safety reporting requirements of the two agencies.)

DATES: Submit written comments by [insert date 90 days after date of publication in the FEDERAL REGISTER]. Submit written comments on the collection of information by [insert date 30 days after date of publication in the FEDERAL REGISTER].

ADDRESSES: Submit written comments to the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852, e-mail: FDADockets@oc.fda.gov or to the Internet at http://www.accessdata.fda.gov/scripts/oc/dockets/comments/commentdocket.cfm. Submit written comments on the information

collection provisions to the Office of Information and Regulatory Affairs, Office of Management and Budget (OMB), New Executive Office Bldg., 725 17th St. NW., rm. 10235, Washington, DC 20503, Attn: Stuart Shapiro, Desk Officer for FDA.

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,
301-594-5626.

For information concerning human biological products:

Miles Braun,
Center for Biologics Evaluation and Research (HFM-220),
Food and Drug Administration,
1401 Rockville Pike,
Rockville, MD 20852-1448,
301-827-6079.

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I. ~~Background~~ insert

In the FEDERAL REGISTER of October 27, 1994 (59 FR 54046), FDA published a proposed rule to amend its expedited and periodic pre- and postmarketing safety reporting regulations for human drug and biological products (the October 1994 proposal). In the FEDERAL REGISTER of October 7, 1997 (62 FR 52237), FDA published a final rule amending its expedited pre- and postmarketing safety

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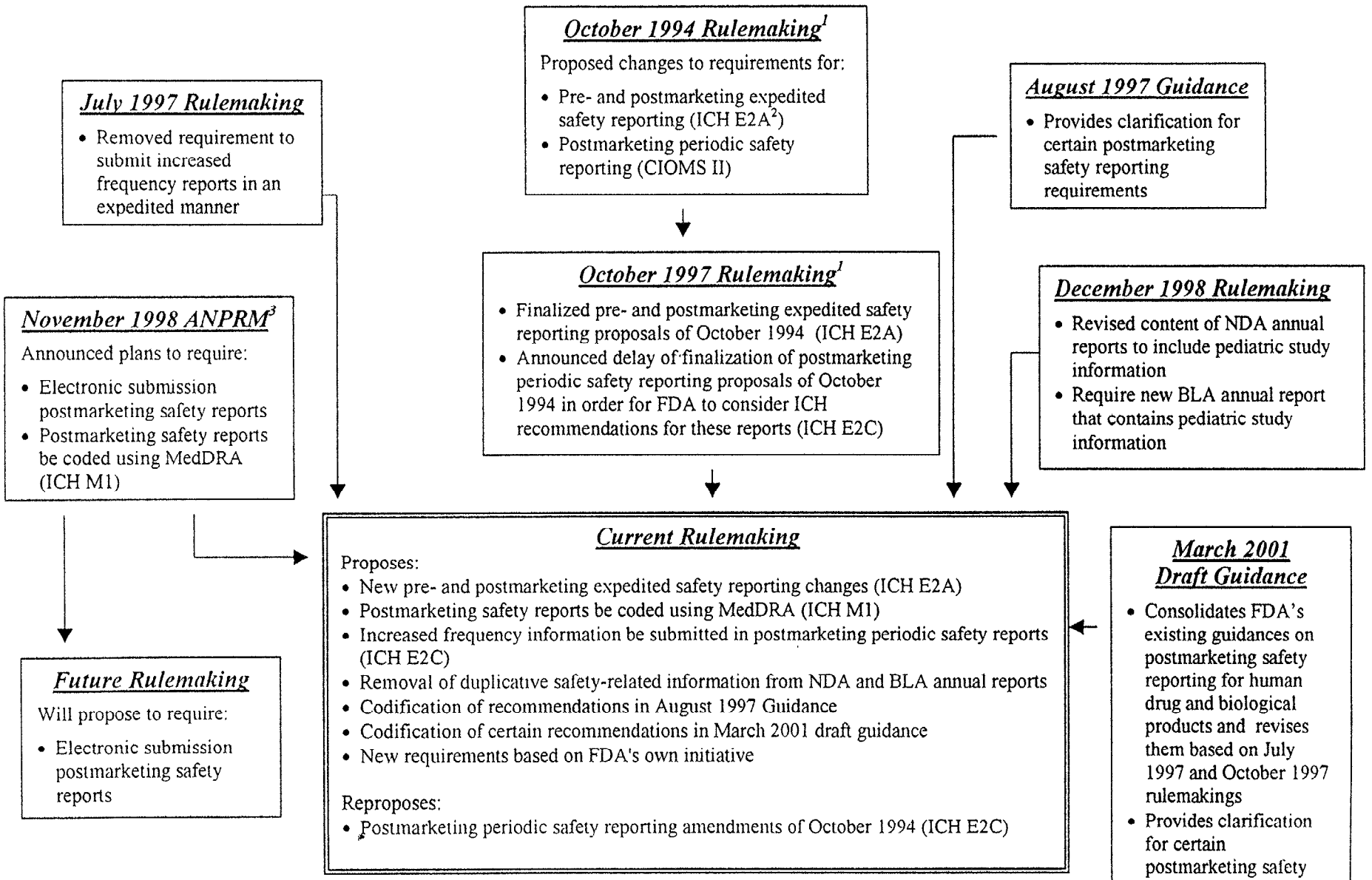
"I. ~~Background~~*Previous Safety Reporting Rulemaking and Current Guidances*

FDA has undertaken a major effort to clarify and revise its regulations regarding pre- and postmarketing safety reporting for human drug and biological products. Since 1990, several rules and guidances have been issued regarding these regulations. Some of these guidances have been issued by international organizations (i.e., ICH and CIOMS), while others have been issued by FDA. In Figure 1, FDA illustrates how these rules and guidances relate to the current proposed rule.

Figure 1. Safety Reporting Rulemaking and Guidances Related to Current Proposed Rule



[1] Includes other amendments not directly related to current rulemaking.
[2] Parentheticals refer to guidance that amendment is based on.
[3] Advanced Notice of Proposed Rulemaking.

reporting regulations for human drug and biological products (the October 1997 final rule). The October 1997 final rule implemented certain international standards recommended in an ICH guidance entitled "Clinical Safety Data Management: Definitions and Standards for Expedited Reporting" (60 FR 11284, March 1, 1995)(the ICH E2A guidance). FDA is now proposing additional amendments to its expedited pre- and postmarketing safety reporting regulations based on recommendations in the ICH E2A guidance that were not included in the October 1994 proposal. Although the ICH E2A guidance pertains to expedited safety reporting during the premarketing phase of drug development, the agency has determined that many of the definitions and standards also should apply to FDA's expedited postmarketing safety reporting requirements.

~~[In the FEDERAL REGISTER of May 19, 1997 (62 FR 27470), FDA published an ICH final guidance entitled "Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs" (the ICH E2C guidance).]~~ As explained in the October 1997 final rule, the agency decided not to finalize the proposed amendments ~~[to the postmarketing periodic safety reporting regulations in the October 1994 proposal]~~ (62 FR 52237 at 52238) until FDA considered ~~the ICH E2C guidance.~~ FDA ~~is now~~ reproposing the postmarketing periodic safety reporting amendments based on recommendations in

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The proposed amendments to the postmarketing periodic safety reporting requirements in the October 1994 proposal were based on recommendations in a CIOMS II report issued in 1992 ("International Reporting of Periodic Drug-Safety Update Summaries") (Ref. 28).

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ICH's recommendations on this topic. ~~the ICH E2C guidance.~~ These recommendations were published in an ICH final guidance entitled "Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs" (PSUR's) (the ICH E2C guidance) (62 FR 27470; May 19, 1997). After review of the ICH E2C guidance,

the ICH E2C guidance and comments submitted in response to the October 1994 proposal.

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Some of the comments submitted in response to the October 1994 proposal noted that several of the proposed amendments to the postmarketing periodic safety reporting regulations would result in duplicative reporting of information currently required in postmarketing approved NDA annual reports. The comments questioned the value of submitting similar information to FDA in two different reports and requested that the agency require inclusion of this information in either one report or the other, but not in both of them. In light of these comments, FDA is proposing to revoke the requirement for safety-related information in postmarketing approved NDA annual reports.

In the FEDERAL REGISTER of December 2, 1998 (63 FR 66632), FDA issued a final rule amending its postmarketing approved new drug application (NDA) annual reports regulations to require reporting of specific information regarding studies in pediatric populations (the 1998 pediatric final rule). The 1998 pediatric final rule also required a new annual report for biological products with approved biologics license applications (BLA's) that contains the same type of information on studies of licensed biological products in pediatric populations. FDA is proposing to amend the annual reporting requirements for licensed biological products ~~to be~~ consistent with the proposed amendments to revoke the requirement to submit safety-related information in these reports. This proposal is

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(67 FR 79939, December 31, 02)

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An addendum to the ICH E2C guidance has been prepared by ICH (the ICH V1 draft guidance) based on experience gained over the past five years in preparation of PSUR reports by companies and review of them by regulators. ~~The ICH V1 draft guidance is available on the Internet at~~ www.ich.org/pdfich/V1step2.pdf. *FDA is interested in harmonizing, to the extent possible, its postmarketing periodic safety reporting regulations with the recommendations in the ICH V1 draft guidance. In this regard, FDA is interested in comment from the public on whether the agency should implement these recommendations (e.g., permit use of summary bridging reports, include an executive summary in PSUR's, permit use of different versions of reference safety information within a reporting interval or use of the version in effect at the end of the reporting interval, ~~redefine how solicited reports must be handled~~).*

to the postmarketing approved NDA annual reporting requirements ~~(i.e., the proposal to revoke the requirement to submit safety-related information)~~.

In the FEDERAL REGISTER of June 25, 1997 (62 FR 34166), FDA published a final rule revoking the postmarketing safety reporting requirement for submission of increased frequency reports in an expedited manner (the increased frequency reports final rule). These reports contained information regarding a significant increase in frequency of an adverse drug experience (synonymous with adverse experience) that is both serious and expected for marketed human drug and licensed biological products.

In the FEDERAL REGISTER of August 27, 1997 (62 FR 45425), FDA published a notice of availability of a guidance for industry entitled "Postmarketing Adverse Experience Reporting for Human Drug and Licensed Biological Products; Clarification of What to Report" (the clarification guidance of 1997). This guidance clarifies the agency's policy concerning certain postmarketing safety reporting requirements for human drugs and licensed biological products. The guidance: (1) Describes the information that should be obtained before an individual case safety report (i.e., FDA Form 3500A, CIOMS I Form, Vaccine Adverse Event Reporting System (VAERS) Form) of an adverse experience should be considered for submission to FDA; (2) clarifies how solicited

FDA is now proposing to amend its regulations to require submission of increased frequency type information for marketed human drugs and licensed biological products in postmarketing periodic safety reports.

safety information from planned contacts with patients should be handled; and (3) informs applicants that FDA will entertain waiver requests for periodic submission of individual case safety reports for adverse experiences that are determined to be nonserious and expected.

FDA received 28 comments from medical centers, physicians, and consumers regarding the clarification guidance of 1997. The agency considered these comments in developing this proposed rule. All of the comments requested that FDA postpone granting waivers ~~for submission of nonserious, expected adverse experiences~~ until the new ~~waiver~~ policy receives more complete public scrutiny and debate. The comments stated that the new waiver policy would deprive the public of access to important safety information about adverse reactions to approved drugs and biological products. The comments noted that, in some cases, adverse reactions classified as "nonserious" may, in fact, be related to very serious reactions. The comments also indicated that the new waiver policy provides industry with an incentive to classify serious reactions as "nonserious" so that the reactions would not have to be reported to FDA.

Even though applicants may currently request waivers for submission of individual case safety reports for nonserious, expected adverse experiences, the agency should continue to receive information regarding these experiences. The

. . . All of these comments pertained to the item regarding waiver requests for periodic submission of individual case safety reports for adverse experiences that are determined to be nonserious and expected.

clarification guidance of 1997 provides that summary tabulations of nonserious, expected adverse experiences be included in postmarketing periodic safety reports. If warranted, FDA could request submission of an individual case safety report for any nonserious, expected adverse experience. Thus, even if a waiver is granted, the agency will continue to receive sufficient information to monitor the safety of marketed drugs and licensed biological products. FDA is now proposing amendments to its postmarketing periodic safety reporting regulations that would require that ~~requirements to codify and clarify FDA's expectations for reporting of~~ nonserious, expected adverse experiences[1] ~~(proposed to be called SADR's in this proposed rule; see section III.A.1 of this document)~~.

In the FEDERAL REGISTER of March 12, 2001 (66 FR 14391), FDA published a notice of availability of a draft guidance for industry entitled "Postmarketing Safety Reporting for Human Drug and Biological Products Including Vaccines" (the draft guidance of 2001). The draft guidance of 2001 represents the agency's current thinking on reporting of postmarketing adverse drug experiences for human marketed drug and biological products including vaccines in accordance with FDA's postmarketing safety reporting regulations for these products in effect at the time the draft guidance of 2001 was issued. The draft guidance of 2001 consolidates the agency's existing guidances on this topic and revises them based on the October 1997 final rule and the

[1] *Adverse experiences are proposed to be called suspected adverse drug reactions (SADR's) in this proposed rule; see section III.A.1 of this document; the term "adverse experiences" or "adverse drug experiences" will be used in this document when discussions pertain to FDA's current regulations and the term "SADR" will used in this document when discussions pertain to proposals in this rule.*

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be submitted to the agency in summary tabulations consistent with the clarification guidance of 1997. At this time, FDA is also proposing to codify the other recommendations in the clarification guidance of 1997 (i.e., require a minimum data set for individual case safety reports, describe how solicited safety information from planned contacts with patients must be handled).

increased frequency reports final rule. The draft guidance of 2001, once finalized, will replace FDA's guidances entitled "Postmarketing Reporting of Adverse Drug Experiences" (57 FR 61437, December 24, 1992) (the guidance of 1992), "Adverse Experience Reporting for Licensed Biological Products" (the guidance of 1993), and the clarification guidance of 1997. The agency will issue a final guidance for industry on this topic after considering the comments received on the draft guidance of 2001.

FDA is now proposing to codify certain expectations described in the draft guidance of 2001 to improve the quality of postmarketing safety reports submitted to the agency for human marketed drug and biological products, and also to clarify certain postmarketing safety reporting requirements. Once this proposed rule is finalized, the draft guidance of 2001, as finalized, will be updated to provide industry with assistance in fulfilling the new safety reporting requirements for human marketed drug and biological products. INSERT A

In the FEDERAL REGISTER of November 5, 1998 (63 FR 59746), FDA published an advance notice of proposed rulemaking announcing that it is considering a proposal to require persons subject to the postmarketing safety reporting regulations to submit postmarketing expedited individual case safety reports and individual case safety reports contained in postmarketing

In June 2001, CIOMS issued a new report entitled, "Current Challenges in Pharmacovigilance: Pragmatic Approaches" (CIOMS V report) (Ref. 29). This report provides recommendations for simplification, clarification, and harmonization of certain drug safety practices. Many of these recommendations serve to provide guidance for industry and would not be subject to requirements of individual regulatory authorities (e.g., FDA). Those that are the subject of our proposed rule are essentially consistent with what we are proposing. However, in some cases, there may be differences (see section III.A.6 of this document for discussion of use of active query and written requests for acquisition of followup information).

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periodic safety reports to the agency electronically using a standardized medical terminology, standardized data elements, and electronic transmission standards recommended by the ICH. Under the auspices of ICH, standard medical terminology for regulatory purposes, MedDRA, the medical dictionary for regulatory activities (ICH M1), has been developed (63 FR 59746 at 59748). On November 24, 1998, an international maintenance and support services organization (MSSO) was established to maintain and update MedDRA in response to medical/scientific advances and regulatory changes and to serve as the licensing agent for distribution of MedDRA. This proposed rule on safety reporting would require that postmarketing individual case safety reports be coded using MedDRA prior to submission to the agency. In a separate rulemaking, FDA plans to propose that postmarketing individual case safety reports be submitted to the agency electronically using standardized data elements and electronic transmission standards. The proposed amendments for electronic submissions are beyond the scope of this proposed rule.

II. Introduction

II.A. Persons Subject to the Safety Reporting Regulations

II.A.1. Premarketing Expedited Safety Reporting Regulations

Section 312.32 (21 CFR 312.32), requires expedited reports of premarketing adverse experiences associated with the use of an investigational human drug or biological product (see table 1).

Sponsors of IND's are subject to the premarketing expedited safety reporting regulations.

Table 1.--Currently Required Premarketing Expedited Safety Reports

Safety Report	Type of Information	21 CFR Section	Submission Timeframe	Persons with Reporting Responsibility
Written IND safety report	• Serious and unexpected adverse experience associated with the use of the drug • Findings from tests in laboratory animals that suggest a significant risk for humans	312.32	15 calendar days	Sponsors
Telephone and facsimile transmission safety report	Unexpected fatal or life-threatening experience associated with the use of the drug	312.32	7 calendar days	Sponsors

II.A.2. Postmarketing Safety Reporting Regulations

Sections 310.305, 314.80, 314.98, and 600.80 (21 CFR 310.305, 314.80, 314.98, and 600.80) require expedited reports of postmarketing adverse drug experiences (see table 2). The

following persons are subject to these postmarketing expedited safety reporting regulations:

- Manufacturers, packers, and distributors (also shared manufacturers, joint manufacturers, or any other participant involved in divided manufacturing for § 600.80) whose name appears on the label of ~~the~~ a product.

~~- Applicants with approved NDA's and Abbreviated New Drug Applications (ANDA's); and~~

~~- Licensed manufacturers with approved BLA's.~~

In this document, the term "applicant" will be used instead of the term "licensed manufacturer" for persons with approved BLA's.

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- *Applicants with approved NDA's (§ 314.80) and Abbreviated New Drug Applications (ANDA's) (§ 314.98);*
- *Licensed manufacturers with approved BLA's (§ 600.80);*

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with an approved NDA, ANDA, or BLA (§§ 314.80, 314.98 and 600.80); and

Manufacturers, packers, and distributors whose name appears on the label of a prescription drug product marketed without an approved NDA or ANDA (§ 310.305).

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Table 2.--Currently Required Postmarketing Safety Reports

Type of Report	Safety Report	Type of Information	21 CFR Section	Submission Timeframe	Persons with Reporting Responsibility
Expedited report	15-day Alert report	Serious and unexpected adverse drug experience[1]	310.305, 314.80, 314.98, 600.80	15 calendar days	Manufacturers[2] and applicants[3]
	15-day Alert report-followup	New information for 15-day Alert report	310.305, 314.80, 314.98, 600.80	15 calendar days	Manufacturers[2] and applicants[3]
	Reports to manufacturer instead of FDA	Serious adverse drug experiences[1]	310.305	5 calendar days	Packers and distributors
	Reports to applicant instead of FDA	Serious adverse drug experiences[1]	314.80, 314.98, 600.80	5 calendar days	Manufacturers, packers, and distributors (§§ 314.80, 314.98, and 600.80) and joint manufacturers, shared manufacturers, or any participant involved in divided manufacturing (§ 600.80)

Table 2.--Currently Required Postmarketing Safety Reports (Continued)

Type of Report	Safety Report	Type of Information	21 CFR Section	Submission Timeframe	Persons with Reporting Responsibility
Expedited report	Blood safety report	Fatalities	606.170	As soon as possible (oral or written) and 7 days (written)	Blood establishments
Periodic report.	Periodic adverse drug experience report	• Narrative summary and analysis of adverse drug experiences that occurred during the reporting interval including 15-day Alert reports previously submitted to FDA[1] • Individual case safety report for each adverse drug experience not submitted to FDA as a 15-day Alert report, excluding reports from postmarketing studies, reports in the scientific literature, and foreign marketing experience[1] • History of actions taken.	314.80, 314.98, 600.80	Quarterly for 3 years from the date of U.S. approval of the application and then annually thereafter	Applicants

[1]For spontaneous reports, adverse drug experiences are submitted whether or not they are considered drug related; for study reports, adverse drug experiences are submitted if there is a reasonable possibility that the drug caused the adverse drug experience.

[2]Section 310.305 also includes packers and distributors.

[3]Sections 314.80 and 314.98 also include manufacturers, packers and distributors. Section 600.80 also includes manufacturers, packers, distributors, joint manufacturers, shared manufacturers, or any participant involved in divided manufacturing.

Applicants with approved NDA's, ANDA's, and BLA's must also submit periodic reports of postmarketing adverse drug experience under §§ 314.80, 314.98 and 600.80 (see table 2). ~~Current safety reporting regulations under §§ 310.305, 314.80, 314.98, and 600.80, as well as the provisions of this proposed rule, do not apply to voluntary reporting of adverse drug experiences to companies or regulatory authorities (e.g., FDA) by an individual (e.g., health care professional, consumer).~~

Existing regulations, under § 606.170 (21 CFR 606.170), require expedited reports of fatalities associated with blood collection or transfusion (see table 2). The report must be submitted to FDA by the collecting facility in the event of a donor reaction and by the facility that performed the compatibility tests in the event of a transfusion reaction.

II.A.3. Terms Used in This Document

The terms "sponsors," "manufacturers," and "applicants" are used in this proposed rule to describe, as appropriate, persons with safety reporting responsibilities. "Sponsors" is used to describe persons subject to the premarketing safety reporting regulations. "Manufacturers" is used, unless otherwise specified, to describe persons subject to the postmarketing safety reporting regulations under § 310.305, for prescription drug products marketed without an approved NDA or ANDA. "Applicants" is used to describe persons subject to the postmarketing safety

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Manufacturers of prescription drug products marketed without an approved NDA or ANDA are not required to submit periodic reports of postmarketing adverse drug experiences (§ 310.305).

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Current safety reporting regulations under §§ 310.305, 314.80, 314.98, 600.80 and 606.170, as well as the provisions of this proposed rule, do not apply to voluntary reporting of adverse drug experiences to companies or regulatory authorities (e.g., FDA) by an individual (e.g., health care professional, consumer).

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reporting regulations under §§ 314.80, 314.98, and 600.80; for § 600.80, "applicants" includes participants involved in divided manufacturing.

II.B. Rationale for This Proposal

II.B.1. International Standards

As explained in the October 1994 proposal and October 1997 final rule, the amendments to FDA's safety reporting regulations are intended to provide consistency with definitions, procedures, formats, and standards developed by ICH and CIOMS (59 FR 54046 at 54047; 62 FR 52237 at 52239). These organizations were formed to facilitate international consideration of issues, particularly safety issues, concerning the use of global 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 offered suggestions on international postmarketing safety reporting by pharmaceutical companies to regulatory authorities.~~ FDA believes the changes recommended by ICH and CIOMS will result in more effective and efficient safety reporting to regulatory authorities worldwide.

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Many of the amendments that are being proposed in this rulemaking are intended to harmonize our safety reporting requirements with international standards developed by CIOMS and ICH (see Table 4 of this document).

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The World Health Organization's CIOMS working groups have been comprised of representatives from regulatory authorities, including FDA, and the pharmaceutical industry. These groups have worked to develop recommendations for standardization of international reporting of postmarketing adverse reactions by the pharmaceutical industry to regulatory authorities.

ICH was organized to provide an opportunity for tripartite harmonization initiatives to be developed with input from regulatory and industry representatives.

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United States. The six ICH sponsors are the European Commission; the European Federation of Pharmaceutical Industry Associations; the Japanese Ministry of Health and Welfare; the Japanese Pharmaceutical Manufacturers Association; the Food and Drug Administration; and the Pharmaceutical Research and Manufacturers of America.

One ICH initiative is to harmonize certain safety reporting requirements of the three regions. Through the ICH process, recommendations have been developed regarding the content, format, and reporting frequency for expedited and periodic safety reports for human drugs and biological products (the ICH E2A and E2C guidances). In addition, a standard medical terminology for regulatory purposes, MedDRA, has been developed (ICH M1). Worldwide implementation of this initiative is in process. FDA, which has been actively involved in the development of these recommendations, has implemented some of them (the October 1997 final rule) and is proposing to implement others in this rulemaking.

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For example, postmarketing periodic safety reports are, for the most part, currently submitted to regulatory authorities in the three regions at different times with different formats and content. International harmonization efforts are beginning to decrease some of these differences, but harmonization of the format and content, as well as the reporting frequency, of these reports by all countries in the three regions is essential to eliminate unnecessary reporting burdens on industry so that companies can focus on the safety profiles of their products and not on the different reporting requirements of different regions. The PSUR recommended for postmarketing periodic safety reporting in the ICH E2C guidance provides regulatory authorities with a comprehensive overview of the safety profile of a product along with other relevant information such as estimates of worldwide patient exposure and worldwide marketing status of the product. In this rulemaking, FDA is proposing to require submission of PSUR's for certain products (see sections III.E.2 and III.E.5.a of this document). FDA is also interested in receipt of additional information and is proposing to require that such information be submitted with these reports as appendices (e.g., copy of current U.S. approved labeling, information on medication errors, resistance to antimicrobial drug products and class action lawsuits) (see section III.E.2.k of this document). Thus, companies can prepare the same core document for all three regions and any additional information required by FDA would simply be attached to this document.

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~~In order to support~~ another international harmonization ~~and~~ standardization ~~efforts,~~ even though FDA is proposing to use MedDRA as the standard medical terminology for reporting purposes under this rule, ~~At the same time, however, FDA~~ the agency recognizes that alternative standard classification systems for clinical information exist in the United States and supports the national health data standardization initiatives underway in the United States under the Health Insurance Portability and Accountability Act.

Although this proposed rule does not impose reporting requirements on health care providers, the agency recognizes that clinicians, medical centers, hospitals and others may report safety information to pharmaceutical companies. These third parties may employ clinical terminology standards that differ from those proposed here. Therefore, the agency invites comment on the unintended potential impact of this proposed rule on those parties not subject to FDA's safety reporting requirements. The agency also invites comment on the potential strategies and approaches for facilitating seamless cross-standard communication ~~harmonization between standards,~~ such as mapping between alternative terminologies and MedDRA.

II.B.2. Quality of Postmarketing Safety Reports

In light of the recommendations of ICH and CIOMS, FDA has reviewed its postmarketing safety reporting regulations for human drugs and licensed biological products and identified additional changes that the agency believes would further enhance

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effort is standardization of medical terminology used for regulatory purposes. As noted above, ICH has developed MedDRA for this purpose. ~~efforts,~~ Currently, companies use various medical terminologies for safety reporting purposes (e.g., World Health Organization's Adverse Reaction Terminology (WHOART), Coding Symbols for a Thesaurus of Adverse Reaction Terms (COSTART), Japan's Adverse Reaction Terminology (J-ART)). The established terminologies have been criticized for a number of reasons, including: Lack of specificity, limited data retrieval options, and an inability to effectively handle complex combinations of signs and symptoms (syndromes). In addition, use of different terminologies at different stages in the development and use of products complicates data retrieval and analysis of information and makes it difficult to effectively cross-reference data through the lifetime of a product. Internationally, communication is impaired between regulatory authorities because of the delays and distortions caused by the translation of data from one terminology to another.

Use of different terminologies also has significant consequences for pharmaceutical firms. Companies operating in more than one jurisdiction have had to adjust to subsidiaries or clinical research organizations that use different terminologies because of variations in data submission requirements. The difficulty of analyzing data comprehensively may be compounded by use of incompatible terminologies and could lead to delays in recognizing potential public health problems.

For these reasons, it is critical that a single medical terminology be used internationally for coding postmarketing safety reports. FDA is proposing to use MedDRA for this purpose (see section III.F.2 of this document). MedDRA is the best choice because it was developed with input from regulatory authorities and industry and the problems associated with the other terminologies were taken into consideration during development of MedDRA. Some companies have begun to voluntarily submit their postmarketing safety reports to FDA coded using MedDRA.

surveillance of marketed products. ~~In recent years, FDA has received an increased number of safety reports, especially for serious adverse drug experiences with insufficient information for evaluation. For timely review of safety reports, complete information is highly important. Thus,~~ for reports of serious adverse drug experiences (proposed to be called SADR's in this proposed rule; see section III.A.1 of this document) ~~FDA would expect due diligence to be used to acquire complete information expeditiously.~~ For SADR's that are determined to be nonserious, not as much information would need to be acquired.

II.B.3. New Postmarketing Expedited Safety Reports

FDA currently requires postmarketing expedited safety reports for serious and unexpected adverse drug experiences (proposed to be called SADR's in this proposed rule; see section III.A.1 of this document). To facilitate identification of significant safety problems, FDA is proposing that additional safety information be submitted expeditiously to the agency for marketed drugs and biological products. ~~This information would include reports of~~ SADR's that are unexpected and for which a determination of serious or nonserious cannot be made (i.e., SADR with unknown outcome). FDA would ~~evaluate these reports on~~ do this by comparing information on the unexpected SADR's with unknown outcome ~~in light of~~ with information on other similar unexpected SADR's with a known serious outcome that are on file

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Many of the postmarketing safety reports that FDA receives are complete and of very high quality. Others are incomplete, of mediocre or poor quality or both, making it difficult to ascertain the significance of these reports. In the latter cases, FDA is unnecessarily spending considerable amounts of time trying to collect additional information for the reports.

To address this problem, FDA is proposing amendments to its postmarketing safety reporting requirements. For most of these amendments, a risk-based approach is being proposed (i.e., greater emphasis and effort would be required

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while less information would be required for nonserious adverse drug experiences (adverse drug experiences

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FDA is proposing that complete information be submitted for reports of serious SADR's (see section III.C.5 of this document) ~~would expect due diligence to be used to acquire complete information expeditiously~~. If complete information is not available, in some cases, a followup report would be required (i.e., for serious, unexpected SADR's) (see section III.D.6 of this document). On the other hand, F

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(see section III.C.5 of this document).

Another amendment would require direct contact with the initial reporter of an SADR by a health care professional at the company for collection of certain postmarketing safety information (e.g., collection of followup information for a serious SADR) (see section III.A.6 of this document). Currently, some companies use this approach for collecting information, whereas others send the initial reporter a letter. The latter case is a passive approach which, in FDA's experience, results in limited acquisition of new information. In most cases, the initial reporter simply does not respond to the letter. Instead, using an active approach, as proposed by FDA, companies would more likely obtain the additional information needed for an SADR. Thus, use of this approach should result in submission of higher quality reports to FDA for review.

Another amendment would require that a licensed physician at the company be responsible for the content of postmarketing safety reports submitted to FDA (see sections III.E.1.h, III.E.2.k.xi and II.F.4 of this document). As in the previous examples, some companies currently use licensed physicians for this purpose, whereas others have their postmarketing safety reports prepared and submitted by clerical personnel with no health care training. The medical significance of postmarketing safety reports warrants review by a licensed physician. The agency believes that licensed physicians would ensure submission of high quality reports to FDA that articulately conveys all clinically relevant information associated with an SADR.

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Some of this information is currently submitted to the agency but not in an

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expedited manner. In other cases, the information is not currently required to be submitted to the agency.

II.B.3.a. Medication errors. In 1999, the Institute of Medicine (IOM) issued a report, "To Err is Human: Building a Safer Health System," that cited studies and articles estimating the number of Americans dying each year as a result of medical mistakes to be between 44,000 and 98,000 (Ref. 10). The IOM report concluded that preventable adverse drug events impose significant medical, personal, and economic costs to the United States.

Requiring medication errors to be reported in an expedited manner to a centralized location would provide a systematic approach for collecting comprehensive information on these errors and result in timely assessment of the information. Various organizations and health care professional associations, including the 1999 IOM report, have advocated mandatory medication error reporting efforts, as well as encouragement of voluntary efforts, aimed at making sure the system continues to be made safer for patients. Such a system would provide the public with a higher level of protection by assuring that the most serious errors are investigated and reported, and that appropriate followup action is taken both by FDA and the company whose product is associated with the error. Second, it would provide companies with an incentive to improve patient safety regarding medication errors associated with their products. Finally, it would require that FDA and the pharmaceutical industry make some level of investment in preventing medication errors and improving patient safety. In some instances, information gathered through this type of a reporting system and analyzed for root causes can lead to various changes within the health care system to prevent or minimize recurrence.

Currently, FDA maintains both a voluntary adverse event reporting system for health care professionals, through MedWatch (the Medical Products Reporting Program), and a mandatory adverse event reporting system for companies subject to the agency's postmarketing safety reporting regulations. Through these systems, FDA receives only about 3,000 reports of medication errors annually. FDA believes that these safety reporting systems do not adequately address the nature and extent of problems caused by medication errors. In most cases, safety reports associated with a medication error are not identified in the report as being associated with an error. Instead, the report only highlights the effect of the medication error (e.g., patient experienced a seizure). This information is not sufficient for FDA to identify medication errors that could be avoided in the future. For cases that involve a medication error, the safety report needs to be identified as a suspected medication error so that the report can be appropriately analyzed and addressed. FDA concludes that an explicit requirement for reporting medication errors by companies subject to the agency's postmarketing safety reporting regulations is needed to adequately assess and respond to the problem.

FDA is therefore proposing to require that these companies submit to the agency expeditiously all domestic reports of actual and potential medication errors (see section III.D.5 of this document). FDA would review information about suspected medication errors to determine an appropriate risk management plan (e.g., changes to the proprietary name, labels, labeling or packaging of the drug or biological product or educational initiatives to protect public health). This proposal, which is consistent with

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one of the Department of Health and Human Services' major health initiatives, would allow FDA to form the framework for building a comprehensive risk assessment and management system for preventable SADR's. This proposal is also responsive to the 1999 IOM report, which states that "the Food and Drug Administration (FDA) should increase attention to the safe use of drugs in both pre and postmarketing process" by "establishing appropriate responses to problems identified through post-marketing surveillance, especially for concerns that are perceived to require immediate response to protect the safety of patients."

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II.B.3.b. Unexpected SADR's with unknown outcome. FDA is also proposing to require that companies subject to the agency's postmarketing safety reporting regulations submit to FDA in an expedited report

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, (see section III.D.3 of this document). This information is currently submitted to FDA, but, in most cases, not in an expedited manner. A company that receives a report of an adverse drug experience is able, in most cases, to determine if it is serious or nonserious (i.e., whether it meets the regulatory definition of serious), but in some cases, this may not be possible. Currently, most companies that are not able to make this determination designate the adverse drug experience as nonserious and include it in their next quarterly or annual postmarketing periodic safety report. In some of these cases, the adverse drug experience is, in fact, serious even though the company was not able to make this determination. FDA needs to receive reports of SADR's with unknown outcome expeditiously if the SADR is unexpected so that the agency can evaluate the report in light of other data and information available to FDA to attempt to determine if the SADR is serious. I

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with the agency. ~~to determine if the SADR with unknown outcome is serious.~~

~~Because of their medical gravity,~~ certain SADR's (e.g., ventricular fibrillation, liver necrosis, transmission of an infectious agent by an approved product) ~~would be submitted to the agency expeditiously for review. These medically significant SADR's, which may jeopardize the patient or subject and/or require medical or surgical intervention to treat the patient or subject, would be submitted to FDA in an expedited manner~~ whether the SADR is unexpected or expected and whether or not the SADR leads to a serious outcome.

~~All domestic reports of actual and potential medication errors would also be submitted to the agency expeditiously for review. FDA would review information of suspected medication errors to determine if changes to the proprietary name, labels, labeling or packaging of the drug or biological product or educational initiatives are necessary to protect public health.~~

~~In addition to reports of fatalities associated with collection and transfusion of blood and blood components, all reports of other serious SADR's associated with these products would be submitted expeditiously to FDA for review. These expedited reports would be used by the agency to monitor the safety of blood collections and transfusions.~~

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II.B.3.c. Always expedited reports. ~~Because of their medical gravity,~~ FDA is also proposing that companies subject to the agency's postmarketing safety reporting regulations always submit to FDA in an expedited report

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which may jeopardize the patient or subject and/or require medical or surgical intervention to treat the patient or subject

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(see section III.D.4 of this document) ~~would be submitted to the agency expeditiously for review~~. Currently, all of these adverse drug experiences are submitted to the agency for review, but only some of them are submitted in an expedited safety report (i.e., if the adverse drug experience is serious and unexpected). FDA is proposing that all of them be submitted expeditiously

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This is because of the medical gravity of these SADR's. For example, even though the labeling for a product indicates that ventricular fibrillation may be associated with use of the product and thus not subject to expedited reporting to FDA (i.e., SADR is expected), the agency needs to review each new report of ventricular fibrillation for this product as quickly as possible to ascertain if there is a qualitative or quantitative change in the nature of the SADR. Information from these reports could result in either new studies being undertaken to evaluate the SADR or appropriate regulatory action by FDA (e.g., labeling change, distribution of Dear Health Care Professional letter, restriction on distribution of product, withdrawal of product from the market).

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II.B.3.d. Blood and blood component safety reports.

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With regard to blood and blood components (e.g., red blood cells, plasma, platelets, cryoprecipitated AHF), FDA is proposing that blood establishments submit reports to the agency for all serious SADR's associated with blood collection and transfusion, in addition to their current requirement at 21 CFR 606.170(b) to submit reports of fatalities (see section III.D.12 of this document). This proposed safety reporting requirement would not impose significant new burdens on blood establishments. This is because under 21 CFR 606.170(a) blood collection and transfusion facilities are currently required to conduct investigations and prepare and maintain reports of all adverse events associated either with the collection or transfusion of blood or blood components. The proposal would simply require that reports of serious SADR's that are currently maintained by the facility, be submitted to the agency within 45 calendar days of occurrence rather than only having these reports be reviewed by FDA at the time of an inspection. Thus, not all serious SADR's are reported to FDA for blood and blood components. FDA believes that it is critical that we receive all such reports to enhance donor safety and also to ensure the safety, purity and potency of blood and blood components for administration to patients.

In the past, the agency has received some voluntary reports that have helped to identify errors in manufacturing and defects in products used to collect blood. For example, in 1997, FDA received reports from a blood establishment of allergic adverse reactions to red blood cells that had been leukoreduced using a bedside filtration method in hematology or oncology patients receiving multiple transfusions. The reactions were related to several lots of Hemasure Leukonet filters. The symptoms included bilateral conjunctival edema, severe headaches, eye pain, nausea sometimes associated with vomiting and joint pain. After investigation and analysis of the reports by FDA, the manufacturer discontinued production of the filter. Voluntary reporting of the adverse reactions by the blood establishment brought the issue to the attention of FDA. However, the time to resolution may have been shortened had these been required to be reported to FDA from all blood centers.

With regard to the safety of donors, FDA review of adverse event reports is important and has resulted in detection and correction of problematic collection procedures.

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During an inspection, FDA field officers identified a blood collection center that had numerous donors with vasovagal reactions that required treatment by emergency medical personnel. In some of these cases, the donors had to be transported to a hospital emergency room for treatment. Upon investigation, FDA determined that the center had failed to establish a lower limit for blood pressure measurements for donors as required by 21 CFR 640.3. Had these serious adverse events been required to be reported to FDA, immediate analysis of them is likely to have identified the problem sooner.

Thus, required reporting of all serious SADR's related to blood collection and transfusion would enhance FDA's ability to take appropriate action to protect the blood supply more consistently. Currently, there is no assurance that FDA will receive reports of serious SADR's that have the potential to adversely affect both the donors and recipients of the nation's blood supply. Such information is essential for evaluating the agency's scientific and regulatory policies and for monitoring industry practices and their implications on blood safety.

II.B.4. Bioavailability and Bioequivalence Studies Not Subject to an Investigational New Drug Application (IND)

FDA is also proposing to amend its bioavailability and bioequivalence regulations under part 320 (21 CFR part 320) (see section III.K of this document). Under the existing regulations at § 320.31, persons conducting a bioavailability or bioequivalence study in humans are only required to comply with the IND requirements of part 312 (21 CFR part 312) for certain products or for certain types of studies. This proposed rule would require submission of expedited safety reports as prescribed under § 312.32 for human bioavailability and bioequivalence studies that are not being conducted under an IND. ~~This proposed amendment would enable the agency to monitor the safety of all drug products being investigated in human bioavailability and bioequivalence studies.~~ OMB

for serious, unexpected adverse experiences (adverse experiences proposed to be called SADR's in this proposed rule; see section III.A.1 of this document)

FDA believes that bioavailability and bioequivalence studies that are not being conducted under an IND are, in general, safe. However, the agency is occasionally made aware of safety-related information associated with these types of studies. This information could either reflect a problem with the drug product being evaluated or with the study design being used. Timely review of serious, unexpected SADR's from these studies is critical to ensure the safety of study subjects. FDA would use this information to determine if the study design needs to be altered or if the study needs to be stopped.

II.C. New Safety Reporting Abbreviations

Table 3 provides a list of new safety reporting abbreviations that are used in this document.

Table 3.--New Safety Reporting Abbreviations

Phrase	Abbreviation	Reference in Section III of this Document
Company core safety information	CCSI	A.9
Interim periodic safety report	IPSR	E.3
Medical dictionary for regulatory activities	MedDRA	F.2
Periodic safety update report	PSUR	E.2
Suspected adverse drug reaction	SADR	A.1
Traditional periodic safety report	TPSR	E.1

II.D. Highlights of Proposed Changes to FDA's Safety Reporting Regulations

Specific changes to FDA's safety reporting requirements, as described in this proposed rule, are identified in table 4.

Table 4.--Highlights of Proposed Changes to FDA's Safety Reporting Requirements

21 CFR Section	Proposed Change (reference in section III of this document)	Is the change based on ICH (ICH guidance)?
Changes apply to: 310.305, 312.32, 314.80, 314.98, and 600.80. 1	• "Associated with the use of the drug" and "adverse drug experience" changed to "suspected adverse drug reaction (SADR)" and "adverse experience" changed to "suspected adverse reaction (SAR)" (A.1)	Yes (E2A)
	• Minimum data set required for all individual case safety reports of SADR's (A.5, B.2.a, C.5, E.4)	Yes (E2A)
	• Reporting requirements for lack of efficacy reports revised (B.2.c, C.7, D.2, E.1.c, E.2.h, E.2.k.vi)	Yes (E2A and E2C)
	• Sources of safety information revised (B.1, C.2, D.8)	No
	• Individual case safety reports from clinical trials based on opinion of either the sponsor/applicant or investigator (B.2.b, B.3, C.6)	Yes (E2A)
	• Narrative format required for safety reports of overall findings or data in the aggregate (B.2.d, F.1)	No

Table 4.--Highlights of Proposed Changes to FDA's Safety Reporting Requirements (Continued)

21 CFR Section	Proposed Change (reference in section III of this document)	Is the change based on ICH (ICH guidance)?
Changes only apply to 312.32	• Determination of a life-threatening SADR based on opinion of either sponsor or investigator (A.2)	Yes (E2A)
	• Expedited reports of findings from tests in laboratory animals revised to include other information sufficient to consider product administration changes (B.2.c)	Yes (E2A)
Changes only apply to 310.305, 314.80, 314.98, and 600.80	<u>New Safety Reports</u> • Expedited report for information sufficient to consider product administration changes (D.2)	Yes (E2A)
	• Expedited report for unexpected SADR's with unknown outcome (A.3, D.3)	No
	• Always expedited reports for certain medically significant SADR's whether unexpected or expected and whether or not the SADR leads to a serious outcome (D.4)	No
	• Expedited report for medication errors (D.5)	No
	• 30-day followup report for initial serious and unexpected SADR reports, always expedited reports, and medication error reports that do not contain a full data set (D.6)	No
	<u>Other Changes</u> • Active query required to acquire certain safety information (A.6, C.5, D.6, D.7)	No
	• Full data set required for reports of serious SADR's, always expedited reports, and medication errors reports (A.5, C.5, D.1, D.4, D.5, E.4)	No
	• Safety reporting requirements for contractors and shared manufacturers (A.4, D.9)	No

Table 4.--Highlights of Proposed Changes to FDA's Safety Reporting Requirements (Continued)

21 CFR Section	Proposed Change (reference in section III of this document)	Is the Change Based on ICH (ICH guidance)?
Changes only apply to 310.305, 314.80, 314.98, and 600.80	• Reporting requirements for spontaneous reports codified (A.7, C.6)	Yes (E2A and E2C)
	• Supporting documentation required for expedited reports concerning a death or hospitalization (D.7)	No
	• FDA request for submission of safety reports at times other than prescribed by regulations (C.4)	No
	• Individual case safety reports required to be coded using MedDRA (F.2).	Yes (M1)
	• SADR information from class action lawsuits (A.7, E.1.e, E.2.k.v, E.3)	No
	• Contact person for postmarketing safety reports (E.1.h, E.2.k.xi, E.3, F.4)	No
	• Use of computer-generated facsimile of FDA Form 3500A or VAERS form permitted without approval by FDA (F.5)	No
	• Location of safety records (D.10, E.1.g, E.2.k.x, E.3)	No
	• FDA request for submission of safety related records (D.7, H).	No

Table 4.--Highlights of Proposed Changes to FDA's Safety Reporting Requirements (Continued)

21 CFR Section	Proposed Change (reference in section III of this document)	Is the Change Based on ICH (ICH guidance)?
Changes only apply to 314.80, 314.98 and 600.80	<u>New or Revised Safety Reports</u> • Semiannual submission of certain spontaneously reported individual case safety reports (E.4, E.5.a)	No
	• TPSR, PSUR, or IPSR for applications approved prior to January 1, 1998 (E.1, E.2, E.3, E.5.a)	No
	• PSUR/IPSR for applications approved on or after January 1, 1998 (E.2, E.3, E.5.a)	Yes (E2C)
	• PSUR/IPSR for pediatric use supplements (E.5.a)	No
	<u>Other Changes</u> • Periodicity of periodic safety reports (E.5.a, I)	Yes (E2C)
	• Submission date for periodic safety reports (A.10, E.5.b, I)	Yes (E2C)
	• CCSI for determination of listed and unlisted SADR's for certain periodic safety reports (A.9, E.2, E.3, E.4)	Yes (E2C)
	• Information in addition to the minimum data set not required to be acquired for nonserious SADR's, except for nonserious SADR's resulting from a medication error, which require a full data set (A.3, C.5, E.4)	No
	• Individual case safety reports forwarded to applicant by FDA required to be included in comprehensive safety analysis (C.2)	No
	• Information on resistance to antimicrobial drug products (E.2.k.vii, E.3)	No
	• Number of copies of periodic safety reports required to be submitted to FDA (C.3)	No

Table 4.--Highlights of Proposed Changes to FDA's Safety Reporting Requirements (Continued)

21 CFR Section	Proposed Change (reference in section III of this document)	Is the Change Based on ICH (ICH guidance)?
Change only applies to 314.81 and 601.37[1]	• Requirement to submit safety-related information in postmarketing annual report revoked (J)	No
Change only applies to 312.64(b)[3]	• Investigator safety reporting requirements revised	No
Change only applies to 320.31(d)[4]	• Submission of expedited safety reports required for human bioequivalence and bioavailability studies which are exempt from submission of an IND (K)	No
Change only applies to 606.170[5]	• All serious SAR's required to be submitted to FDA for blood and blood products (D.12).	No

[1]Section 310.305 describes postmarketing safety reporting regulations for prescription drug products marketed for human use without an approved application; § 312.32 describes premarketing safety reporting regulations for investigational drugs and biological products; § 314.80 describes postmarketing safety reporting regulations for human drugs with approved NDA's; § 314.98 describes postmarketing safety reporting regulations for human drugs with approved ANDA's; and § 600.80 describes postmarketing safety reporting regulations for human licensed biological products with approved BLA's.

[2]Section 314.81 describes postmarketing annual reporting regulations for human marketed drugs with approved NDA's; § 601.37 describes postmarketing annual reporting regulations for pediatric studies of human licensed biological products with approved BLA's.

[3]Section 312.64(b) describes requirements for safety reporting to sponsors by investigators.

[4]Section 320.31 (d) describes bioequivalence and bioavailability requirements for studies which are exempt from submission of an IND.

[5]Section 606.170 describes safety reporting and recordkeeping requirements for blood and blood products.

III. Description of the Proposed Rule

III.A. Definitions

III.A.1. Suspected Adverse Drug Reaction (SADR)

FDA's existing premarketing safety reporting regulations in § 312.32(a) define "associated with the use of the drug" to mean: "There is a reasonable possibility that the experience may have been caused by the drug."

FDA's existing postmarketing safety reporting regulations in §§ 310.305(b), 314.80(a), and 600.80(a) define "adverse drug experience ("adverse experience" for § 600.80(a))" to mean:

> Any adverse event associated with the use of a drug ("biological product" for § 600.80(a)) in humans, whether or not considered drug ("product" for § 600.80(a)) related, including the following: An adverse event occurring in the course of the use of a drug ("biological" for § 600.80(a)) product in professional practice; an adverse event occurring from drug overdose ("from overdose of the product" for § 600.80(a)) whether accidental or intentional; an adverse event occurring from drug abuse ("from abuse of the product" for § 600.80(a)), an adverse event occurring from drug withdrawal ("from

withdrawal of the product" for § 600.80(a));
and any failure of expected pharmacological action.

Proposed § 312.32(a) would replace the term "associated with the use of the drug" with the term "suspected adverse drug reaction (SADR)." Proposed §§ 310.305(a) and 314.80(a) would replace the term "adverse drug experience" with the term "suspected adverse drug reaction (SADR)" (see section III.C.1 of this document regarding reorganization of § 310.305). Proposed § 600.80(a) would replace the term "adverse experience" with the term "suspected adverse reaction (SAR)." In this document the term "adverse drug experience" is synonymous with the term "adverse experience" and the abbreviation "SADR" will be used for both "SADR" and "SAR," except when reference is only being made to an "SAR," in which case the abbreviation "SAR" will be used. Proposed §§ 310.305(a), 312.32(a), 314.80(a), and 600.80(a) would also replace the definitions for "associated with the use of the drug," "adverse drug experience" and "adverse experience" with the following definition for "SADR":

> A noxious and unintended response to any dose of a drug ("biological" for proposed § 600.80(a)) product for which there is a reasonable possibility that the product caused the response. In this definition, the

phrase "a reasonable possibility" means that the relationship cannot be ruled out.

The phrase "the relationship cannot be ruled out" clarifies which individual cases would be reported to FDA. Classifying a case as "probably related," "possibly related," "remotely related," or "unlikely related" to the drug or biological product would signify that a causal relationship between the product and an adverse event could not be ruled out and, thus, the adverse event would be considered an SADR. For example, in some cases an adverse event may most probably have occurred as a result of a patient's underlying disease and not as a result of a drug or biological product the patient was taking, but it cannot usually be said with certainty that the product did not cause the adverse event. Therefore, such an adverse event would be classified as an SADR because there would be at least a "reasonable possibility" that the drug or biological product may have caused the adverse event. Of course, this classification would not establish causality (attributability) by itself, it would only indicate that causality could not be ruled out with certainty.

These proposed changes are consistent with the ICH E2A guidance (60 FR 11284 at 11285), which defines "adverse drug reaction" as:

All noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug

reactions. The phrase "response to medicinal products" means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out.

These proposed amendments would harmonize the agency's premarketing and postmarketing safety reporting definition for SADR, as well as safety reporting worldwide ~~but the effect on~~ safety ~~reporting~~ to FDA from spontaneous sources ~~and~~ clinical studies ~~would be different~~.

Although FDA is proposing to remove the definition for "adverse drug experience" from its postmarketing safety reporting regulations and replace it with the definition for "SADR," this change would not affect the number of safety reports from spontaneous sources that would be submitted to the agency because every spontaneous report currently must be submitted to FDA, irrespective of whether the manufacturer or applicant considers it to be drug related (see current definition of adverse drug experience at §§ 310.305(c), 314.80(c), and 600.80(c)). Under this proposed rule, every spontaneous report would continue to be submitted to FDA, because, for spontaneous reports, manufacturers and applicants would always be required to assume, for safety reporting purposes only, that there was at least a reasonable possibility in the opinion of the initial reporter that the drug or biological product caused the spontaneously reported event

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Even though FDA has harmonized its proposed definition of SADR with the definition of adverse drug reaction recommended by ICH, the agency would like comment on an alternative definition for SADR:

> *A noxious and unintended response to any dose of a drug product for which a relationship between the product and the response to the product cannot be ruled out.*

The alternative and proposed definitions for SADR have the same meaning (i.e., a response to a product is an SADR unless one is sure that the product did not cause the response). The difference between these definitions is that the alternative definition of SADR does not include the phrase "a reasonable possibility." This is because use of this phrase is potentially confusing. The phrase "a reasonable possibility" might be interpreted differently than the phrase "the relationship cannot be ruled out." The agency defines "a reasonable possibility" as "the relationship cannot be ruled out" to be consistent with ICH. FDA seeks comment as to whether the agency should use the alternative definition of SADR instead of the proposed definition of SADR.

~~, but the effect on~~ ~~While~~ the proposed definition of SADR would not affect the number

The agency also requests comment from sponsors, manufacturers and applicants if their interpretation of these definitions is different than FDA's interpretation.

As explained below, FDA believes that

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FDA seeks comment

as to whether use of the proposed or alternative definition of SADR would lead to significant increases in reporting to the agency beyond what FDA has identified below. FDA is particularly interested in learning of examples of events beyond those identified by the agency that are not currently reported to FDA but would be required to be reported under these definitions.

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(see sections III.A.7 and III.C.6 of this document for the proposed definition of spontaneous report and for discussion of the proposed reporting requirement for SADRs from spontaneous sources).

On the other hand, with regard to clinical studies of investigational and marketed drugs and biological products, the proposed definition of SADR is likely to result in an increase in the number of safety reports that are currently submitted to FDA from some studies. Current regulations at §§ 310.305(c)(1)(ii), 312.32(c)(1), 314.80(e)(1), and 600.80(e)(1) require that serious, unexpected adverse experiences from a study be reported to FDA only if there is a reasonable possibility that the drug caused the adverse experience. The phrase "reasonable possibility" is typically interpreted by sponsors, manufacturers and applicants to mean that there is a possible causal relationship between an adverse experience and a drug or biological product. It would not include adverse experiences considered to be unlikely or remotely related to the product. The proposed definition of SADR maintains the phrase "reasonable possibility" as part of the definition, but defines the phrase to mean that the relationship between a product and a response to the product cannot be ruled out. In some cases, this proposed change would result in submission of more safety reports to FDA. For example, under the current regulations if a sponsor or

applicant concludes that the existence of a causal relationship between a drug and an adverse event is unlikely or remote, but not impossible, (e.g., because the event is a recognized consequence of the patient's underlying disease) it would not submit a safety report to FDA. In contrast, under the proposed rule, the sponsor or applicant would be required to submit a safety report to the agency for this SADR, because, although the relationship of the adverse event to the drug is unlikely or remote because of the patient's underlying disease, a causal relationship cannot, nonetheless, be ruled out. FDA is proposing the new definition for SADR to minimize situations in which an adverse event that proves ultimately to be due to a drug or biological product is not reported as soon as possible to the agency because the etiology of the adverse event is attributed to the patient's underlying disease by the sponsor, manufacturer or applicant (e.g., a patient's hepatic deterioration is judged to be related to the patient's viral hepatitis and not to the hepatotoxicity of the drug the patient received.)

FDA recognizes, however, that particularly for those patients who have certain diseases (e.g., fatal diseases such as cancer), the proposed definition of SADR may result in submission of numerous safety reports to the agency for which the reported SADR is not informative as a single report because it is very likely to have been a consequence of the patient's disease. This would be true, for example, for most non-acute deaths in a

clinical trial evaluating a drug in cancer patients. These deaths would have to be reported to FDA as SADRs because a relationship between the drug and the deaths could not be ruled out with certainty. Because such "over-reporting" may make it more difficult for FDA and the sponsor, manufacturer or applicant to recognize adverse events that are really caused by a drug or biological product, the agency wants to minimize receipt of this type of safety report, but in a way that does not compromise receipt of useful safety reports that are perceived as remotely related to an administered drug or biological product but that occur, in fact, as a result of the product. If sponsors, manufacturers or applicants believe that, in a specific situation, there is an alternative way(s) to handle adverse events occurring during clinical studies that would minimize "over-reporting" while assuring that reporting of SADRs would not be compromised, they are invited to propose any such alternative(s) reporting method to the agency. In such situations, if FDA does not oppose the proposed alternative reporting method, the sponsor, manufacturer or applicant would be permitted to report SADRs to the agency according to the alternative method. For example, one such alternative would be to include in study protocols or other documentation a list of known consequences of the disease that would not be submitted to FDA in an expedited manner as individual case safety reports (e.g., events that are the endpoints of the study). These

adverse events would, however, be monitored by the sponsor, manufacturer, or applicant and, if they indicated in the aggregate by comparison to a control group or historical experience, that the product in the clinical study may be causing these events, the information would be submitted to FDA in an expedited manner as an information sufficient to consider product administration changes report (see sections III.B.2.c and III.D.2 of this document for discussion of this type of report). FDA invites comment from the public on this alternative and requests suggestions for other alternatives as well that would minimize "over-reporting" of uninformative events and assure submission of meaningful reports of unexpected events. FDA also invites comment on reporting of these types of clinical events that occur in studies not being conducted under an IND (e.g., drug or biological product is marketed in the United States for a particular indication and being investigated in a clinical trial abroad for the same or other indication).

The proposed definition of SADR may result in submission to FDA of some reports from clinical studies and the scientific literature in which the reported SADR is suspected to be associated with the product, but, in fact, it is ultimately demonstrated not to be due to the product. This is also true for reports from spontaneous sources in which manufacturers and applicants must always assume, for safety reporting purposes, that there is at least a reasonable possibility that the drug or

biological product caused the spontaneously reported event and submit the report to FDA. Thus, SADR reports are required to be submitted to FDA based on a suspected, not established, causal relationship between an adverse event and a drug. This type of reporting program allows the agency to determine more quickly which SADRs warrant regulatory action by FDA to protect public health (e.g., change in product labeling, withdrawal of product from the market). FDA receives hundreds of thousands of such reports each year, most of which do not result in any regulatory action. But for those reports that do represent a significant change in the benefit-to-risk profile of a product, this system is critical for developing a signal necessitating further evaluation of an SADR.

Some members of the public have maintained that submission of voluntary SADR reports by health care professionals or consumers to manufacturers or to FDA might be discouraged because of concern that a person or entity might be implicated in a product liability action. In addition, industry has expressed its concern that these reports, taken out of context and used in a manner for which they were never intended, can create a product liability vulnerability. FDA is concerned that such liability misuse of these reports could imperil the credibility and functionality of this critical public health reporting system.

Our current safety reporting regulations at §§ 310.305(g), 312.32(e), 314.80(k), and 600.80(l) provide manufacturers,

applicants, and sponsors with a disclaimer that permits them to deny that the safety report or other information required to be submitted to FDA under these regulatory provisions constitutes an admission that the drug or biological product caused or contributed to an adverse effect. For example, § 314.80(k) currently reads in pertinent part:

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

Additionally, a "disclaimer" is included on the first page of the voluntary reporting form used by health care professionals and consumers, FDA Form 3500, stating "Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event." A similar disclaimer is included on the mandatory reporting form used by manufacturers and applicants, FDA Form 3500A. In its notice of availability announcing FDA Form 3500 and 3500A, the agency reiterated that "Although the underlying information may be relevant to product liability issues, submitting the form itself, as is clearly

stated on the form, does not constitute an admission that the product caused the adverse event." (58 FR 31596 at 31600, June 3, 1993).

FDA seeks comment as to whether these "disclaimers" are sufficient to protect manufacturers, applicants, and sponsors, from the use of SADR reports in product liability actions. For instance, perhaps the agency should consider also prohibiting use of SADR reports the agency receives in product liability actions. Accordingly, FDA seeks comment on the need for any further action to promote submission of SADR reports to the agency and guard against their misuse, as well as FDA's legal authority to take any such action.

FDA is proposing to remove the current provisions in §§ 310.305(c)(1)(ii), 314.80(e)(1), and 600.80(e)(1). The agency is proposing this amendment because the information contained in these paragraphs is included in the proposed definition of SADR.

III.A.2. A Life-Threatening SADR

FDA's existing premarketing safety reporting regulations at § 312.32(a) define a life-threatening adverse drug experience as:

> 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.

FDA is proposing to amend this definition by adding the phrase "or sponsor" after the word "investigator." Thus, reports of life-threatening SADR's would be based on the opinion of either the investigator or sponsor. In some cases, the opinions of the investigator and sponsor may be discordant. In these situations, the sponsor would submit an IND safety report to FDA for the life-threatening SADR and include in the report the reason(s) for any differences in opinions. This proposed revision is consistent with the ICH E2A guidance (60 FR 11286): "Causality assessment is required for clinical investigation cases. All cases judged by either the reporting health care professional or the sponsor as having a reasonable suspected causal relationship to the medicinal product qualify as ADR's [adverse drug reactions]."

FDA's existing postmarketing safety reporting regulations at §§ 310.305(b), 314.80(a), and 600.80(a) define a "life-threatening adverse drug experience" as:

> Any adverse [drug] experience that places the patient, in the view of the initial reporter, at <u>immediate</u> 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.

Proposed §§ 310.305(a), 312.32(a), 314.80(a), and 600.80(a) would amend the premarketing and postmarketing definition of life-threatening adverse drug experience by making minor revisions. FDA is proposing to move the phrase "places the patient" ("patient or subject" for proposed § 312.32(a)) before the phrase "at immediate risk of death" and also to replace the phrase "adverse drug experience" with the abbreviation "SADR."

III.A.3. Serious SADR, Nonserious SADR, and SADR With Unknown Outcome

FDA's existing premarketing and postmarketing safety reporting regulations at §§ 310.305(b), 312.32(a), 314.80(a), and 600.80(a) define a serious adverse drug experience as:

> 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. * * *

Proposed §§ 310.305(a), 312.32(a), 314.80(a), and 600.80(a) would amend this definition by removing the phrase "occurring at any dose," because the proposed definition of SADR includes the

phrase "response to any dose of a drug ("biological" for proposed § 600.80(a)) product" and it is unnecessary to refer to "any dose" in both definitions. FDA is also proposing to amend this definition by replacing the phrase "adverse drug experience" with the abbreviation "SADR" for consistency as proposed previously.

Under proposed §§ 310.305(a), 314.80(a), and 600.80(a), FDA would amend its postmarketing safety reporting regulations to define the term "nonserious SADR" to mean: "Any SADR that is determined not to be a serious SADR." FDA is proposing to add this definition to clarify what constitutes a nonserious SADR. SADR's would only be classified as "nonserious" if manufacturers and applicants have determined that the reaction does not meet the definition of a serious SADR. If the outcome for an SADR is not known, a determination of seriousness cannot be made; the SADR would not default to a "nonserious" designation, but would rather be classified as an "SADR with unknown outcome" as described below.

Under proposed §§ 310.305(a), 314.80(a), and 600.80(a), FDA would amend its postmarketing safety reporting regulations to define the term "SADR with unknown outcome" to mean: "An SADR that cannot be classified, after active query, as either serious or nonserious." FDA is proposing to define this term to describe those SADR's for which an outcome (i.e., classification as either serious or nonserious) cannot be determined. FDA believes that, in most cases, manufacturers and applicants are usually able to

determine the outcome of an SADR. However, in a few cases, this may not be possible, even after active query, and these SADR's would be designated as "SADR with unknown outcome" (see section III.A.6 of this document for proposed definition of active query).

III.A.4. Contractor

Under proposed § 310.305(a), FDA would amend its postmarketing safety reporting regulations to define the term "contractor" to mean:

> Any person (e.g., packer or distributor whether or not its name appears on the label of the product; licensee; contract research organization) that has entered into a contract with the manufacturer to manufacture, pack, sell, distribute, or develop the drug or to maintain, create, or submit records regarding SADR's or medication errors.

Under proposed § 314.80(a), the term "contractor" is defined as persons (e.g., manufacturer, packer, or distributor whether or not its name appears on the label of the product; licensee; contract research organization) that have entered into a contract with the applicant. Under proposed § 600.80(a), the term "contractor" is defined as persons (e.g., manufacturer, joint manufacturer, packer, or distributor whether or not its name

appears on the label of the product; licensee; contract research organization) that have entered into a contract with the applicant (includes participants involved in divided manufacturing). FDA would define this term to specify which contractors would be subject to the agency's postmarketing safety reporting requirements under proposed §§ 310.305(c)(2)(xi), 314.80(c)(2)(x), and 600.80(c)(2)(x) (see section III.D.9 of this document). Persons under contract to manufacture, pack, sell, distribute, or develop the drug or licensed biological product, or to maintain, create, or submit records regarding SADR's or medication errors (whether or not the medication error results in an SADR; see section III.A.8 of this document) would have postmarketing safety reporting responsibilities.

III.A.5. Minimum Data Set and Full Data Set for an Individual Case Safety Report

Proposed §§ 310.305(a), 312.32(a), 314.80(a), and 600.80(a), would amend FDA's premarketing and postmarketing safety reporting regulations to define the term "minimum data set." A "minimum data set" for an individual case safety report of an SADR would include: an identifiable patient, an identifiable reporter, a suspect drug (biological for proposed § 600.80(a)) product, and an SADR.

Proposed §§ 310.305(a), 314.80(a), and 600.80(a), would also amend FDA's postmarketing safety reporting regulations to define

the term "full data set." A "full data set" for a postmarketing individual case safety report would include:

> Completion of all the applicable elements on FDA Form 3500A (or the Vaccine Adverse Event Reporting System (VAERS) form for proposed § 600.80(a))(or on a Council for International Organizations of Medical Sciences (CIOMS) I form for reports of foreign SADR's) including a concise medical narrative of the case (i.e., an accurate summary of the relevant data and information pertaining to an SADR or medication error).

The proposed rule would define these terms to clarify the type of information that manufacturers and applicants would be required to submit to FDA for SADR's and medication errors. The proposed rule would, as described below, require at least a minimum data set for all individual case safety reports, except for certain reports of medication errors (see sections III.B.2.a and III.C.5 of this document). In addition, a full data set would be required for postmarketing individual case safety reports of serious SADR's, always expedited reports, and medication error reports (see sections III.C.5, III.D.1, III.D.4, III.D.5, and III.E.4 of this document). Reports of nonserious SADR's with a minimum data set would include All safety information received or otherwise obtained ~~for SADR's that are determined to be nonserious would be submitted to FDA even though manufacturers~~ by the manufacturer or applicant for the SADR. However, except for reports of nonserious SADR's resulting from a medication error,

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~~and applicants would not be required to obtain~~ information in addition to the minimum data set, ~~except~~ for reports of nonserious SADR's resulting from a medication error ~~for which a full data set would be required~~ (see sections III.C.5 and III.D.5 ~~and III.E.4~~ of this document).

As noted above, for each individual case safety report, a suspect product would be required to be identified. Reports from blinded clinical studies (i.e., the sponsor and investigator are blinded to individual patient treatment) should be submitted to FDA only after the code is broken for the patient or subject that experiences an SADR. The blind should be broken for each patient or subject who experiences a serious, unexpected SADR unless arrangements have been made otherwise with the FDA review division that has responsibility for review of the IND (e.g., the protocol or other documentation clearly defines specific alternative arrangements for maintaining the blind). Exceptions to breaking the blind for a study usually involve situations in which mortality or certain serious morbidities are indeed the clinical endpoint of the study. This is consistent with the discussion of managing blinded therapy cases in the ICH E2A guidance (60 FR 11266):

> * * * Although it is advantageous to retain the blind for all patients prior to final study analysis, when a serious adverse reaction is judged reportable on an expedited basis, it is recommended that the blind be broken only for the

would not be required to be acquired by the manufacturer or applicant (see sections III.C.5 and III.E.4 of this document). Manufacturers and applicants would be required to submit a full data set;

specific patient by the sponsor even if the investigator has not broken the blind. * * * However, when a fatal or other "serious" outcome is the primary efficacy endpoint in a clinical investigation, the integrity of the clinical investigation may be compromised if the blind is broken. Under these and similar circumstances, it may be appropriate to reach agreement with regulatory authorities in advance concerning serious events that would be treated as disease-related and not subject to routine expedited reporting.

In addition to the exception for breaking the blind mentioned above, FDA is also interested in considering whether the blind should be broken for other serious SADRs that are not the clinical endpoint of the study, but occur at a rate high enough that the overall study blind would be threatened if each such case were individually unblinded. FDA invites comment from the public on how reporting of these SADRs should be handled.

III.A.6. Active Query

Under proposed §§ 310.305(a), 314.80(a), and 600.80(a), FDA would amend its postmarketing safety reporting regulations to define the term "active query" to mean:

> Direct verbal contact (i.e., in person or by telephone or other interactive means such as a videoconference) with the initial reporter of a suspected adverse drug reaction (SADR)

or medication error by a health care professional (e.g., physician, physician assistant, pharmacist, dentist, nurse) representing the manufacturer (applicant for proposed §§ 314.80(a) and 600.80(a)). For SADR's, active query entails, at a minimum, a focused line of questioning designed to capture clinically relevant information associated with the drug product (licensed biological product for proposed § 600.80(a)) and the SADR, including, but not limited to, information such as baseline data, patient history, physical exam, diagnostic results, and supportive lab results.

The agency would define this term to describe the process that manufacturers and applicants would be required to use to acquire safety information expeditiously. Active query would be used to:

- Determine whether an SADR is serious or nonserious (see section III.C.5 of this document),
- Obtain at least the minimum data set for all SADR's and the minimum information for medication errors that do not result in an SADR (see section III.C.5 of this document),
- Obtain a full data set for individual case safety reports of serious SADR's, always expedited reports,

and medication error reports (see section III.C.5 of this document), and

- Obtain supporting documentation for a report of a death or hospitalization (e.g., autopsy report, hospital discharge summary) (see section III.D.7 of this document).

Active query would entail direct verbal contact either in person or by telephone or other interactive means (e.g., a videoconference) with the initial reporter of an SADR or medication error. FDA believes that, in many cases, use of active query during initial contact with these reporters would provide manufacturers and applicants with adequate safety information and could eliminate or decrease followup time expended by manufacturers, applicants, and the agency. The agency does not believe that it is sufficient for manufacturers and applicants just to send a letter to reporters of SADR's and medication errors requesting further information. These reporters could, however, submit written materials to manufacturers and applicants to clarify or provide support for verbal discussions.

Active query would be conducted by a health care professional, such as a physician, physician's assistant, pharmacist, dentist, or nurse. The agency believes that a health care professional would be able to understand better the medical consequences of a case and ask reporters of SADR's and medication

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Even though the agency is not proposing that manufacturers and applicants request followup information for SADR and medication error reports in writing, the CIOMS V report describes instances when it might be appropriate to do so. FDA seeks comment as to whether the agency should permit written requests for followup information and, if so, in which situations should these requests be permitted.

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errors appropriate questions to acquire more complete safety information effectively and rapidly.

The proposed definition of active query would provide that, at a minimum, a focused line of questioning be used to acquire further information on SADR's. For this purpose, questions would be designed to capture clinically relevant information associated with the drug or licensed biological product and the SADR. This information would include, but would not be limited to, baseline data, patient history, physical exam, diagnostic results, and supportive lab results.

III.A.7. Spontaneous Report

Under proposed §§ 310.305(a), 314.80(a), and 600.80(a), FDA would amend its postmarketing safety reporting regulations to define the term "spontaneous report" to mean:

> A communication from an individual (e.g., health care professional, consumer) to a company or regulatory authority that describes an SADR or medication error. It does not include cases identified from information solicited by the manufacturer or contractor (applicant or contractor for proposed § 314.80(a); applicant, shared manufacturer, or contractor for proposed § 600.80(a)), such as individual case safety reports or findings derived from a study,

company-sponsored patient support program, disease management program, patient registry, including pregnancy registries, or any organized data collection scheme. It also does not include information compiled in support of class action lawsuits.

The agency would define this term to clarify which reports would be considered "spontaneous." Over the years, changes in marketing practices in the United States have led to expanded contacts between consumers and manufacturers, applicants, contractors, and shared manufacturers. This has resulted in the acquisition of new types of solicited safety information. Under the proposed rule, only unsolicited safety information from an individual, such as a health care professional or consumer, to a company or regulatory authority would be considered a "spontaneous report."

Cases identified from information solicited by companies, such as individual case safety reports or findings obtained from a study, company-sponsored patient support program, disease management program, patient registry, including pregnancy registries, or any organized data collection scheme would not be considered spontaneous. Instead, safety information from these sources would be considered "study" information and would be handled according to the postmarketing safety reporting

requirements for a "study." As proposed, study information would be subject to reporting as discussed below:

- Expedited reports for serious and unexpected SADR's from a study (see section III.D.1 of this document),
- Expedited reports for information from a study that would be sufficient to consider product administration changes (see section III.D.2 of this document),
- Expedited reports for an unexpected SADR with unknown outcome from a study (see section III.D.3 of this document),
- Always expedited reports from a study (see section III.D.4 of this document),
- Medication error reports from a study (see section III.D.5 of this document),
- Summary tabulations of all serious SADR's from studies or individual patient IND's in PSUR's (see section III.E.2.f.ii of this document), and
- Discussion of important safety information from studies in PSUR's and IPSR's (see sections III.E.2.g and III.E.3 of this document).

The proposed rule would consider SADR information compiled in support of class action lawsuits to be neither spontaneous nor "study" information. FDA believes that the vast majority of SADR information from class action lawsuits is duplicative (i.e., the same SADR information is reported by multiple individuals). In

many cases, information in addition to the minimum data set is not available for these SADR reports and followup is unlikely to result in acquisition of new information. For these reasons, the agency is proposing to require in TPSR's, PSUR's and IPSR's summary information for SADR's from class action lawsuits (see sections III.E.1.e, III.E.2.k.v, and III.E.3 of this document).

Any safety information obtained from an individual (e.g., health care professional, consumer) who has initiated contact with a company or regulatory authority would be considered spontaneous. For example, if an individual calls a company and asks if a particular SADR has been observed with one of the company's drug or licensed biological products because the individual or someone the individual knows has experienced such an SADR, the call would be considered spontaneous. The agency would consider these calls spontaneous because the individual making the call has a belief or suspicion that the drug or licensed biological product may have caused the SADR.

The proposed definition for spontaneous report is consistent with the definition of "spontaneous report or spontaneous notification" in the ICH E2C guidance (62 FR 27475)):

> An unsolicited communication to a company, regulatory authority, or other organization that describes an adverse reaction in a patient given one or more medicinal products

and which does not derive from a study or any organized data collection scheme.

III.A.8. Medication Error

Proposed §§ 310.305(a), 314.80(a), and 600.80(a) would amend FDA's postmarketing safety reporting regulations to define the terms "medication error," "actual medication error," and "potential medication error." A "medication error" would be defined as:

> Any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer. Such events may be related to professional practice, health care products, procedures, and systems including: Prescribing; order communication; product labeling, packaging, and nomenclature; compounding; dispensing; distribution; administration; education; monitoring; and use.

An "actual medication error" would be defined as:

> A medication error that involves an identifiable patient whether the error was prevented prior to administration of the product or, if the product was administered,

whether the error results in a serious SADR, nonserious SADR, or no SADR.

A "potential medication error" would be defined as:

> An individual case safety report of information or complaint about product name, labeling, or packaging similarities that does not involve a patient.

The proposed rule would define these terms to clarify what would be considered a medication error. The proposed definition for "medication error" was developed by the National Coordinating Council for Medication Error Reporting and Prevention, of which FDA is a member. The proposed definitions for actual and potential medication errors were developed by FDA. Actual medication errors involve an identifiable patient whether or not the product is administered and, if the product is administered, whether or not an SADR occurs. Potential medication errors do not involve a patient, but rather describe information or complaint about product name, labeling, or packaging similarities that could result in a medication error in the future.

III.A.9. Company Core Data Sheet, Company Core Safety Information (CCSI), Listed SADR, Unlisted SADR, and Unexpected SADR

Proposed §§ 314.80(a) and 600.80(a) would amend FDA's postmarketing safety reporting regulations to define the terms "company core data sheet," "company core safety information

(CCSI)," "listed SADR," and "unlisted SADR." The "company core data sheet" would be defined as:

> A document prepared by the applicant containing, in addition to safety information, material relating to indications, dosing, pharmacology, and other information concerning the drug substance (biological product for proposed § 600.80(a)). The only purpose of this document is to provide the company core safety information (CCSI) for periodic safety update reports (PSUR's), interim periodic safety reports (IPSR's), and certain individual case safety reports--semiannual submissions (i.e., if PSUR's are submitted for the product).

The "CCSI" would be defined as:

> All relevant safety information contained in the company core data sheet that the applicant proposes to include in the approved product labeling in all countries where the applicant markets the drug substance (biological product for proposed § 600.80(a)). It is the reference information by which an SADR is determined to

be "listed" or "unlisted" for PSUR's, IPSR's, and certain individual case safety reports--semiannual submissions (i.e., if PSUR's are submitted for the product).

A "listed SADR" would be defined as: "an SADR whose nature, specificity, severity, and outcome are consistent with the information in the CCSI."

An "unlisted SADR" would be defined as: "an SADR whose nature, specificity, severity, or outcome is not consistent with the information included in the CCSI."

The proposed rule would define these terms to help applicants determine which SADR's must be reported in PSUR's, IPSR's, and certain individual case safety reports--semiannual submissions (i.e., if PSUR's are submitted for the product) (see sections III.E.2, III.E.3, and III.E.4 of this document). For this purpose, the CCSI would be used as the reference document by which an SADR would be judged as "listed" or "unlisted."

Company core data sheets would usually be prepared by applicants for a drug substance rather than a drug product because postmarketing PSUR's and IPSR's would be based on a drug substance. Under the existing regulations at § 314.3(b) (21 CFR 314.3(b)), a drug substance is defined as:

> An active ingredient that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure,

> mitigation, treatment, or prevention of disease or to affect the structure or any function of the human body, but does not include intermediates use[d] in the synthesis of such ingredient.

Under these same regulations, a drug product is defined as:

> a finished dosage form, for example, tablet, capsule, or solution, that contains a drug substance, generally, but not necessarily, in association with one or more other ingredients.

Thus, drug substances refer to active moieties of drug products.

In the United States, the company core data sheet would be used only to provide the CCSI for a drug or biological product to determine whether an SADR is listed or unlisted. Company core data sheets would not require approval from FDA, unlike the U.S. labeling for a marketed drug or licensed biological product which does require approval from FDA. Company core data sheets would not be used in the United States as the labeling for an approved drug or licensed biological product. FDA believes that preparation of a company core data sheet would not impose a new burden on most applicants because it codifies a common practice in the pharmaceutical industry (see the ICH E2C guidance, 62 FR 27470 at 27472).

Postmarketing PSUR's may be submitted by applicants to multiple countries, and the drug or licensed biological product may have different approved labeling in the different countries. The CCSI for the product should not be a compilation of all the safety information contained in the various approved labelings for the product. Instead, the CCSI should contain the critical safety information for the product that would be relevant in all countries where the product is approved for marketing. In some cases, the CCSI and an approved labeling for the product would contain the same safety information (i.e., all the safety information in an approved labeling for the product is relevant in all countries where the product is approved for marketing or the product is only approved for marketing in one country). In other cases, an approved labeling for a product may contain more safety information than the CCSI for the product because the labeling may contain safety information specific to the country in which the product is approved for marketing (e.g., safety information regarding a specific indication for which the product is approved for marketing in one country but not other countries). In these cases, the use of the CCSI as the reference document for determining whether an SADR is listed or unlisted for the postmarketing PSUR's may result in overreporting of some SADR's to FDA as "unlisted" when they actually are "expected" by the approved U.S. labeling.

This proposal would not affect the reference document used to determine expectedness (i.e., unexpected or expected SADR) for SADR's reported in premarketing IND safety reports, postmarketing expedited reports, postmarketing TPSR's, and certain postmarketing individual case safety reports--semiannual submissions (i.e., if TPSR's are submitted for the product) (see table 5 and sections III.B, III.D, III.E.1, and III.E.4 of this document). Under the existing regulations at §§ 310.305(b), 314.80(a), and 600.80(a), the definition of "unexpected adverse drug experience" designates the current approved labeling for the drug or licensed biological product as the reference document to be used to determine what would be considered "unexpected." Proposed §§ 310.305(a), 314.80(a), and 600.80(a) would include in the definition of "unexpected SADR" the abbreviation "U.S." before the word "labeling" to clarify that the approved U.S. labeling would be used to determine whether or not an SADR is "unexpected." FDA would also amend this definition by replacing the word "event" with the word "reaction" and by clarifying that the phrase "differ from the event because of greater severity or specificity" refers to a "labeled reaction." Under proposed §§ 310.305(a), 312.32(a), 314.80(a), and 600.80(a), the agency would also replace the word "listed" with the word "included" in the definition of "unexpected SADR" to minimize confusion with "listed SADR's" in the CCSI. FDA would also revise the sentence "Unexpected, as used in this definition, refers to an SADR that

has not been previously observed * * * rather than from the perspective of such reaction not being anticipated from the pharmacological properties of the drug product" in this definition for clarity.

Table 5.--Proposed Reference Documents for Safety Reports

Marketing Status	Safety Report		Reference Document
Premarketing	IND safety report		Investigator's brochure. If not available, risk information in general investigational plan or elsewhere in the current application.
Postmarketing	Expedited reports		U.S. labeling
	TPSR's		U.S. labeling
	PSUR's and IPSR's		CCSI
	Individual case safety reports--semiannual submission	If TPSR is submitted for the product	U.S. labeling
		If PSUR is submitted for the product	CCSI

These proposed amendments are consistent with the ICH E2C guidance (62 FR 27470 at 27472):

> For purposes of periodic safety reporting, CCSI forms the basis for determining whether an ADR is already Listed or is still Unlisted, terms that are introduced to distinguish them from the usual terminology of "expectedness" or "labeledness" that is used in association with official labeling. Thus, the local approved product information continues to be the reference document upon which labeledness/expectedness is based for

the purpose of local expedited postmarketing safety reporting.

Under proposed §§ 310.305(a), 312.32(a), 314.80(a), and 600.80(a), FDA would include the following sentence in the definition of "unexpected SADR:"

> SADR's that are mentioned in the U.S. labeling (investigator's brochure for proposed § 312.32(a)) as occurring with a class of drugs (products for proposed § 600.80(a)) but not specifically mentioned as occurring with the particular drug (product for proposed § 600.80(a)) are considered unexpected.

This information is currently included in the draft guidance of 2001. FDA is now proposing to codify this information to clarify which SADR's would be considered "unexpected."

III.A.10. Data Lock Point and International Birth Date

Proposed §§ 314.80(a) and 600.80(a) would amend FDA's postmarketing safety reporting requirements to define the terms "data lock point" and "international birth date." The "data lock point" would be defined as:

> The date designated as the cut-off date for data to be included in a postmarketing periodic safety report.

The "international birth date" would be defined as:

The date the first regulatory authority in the world approved the first marketing application for a human drug product containing the drug substance (human biological product for proposed § 600.80(a)).

The agency would define these terms to help standardize the submission date (i.e., month and day of submission) for postmarketing periodic safety reports (i.e., PSUR's, IPSR's, TPSR's, individual case safety reports--semiannual submissions). The data lock point would signify the end of a reporting period for data to be included in a specific postmarketing periodic safety report. The month and day of the international birth date would serve as a reference point for determining the data lock point. On the date of the data lock point, safety information that is available to applicants would be reviewed and evaluated prior to being submitted to FDA. Postmarketing periodic safety reports would be submitted to FDA within 60 days of the data lock point (see section III.E.5.b. of this document). For example, for a drug or biological product approved by FDA on June 15 with a 6-month periodic reporting period and an international birth date of April 1, the first data lock point would be October 1, which is less than 6 months after FDA approval, but is the 6-month anniversary of the international birth date. Therefore, the first postmarketing periodic safety report would cover the period from April 1 through October 1 even though the product

had only been approved in the United States on June 15. The second periodic report would cover the period from October 2 through April 1.

An international birth date would be determined and declared by applicants. Applicants would determine an international birth date for a product based on the date of approval of the first marketing application in the world for a human drug product containing the drug substance or a biological product. A single international birth date would encompass all different dosage forms, formulations, or uses (e.g., indications, routes of administration, populations) of a drug substance or licensed biological product. Thus, postmarketing periodic safety reports for different drug products containing the same drug substance would be submitted to FDA at the same time.

The month and day of the international birth date would be used, as noted previously, to determine the data lock point (i.e., month and day) for postmarketing periodic safety reports. It would not, except as noted below, be used to determine the frequency for submission of these reports (i.e., 6-month intervals or multiples of 6 months). Instead, the date (i.e., year) of U.S. approval of the application for the drug or biological product (e.g., NDA, ANDA, BLA) would be used to determine the frequency for submission of postmarketing periodic safety reports to FDA (see section III.E.5.a of this document). The international birth date would be used to determine both the

data lock point and reporting frequency for postmarketing periodic safety reports only when the U.S. approval date is used to determine the international birth date (e.g., FDA is the first regulatory authority in the world to approve the human drug product containing the drug substance or biological product for marketing).

The use of a standardized submission date (i.e., month and day), which is consistent with the ICH E2C guidance (62 FR 27470 at 27472), would enable applicants to submit a single core report (PSUR excluding appendices) to regulatory authorities worldwide. Currently, different regulatory authorities require submission of postmarketing periodic safety reports on varying time schedules. The submission of a single core report to multiple regulatory authorities would significantly reduce the time spent preparing these reports, thereby permitting more time for the evaluation of the medical significance of any safety information reported.

III.B. IND Safety Reports

III.B.1. Review of Safety Information

Current IND safety reporting regulations in § 312.32(b) require that sponsors promptly review all information relevant to the safety of the drug under investigation obtained or otherwise received by the sponsor from any source, foreign or domestic. Sources of information include any clinical or epidemiological investigations, animal investigations, commercial marketing experience, reports in the scientific literature, and unpublished

scientific papers, and reports from foreign regulatory authorities that have not already been previously reported to FDA by the sponsor. FDA is proposing to amend this requirement by adding "in vitro studies" to the list of examples because some in vitro studies report relevant safety-related information (e.g., carcinogenicity studies performed in cell lines). FDA is also proposing to move the phrase "commercial marketing experience" to the end of the list and to revise it to read "and reports of foreign commercial marketing experience for drugs that are not marketed in the United States" to clarify that sponsors are not required to review safety information from commercial marketing experience for drugs that are marketed in the United States and are being further studied under an IND. Safety reports from commercial marketing experience for these drugs would be reviewed for safety information as prescribed by FDA's postmarketing safety reporting regulations (see section III.C.2 of this document). This proposed revision is consistent with existing regulations at § 312.32(c)(4) and proposed amendments to § 312.32(c)(4) described below (see section III.B.4 of this document). The proposed amendments would further clarify some of the types of safety information that must be examined to determine whether the information must be submitted in an IND safety report.

III.B.2. Written IND Safety Reports

Current IND safety reporting regulations at § 312.32(c)(1)(i) require sponsors to notify FDA and all participating investigators in a written IND safety report of 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. These written IND safety reports must be made as soon as possible and in no event later than 15 calendar days after the sponsor's initial receipt of the information. For clarity, FDA is proposing to amend § 312.32(c)(1) by reorganizing and renumbering this paragraph.

III.B.2.a. Minimum data set. FDA is proposing to amend § 312.32(c) to state that sponsors must not submit an IND safety report for an SADR to the agency if the report does not contain a minimum data set (i.e., identifiable patient, identifiable reporter, suspect drug or biological product, and SADR). If a minimum data set is not available, a sponsor would be required to maintain records of any information received or otherwise obtained for the SADR along with a record of its efforts to obtain a minimum data set for the IND safety report. This proposed amendment would clarify for sponsors that, at a minimum, certain information must be submitted to FDA for each IND safety report of an SADR to allow an initial evaluation of the

significance of the SADR. This proposed revision is consistent with the ICH E2A guidance (60 FR 11284 at 11287):

> The minimum information required for expedited reporting purposes is: an identifiable patient; the name of a suspect medicinal product; an identifiable reporting source; and an event or outcome * * *.

III.B.2.b. Serious and unexpected SADR's. FDA is also proposing to amend § 312.32(c)(1)(i) by replacing the phrase "any adverse experience associated with the use of the drug that is both serious and unexpected" with the phrase "any SADR that, based on the opinion of the investigator or sponsor, is both serious and unexpected, as soon as possible, but in no case later than 15 calendar days after receipt by the sponsor of the minimum data set for the serious, unexpected SADR." This proposed amendment would require that the determination of the possibility of causality (attributability) of an SADR to an investigational drug be based on the opinion of either the investigator or sponsor, which is consistent with the ICH E2A guidance (60 FR 11284 at 11286):

> Causality assessment is required for clinical investigation cases. All cases judged by either the reporting health care professional or the sponsor as having a reasonable

suspected causal relationship to the medicinal product qualify as ADR's.

In situations in which a sponsor does not believe that there is a reasonable possibility that an investigational drug caused a response, but an investigator believes that such a possibility exists, the proposed rule would require that the sponsor submit a written IND safety report to FDA for the SADR. In the opposite situation, the same would also be true.

The proposed rule would also require that written IND safety reports be submitted to FDA no later than 15 calendar days after receipt by the sponsor of the minimum data set for the serious, unexpected SADR. This proposed revision would clarify when the 15 calendar day timeframe would begin. FDA expects sponsors to use due diligence to acquire immediately the minimum data set for a report and to determine the outcome (whether the SADR is serious or nonserious) and expectedness of an SADR upon initial receipt of the SADR. Sponsors should include in any written IND safety reports subsequently filed with FDA a chronological history of their efforts to acquire this information if there is a delay in obtaining the information (it is not necessary to include the chronological history in IND safety reports sent to investigators). This proposed amendment is consistent with the ICH E2A guidance (60 FR 11284 at 11286):

> Information for final description and evaluation of a case report may not be

available within the required timeframes for reporting * * *. Nevertheless, for regulatory purposes, initial reports should be submitted within the prescribed time as long as the following minimum criteria are met: An identifiable patient; a suspect medicinal product; an identifiable reporting source; and an 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. * * *

FDA is also proposing to amend § 312.32(c)(1)(i) by removing the following sentence: "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." The agency is proposing this revision because the information in this sentence is redundant with a provision of proposed § 312.32(c)(1)(i).

III.B.2.c. Information sufficient to consider product administration changes. Under proposed § 312.32(c)(1)(ii), FDA would amend § 312.32(c)(1)(i) by replacing the phrase "Any finding from tests in laboratory animals that suggests a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity" with the sentence: