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**Department of
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Food and Drug Administration

**21 CFR Parts 310, 312, et al.
Safety Reporting Requirements for
Human Drug and Biological Products;
Proposed Rule**

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 (WHO'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 July 14, 2003. Submit written comments on the collection of information by April 14, 2003.

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>. FAX 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, 202-395-6974.

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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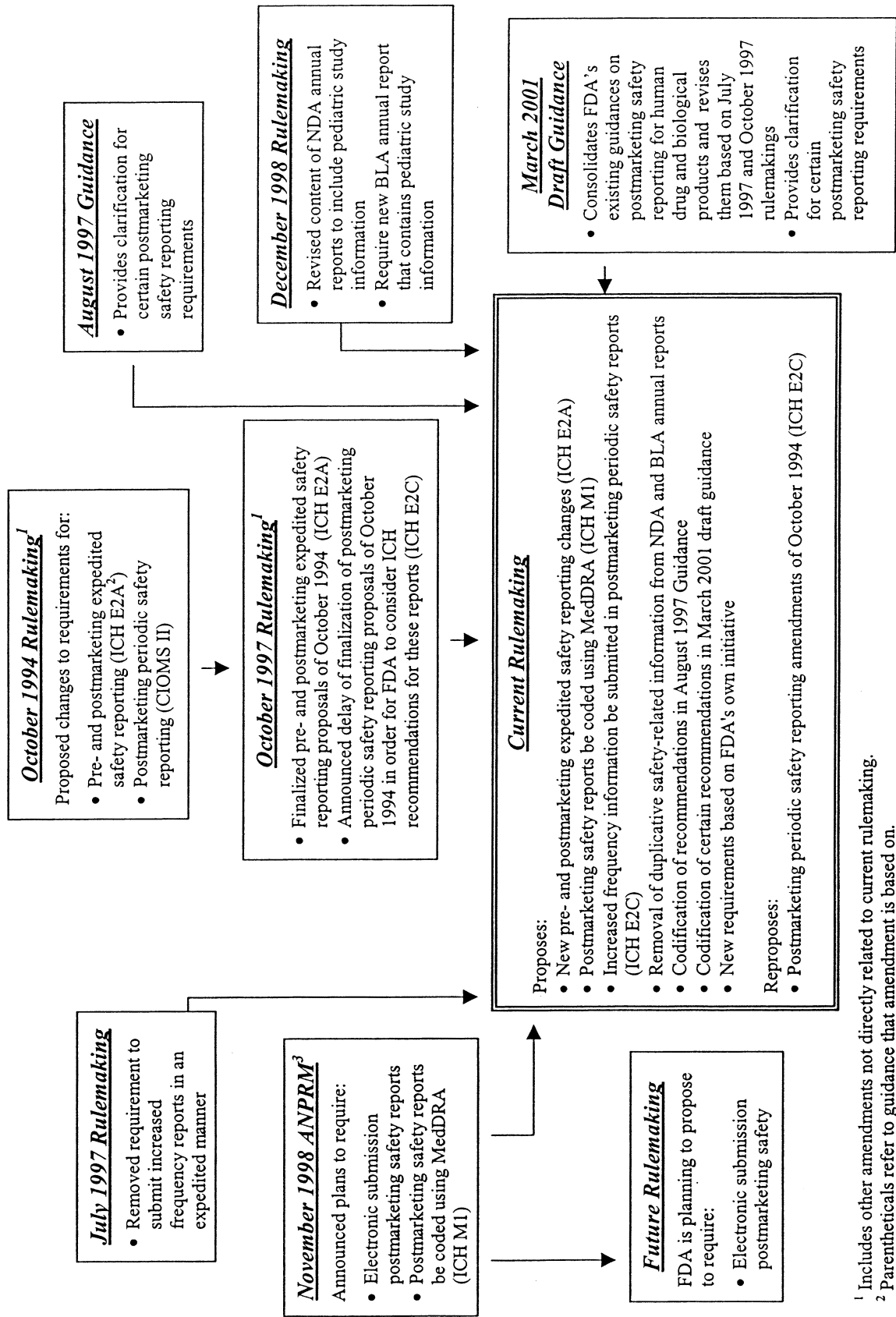
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I. Previous Safety Reporting Rulemaking and Current Guidances

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 of this document, FDA illustrates how these rules and guidances relate to the current proposed rule.

BILLING CODE 4160-01-P

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.

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 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.

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). As explained in the October 1997 final rule, the agency decided not to finalize these proposed amendments (62 FR 52237 and 52238) until FDA considered ICH's recommendations on this topic. These recommendations were published in an ICH final guidance entitled "Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs" (PSURs) (the ICH E2C guidance) (62 FR 27470, May 19, 1997). After review of the ICH E2C guidance, FDA decided to repropose the postmarketing periodic safety reporting amendments in the October 1994 proposal. These amendments are being repropose in this rulemaking based on recommendations in the ICH E2C guidance and comments submitted in response to the October 1994 proposal.

An addendum to the ICH E2C guidance has been prepared by ICH based on experience gained over the past 5 years in preparation of PSUR reports by companies and review of them by regulators (the ICH V1 draft guidance) (67 FR 79939; December 31, 2002). 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 PSURs, 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).

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 new drug application (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 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 (BLAs) 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 revoke the requirement to submit safety-related information in these reports. This proposal is consistent with the proposed amendments to the postmarketing approved NDA annual reporting requirements.

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. 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.

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 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. 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. The agency considered these comments in developing this proposed rule. All of the comments requested that FDA postpone granting these waivers until this new 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 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 nonserious, expected adverse experiences¹ 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).

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 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.

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).

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 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 INDs 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	<ul style="list-style-type: none"> 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.

¹ Adverse experiences are proposed to be called suspected adverse drug reactions (SADRs) 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 be used in this document when discussions pertain to proposals in this rule.

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:

- Applicants with approved NDAs (§ 314.80) and abbreviated new drug applications (ANDAs) (§ 314.98);
- Licensed manufacturers with approved BLAs (§ 600.80);
- 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 a product 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). In this document, the term “applicant” will be used instead of the term “licensed manufacturer” for persons with approved BLAs.

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 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).
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.	<ul style="list-style-type: none"> • 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 NDAs, ANDAs, and BLAs must also submit periodic reports of postmarketing adverse drug experiences under §§ 314.80, 314.98 and 600.80 (see table

2). 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).

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.

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).

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 reporting regulations under §§ 314.80, 314.98, and 600.80 for products with an approved NDA, ANDA, or BLA; for § 600.80, “applicants” includes participants involved in divided manufacturing.

II.B. Rationale for This Proposal

II.B.1. International Standards

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). 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.

The 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. 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. 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; FDA; 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.

FDA believes the changes recommended by ICH and CIOMS will result in more effective and efficient safety reporting to regulatory authorities worldwide. 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 PSURs 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.

Another international harmonization effort is standardization of medical terminology used for regulatory purposes. As noted previously, ICH has developed MedDRA for this purpose. Currently, companies use various medical terminologies for safety reporting purposes (e.g., WHO'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.

Even though FDA is proposing to use MedDRA as the standard medical terminology for reporting purposes under this rule, 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 communications, 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 surveillance of marketed products. 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 for reports of serious adverse drug experiences while less information would be required for nonserious adverse drug experiences (adverse drug experiences proposed to be called SADR in this proposed rule; see section III.A.1 of this document)). For example, FDA is proposing that complete information be submitted for reports of serious SADR

(see section III.C.5 of this document). If complete information is not available, in some cases, a followup report would be required (*e.g.*, for serious, unexpected SADR) (see section III.D.6 of this document). On the other hand, for SADR that are determined to be nonserious, not as much information would need to be acquired (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.

II.B.3. New Postmarketing Expedited Safety Reports

FDA currently requires postmarketing expedited safety reports for serious and unexpected adverse drug experiences (adverse drug experiences proposed to be called SADR 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. Some of this information is currently submitted to the agency but

not in an 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 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 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 SADRs. 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 postmarketing surveillance, especially for concerns that are perceived to require immediate response to protect the safety of patients."

II.B.3.b. *Unexpected SADRs 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 SADRs that are unexpected and for which a determination of serious or nonserious cannot be made (i.e., SADR with unknown outcome) (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 SADRs 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. FDA would do this by comparing information on the unexpected SADR with unknown outcome with information on other similar unexpected SADRs with a known serious outcome that are on file with the agency.

II.B.3.c. *Always expedited reports.* FDA is also proposing that companies subject to the agency's postmarketing safety reporting regulations always submit to FDA in an expedited report certain SADRs, which may jeopardize the patient or subject and/or require medical or surgical intervention to treat the patient or subject (e.g., ventricular fibrillation, liver necrosis, transmission of an infectious agent by an approved product) (see section III.D.4 of this document). 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 whether the SADR is unexpected or expected and whether or not the SADR leads to a serious outcome. This is because of the medical gravity of these SADRs. 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).

II.B.3.d. *Blood and blood component safety reports.* 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 SADRs associated

with blood collection and transfusion, in addition to their current requirement at § 606.170(b) (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 § 606.170(a) (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 SADRs 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 SADRs 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 Hemosure 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. 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 SADRs 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 SADRs 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 for serious, unexpected adverse experiences (adverse experiences proposed to be called SADRs in this proposed rule; see section III.A.1 of this document) as prescribed under § 312.32 for human bioavailability and bioequivalence studies that are not being conducted

under an IND. 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 SADRs 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 SADRs (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
	Changes only apply to 312.32	• Determination of a life-threatening SADR based on opinion of either sponsor or investigator (A.2).
• 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, 600.80.	New Safety Reports	Yes (E2A)
	• Expedited report for information sufficient to consider product administration changes (D.2).	
	• Expedited report for unexpected SADRs with unknown outcome (A.3, D.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)?
Changes only apply to 310.305, 314.80, 314.98, and 600.80.	<ul style="list-style-type: none"> • Always expedited reports for certain medically significant SADRs whether unexpected or expected and whether or not the SADR leads to a serious outcome (D.4). • Expedited report for medication errors (D.5) • 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). <i>Other Changes</i> • Active query required to acquire certain safety information (A.6, C.5, D.6, D.7). • Full data set required for reports of serious SADRs, always expedited reports, and medication error reports (A.5, C.5, D.1, D.4, D.5, E.4). • Safety reporting requirements for contractors and shared manufacturers (A.4, D.9). • Reporting requirements for spontaneous reports codified (A.7, C.6) 	<p>No</p> <p>No</p> <p>No</p> <p>No</p> <p>No</p> <p>No</p> <p>Yes (E2A and E2C)</p>
Changes only to apply to 314.80, 314.98 and 600.80.	<ul style="list-style-type: none"> • Supporting documentation required for expedited reports concerning a death or hospitalization (D.7). • FDA request for submission of safety reports at times other than prescribed by regulations (C.4). • Individual case safety reports required to be coded using MedDRA (F.2). • SADR information from class action lawsuits (A.7, E.1.e, E.2.k.v, E.3) • Contact person for postmarketing safety reports (E.1.h, E.2.k.xi, E.3, F.4) • Use of computer-generated facsimile of FDA Form 3500A or VAERS form permitted without approval by FDA (F.5). • Location of safety records (D.10, E.1.g, E.2.k.x, E.3) • FDA request for submission of safety related records (D.7, H) <i>New or Revised Safety Reports</i> • Semiannual submission of certain spontaneously reported individual case safety reports (E.4, E.5.a). • TPSR, PSUR, or IPSR for applications approved prior to January 1, 1998 (E.1, E.2, E.3, E.5.a). • PSUR/IPSR for applications approved on or after January 1, 1998 (E.2, E.3, E.5.a). • PSUR/IPSR for pediatric use supplements (E.5.a) <i>Other Changes</i> • Periodicity of periodic safety reports (E.5.a, I) • Submission date for periodic safety reports (A.10, E.5.b, I) • CCSI for determination of listed and unlisted SADRs for certain periodic safety reports (A.9, E.2, E.3, E.4). • Information in addition to the minimum data set not required to be acquired for nonserious SADRs, except for nonserious SADRs resulting from a medication error, which require a full data set (A.3, C.5, E.4). • Individual case safety reports forwarded to applicant by FDA required to be included in comprehensive safety analysis (C.2). • Information on resistance to antimicrobial drug products (E.2.k.vii, E.3) • Number of copies of periodic safety reports required to be submitted to FDA (C.3). 	<p>No</p> <p>No</p> <p>Yes (M1)</p> <p>No</p> <p>No</p> <p>No</p> <p>No</p> <p>No</p> <p>No</p> <p>No</p> <p>No</p> <p>No</p> <p>No</p> <p>No</p> <p>Yes (E2C)</p> <p>Yes (E2C)</p> <p>Yes (E2C)</p> <p>No</p> <p>No</p>
Change only applies to 314.81 and 601.28 ² .	<ul style="list-style-type: none"> • Requirement to submit safety-related information in postmarketing annual report revoked (J). 	<p>No</p>
Change only applies to 312.64(b) ³	<ul style="list-style-type: none"> • Investigator safety reporting requirements revised 	<p>No</p>
Change only applies to 320.31(d) ⁴	<ul style="list-style-type: none"> • Submission of expedited safety reports required for human bioequivalence and bioavailability studies which are exempt from submission of an IND (K). 	<p>No</p>
Change only applies to 606.170 ⁵	<ul style="list-style-type: none"> • All serious SARs required to be submitted to FDA for blood and blood products (D.12). 	<p>No</p>

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 NDAs; § 314.98 describes postmarketing safety reporting regulations for human drugs with approved ANDAs; and § 600.80 describes postmarketing safety reporting regulations for human licensed biological products with approved BLAs.

² Section 314.81 describes postmarketing annual reporting regulations for pediatric studies of human marketed drugs with approved NDAs; § 601.28 describes postmarketing annual reporting regulations for pediatric studies of human licensed biological products with approved BLAs.

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.

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

As explained in the following paragraphs, FDA believes that the proposed definition of SADR would not affect the number of safety reports that are currently submitted to FDA from spontaneous sources, but it could increase the number of safety reports that would be submitted from clinical studies. 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 in the following paragraphs. 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.

Although FDA is proposing to remove the definition for "adverse drug experience" from its postmarketing safety reporting regulations and replace it with the proposed 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 (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 SADR 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 SADRs 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 immediate risk of death from the adverse [drug] experience as it occurred, *i.e.*, it does not include an adverse [drug] experience that, had it occurred in a more severe form, might have caused death.

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. SADRs 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 SADRs 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 SADRs 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 SADRs 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 SADRs 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 SADRs) 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 SADRs 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 SADRs, 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 SADRs with a minimum data set would include all safety information received or otherwise obtained by the manufacturer or applicant for the SADR. However, except for reports of nonserious SADRs resulting from a medication error, information in addition to the minimum data set 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 for reports of nonserious SADRs resulting from a medication error (see sections III.C.5 and III.D.5 of this document).

As noted previously, 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 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, any individual with some form of health care training) representing the manufacturer (applicant for proposed §§ 314.80(a) and 600.80(a)). For SADRs, 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 if the manufacturer or applicant is not able to immediately make this determination (see section III.C.5 of this document),
- Obtain at least the minimum data set for all SADRs and the minimum information for medication errors that do not result in an SADR if the manufacturer or applicant is not able to immediately obtain this information (see section III.C.5 of this document),
- Obtain a full data set for individual case safety reports of serious SADRs, always expedited reports, and medication error reports if a full data set is not available for the report (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 SADRs 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.

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.

Active query would be conducted by a health care professional, such as a physician, physician's assistant, pharmacist, dentist, nurse, or any individual with some form of health care training. The agency believes that a health care professional would be able to understand better the medical consequences of a case and ask reporters of SADRs and medication 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 SADRs. 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 SADRs 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 SADRs from studies or individual patient INDs in PSURs (see section III.E.2.f.ii of this document), and
- Discussion of important safety information from studies in PSURs and IPSRs (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 TPSRs, PSURs and IPSRs summary information for SADRs 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. FDA would not consider a case in which a patient deliberately took an overdose of a drug to be a “medication error” because the agency does not believe that this type of situation is “preventable.” Instead, it would be considered a “non-accidental overdose.”

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 (PSURs), interim periodic safety reports (IPSRs), and certain individual case safety reports—semiannual submissions (*i.e.*, if PSURs 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 PSURs, IPSRs, and certain individual case safety reports—semiannual submissions (*i.e.*, if PSURs 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 SADRs must be reported in PSURs, IPSRs, and certain individual case safety reports—semiannual submissions (*i.e.*, if PSURs 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 PSURs and IPSRs 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 PSURs 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 PSURs may result in overreporting of some SADRs 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 SADRs reported in premarketing IND safety reports, postmarketing expedited reports, postmarketing TPSRs, and certain postmarketing individual case safety reports—semiannual submissions (*i.e.*, if TPSRs 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” 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.
	TPSRs	U.S. labeling.
	PSURs and IPSRs	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:”

SADRs 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 SADRs 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.*, PSURs, IPSRs, TPSRs, 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 SADRs.* 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:

The sponsor must also notify FDA and all participating investigators in a written IND safety report of information that, based upon appropriate medical judgment, might materially influence the benefit-risk assessment of an investigational drug or that would be sufficient to consider changes in either product administration or in the overall conduct of a clinical investigation. The sponsor must submit this information to FDA and all participating investigators as soon as possible, but in no case later than 15 calendar days after determination by the sponsor that the information qualifies for reporting under this paragraph. Examples of such information include any significant unanticipated safety finding or data in the aggregate from an in vitro, animal, epidemiological, or clinical study, whether or not conducted under an IND, that suggests a significant human risk, such as reports of mutagenicity, teratogenicity, or carcinogenicity or reports of a lack of efficacy with a drug product used in treating a life-threatening or serious disease.

This proposed amendment is consistent with the ICH E2A guidance (60 FR 11284 at 11286):

There are situations in addition to single case reports of "serious" adverse events or reactions that may necessitate rapid communication to regulatory authorities; appropriate medical and scientific judgment should be applied for each situation. In general, information that might materially influence the benefit-risk assessment of a medicinal product or that would be sufficient to consider changes in medicinal product administration or in the overall conduct of a clinical investigation represents such situations. Examples include:

- a. For an "expected, serious ADR, ["] an increase in the rate of occurrence which is judged to be clinically important.
- b. A significant hazard to the patient population, such as lack of efficacy with a medicinal product used in treating life-threatening disease.
- c. A major safety finding from a newly completed animal study (such as carcinogenicity).

In contrast to the ICH recommendations, the proposed rule would not require reports of an increase in the rate of occurrence of expected, serious SADR to be submitted to the

agency in an expedited manner. However, sponsors should report this information to FDA in their IND annual reports under § 312.33(b)(1). Proposed § 312.32(c)(1)(ii) would be consistent with the increased frequency reports final rule that revoked the postmarketing safety reporting requirement for submission of increased frequency reports in an expedited manner. Although the increased frequency reports final rule pertains to postmarketing expedited safety reporting, FDA has decided to apply this rule to its requirements for premarketing expedited safety reports because of the limited reliability of increased frequency reports. See the increased frequency reports final rule (62 FR 34166) for a discussion of the limited reliability of increased frequency reports. With regard to premarketing clinical trials in progress, FDA does not believe that baseline incidence rates would be available for serious expected SADR which would make it difficult for sponsors to predict an increase in the rate of occurrence of these SADR.

III.B.2.d. *Reporting format.* Current IND safety reporting regulations at § 312.32(c)(1)(i) require sponsors to submit written IND safety reports from animal or epidemiological studies in a narrative format. Proposed § 312.32(c)(1)(iii) would amend these regulations by replacing the phrase "reports from animal or epidemiological studies" with the phrase "reports of overall findings or data in the aggregate from published and unpublished in vitro, animal, epidemiological, or clinical studies." The proposed rule would require sponsors to submit reports of overall findings or data in the aggregate in a narrative format rather than on FDA Form 3500A because the form is designed for reporting safety information for an individual case.

III.B.3. Telephone Safety Reports

Current IND safety reporting regulations at § 312.32(c)(2) require sponsors to notify FDA by telephone or by facsimile transmission of any unexpected fatal or life-threatening experience associated with the use of an investigational drug as soon as possible but in no event later than 7 calendar days after the sponsor's initial receipt of the information. FDA is proposing to amend this requirement to read:

The sponsor must also notify FDA by telephone or by facsimile transmission of any unexpected fatal or life-threatening SADR based on the opinion of the investigator or sponsor as soon as possible but in no case later than 7 calendar days after receipt by the

sponsor of the minimum data set for the unexpected fatal or life-threatening SADR.

These proposed revisions are consistent, as described previously, with the proposed amendments to § 312.32(c)(1)(i) for written IND safety reports and the ICH E2A guidance (60 FR 11284 at 11286).

III.B.4. IND Safety Reporting for Drugs Marketed in the United States

Current IND safety reporting regulations at § 312.32(c)(4) state that a sponsor of a clinical study of a marketed drug is not required to make a safety report for any adverse experience associated with the use of the drug that is not from the clinical study itself. FDA is proposing to amend this regulation by making the following revisions:

A sponsor of a clinical study under an IND for a drug marketed in the United States is only required to submit IND safety reports to FDA (review division that has responsibility for the IND) for SADR from the clinical study itself, whether from domestic or foreign study sites of the IND. The sponsor must also submit to FDA safety information from these clinical studies as prescribed by the postmarketing safety reporting requirements under §§ 310.305, 314.80, and 600.80 of this chapter.

FDA is proposing this change to clarify, for sponsors investigating under an IND drugs and biological products that are already marketed in the United States, what SADR must be reported in IND safety reports under § 312.32. The agency notes that sponsors investigating under an IND drug and biological products that are not marketed in the United States are required, under § 312.32, to report to FDA safety information obtained or otherwise received for the product from any source, domestic or foreign, including safety information from foreign commercial marketing experience (see section III.B.1 of this document). Proposed § 312.32(c)(4) also clarifies that sponsors investigating under an IND drugs and biological products that are already marketed in the United States must submit safety information for these clinical studies as prescribed by the postmarketing safety reporting requirements in §§ 310.305, 314.80, and 600.80.

III.B.5. Investigator Reporting

Current investigator safety reporting regulations at § 312.64(b) state that the investigator shall promptly report to the sponsor any adverse effect that may reasonably be regarded as caused by, or probably caused by, the drug. If the adverse effect is alarming, the investigator shall report the adverse

effect immediately. FDA is proposing to revise this requirement as follows:

An investigator must report to the sponsor any serious SADR (as defined in § 312.32(a)) immediately and any other SADR (as defined in § 312.32(a)) promptly unless the protocol or investigator's brochure specifies a different timetable for reporting the SADR.

FDA is proposing this revision to be consistent with the proposed definition for SADR and to clarify what information investigators must submit to sponsors expeditiously.

III.C. Postmarketing Safety Reporting

III.C.1. Prescription Drugs Marketed for Human Use Without an Approved Application

Current regulations (§ 310.305) require manufacturers, packers, and distributors of marketed prescription drug products that are not the subject of an approved NDA or ANDA to establish and maintain records of and report to FDA all serious, unexpected adverse drug experiences associated with the use of their drug products. The proposed rule would amend these regulations by revising the language in this section to be consistent with the language for the postmarketing expedited safety reporting requirements under § 314.80. FDA is also proposing to reorganize and renumber § 310.305 to be consistent with § 314.80. FDA is proposing these revisions to harmonize, to the extent possible, the postmarketing expedited safety reporting requirements for human marketed drugs with approved applications (*i.e.*, NDAs, ANDAs) and prescription drugs marketed for human use without an approved application.

III.C.2. Review of Safety Information

Current postmarketing safety reporting regulations under §§ 314.80(b) and 600.80(b) require applicants to promptly review all safety information obtained or otherwise received from any source, foreign or domestic, including information derived from commercial marketing experience, postmarketing clinical investigations, postmarketing epidemiological/surveillance studies, reports in the scientific literature, and unpublished scientific papers. FDA is proposing to amend these regulations by adding "animal and in vitro studies," "electronic communications with applicants via the Internet (*e.g.*, e-mail)," and "reports from foreign regulatory authorities that have not been previously reported to FDA by the applicant" to the list of examples. FDA is proposing to add animal and in vitro studies to the list of examples because many of these studies report relevant

safety-related information (*e.g.*, carcinogenicity, mutagenicity, teratogenicity).

FDA is proposing to add electronic communications with applicants via the Internet (*e.g.*, e-mail) to the list of examples to clarify for applicants what safety information on the Internet would be required to be reviewed. An applicant would be required to review information received on an Internet site(s) that it sponsors, but would not be required to review Internet sites that it does not sponsor. However, if an applicant becomes aware of safety information on an Internet site that it does not sponsor, the applicant would be responsible for reviewing the information.

FDA would not expect applicants to review safety data bases generated by foreign regulatory authorities. However, proposed §§ 314.80(b)(1) and 600.80(b)(1) would require that any safety information acquired or received from a foreign regulatory authority be reviewed to determine whether the information must be reported to FDA. The agency is proposing these amendments to further clarify some of the types of safety information that must be examined to determine whether the information must be submitted in postmarketing safety reports.

Proposed § 310.305(b)(1) would amend FDA's postmarketing safety reporting regulations for prescription drugs marketed for human use without an approved application by adding the following sentence:

Each manufacturer of a prescription drug product marketed for human use without an approved application must promptly review all safety information pertaining to its product obtained or otherwise received by the manufacturer from any source, foreign or domestic, including information derived from commercial marketing experience, postmarketing clinical investigations, postmarketing epidemiology/surveillance studies, animal or in vitro studies, electronic communications with manufacturers via the Internet (*e.g.*, e-mail), reports in the scientific literature, and unpublished scientific papers, as well as reports from foreign regulatory authorities that have not been previously reported to FDA by the manufacturer.

This proposed amendment would further clarify some of the types of safety information that must be examined to determine whether the information must be submitted in postmarketing expedited safety reports (see section III.D of this document). This proposed revision would provide uniformity between FDA's safety reporting requirements for human marketed drugs with approved applications (*i.e.*, NDAs, ANDAs) and prescription drugs marketed for human

use without an approved application (*i.e.*, without an approved NDA or ANDA).

Current postmarketing safety reporting regulations in §§ 314.80(b) and 600.80(b) state that applicants are not required to resubmit to FDA safety reports forwarded to the applicant by FDA; however, applicants must submit all followup information on such reports. Proposed §§ 314.80(b)(2) and 600.80(b)(2) would amend these regulations to state that individual case safety reports forwarded to the applicant by FDA must not be resubmitted to the agency by applicants. FDA is proposing this revision to prevent duplicate reports from being entered into the agency's safety reporting database. Applicants that inadvertently resubmit such reports to FDA will be informed not to do so in the future.

Proposed §§ 314.80(b)(2) and 600.80(b)(2) would also amend these regulations to require that applicants include information from individual case safety reports forwarded to the applicant by FDA in any comprehensive safety analysis subsequently submitted to the agency. This proposed amendment, which was discussed in the preamble but inadvertently omitted from the codified section of the October 1994 proposal (59 FR 54046 at 54053), would clarify how safety information received from FDA must be handled.

Current postmarketing safety reporting regulations at §§ 314.80(b) and 600.80(b) state that applicants must develop written procedures for the surveillance, receipt, evaluation, and reporting of postmarketing adverse drug experiences to FDA. FDA is proposing to amend this provision by adding the phrase "and maintain" after the phrase "must develop." This proposed amendment would clarify that applicants must maintain records of the written procedures for review by FDA. FDA would review the written procedures either upon request by the agency (proposed §§ 314.80(f) and 600.80(f)) or during inspections by the agency. FDA is also proposing to replace the phrase "adverse drug experiences" with the phrase "postmarketing safety information." For organizational purposes, FDA is proposing to move the written procedures provision to proposed §§ 314.80(g) and 600.80(g). FDA is proposing the same type of amendments to § 310.305.

Current § 314.80(b) applies to applicants having an approved application under § 314.50 or, in the case of a 505(b)(2) application, an effective approved application. FDA is proposing to amend this provision by replacing the phrase "under § 314.50 or,

in the case of a 505(b)(2) application, an effective approved application” with the phrase “under section 505(c) of the act.” Although NDAs, including those referred to in section 505(b)(2) of the Federal Food, Drug and Cosmetic Act (the act) (21 U.S.C. 355(b)(2)) are filed under section 505(b)(1) of the act, they are approved under section 505(c) of the act. FDA is proposing to use the phrase “section 505(c) of the act” because it more appropriately references the cite for approval of NDAs.

The agency is proposing to remove the phrase “in the case of a 505(b)(2) application, an effective approved application” because FDA no longer issues approvals with a delayed effective date for 505(b)(2) applications, as it did at the time this regulation was issued. The agency now issues tentative approvals for 505(b)(2) applications when the (final) approval is blocked by patent or exclusivity rights. As described in the preamble to the final rule on “Abbreviated New Drug Application Regulations; Patent and Exclusivity Provisions” (59 FR 50338 at 50351 to 50352, October 3, 1994), a 505(b)(2) application that has a tentative approval is not approved for marketing until a final approval letter for the drug product is received from FDA. Thus, applicants having a 505(b)(2) application with a tentative approval would not be subject to the postmarketing safety reporting

requirements under § 314.80 until final approval of the application is in effect. For consistency, FDA is proposing a similar change to § 314.98(a).

III.C.3. Reporting Requirements

Current postmarketing safety reporting requirements at §§ 310.305(c), 314.80(c), and 600.80(c) state that persons subject to these requirements shall report to FDA adverse drug experience information as described under these sections. FDA is proposing to remove these provisions from its postmarketing safety reporting regulations because they are redundant (see proposed §§ 310.305(c), 314.80(c), and 600.80(c)).

Current postmarketing safety reporting requirements at §§ 314.80(c) and 600.80(c) state that two copies of each report must be submitted to FDA. For drug products, proposed § 314.80(c) would require that applicants submit to FDA two copies of each postmarketing expedited report and one copy of each postmarketing periodic safety report of an individual case safety reports—semiannual submission pertaining to its product (see tables 6 and 7 for proposed postmarketing expedited and periodic safety reports). For nonvaccine biological products, proposed § 600.80(c) would require that applicants submit to FDA two copies of each postmarketing expedited report and each postmarketing periodic safety

report of an individual case safety reports—semiannual submission pertaining to its product. For drugs and nonvaccine biologics, proposed §§ 314.80(c) and 600.80(c) would also require that one copy of a PSUR, IPSR, or TPSR be submitted to FDA along with one copy for each approved application for a human drug or licensed biological product (e.g., NDA, ANDA, BLA) covered by the report (see table 7 for proposed postmarketing periodic safety reports). For vaccines, proposed § 600.80(c) would require that applicants submit to VAERS two copies of each safety report required under § 600.80 and pertaining to its product. These proposed amendments would provide FDA with enough copies of safety reports for efficient review by the agency. Electronic submission of these reports will obviate the need for submission of two copies. At this time, manufacturers and applicants can voluntarily submit certain postmarketing safety reports in an electronic format (see Docket 92S–0251 regarding postmarketing expedited and periodic individual case safety reports; available on the Internet at <http://www.fda.gov/ohrms/dockets/dockets/92s0251/92s0251.htm>). Capabilities for electronic submission of other postmarketing safety reports (e.g., safety reports for vaccines) will be available in the future.

TABLE 6.—PROPOSED POSTMARKETING EXPEDITED SAFETY REPORTS

Expedited Safety Report	Type of Information	Submission to FDA—Timeframe	Persons with Reporting Responsibility	Reference in Section III of this Document
Serious & unexpected SADR.	Individual case safety reports.	15 calendar days.	Manufacturers and applicants.	D.1
Information sufficient to consider product administration changes.	Information based upon appropriate medical judgment. For example, any significant unanticipated safety finding or data in the aggregate from an in vitro, animal, epidemiological, or clinical study that suggests a significant human risk.	15 calendar days.	Manufacturers and applicants.	D.2
Unexpected SADR with unknown outcome.	Individual case safety reports of unexpected SADR for which a determination of serious or nonserious cannot be made..	45 calendar days.	Manufacturers and applicants.	D.3
Always expedited reports.	Individual case safety reports of certain medically significant SADR whether unexpected or expected and whether or not the SADR leads to a serious outcome.	15 calendar days.	Manufacturers and applicants.	D.4
Medication errors	All domestic reports of medication errors, whether actual or potential..	15 calendar and days.	Manufacturers and applicants.	D.5
30-day followup ...	Followup report for initial serious and unexpected SADR reports, always expedited reports and medication error reports that do not contain a full data set.	30 calendar days.	Manufacturers and applicants.	D.6
15-day followup ...	New information for expedited or followup reports, except initial expedited reports for which 30-day followup reports must be submitted.	15 calendar days.	Manufacturers and applicants.	D.6
SADR reports to manufacturer.	All SADR	5 calendar days to manufacturer.	Contractors	D.9
SADR reports to applicant.	All SADR	5 calendar days to applicant.	Contractors and shared manufacturers.	D.9

TABLE 6.—PROPOSED POSTMARKETING EXPEDITED SAFETY REPORTS—Continued

Expedited Safety Report	Type of Information	Submission to FDA—Timeframe	Persons with Reporting Responsibility	Reference in Section III of this Document
Blood safety—oral or written.	Fatalities	As soon as possible.	Blood establishments.	D.12
Blood safety—written.	Fatalities	7 calendar days	
	All serious SARs except fatalities	45 calendar days.	

TABLE 7.—PROPOSED POSTMARKETING PERIODIC SAFETY REPORTS

Periodic safety report	Type of information	Submission to FDA—timeframe	Persons with reporting responsibility	Reference in section III of this document
Individual case safety reports—semiannual submission.	<ul style="list-style-type: none"> • Serious, expected SADRs (domestic and foreign) and nonserious, unexpected SADRs (domestic) if TPSR is submitted for the product.¹ • Serious, listed SADRs (domestic and foreign) and nonserious, unlisted SADRs (domestic) if PSUR is submitted for the product.² 	Every 6 months after U.S. approval of application. ³	Applicants	E.4
TPSR—for applications approved before January 1, 1998. ⁴	<ul style="list-style-type: none"> • Narrative summary and analysis of individual case safety reports • Increased frequency reports • Safety-related actions to be taken • Summary tabulations of individual case safety reports • History of safety-related actions taken • Location of safety records • Contact person information 	At 5, 7.5, 10, 12.5, and 15 years after U.S. approval of application and then every 5 years thereafter. ³	Applicants	E.1
PSUR—for applications approved on or after January 1, 1998.	<p>Core Document</p> <ul style="list-style-type: none"> • Introduction • Worldwide marketing status • Actions taken for safety reasons • Changes to CCSI • Worldwide patient exposure • Summary tabulations • Safety studies • Other information • Overall safety evaluation • Conclusion <p>Appendices</p> <ul style="list-style-type: none"> • Company core data sheet • U.S. labeling • Spontaneous reports from individuals other than health care professionals • SADRs with unknown outcome • SADRs from class action lawsuits • Lack of efficacy reports • Information on resistance to antimicrobial drug products • Medication errors • U.S. patient exposure • Location of safety records • Contact person 	Every 6 months after U.S. approval of application for 2 years, annually for the next 3 years, and then every 5 years thereafter. ³	Applicants	E.2
IPSR—for applications approved on or after January 1, 1998.	An “abbreviated PSUR;” same information as PSUR excluding summary tabulations.	At 7.5 and 12.5 years after U.S. approval of application. ³	Applicants	E.3

¹ Nonserious, expected SARs (domestic) and expected SARs with unknown outcome (domestic) would also be submitted for vaccines.

² Nonserious, listed SARs (domestic) and listed SARs with unknown outcome (domestic) would also be submitted for vaccines.

³ The data lock point for the report would be the month and day of the international birth date or any other month and day agreed on by the applicant and FDA. The submission date for the report would be within 60 calendar days of the data lock point.

⁴ A PSUR may be submitted in lieu of a TPSR if an applicant so desires.

Current §§ 310.305(c), 314.80(c), 314.98(b), and 600.80(c) provide mailing addresses for the submission of

postmarketing safety reports. FDA is proposing to remove the mailing addresses from §§ 310.305(c), 314.80(c),

314.98(b), and 600.80(c) because this information is provided in the draft guidance of 2001.

III.C.4. Request for Alternative Reporting Frequency

FDA is proposing to amend its postmarketing safety reporting regulations at §§ 310.305(c), 314.80(c), and 600.80(c) to state that, upon written notice, the agency may require, when appropriate, that manufacturers and

applicants submit postmarketing safety reports (*i.e.*, expedited, followup, or periodic safety reports) to FDA at times other than prescribed by the regulations (see tables 8 and 9 regarding proposed reporting frequencies for postmarketing safety reports). In most cases, FDA would not request alternative reporting

periods for these safety reports. In some cases, however, FDA may need to receive reports more frequently (*e.g.*, marketed product approved for a new indication, dosage form, or population) or less frequently (*e.g.*, product on the market for over 30 years with no new safety concerns identified).

TABLE 8.—PROPOSED REPORTING FREQUENCY FOR POSTMARKETING EXPEDITED SAFETY REPORTS

Submit as soon as possible	Submit within 5 calendar days	Submit within 7 calendar days	Submit within 15 calendar days	Submit within 30 calendar days	Submit within 45 calendar days
<ul style="list-style-type: none"> Blood safety report— telephone (fatality) (D.12).¹ 	<ul style="list-style-type: none"> Individual case safety reports from contractors to manufacturer (D.9). Individual case safety reports from contractors and shared manufacturers to applicant (D.9). 	<ul style="list-style-type: none"> Blood safety report—written (fatality) (D.12). 	<ul style="list-style-type: none"> Serious and unexpected SADR report (D.1). Information sufficient to consider product administration changes (D.2). Always expedited report (D.4). Medication error report (D.5). 15-day followup report (D.6). 	<ul style="list-style-type: none"> 30-day followup report (D.6). 	<ul style="list-style-type: none"> Unexpected SADR with unknown outcome (D.3). Blood safety report—written (all serious SARs except fatalities) (D.12).

¹ References in parentheses refer to location in section III of this document.

TABLE 9.—PROPOSED REPORTING FREQUENCY FOR POSTMARKETING PERIODIC SAFETY REPORTS

Persons with reporting responsibility	Submit every 6 months	Submit at 0.5, 1, 1.5, 2, 3, 4, and 5 years	Submit at 7.5 and 12.5 years	Submit at 10 years and every 5 years thereafter
Applicants with NDAs ¹ or BLAs approved on or after 1/1/98 and applicants with approved pediatric use supplements.	Individual case safety reports—semiannual submission (E.4) ² .	PSUR (E.2)	IPSR (E.3)	PSUR.
Applicants with NDAs or BLAs approved before 1/1/98.	Individual case safety reports—semiannual submission.	NA	TPSR (E.1) or IPSR.	TPSR or PSUR.

¹ Applicants with approved ANDAs would determine the type of postmarketing periodic safety report required to be submitted to FDA (*i.e.*, TPSR, PSUR, IPSR) and the frequency of submission for these reports based on the U.S. approval date of the application for the innovator NDA product (see section III.I of this document).

² References in parentheses refer to section III of this document.

FDA is also proposing to amend its postmarketing safety reporting regulations at §§ 314.80(c) and 600.80(c) to state that applicants who wish to submit postmarketing safety reports at times other than prescribed by these regulations may request a waiver for this purpose under §§ 314.90 or 600.90. This proposed revision does not represent a new provision, but rather provides a cross-reference to the existing waiver requirements under §§ 314.90 and 600.90.

FDA is also proposing to amend its postmarketing periodic safety reporting regulations at §§ 314.80(c)(2)(i) and 600.80(c)(2)(i) by removing the third and fourth sentences in these paragraphs. These sentences state that, upon written notice, FDA may request submission of periodic safety reports at different times than stated under §§ 314.80(c)(2)(i) and 600.80(c)(2)(i)

(*e.g.*, following the approval of a major supplement). FDA is proposing to remove these sentences because this information would now be stated under proposed §§ 314.80(c) and 600.80(c). This proposed revision represents an organizational change that clarifies that FDA may request a different time period for submission of not only postmarketing periodic safety reports, but also postmarketing expedited safety reports.

III.C.5. Determination of Outcome, Minimum Data Set, and Full Data Set

Proposed §§ 310.305(c)(1)(i)(A), 314.80(c)(1)(i)(A), and 600.80(c)(1)(i)(A) would amend FDA's postmarketing safety reporting regulations to require that manufacturers and applicants immediately, upon initial receipt of an SADR report, determine the outcome for the SADR (whether the SADR is serious

or nonserious) and at least the minimum data set for the individual case safety report (*i.e.*, identifiable patient, identifiable reporter, suspect drug or biological product, and SADR). If the manufacturer or applicant is not able to immediately determine this information, active query would be required to be used by the manufacturer or applicant to obtain the information as soon as possible. FDA is proposing this change to clarify that timely acquisition of information is critical to determine whether an SADR must be submitted to FDA and, for those reactions that would be reported, whether the SADR would be submitted in a postmarketing expedited safety report or a postmarketing periodic safety report.

Proposed §§ 310.305(c)(1)(i)(A), 314.80(c)(1)(i)(A), and 600.80(c)(1)(i)(A) would also require manufacturers and applicants to immediately determine the

minimum information for actual medication errors that do not result in an SADR and potential medication errors (minimum information described below and at proposed

§§ 310.305(c)(1)(iii)(B) and (c)(1)(iii)(C), 314.80(c)(1)(iii)(B) and (c)(1)(iii)(C), and 600.80(c)(1)(iii)(B) and (c)(1)(iii)(C)). If the manufacturer or applicant is not able to immediately determine this information, active query would be required to be used by the manufacturer or applicant to obtain the information as soon as possible.

Proposed §§ 310.305(c)(1)(ii), 314.80(c)(1)(ii), and 600.80(c)(1)(ii) would require manufacturers and applicants who are unable to immediately determine the outcome of an SADR (whether the SADR is serious or nonserious) to continue to use active query to attempt to determine the outcome within 30 calendar days after initial receipt of the SADR report by the manufacturer or applicant. The proposed rule would require that manufacturers and applicants maintain records of their efforts to obtain this information. These proposed revisions clarify that due diligence must be used to obtain the outcome for SADRs. Unknown outcomes should not be classified arbitrarily as nonserious SADRs. Instead, each of the outcomes in the definition of serious SADR should be considered as a possibility.

Under proposed §§ 310.305(c)(1)(iii)(A), 314.80(c)(1)(iii)(A), and 600.80(c)(1)(iii)(A), individual case safety reports for SADRs that do not contain a minimum data set would not be submitted to the agency. Instead, the proposed rule would require that manufacturers and applicants maintain records of any information received or otherwise obtained for the SADR along with a record of their efforts to obtain a minimum data set for the individual case safety report. These proposed amendments are consistent with proposed revisions to the premarketing safety reporting regulations at proposed § 312.32(c) (see section III.B.2.a of this document). This change would clarify that, at a minimum, certain information must be submitted to FDA to provide the agency with enough information to allow an initial evaluation of the significance of an SADR.

Proposed §§ 310.305(c)(1)(iii)(B), 314.80(c)(1)(iii)(B), and 600.80(c)(1)(iii)(B) would require that reports of actual medication errors that do not result in an SADR be submitted to FDA even though the report does not contain a minimum data set (*i.e.*, does not have an SADR). In these cases, individual case safety reports would be

required to contain at least an identifiable patient, an identifiable reporter, and a suspect drug or biological product.

Proposed §§ 310.305(c)(1)(iii)(C), 314.80(c)(1)(iii)(C), and 600.80(c)(1)(iii)(C) would require that reports of potential medication errors be submitted to FDA even though the report does not contain a minimum data set (*i.e.*, does not have an identifiable patient or an SADR). In these cases, individual case safety reports would be required to contain at least an identifiable reporter and a suspect drug or biological product.

FDA is requiring submission of individual case safety reports for actual medication errors that do not result in an SADR and potential medication errors because of their potential significance and the need for intervention to minimize future errors. For example, if an adult is given the wrong medication, no SADR may occur, but if the same error occurs with a child, an SADR may occur. Also, if an error is prevented prior to administration of a product, this information could be used to prevent the error from occurring in other situations. For example, the proprietary name, label, labeling or packaging of the product could be changed if sufficient evidence suggests such a change is warranted, or education announcements could be communicated to health care professionals and/or consumers.

Proposed §§ 310.305(c)(1)(iv), 314.80(c)(1)(iv), and 600.80(c)(1)(iv) state that, for reports of serious SADRs, always expedited reports, and medication error reports, manufacturers and applicants would be required to submit a full data set for the report (see section III.D.4 of this document for discussion of always expedited reports and section III.D.5 of this document for discussion of medication error reports). If a full data set is not available for the report, the manufacturer or applicant would be required to use active query to obtain this information. If a full data set is not available, after active query, the manufacturer or applicant would provide the following information:

- All safety information, received or otherwise obtained, for the report;
- The reason(s) for their inability to acquire a full data set; and
- Documentation of their efforts to obtain a full data set (*i.e.*, description of unsuccessful steps taken to obtain this information).

In some cases, the agency has received incomplete safety reports for serious SADRs, making interpretation of their significance difficult. This proposed

amendment would require submission of complete information for reports of serious SADRs, always expedited reports, and medication error reports, which would facilitate their expeditious review.

Proposed §§ 310.305(c)(1)(v), 314.80(c)(1)(v), and 600.80(c)(1)(v) state that:

For a serious SADR that was not initially reported to the manufacturer (applicant for proposed §§ 314.80(c)(1)(v) and 600.80(c)(1)(v)) by a health care professional (*e.g.*, report from a consumer), the manufacturer (applicant for proposed §§ 314.80(c)(1)(v) and 600.80(c)(1)(v)) must contact the health care professional associated with the care of the patient using active query to gather further medical perspective on the case and to acquire a full data set for the report. If the manufacturer (applicant for proposed §§ 314.80(c)(1)(v) and 600.80(c)(1)(v)) is unable to contact the health care professional, it must include in the report for the serious SADR: (A) The reason(s) for its inability to contact the health care professional and (B) a description of its efforts to contact the health care professional.

The agency believes that contact with a health care professional is warranted for serious SADRs because of the critical nature of these reactions. However, in those situations in which a manufacturer or applicant is unable to contact the health care professional (*e.g.*, health care professional does not return phone calls, consumer does not permit manufacturer or applicant to contact its health care provider), it would include in its report to FDA the reason(s) for its inability to contact the health care professional and a description of its efforts to contact the health care professional.

For nonserious SADRs with a minimum data set, proposed §§ 314.80(c)(1)(vi) and 600.80(c)(1)(vi) would require applicants to submit to FDA all safety information received or otherwise obtained. Applicants would not be required to acquire information in addition to the minimum data set, except that reports of nonserious SADRs resulting from a medication error would require a full data set. Thus, followup would not be required for reports of nonserious SADRs that contain a minimum data set and do not occur because of a medication error.

III.C.6. Spontaneous Reports and Reports From Clinical Trials

Proposed §§ 310.305(c)(1)(i)(B), 314.80(c)(1)(i)(B), and 600.80(c)(1)(i)(B) would require that, for spontaneous reports, manufacturers and applicants must always assume, for safety reporting purposes only, that there is at least a reasonable possibility, in the opinion of the initial reporter, that the drug or

biological product caused the spontaneously reported event. Proposed §§ 310.305(c)(1)(i)(C), 314.80(c)(1)(i)(C), and 600.80(c)(1)(i)(C) state that, for a clinical trial, the possibility that the drug or biological product caused the SADR or that a medication error has occurred would be assumed if either the investigator or the applicant/manufacturer believes that such a reasonable possibility exists.

These proposed changes would clarify that all spontaneous reports received by manufacturers and applicants that contain a minimum data set (minimum information for a report of a medication error that does not result in SADR) would be reported to FDA (*i.e.*, as an individual case safety report and/or in a summary tabulation). These changes are consistent with the premarketing safety reporting requirements described in section III.B.2.b of this document (*i.e.*, determination of the possibility of causality (attributability) of an SADR to the drug or biological product in a clinical investigation would be based on the opinion of either the applicant/sponsor or investigator). These proposed amendments are also 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. For purposes of reporting, adverse event reports associated with marketed drugs (spontaneous reports) usually imply causality.

III.C.7. Lack of Efficacy Reports

With regard to reports of a lack of efficacy for an approved drug or biological product, the guidance of 1992 and guidance of 1993 advise applicants to submit all individual cases of such reports that occur in the United States in postmarketing periodic safety reports. In this proposed rule, FDA would not require submission of individual case safety reports for reports of a lack of efficacy. Instead, applicants would be required to submit to FDA expedited reports of information sufficient to consider a product administration change, based upon appropriate medical judgement, for any significant unanticipated safety finding or data in the aggregate from a study that suggests a significant human risk. For example, applicants would be required to submit information concerning reports of a lack of efficacy with a drug or biological product used in treating a life-threatening or serious disease (see section III.D.2 of this document). In addition, applicants would be required

to include in postmarketing periodic safety reports (*i.e.*, TPSRs, PSURs, IPSRs) an assessment of whether it is believed that the frequency of lack of efficacy reports is greater than would be predicted by the premarketing clinical trials for the drug or biological product (see sections III.E.1.c, III.E.2.k.vi, and III.E.3 of this document). This assessment would be provided for reports of a lack of efficacy whether a serious SADR, nonserious SADR, or no SADR occurs. Applicants that submit PSURs and IPSRs to FDA would also include in these reports a discussion of medically relevant lack of efficacy reports (*e.g.*, might represent a significant hazard to the treated population) for a product(s) used to treat serious or life-threatening diseases (see sections III.E.2.h and III.E.3 of this document).

III.D. Postmarketing Expedited Reports

Current postmarketing expedited safety reporting regulations at §§ 310.305(c), 314.80(c), and 600.80(c) require submission of "15-day Alert reports" to FDA. FDA is proposing to amend these regulations by removing the term "15-day Alert report" and replacing it with the term "expedited report" to be consistent with terminology used in the ICH E2A guidance. FDA is also proposing the following revisions to its postmarketing expedited safety reporting regulations.

III.D.1. Serious and Unexpected SADR's

Under the existing postmarketing expedited safety reporting regulations at § 310.305(c)(1)(i), persons subject to this requirement must report to FDA each adverse drug experience received or otherwise obtained that is both serious and unexpected as soon as possible, but in no case later than 15 calendar days of initial receipt of the information by the person. Under the existing postmarketing expedited safety reporting regulations at §§ 314.80(c)(1)(i) and 600.80(c)(1)(i), persons subject to these requirements must report each adverse drug experience that is both serious and unexpected, whether foreign or domestic, as soon as possible, but in no case later than 15 calendar days of initial receipt of the information by the person.

FDA is proposing minor revisions to these regulations for consistency. Proposed § 310.305(c)(2)(i) would amend § 310.305(c)(1)(i) by adding the phrase "whether foreign or domestic" after the phrase "that is both serious and unexpected." Proposed §§ 314.80(c)(2)(i) and 600.80(c)(2)(i) would amend §§ 314.80(c)(1)(i) and

600.80(c)(1)(i) by adding the phrase "to FDA" after the word "report" and by adding the phrase "received or otherwise obtained" before the phrase "that is both serious and unexpected."

Proposed §§ 310.305(c)(2)(i), 314.80(c)(2)(i), and 600.80(c)(2)(i) would amend §§ 310.305(c)(1)(i), 314.80(c)(1)(i), and 600.80(c)(1)(i) by removing the phrase "of initial receipt of the information by the person whose name appears on the label ("by the applicant" for § 314.80(c)(1)(i), and "by the licensed manufacturer" for § 600.80(c)(1)(i)) and replacing it with the phrase "after receipt by the manufacturer ("applicant" for proposed §§ 314.80(c)(2)(i), and 600.80(c)(2)(i)) of the minimum data set for the serious, unexpected SADR." This proposed amendment is consistent with proposed revisions to the premarketing expedited safety reporting regulations at proposed § 312.32(c)(1)(i) (see section III.B.2.b of this document). The amendment would clarify that the 15 calendar day timeframe would begin as soon as manufacturers and applicants have knowledge of the minimum data set for an SADR that is serious and unexpected. Manufacturers and applicants must use due diligence to acquire this information. For this purpose, they would be required, as described in section III.C.5 of this document, to use active query to determine the outcome for the SADR (whether the SADR is serious or nonserious) and acquire at least the minimum data set for the individual case safety report if they are not able to immediately obtain this information. Manufacturers and applicants should include in postmarketing expedited safety reports a chronological history of their efforts to acquire a minimum data set and to determine the seriousness and expectedness of an SADR if there is a delay in obtaining such information.

Proposed §§ 310.305(c)(2)(i), 314.80(c)(2)(i) and 600.80(c)(2)(i) state that if a full data set is not available for a serious and unexpected SADR report at the time of initial submission of the report to FDA, manufacturers and applicants must submit the information required under proposed §§ 310.305(c)(1)(iv), 314.80(c)(1)(iv) and 600.80(c)(1)(iv) as described in section III.C.5 of this document and also submit a 30-day followup report as described in section III.D.6 of this document. FDA is proposing this action to clarify the importance of acquiring complete information for serious SADR's.

III.D.2. Information Sufficient To Consider Product Administration Changes

Proposed §§ 310.305(c)(2)(ii), 314.80(c)(2)(ii), and 600.80(c)(2)(ii) would require that manufacturers and applicants submit to FDA information, received or otherwise obtained, whether foreign or domestic, that would be sufficient, based upon appropriate medical judgment, to consider changes in product administration. Manufacturers and applicants would be required to submit this information to the agency as soon as possible, but in no case later than 15 calendar days after the manufacturer or applicant determines that the information qualifies for expedited reporting. Examples of such information include any significant unanticipated safety finding or data in the aggregate from an *in vitro*, animal, epidemiological, or clinical study, whether or not conducted under an IND, that suggests a significant human risk, such as reports of mutagenicity, teratogenicity, or carcinogenicity, or reports of a lack of efficacy with a drug or biological product used in treating a life-threatening or serious disease. The proposed rule would require that manufacturers and applicants maintain records of their efforts to determine whether information that they have received or otherwise obtained would qualify for expedited reporting under this proposed requirement. This proposed requirement is consistent with the proposed revisions to the premarketing expedited safety reporting regulations at proposed § 312.32(c)(1)(ii) (see section III.B.2.c of this document) and with the ICH E2A guidance (60 FR 11284 at 11286). The proposed amendment would further clarify some of the types of safety information that must be submitted to FDA in an expedited manner.

III.D.3. Unexpected SADRs With Unknown Outcome

FDA expects that, in most cases, manufacturers and applicants will be able to determine the outcome for an SADR (whether the SADR is serious or nonserious). However, in those few cases where a determination may not be possible, FDA would require submission of unexpected SADRs with unknown outcome in an expedited manner (proposed §§ 310.305(c)(2)(iii), 314.80(c)(2)(iii), and 600.80(c)(2)(iii)). Expedited safety reports for unexpected SADRs with unknown outcome would be submitted to FDA within 45 calendar days after initial receipt by the manufacturer or applicant of the minimum data set for the unexpected

SADR. FDA is proposing this action to expedite review of potentially serious SADRs.

The proposed rule would require that manufacturers and applicants reporting an unexpected SADR with unknown outcome include in the expedited safety report the reason(s) for their inability to classify an SADR as either serious or nonserious (*i.e.*, unknown outcome). For this purpose, manufacturers and applicants should include in the expedited report a chronological history of their efforts to determine the outcome of the SADR.

Manufacturers and applicants reporting an unexpected SADR with unknown outcome must exercise due diligence to determine the expectedness for the SADR and to acquire at least the minimum data set for the individual case safety report. For this purpose, these persons would be required to use active query to acquire this information (see section III.C.5 of this document). These persons should include in postmarketing expedited safety reports a chronological history of their efforts to acquire this information if there is a delay in obtaining it.

III.D.4. Always Expedited Reports

Proposed §§ 310.305(c)(2)(iv), 314.80(c)(2)(iv), and 600.80(c)(2)(iv) would require manufacturers and applicants to submit to FDA individual case safety reports for SADRs, received or otherwise obtained, whether foreign or domestic, that are the subject of an always expedited report. These always expedited reports would be submitted to the agency as soon as possible, but in no case later than 15 calendar days after receipt by the manufacturer ("applicant" for proposed §§ 314.80(c)(2)(iv), and 600.80(c)(2)(iv)) of the minimum data set for the report. The following medically significant SADRs, which may jeopardize the patient or subject and/or require medical or surgical intervention to treat the patient or subject, would be subject to an always expedited report:

- Congenital anomalies,
- Acute respiratory failure,
- Ventricular fibrillation,
- Torsades de pointe,
- Malignant hypertension,
- Seizure,
- Agranulocytosis,
- Aplastic anemia,
- Toxic epidermal necrolysis,
- Liver necrosis,
- Acute liver failure,
- Anaphylaxis,
- Acute renal failure,
- Sclerosing syndromes,
- Pulmonary hypertension,
- Pulmonary fibrosis,

- Confirmed or suspected transmission of an infectious agent by a marketed drug or biological product,

- Confirmed or suspected endotoxin shock, and

- Any other medically significant SADR that FDA determines to be the subject of an always expedited report (*i.e.*, may jeopardize the patient or subject and/or require medical or surgical intervention to treat the patient or subject).

These SADRs would be submitted to the agency in an expedited manner whether unexpected or expected and whether or not the SADR leads to a serious outcome. The medical gravity of these SADRs requires expedited reporting.

The agency is proposing that a confirmed or suspected transmission of an infectious agent by a marketed drug or biological product would be the subject of an always expedited report. Examples of such transmissions include human immunodeficiency virus (HIV) transmission by anti-hemophilic factor, hepatitis C transmission by intravenous immunoglobulin, bacterial contamination of albumin leading to sepsis, and parvovirus contamination of anti-hemophilic factor causing an SADR. These SADRs indicate a public health problem that requires expedited review by the agency.

The proposal provides that the agency could make a new SADR the subject of an always expedited report. Such an SADR would only become the subject of these reports if FDA determines that the SADR is medically significant (*i.e.*, may jeopardize the patient or subject and/or require medical or surgical intervention to treat the patient or subject). New SADRs that become the subject of always expedited reports would be included in the agency's current guidance for industry on postmarketing safety reporting for human drugs and licensed biological products.

Proposed §§ 310.305(c)(2)(iv)(B), 314.80(c)(2)(iv)(B), and 600.80(c)(2)(iv)(B) would require that if a full data set is not available for always expedited reports at the time of initial submission of the report to FDA, manufacturers and applicants would submit the information required under proposed §§ 310.305(c)(1)(iv), 314.80(c)(1)(iv) and 600.80(c)(1)(iv) as described in section III.C.5 of this document and also submit a 30-day followup report as described in section III.D.6 of this document. FDA is proposing this action to clarify the importance of acquiring complete information for medically significant SADRs that are the subject of always expedited reports.

III.D.5. Medication Errors

Proposed §§ 310.305(c)(2)(v)(A), 314.80(c)(2)(v)(A), and 600.80(c)(2)(v)(A) would require that each domestic report of an actual medication error, received or otherwise obtained, be submitted to the agency as soon as possible, but in no case later than 15 calendar days after receipt by the manufacturer ("applicant" for proposed §§ 314.80(c)(2)(v)(A) and 600.80(c)(2)(v)(A)) of the minimum data set for a report of an SADR or, if an SADR does not occur, the minimum information for the report as described in section III.C.5 of this document (*i.e.*, an identifiable patient, an identifiable reporter, and a suspect drug or biological product). For postmarketing safety reporting purposes, all reports of medication errors would be considered unexpected. FDA is proposing this new type of expedited report to protect public health.

Proposed §§ 310.305(c)(2)(v)(B), 314.80(c)(2)(v)(B), and 600.80(c)(2)(v)(B) would require that reports of potential medication errors, received or otherwise obtained, be submitted to the agency as soon as possible, but in no case later than 15 calendar days after receipt by the manufacturer ("applicant" for proposed §§ 314.80(c)(2)(v)(B) and 600.80(c)(2)(v)(B)) of the minimum information described in section III.C.5 of this document (*i.e.*, an identifiable reporter and a suspect drug or biological product). FDA is proposing submission of this information to the agency in an expedited manner to attempt to prevent actual medication errors.

Proposed §§ 310.305(c)(2)(v)(C), 314.80(c)(2)(v)(C), and 600.80(c)(2)(v)(C) state that if a full data set is not available for an actual or potential medication error report at the time of initial submission of the report to FDA, manufacturers and applicants would submit the information required under proposed §§ 310.305(c)(1)(iv), 314.80(c)(1)(iv) and 600.80(c)(1)(iv) as described in section III.C.5 of this document and also submit a 30-day followup report as described in section III.D.6 of this document. FDA is proposing this action to clarify the importance of acquiring complete information for reports of medication errors.

III.D.6. Followup Reports

Current postmarketing expedited safety reporting regulations at §§ 310.305(c)(2), 314.80(c)(1)(ii), and 600.80(c)(1)(ii) require persons subject to these regulations to promptly investigate all serious, unexpected adverse drug experiences that are the

subject of expedited reports and to submit followup reports within 15 calendar days of receipt of new information or as requested by FDA. If additional information is not obtainable, records should be maintained of the unsuccessful steps taken to seek additional information. Thus, followup reports are currently only required to be submitted to FDA if requested by the agency or if new information is obtained or otherwise received by the manufacturer or applicant for an adverse drug experience previously reported to FDA.

In this rulemaking, FDA continues to require submission of these followup reports. In addition, as described in the following paragraph, a 30-day followup report would be required to be submitted in certain cases (*i.e.*, initial serious and unexpected SADR reports, always expedited reports and medication error reports that do not contain a full data set). If a 30-day followup report is required and no new information is available for the report, then the manufacturer or applicant would still be required to submit the 30-day followup report, indicate in the report that no new information was available and include a description of the reason(s) for its inability to acquire complete information and its efforts to obtain complete information. In all other cases, if there is no new information to report to FDA on a previously submitted SADR no followup report would be required to be submitted to the agency.

Proposed §§ 310.305(c)(2)(vi), 314.80(c)(2)(vi), and 600.80(c)(2)(vi) would require manufacturers and applicants to use active query to obtain additional information for any serious and unexpected SADR submitted to FDA in an expedited report under proposed §§ 310.305(c)(2)(i), 314.80(c)(2)(i), and 600.80(c)(2)(i) that does not contain a full data set. The proposed amendment would also require these persons to use active query to obtain additional information for any always expedited report under proposed §§ 310.305(c)(2)(iv), 314.80(c)(2)(iv), and 600.80(c)(2)(iv) or any medication error report under proposed §§ 310.305(c)(2)(v), 314.80(c)(2)(v), and 600.80(c)(2)(v) that does not contain a full data set. This information would be submitted to the agency in a followup report within 30 calendar days after initial submission of the expedited report to FDA by the manufacturer or applicant (30-day followup report). This proposed amendment would provide the agency with timely acquisition of more complete information for SADRs

and medication errors that are the subject of these reports.

Proposed §§ 310.305(c)(2)(vi), 314.80(c)(2)(vi), and 600.80(c)(2)(vi) would also state that:

* * * If a full data set is still not obtainable, the 30-day followup report must contain the information required under paragraph (c)(1)(iv) of this section. Any new safety information in the 30-day followup report must be highlighted. Any new information, received or otherwise obtained, after submission of a 30-day followup report must be submitted to FDA as a 15-day followup report under paragraph (c)(2)(vii) of this section.

This proposed amendment would clarify the information that would be required in a 30-day followup report if a full data set is still not available for the report. It would also clarify that FDA would require a 15-day followup report, as described in the paragraphs that follow, for any new information obtained or otherwise received for the report after submission of the 30-day followup report. The proposed amendment would ensure that manufacturers and applicants would exercise due diligence to obtain complete information for SADRs that are the subject of 30-day followup reports.

Proposed §§ 310.305(c)(2)(vii), 314.80(c)(2)(vii), and 600.80(c)(2)(vii) would amend §§ 310.305(c)(2), 314.80(c)(1)(ii), and 600.80(c)(1)(ii) to clarify that manufacturers and applicants must submit 15-day followup reports to FDA of any new information received or otherwise obtained for any expedited or followup report (except for initial expedited reports under proposed §§ 310.305(c)(2)(i), (c)(2)(iv), and (c)(2)(v), 314.80(c)(2)(i), (c)(2)(iv), and (c)(2)(v), and 600.80(c)(2)(i), (c)(2)(iv), and (c)(2)(v) that do not contain a full data set) within 15 calendar days of initial receipt of new information by the manufacturer or applicant. Proposed §§ 310.305(c)(2)(vii), 314.80(c)(2)(vii), and 600.80(c)(2)(vii) would also state that:

* * * Expedited reports under paragraphs (c)(2)(i), (c)(2)(iv), and (c)(2)(v) of this section that do not contain a full data set at the time of initial submission of the report to FDA are subject to the 30-day followup reporting requirements under paragraph (c)(2)(vi) of this section rather than the 15-day followup reporting requirements under this paragraph.

Thus, 15-day followup reports would be submitted for the following types of expedited and followup reports:

- Serious and unexpected SADR reports that contain a full data set,
- Information sufficient to consider product administration changes,

- Unexpected SADRs with unknown outcomes,
- Always expedited reports that contain a full data set,
- Actual and potential medication error reports that contain a full data set,
- 30-day followup reports, and
- 15-day followup reports.

These proposed revisions clarify the types of expedited reports that would be subject to the 15-day followup reporting requirements.

FDA notes that a 15-day followup report, rather than a serious and unexpected SADR report, should be submitted to FDA for an SADR that is initially reported to the agency as serious and expected or nonserious and unexpected, but is subsequently determined to be serious and unexpected. In these cases, manufacturers and applicants should include in the 15-day followup report a chronological history describing the events that transpired which resulted in determination of the serious and unexpected character of the SADR.

FDA is proposing to amend its postmarketing expedited safety reporting regulations at §§ 310.305(c)(2), 314.80(c)(1)(ii), and 600.80(c)(1)(ii) by removing the second sentence in these paragraphs regarding maintaining records if additional information is not obtainable for a serious and unexpected adverse drug experience. The agency is proposing this amendment because postmarketing safety reporting requirements for serious and unexpected SADR reports that do not contain a full data set are now prescribed under proposed §§ 310.305(c)(1)(iv) and (c)(2)(vi), 314.80(c)(1)(iv) and (c)(2)(vi), and 600.80(c)(1)(iv) and (c)(2)(vi).

III.D.7. Supporting Documentation

Proposed §§ 310.305(c)(2)(viii)(A), 314.80(c)(2)(viii)(A), and 600.80(c)(2)(viii)(A) would require that manufacturers and applicants submit to FDA, if available, a copy of the autopsy report if the patient dies. If an autopsy report is not available, the proposed rule would require that manufacturers and applicants submit a death certificate to FDA. If an autopsy report becomes available after the manufacturer or applicant has submitted a death certificate to the agency, the manufacturer or applicant must submit the autopsy report to FDA. If the patient was hospitalized, manufacturers and applicants would be required to submit to FDA, if available, a copy of the hospital discharge summary. If any of these documents is not in English, an English translation of the document would be required. FDA is proposing

that manufacturers and applicants submit these documents to provide the agency with complete information for SADRs that result in a death or hospitalization.

Proposed §§ 310.305(c)(2)(viii)(A), 314.80(c)(2)(viii)(A), and 600.80(c)(2)(viii)(A) would require that manufacturers and applicants use active query to obtain the documents required to be submitted to FDA under this paragraph. These documents would be required to be submitted to FDA as 15-day followup reports (see section III.D.6 of this document) within 15 calendar days of initial receipt of the document by the manufacturer or applicant. In instances when a document is not submitted to FDA in a 15-day followup report within 3 months after submission of the initial expedited report for the death or hospitalization, the agency would assume that active query by the manufacturer or applicant did not result in access to these documents. In this case, a record of the reason(s) for the lack of documentation and the effort that was made to obtain the documentation would be required to be maintained by the manufacturer and applicant.

Proposed §§ 310.305(c)(2)(viii)(B), 314.80(c)(2)(viii)(B), and 600.80(c)(2)(viii)(B) would require that each expedited report contain in the narrative a list of other relevant documents (e.g., medical records, laboratory results, data from studies) regarding the report that are maintained by manufacturers and applicants. FDA may require, when appropriate, that copies of one or more of these documents be submitted to the agency within 5 calendar days after receipt of the request. FDA would usually request such records in response to a suspected safety problem associated with the use of a drug or licensed biological product.

III.D.8. Scientific Literature

Current postmarketing expedited safety reporting regulations at §§ 314.80(d)(1) and 600.80(d)(1) require that expedited reports based on information from the scientific literature be accompanied by a copy of the published article. These regulations apply only to reports found in scientific and medical journals either as case reports or as the result of a formal clinical trial. Proposed §§ 314.80(c)(2)(ix) and 600.80(c)(2)(ix) would amend the current regulations by removing the phrase "either as case reports or as the result of a formal clinical trial" to clarify that all reports from the scientific literature, including case reports, and results of a formal clinical trial, epidemiological study, in

vitro study, or animal study, that qualify for expedited reporting under proposed §§ 314.80(c)(2) and 600.80(c)(2) would be required to be submitted to FDA.

The proposed rule would also remove §§ 314.80(d)(2) and 600.80(d)(2). These paragraphs provide that reports based on the scientific literature must be submitted on FDA Form 3500A or comparable format prescribed by the regulations and that, in cases where persons subject to the postmarketing safety reporting regulations believe that preparing the FDA Form 3500A constitutes an undue hardship, arrangements can be made with the agency for use of an acceptable alternative reporting format. FDA is proposing to remove these paragraphs because the reporting format for reports based on information in the scientific literature would be specified under proposed §§ 314.80(c)(4) and 600.80(c)(4) (see section III.F of this document).

For organizational purposes, FDA is proposing to move §§ 314.80(d) and 600.80(d), as revised by this proposed rule, to proposed §§ 314.80(c)(2)(ix) and 600.80(c)(2)(ix). Proposed § 310.305(c)(2)(ix) would amend § 310.305(c) by adding the paragraph:

Scientific literature. An expedited report based on information from the scientific literature applies only to reports found in scientific and medical journals. These expedited reports must be accompanied by a copy of the published article.

This proposed amendment would clarify for prescription drug products marketed for human use without an approved application the types of safety information found in scientific literature that would qualify for expedited reporting. The proposed amendment would also require that these reports include a copy of the published article that is the subject of the expedited report. The proposed amendment would provide the agency with more complete information for review of safety information from the scientific literature and would also provide uniformity between FDA's postmarketing expedited safety reporting requirements for prescription drugs marketed for human use without an approved application and marketed drugs with an approved application.

III.D.9. Contractors and Shared Manufacturers

Current regulations at §§ 310.305(c)(1)(i) and (c)(3), 314.80(c)(1)(iii), and 600.80(c)(1)(iii) require any person whose name appears on the label of a marketed drug product or licensed biological product as a packer or distributor to submit either

expedited reports of serious and unexpected adverse drug experiences directly to FDA or reports of all serious adverse drug experiences to the manufacturer (§ 310.305(c)(3) or applicant (§§ 314.80(c)(1)(iii) and 600.80(c)(1)(iii)) instead of FDA in 5 calendar days. This provision also applies to manufacturers for §§ 314.80(c)(1)(iii) and 600.80(c)(1)(iii) and to shared manufacturers, joint manufacturers, and any participants involved in divided manufacturing for § 600.80(c)(1)(iii). Proposed §§ 310.305(c)(2)(xi)(A), 314.80(c)(2)(x)(A), and 600.80(c)(2)(x)(A) would amend these regulations to require contractors, as defined in proposed §§ 310.305(a), 314.80(a) and 600.80(a) (see section III.A.4 of this document), to submit to the manufacturer (proposed § 310.305(c)(2)(xi)(A)) or applicant (proposed §§ 314.80(c)(2)(x)(A) and 600.80(c)(2)(x)(A)) safety reports of all SADR (serious and nonserious) and medication errors for the manufacturer's (proposed § 310.305(c)(2)(xi)) or applicant's (proposed §§ 314.80(c)(2)(x) and 600.80(c)(2)(x)) drug or biological product, obtained or otherwise received, within 5 calendar days of initial receipt of the report by the contractor. This provision would also apply to shared manufacturers of licensed biological products for proposed § 600.80(c)(2)(x)(A) (*i.e.*, all SARs and medication errors would be required to be submitted to the applicant within 5 calendar days). The contractor would be required to submit a report of an SADR to the manufacturer (proposed § 310.305(c)(2)(xi)(A)) or applicant (proposed §§ 314.80(c)(2)(x)(A) and 600.80(c)(2)(x)(A)) even if the report does not contain a minimum data set. Contractors and shared manufacturers would only be required to convey to manufacturers (proposed § 310.305(c)(2)(xi)(A)) or applicants (proposed §§ 314.80(c)(2)(x)(A) and 600.80(c)(2)(x)(A)) whatever safety information was obtained or otherwise received. They would not be required to use active query to acquire safety information, to conduct followup, or to submit postmarketing safety reports to FDA. Upon receipt of a safety report from a contractor or shared manufacturer, the manufacturer (proposed § 310.305(c)(2)(xi)(A)) or applicant (proposed §§ 314.80(c)(2)(x)(A) and 600.80(c)(2)(x)(A)) would be required to comply with the postmarketing safety reporting requirements under proposed §§ 310.305, 314.80 and 600.80 (*e.g.*, use active query, if necessary, to acquire

safety information, conduct followup, submit postmarketing safety reports to FDA). These proposed amendments would provide manufacturers and applicants with complete safety information regarding its products.

Proposed §§ 310.305(c)(2)(xi)(B), 314.80(c)(2)(x)(B), and 600.80(c)(2)(x)(B) would require that contracts between manufacturers and contractors (§ 310.305(c)(2)(xi)(B)) and applicants and contractors (§§ 314.80(c)(2)(x)(B) and 600.80(c)(2)(x)(B)) specify the postmarketing safety reporting responsibilities of the contractor. Although contractors and shared manufacturers have postmarketing safety reporting responsibilities, the manufacturer (proposed § 310.305(c)(2)(xi)(B)) or applicant (proposed §§ 314.80(c)(2)(x)(B) and 600.80(c)(2)(x)(B)) would be responsible for ensuring that the contractors and shared manufacturers of its products comply with these postmarketing safety reporting responsibilities. FDA believes that, in general, this proposal represents a practice that is already customary and usual in the pharmaceutical industry because contractors are typically considered agents of the manufacturer or applicant.

Proposed §§ 310.305(c)(2)(xi)(C), 314.80(c)(2)(x)(C), and 600.80(c)(2)(x)(C) would require that contractors and shared manufacturers maintain records of SADR reports and medication errors. This proposal is consistent with current postmarketing safety reporting requirements.

Proposed §§ 310.305(c)(2)(xi)(D), 314.80(c)(2)(x)(D), and 600.80(c)(2)(x)(D) state that the recordkeeping, written procedures, and disclaimer provisions under proposed §§ 310.305, 314.80 and 600.80 would apply to contractors and shared manufacturers. This proposal clarifies for contractors and shared manufacturers which of the postmarketing safety reporting provisions would apply to them.

III.D.10. Prescription Drugs Marketed for Human Use Without an Approved Application

Proposed § 310.305(c)(2)(x) would amend § 310.305(c)(1)(i) to require that expedited reports for prescription drugs marketed for human use without an approved application be accompanied by a list of the current addresses where all safety reports and other safety-related records for the drug product are maintained by manufacturers and contractors. In the October 1994 proposal, FDA proposed to include, under §§ 314.80(c)(2) and 600.80(c)(2), a section in its postmarketing periodic safety reports on location of adverse

drug experience records (59 FR 54046 at 54061). FDA is now repropounding this amendment for its postmarketing periodic safety reports (see sections III.E.1.g, III.E.2.k.x, and III.E.3 of this document). The agency is also proposing to require the list of addresses in expedited reports for drugs covered under § 310.305 because manufacturers of these drugs are not required to submit postmarketing periodic safety reports to FDA. The list of addresses would provide rapid access to safety-related records for FDA inspections and for requests by FDA for additional information concerning safety issues.

III.D.11. Class Action Lawsuits

Manufacturers and applicants should not submit SADR from class action lawsuits to FDA in an expedited report. The agency believes that SADR from class action lawsuits would be submitted to FDA from other sources (*e.g.*, spontaneous reports) prior to initiation of the class action lawsuit. Summary tabulations of SADR from class action lawsuits would be required in postmarketing periodic safety reports (see sections III.E.1.e and III.E.2.k.v of this document).

III.D.12. Blood and Blood Component Safety Reports

Current § 606.170(a) requires a blood establishment to thoroughly investigate any complaint of an adverse reaction arising as a result of blood collection or transfusion and to prepare and maintain a written report of the investigation, including followup and conclusions, as part of the record for that lot or unit of final product. If appropriate, the report must be forwarded to the manufacturer of the blood or blood component or the collection facility. Under § 606.170(b), a complication of a blood collection or blood transfusion resulting in a fatality must be reported to FDA as soon as possible by telephone or other rapid means of communication, and a written report of the investigation must be submitted to FDA within 7 days of the fatality. Each year, in accordance with § 606.170(b), FDA receives between 50 and 80 reports of fatalities.

Current § 606.171 requires licensed manufacturers of blood and blood components, unlicensed registered blood establishments and transfusion services to report biological product deviations. A biological product deviation is an event that represents either: (1) A deviation from current good manufacturing practices, applicable regulations, applicable standards, or established specifications that may affect the safety, purity, or potency of a product; or (2) an unexpected or

unforeseeable event that may affect the safety, purity, or potency of a product. In some cases, a biological product deviation reportable under § 606.171 may actually result in an adverse reaction in the transfusion recipient. In many other cases, the biological product deviation may be discovered before the affected products are administered or administration of the product may not result in an adverse reaction.

Although manufacturers of blood and blood components are currently exempt from the safety reporting requirements under § 600.80, FDA receives reports of fatal adverse reactions related to blood and blood components and may receive some additional information through biological product deviation reporting. However, the agency does not currently receive adequate information to monitor and assess safety-related information concerning the collection and transfusion of blood and blood components. Such information is essential for evaluating the agency's scientific and regulatory policies and for monitoring industry practices and their implications on blood safety. For these purposes, FDA is proposing to amend § 606.170 to require the reporting of all serious SARs, in addition to fatalities, that are related to the collection or transfusion of blood and blood components (*e.g.*, red blood cells, plasma, platelets, and cryoprecipitate). For fatal SARs, proposed § 606.170(c) would continue the current requirement that a fatal SAR be reported immediately by telephone, facsimile, express mail, or electronically transmitted mail and in a written report within 7 calendar days of the fatality. Because blood establishments are already required to investigate all complaints of an adverse reaction related to the collection and transfusion of blood and blood components and many of these reactions are well recognized and understood by blood establishments and by FDA, the agency is not proposing to require the submission of postmarketing periodic safety reports (*i.e.*, TPSRs, PSURs, IPSRs and individual case safety reports—semiannual submissions).

Specifically, FDA is proposing to amend § 606.170 by revising the title of the section to read "Suspected adverse reaction investigation and reporting"; by making editorial changes to § 606.170(a), which prescribes requirements for the investigation and recording of any complaint of an SAR related to the collection or transfusion of blood or blood components; by adding a new requirement for reporting of serious SARs related to transfusion or collection procedures (proposed

§ 606.170(b)); and by redesignating current § 606.170(b) as § 606.170(c) and revising the paragraph as discussed below. FDA is also proposing that the terms "SAR" and "serious SAR," as used in proposed § 606.170, have the same meaning as defined in proposed § 600.80(a) (see sections III.A.1 and III.A.3 of this document).

In general, FDA believes that any SAR related to blood donation or transfusion that requires immediate medical intervention or followup medical attention should be reported. For the purpose of reporting serious SARs related to blood collection, FDA interprets the term to include:

- Vasovagal reactions with syncope (hypotension and bradycardia) requiring medical intervention;
- Citrate reactions requiring significant medical intervention;
- Anaphylaxis or any major allergic reactions;
- Seizure of any type or duration;
- Cerebrovascular accidents;
- Cardiac arrhythmia, angina of any duration, myocardial infarction, or cardiac arrest;
- Clinically significant hypotension;
- Bronchospasm, respiratory insufficiency;
- Arterial puncture, air embolus;
- Phlebotomy-related nerve damage; and,
- Thrombophlebitis, phlebitis, or any procedure-related infection.

For SARs related to donation, FDA interprets the term "serious SAR" not to include:

- Self-limited vasovagal reactions (hemodynamically stable);
- Self-limited citrate reactions;
- Localized hematoma, uncomplicated; and,
- Localized skin irritation, uncomplicated.

For the purposes of reporting serious SARs related to receipt of a blood transfusion, FDA interprets the term to include:

- Any complication from the use of an unsuitable unit, including infusion of hemolyzed blood;
- Any complication from improper blood administration, including failure to use a standard blood filter (*e.g.*, air embolism);
- Induced hemolysis, acute or delayed;
- Transmitted infections, including bacterial infections;
- Associated graft versus host disease;
- Related hypersensitivity with respiratory insufficiency and/or hypotension (*e.g.*, anaphylaxis);
- Transfusion-related acute lung injury (TRALI);

- Induced alloimmunization which prevents effective transfusion therapy (*e.g.*, posttransfusion purpura);
- Induced congestive heart failure; and

and

- Induced cardiac arrhythmias, including those resulting from metabolic imbalance.

For SARs related to receipt of a blood transfusion, FDA interprets the term "SAR" not to include:

- Febrile nonhemolytic transfusion reactions;
- Related hypersensitivity without respiratory insufficiency nor hypotension;
- Induced alloimmunization which does not prevent effective transfusion therapy;
- Infections not clinically significant to the recipient, such as cytomegalovirus (CMV) infection in an immunocompetent adult; and,
- Induced hemochromatosis.

FDA is proposing to require that for a serious SAR related to blood collection, the establishment performing the blood collection be responsible for reporting the serious SAR to FDA, and for a serious SAR related to transfusion, the establishment responsible for the compatibility testing be responsible for reporting the serious SAR to FDA (proposed § 606.170(b)). FDA is proposing to require that reports of serious SARs, including fatal SARs under proposed § 606.170(c), be reported to FDA using the reporting format described in proposed § 600.80(c)(4). Thus the reporting facility would be required to submit a report for each individual patient on FDA Form 3500A or a computer-generated facsimile of FDA Form 3500A using the appropriate "preferred term" in the latest version of MedDRA (see section III.F of this document).

Current § 606.171 requires reports of biological product deviations be submitted as soon as possible, but not to exceed 45 calendar days. Because there will be instances when an SAR occurs and a biological product deviation may have contributed to an SAR, FDA is proposing to require reporting of serious SARs to the agency within 45 calendar days (for fatal SARs, within 7 calendar days) of the determination that a serious SAR related to blood collection or transfusion has occurred. This will permit a blood establishment to investigate and report both a biological product deviation and an SAR related to the biological product deviation at the same time and will limit the reporting burden. In the case of a reported serious SAR that subsequently results in a fatality, FDA would not require two separate reports,

one reporting the serious SAR and the other reporting the fatality. However, if the fatality occurs after the report of the serious SAR is submitted to the agency, the blood establishment should update the initial report to report the fatality.

III.E. Postmarketing Periodic Safety Reporting

The proposed rule would require all applicants to submit to FDA semiannually on an FDA Form 3500A (VAERS form for vaccines, CIOMS I Form, if desired, for foreign SADR) certain spontaneously reported SADR (see tables 7 and 9 and section III.E.4 of this document regarding individual case safety reports—semiannual submissions). Applicants would also be required to submit other postmarketing periodic safety reports (*i.e.*, traditional periodic safety reports (TPSRs), periodic safety update reports (PSURs), or interim periodic safety reports (IPSRs)) to FDA with a frequency as described in section III.E.5.a of this document (see tables 7 and 9). PSURs, IPSRs, and TPSRs would provide FDA with an overview or summary of the safety profile of a drug or licensed biological product (excluding individual case safety reports). A TPSR would essentially contain the same format and content as the periodic safety report currently required by the agency's postmarketing periodic safety reporting regulations (see table 10 and section III.E.1 of this document). A PSUR would essentially be consistent with the format and content of the periodic safety report described in the ICH E2C guidance (see section III.E.2 of this document), and an IPSR would represent an abbreviated form of a PSUR (see section III.E.3 of this document). Applicants with drugs and licensed biological products approved prior to January 1, 1998, would have the option to submit either a TPSR or PSUR to FDA, whereas applicants with products approved on or after January 1, 1998, would be required to submit a PSUR (see tables 7 and 9 and section III.E.5.a of this document). FDA is proposing to require submission of periodic safety reports in a PSUR format for products approved on or after January 1, 1998, to be consistent with the ICH E2C guidance. FDA is not proposing to require submission of PSURs for products approved prior to January 1, 1998, because the agency recognizes that the most significant new safety information on a product is usually acquired in the first few years after it has been on the market. It is not necessary for applicants to reformat periodic safety reports for products approved prior to January 1, 1998. In addition, in some cases, it will be

sufficient for FDA to review an abbreviated form of the PSUR (*i.e.*, at 7.5 and 12.5 years after U.S. approval of a product). For these cases, the agency is proposing to require submission of an IPSR instead of a PSUR (see tables 7 and 9 and sections III.E.3 and III.E.5.a of this document).

III.E.1. Traditional Periodic Safety Reports (TPSRs)

Current regulations (§§ 314.80(c)(2)(ii)(a) through (c)(2)(ii)(c) and 600.80(c)(2)(ii)(A) through (c)(2)(ii)(C)) require the submission of postmarketing periodic adverse drug experience reports that contain:

- A narrative summary and analysis of the information in the report and an analysis of the 15-day postmarketing Alert reports submitted during the reporting period (all 15-day Alert reports being appropriately referenced by the applicant's patient identification number, adverse reaction term(s), and date of submission to FDA);
- An FDA Form 3500A describing each adverse drug experience not previously reported (with an index consisting of a line listing of the applicant's patient identification number and adverse reaction term(s)); and
- A history of actions taken since the last periodic report.

Proposed §§ 314.80(c)(3)(i) and 600.80(c)(3)(i) would amend these regulations by replacing the term "periodic adverse drug experience report" with the term "traditional periodic safety report (TPSR)." FDA is proposing this revision to differentiate the existing postmarketing periodic safety report from the proposed new postmarketing periodic safety reports (*i.e.*, PSURs and IPSRs, see sections III.E.2 and III.E.3 of this document).

III.E.1.a. *Narrative summary and analysis of individual case safety reports.* Proposed §§ 314.80(c)(3)(i)(A) and 600.80(c)(3)(i)(A) would amend §§ 314.80(c)(2)(ii)(a) and 600.80(c)(2)(ii)(A) by providing paragraph headings and reorganizing and revising these paragraphs. Proposed §§ 314.80(c)(3)(i)(A)(1) and 600.80(c)(3)(i)(A)(1) would amend §§ 314.80(c)(2)(ii)(a) and 600.80(c)(2)(ii)(A) by replacing the phrase "the information in the report" with the following:

serious, expected SADR and nonserious, unexpected SADR occurring in the United States that were submitted to the applicant during the reporting period from all spontaneous sources (*i.e.*, health care professionals and other individuals) (with an index consisting of a line listing of the applicant's manufacturer report number and

SADR term(s)). The narrative summary and analysis would include spontaneous reports submitted to the applicant by health care professionals and other individuals (*e.g.*, consumers).

Proposed §§ 314.80(c)(3)(i)(A)(2) and 600.80(c)(3)(i)(A)(2) would amend §§ 314.80(c)(2)(ii)(a) and 600.80(c)(2)(ii)(A) by replacing the phrase "an analysis of the 15-day Alert reports * * * date of submission to FDA)" with the phrase:

An analysis of the expedited reports submitted during the reporting period under paragraphs (c)(2)(i) through (c)(2)(vii) of this section (all expedited reports must be appropriately referenced by the applicant's manufacturer report number, SADR term(s), if appropriate, and date of submission to FDA).

Current regulations at §§ 314.80(c)(2)(iii) and 600.80(c)(2)(iii) state that periodic reporting, except for information regarding 15-day Alert reports, does not apply to adverse drug experience information obtained from postmarketing studies (whether or not conducted under an IND), from reports in the scientific literature, and from foreign marketing experience. FDA is proposing to remove this statement because proposed §§ 314.80(c)(3)(i)(A)(1) and 600.80(c)(3)(i)(A)(1) specifies the type of information that FDA would require in a TPSR.

III.E.1.b. *Individual case safety reports.* FDA is also proposing to remove §§ 314.80(c)(2)(ii)(b) and 600.80(c)(2)(ii)(B) from these regulations. FDA is proposing this change because the requirement to submit individual case safety reports to FDA on FDA Form 3500A (VAERS form for vaccines) would be required in a separate submission on a semiannual basis (see section III.E.4 of this document).

III.E.1.c. *Increased frequency reports.* Proposed §§ 314.80(c)(3)(i)(A)(3) and 600.80(c)(3)(i)(A)(3) would amend §§ 314.80(c)(2)(ii)(a) and 600.80(c)(2)(ii)(A) to require applicants to include in TPSRs a discussion of any increased reporting frequency of serious, expected SADR, including comments on whether it is believed that the data reflect a meaningful change in SADR occurrence. Even though the agency has revoked the requirement to submit increased frequency reports in an expedited manner (62 FR 34166), FDA is interested in reviewing periodically information on increased frequencies of serious, expected SADR and is proposing that this type of information be submitted to the agency in TPSRs.

The proposed rule would also require that this section of the TPSR include an assessment of whether it is believed that the frequency of lack of efficacy reports, obtained or otherwise received during the reporting period, is greater than would be predicted by the premarketing clinical trials for the drug or biological product. This assessment would be provided whether a serious SADR, nonserious SADR, or no SADR occurs as a result of a lack of efficacy of the product.

III.E.1.d. *Safety-related actions to be taken.* Proposed §§ 314.80(c)(3)(i)(A)(4) and 600.80(c)(3)(i)(A)(4) would require applicants to include in TPSRs the applicant's conclusion as to what, if any, safety-related actions should be taken based on the analysis of the safety data in the TPSR (e.g., labeling changes, studies initiated). FDA is proposing this amendment to highlight safety-related actions that may be necessary.

III.E.1.e. *Summary tabulations.* Proposed §§ 314.80(c)(3)(i)(B), and 600.80(c)(3)(i)(B) would require that a new section of summary tabulations (i.e., lists of all SADR terms and counts of occurrences) be included in TPSRs for all serious, expected SADRs; nonserious, unexpected SADRs; nonserious, expected SADRs; and expected SADRs with unknown outcome occurring in the United States that are submitted to the applicant during the reporting period from all spontaneous sources (i.e., health care professionals and other individuals). These tabulations would include SADRs that were previously submitted to FDA in an expedited report (i.e., serious, unexpected SADRs, unexpected SADRs with unknown outcome, and always

expedited reports) and reports of SADRs not previously submitted to FDA by applicants (e.g., reports submitted to applicants by FDA; reports obtained from FDA from freedom of information requests at the discretion of applicants; reports from class action lawsuits). The proposed rule would require that cumulative data be provided for SADRs that are determined to be both serious and unexpected (i.e., all cases reported to date). These summary tabulations would be presented by body system or standard organ system classification scheme (e.g., cardiovascular, central nervous system, endocrine, renal). The proposed rule would also require summary tabulations for all domestic reports of actual medication errors (i.e., serious SADRs, nonserious SADRs, no SADRs) and potential medication errors (i.e., number of reports for specific errors) that were previously submitted to the agency as an expedited report.

In the guidance of 1992, FDA advises applicants to include in their postmarketing periodic safety reports a listing by body system of all adverse drug experience terms and counts of occurrences submitted during the reporting period. FDA is now proposing to clarify and codify this expectation.

III.E.1.f. *History of safety-related actions taken.* Proposed §§ 314.80(c)(3)(i)(C), and 600.80(c)(3)(i)(C) would amend §§ 314.80(c)(2)(ii)(c) and 600.80(c)(2)(ii)(C) by adding the phrase "safety-related" before the word "actions" and by removing the phrase "because of adverse drug experiences." FDA is proposing these changes because actions may be taken for safety-related reasons other than SADRs. The

proposed rule would also amend these regulations by adding the phrase "periodic safety" before the word "report" for clarification.

III.E.1.g. *Location of safety records.* Proposed §§ 314.80(c)(3)(i)(D) and 600.80(c)(3)(i)(D) would require another new section in TPSRs that would contain a list of the current address(es) where all safety reports and other safety-related records for the drug product or licensed biological product are maintained. FDA is proposing to require a list of these addresses to provide rapid access to safety-related records for FDA inspections and for requests by FDA for additional information concerning safety issues.

III.E.1.h. *Contact person.* Proposed §§ 314.80(c)(3)(i)(E) and 600.80(c)(3)(i)(E) would require another new section in TPSRs that would contain the name and telephone number of the licensed physician or licensed physicians responsible for the content and medical interpretation of the data and information contained within the TPSR. The fax number and e-mail address for the licensed physician would also be included, if available. This proposal would provide the agency with someone to contact with any questions that may arise during review of a TPSR. FDA is proposing that the contact persons be licensed physicians because of their crucial knowledge of the medical significance of the information provided in a TPSR.

Table 10 highlights the differences in content between the currently required postmarketing periodic adverse drug experience reports and proposed TPSRs.

TABLE 10.—DIFFERENCES BETWEEN THE CURRENT REQUIREMENT FOR THE CONTENT OF POSTMARKETING PERIODIC ADVERSE DRUG EXPERIENCE REPORTS AND THE PROPOSED CONTENT OF TPSRS.

Content of periodic adverse drug experience report	Proposed revisions to content of periodic adverse drug experience report (proposed TPSRs)
Narrative summary and analysis of the information contained in the report.	Excludes nonserious expected SADRs. Includes discussion of increased frequency of serious expected SADRs and lack of efficacy reports. Includes applicant's recommendations for safety-related actions to be taken.
Analysis of expedited reports submitted to FDA during the reporting interval.	Not revised.
FDA Form 3500A (VAERS form for vaccines) for each adverse drug experience not submitted to FDA as an expedited report.	Revoked requirement. ¹
Index consisting of a line listing of the applicant's patient identification number and adverse reaction term(s).	Not revised.
History of actions taken since the last report because of adverse drug experiences.	Not revised. Require submission summary tabulations. ² New section added for location of safety records. New section added for contact information for licensed physician responsible for information in TPSR.

¹ Individual case safety reports would be submitted to FDA separately on a semiannual basis (see section III.E.4 of this document).

² Summary tabulations are currently requested (see the guidance of 1992) but not required for postmarketing periodic adverse drug experience reports.

III.E.2. Periodic Safety Update Reports (PSURs)

Proposed §§ 314.80(c)(3)(ii) and 600.80(c)(3)(ii) would amend FDA's postmarketing periodic safety reporting regulations by adding a new type of postmarketing periodic safety report. This new report would be identified as a "periodic safety update report (PSUR)." The proposed content and format for the PSUR, as described below, are consistent with the ICH E2C guidance (62 FR 27470) and would enable applicants to submit a single core document (PSUR excluding appendices) to regulatory authorities worldwide. All dosage forms, formulations, and indications for which applicants hold an approved application (*i.e.*, NDA, ANDA, BLA) for a given drug substance or licensed biological product should usually be covered in one PSUR. The PSUR may include separate presentations of these data as well as other data (*e.g.*, populations) if such presentations would facilitate review of the PSUR. FDA is proposing that a PSUR contain the following information:

III.E.2.a. *Title page, table of contents, and introduction.* The title page would include, at a minimum, the following information:

- Name and international birth date of the drug substance or licensed biological product that is the subject of the PSUR,
- Various dosage forms and formulations of the drug substance or biological product covered by the PSUR,
- Name and address of the applicant,
- Reporting period covered by the PSUR, and
- Date of the PSUR.

The introduction would provide a brief description of how this PSUR relates to previous reports and circumstances, would reference relevant drug products, drug substances, or biological products reported in other periodic safety reports (*e.g.*, a combination product reported in a separate PSUR), and would indicate any data duplication with other PSURs. If two or more companies co-market the same drug substance or licensed biological product, the safety reporting responsibilities of each of the companies should be specified clearly in the introduction.

III.E.2.b. *Worldwide marketing status.* This section of the PSUR would contain a table of the chronological history of the worldwide marketing status of the drug or biological product(s) covered by the PSUR from the date the product was first approved (*i.e.*, the international birth date) through its current status

(*i.e.*, cumulative information). The table would include:

- Dates of drug or biological product approval and renewal,
- Safety-related restrictions on product use,
- Indications for use and special populations covered by the drug or biological product approval,
- Lack of approval of the drug substance or biological product in any dosage form or for any indication for use by any regulatory authority(ies),
- Withdrawal of a pending drug or biological product marketing application by the applicant for safety- or efficacy-related reasons,
- Dates of market launches, and
- Trade name(s).

Drug or biological products that are approved in a country for a particular indication, population, or dosage form that may result in different types of patient exposure in that country should be identified, particularly if there are meaningful differences in the safety information reported in the PSUR due to the difference in patient exposures.

III.E.2.c. *Actions taken for safety reasons.* This section of the PSUR would contain details on regulatory authority-initiated (*e.g.*, FDA) and/or applicant-initiated actions related to safety that were taken during the period covered by the PSUR and between the data lock point and PSUR submission (*i.e.*, "late-breaking" safety concerns) including:

- Withdrawal or suspension of product approval or indication for use approval,
- Failure to obtain a marketing authorization renewal or to obtain an approval for a new indication for use,
- Restrictions on distribution (*e.g.*, products recalled for safety reasons),
- Clinical trial suspension,
- Dosage modification,
- Changes in target population or indications, and
- Formulation changes.

This section of the PSUR would also contain a narrative identifying the safety-related reasons that led to these actions with relevant documentation appended when appropriate. Any communication with health care professionals (*e.g.*, Dear Healthcare Professional letters) resulting from such actions would also be described with copies appended.

III.E.2.d. *Changes to CCSI.* This section of the PSUR would describe changes to the CCSI (*e.g.*, new contraindications, precautions, warnings, SADR, or interactions) made during the period covered by the PSUR. A copy of any modified section of the

CCSI would be included. Applicants would use the CCSI in effect at the beginning of the reporting period for the PSUR. The revised CCSI would be used as the reference document for the next reporting period.

III.E.2.e. *Worldwide patient exposure.* This section of the PSUR would include, for the reporting period, an estimate of the worldwide patient exposure to the drug or biological product(s) covered by the PSUR (*i.e.*, number of patients, average or median dose received, and average or median length of treatment). In many cases, accurate patient exposure data for a reporting period may be difficult to obtain. However, applicants should exercise due diligence to obtain an estimate of this exposure. The method used to estimate patient exposure would always be described. If the patient exposure is impossible to estimate or is meaningless, an explanation of and justification for such conclusions would be provided. If patient exposure is impossible to estimate, other measures of exposure, such as patient-days, number of prescriptions, or number of dosage units, could be used. If these or other more precise measures are not available and an adequate explanation for the lack of such information is provided, bulk sales could be used with estimates of what such numbers may mean in terms of patient exposure.

When possible, data broken down by gender and age (especially pediatric versus adult) would be provided. Data for the pediatric population would be reported, if possible, by age group (*e.g.*, neonates, infants, children, adolescents). If these data are not available, an explanation for the lack of such information would be included. In addition, when a pattern of reports indicates a potential problem, details by country (with locally recommended dosage regimens) or other segmentation (*e.g.*, indication, dosage form) would also be presented.

Patient exposure for clinical studies should also be provided when SADR data from these types of studies are included in the PSUR. For ongoing or blinded clinical studies, an estimate of patient exposure should be provided.

III.E.2.f. *Individual case safety reports.*

III.E.2.f.i. *Line listings.* Individual line listings of various data points from individual case safety reports are included as part of the format for international PSURs agreed to by ICH (ICH E2C guidance, 62 FR 27470 at 27473 and 27474). FDA will not require submission of such line listings in PSURs because, instead, the agency is proposing to require a separate

semiannual submission of certain individual case safety reports on FDA Form 3500A (VAERS form for vaccines, CIOMS I form, if desired, for foreign SADRs) (*see* section III.E.4 of this document). However, FDA is willing to accept line listings in PSURs as described in the ICH E2C guidance if applicants wish to include them. FDA believes that such an approach will help further the goal of harmonizing PSUR generation, formatting, and submission globally.

III.E.2.f.ii. *Summary tabulations.* This section of the PSUR would consist of summary tabulations of individual case safety reports (*e.g.*, serious unlisted SADRs, serious listed SADRs, nonserious unlisted SADRs, nonserious listed SADRs) for the following SADRs obtained or otherwise received during the reporting period:

- All serious and nonserious SADRs from spontaneous sources that were submitted to applicants by a health care professional,
- All serious SADRs from studies, individual patient INDs, or, in foreign countries, from named-patient “compassionate” use,
- All serious SADRs and nonserious unlisted SADRs from the scientific literature,
- All serious SADRs from regulatory authorities, and
- Serious SADRs from other sources such as reports created by poison control centers and epidemiological data bases.

These summary tabulations would be made up of lists by body system or standard organ system classification scheme (*e.g.*, cardiovascular, central nervous system, endocrine, renal) of all SADR terms and counts of occurrences. For SADRs that are determined to be both serious and unlisted, cumulative data would also be provided (*i.e.*, all cases reported to date). Applicants may provide information for this section of the PSUR in a narrative rather than a summary tabulation if the number of cases is small or the information is inadequate for any of the tabulations.

As noted previously, FDA would consider “study” information to include the following: safety information from company-sponsored patient support programs, disease management programs, patient registries, including pregnancy registries, or any organized data collection scheme (*see* section III.A.7 of this document). FDA is proposing to include summary tabulations for serious listed SADRs from study information in PSURs to be consistent with the ICH E2C guidance (62 FR 27470 at 27474), even though the

agency indicated in the clarification guidance of 1997 that only serious and unexpected adverse drug experiences for which there is a reasonable possibility that the drug or biological product caused the adverse drug experience should be reported to FDA from studies.

This section of the PSUR would also contain a brief discussion of the individual case data in the summary tabulations (*e.g.*, discussion of medical significance or mechanism). This section of the PSUR should be used to comment on specific cases rather than to provide an overall assessment of the cases.

III.E.2.g. *Safety studies.* This section of the PSUR would contain a discussion (not just a listing of the studies) of nonclinical, clinical, and epidemiological studies concerning important safety information including:

- All applicant-sponsored studies newly analyzed during the reporting period;
- New studies specifically planned, initiated, or continuing during the reporting period that examine a safety issue, whether actual or hypothetical; and
- Published safety studies in the scientific and medical literature, including relevant published abstracts from meetings (provide citations for all reports from the literature).

As noted previously, FDA would consider “study” information to include the following: safety information from company-sponsored patient support programs, disease management programs, patient registries, including pregnancy registries, or any organized data collection scheme (*see* section III.A.7 of this document).

The study design and results of newly analyzed studies should be clearly and concisely presented with attention to the usual standards of data analysis and description that are applied to nonclinical and clinical study reports. Copies of full reports for these studies should be appended only if new safety issues are raised or confirmed. FDA may request copies of other studies, if necessary.

For new or ongoing studies, the objective, starting date, projected completion date, number of subjects (planned and enrolled), and protocol abstract for each study should be provided. When possible and relevant, interim results of ongoing studies should be presented.

III.E.2.h. *Other information.* This section of the PSUR would contain a discussion of medically relevant lack of efficacy reports (*e.g.*, might represent a

significant hazard to the treated population) for a product(s) used to treat serious or life-threatening diseases, or any important new information received after the data lock point (*e.g.*, significant new cases).

III.E.2.i. *Overall safety evaluation.* This section of the PSUR would contain a concise, yet comprehensive, analysis of all of the safety information provided in the PSUR, including new information provided under the section entitled “Other Information.” In addition, the section would include an assessment by applicants of the significance of the data collected during the reporting period, as well as from the perspective of cumulative experience. Applicants would highlight any new information on:

- Serious, unlisted SADRs;
 - Increased reporting frequencies of listed SADRs, including comments on whether it is believed that the data reflect a meaningful change in SADR occurrence;
 - A change in characteristics of listed SADRs (*e.g.*, severity, outcome, target population); and
 - Nonserious, unlisted SADRs.
- As part of the overall safety evaluation, applicants would also explicitly address any new safety issue including but not limited to the following:
- Drug interactions;
 - Experience with overdose, whether deliberate or accidental, and its treatment;
 - Drug abuse or intentional misuse;
 - Positive or negative experiences during pregnancy or lactation;
 - Effects with long-term treatment; and
 - Experience in special patient groups (*e.g.*, pediatric population evaluated, if possible, by age group; geriatric; organ impaired).

Applicants would note a lack of significant new information for any of these categories.

III.E.2.j. *Conclusion.* This section of the PSUR would indicate new safety information that is not in accord with previous cumulative experience and with the CCSI in use at the beginning of the reporting period (*e.g.*, new evidence that strengthens a possible causal relationship between the drug or biological product and an SADR, such as positive rechallenge, an epidemiological association, or new laboratory studies). This section of the PSUR would also specify and justify any action recommended or initiated, including changes in the CCSI.

III.E.2.k. *Appendices.* This section of the PSUR would include the following information as appendices:

III.E.2.k.i. *Company core data sheet.* A copy of the company core data sheet covered by the PSUR (*i.e.*, in effect at the beginning of the period covered by the PSUR) would be provided. The company core data sheet would be numbered and dated and include the date of last revision. In addition, a copy of the company core data sheet for the next reporting period would be provided.

III.E.2.k.ii. *U.S. labeling.* A copy of the current approved U.S. labeling would be provided. Any safety information that is included in the CCSI but not in the U.S. labeling would be identified and an explanation for the discrepancy provided. Any safety-related changes or proposed changes to the U.S. labeling made during the reporting period would be described, including the supplement numbers and dates of submission for the supplements. Any suggested change or changes in the U.S. labeling that should be considered based on the safety analysis in the PSUR would also be described. (If appropriate, a supplemental application would be filed with FDA concerning those changes as prescribed under §§ 314.70 or 601.12.)

III.E.2.k.iii. *Spontaneous reports submitted to the applicant by an individual other than a health care professional.* This appendix would contain summary tabulations (*e.g.*, serious unlisted SADR, serious listed SADR, nonserious unlisted SADR, nonserious listed SADR) for all spontaneously reported serious SADR, whether domestic or foreign, and all spontaneously reported nonserious SADR occurring in the United States, obtained or otherwise received during the reporting period by the applicant from an individual other than a health care professional (*e.g.*, SADR reports from consumers). These summary tabulations would consist of lists by body system or by standard organ system classification scheme (*e.g.*, cardiovascular, central nervous system, endocrine, renal) of all SADR terms and counts of occurrences. For those SADR that are determined to be both serious and unlisted, cumulative data (*i.e.*, all cases reported to date by individuals other than a health care professional) would also be provided. The impact of these spontaneous reports on the overall safety evaluation would be discussed briefly. FDA may require applicants to submit to the agency, when appropriate, SADR reports (*e.g.*, FDA Form 3500As), within 5 calendar days after receipt of the request, for any or all of the SADR contained within this appendix (*see* section III.H of this document).

III.E.2.k.iv. *SADRs with unknown outcome.* This appendix would contain summary tabulations for unlisted and listed SADR with unknown outcome from all spontaneous sources (*i.e.*, health care professionals and other individuals), obtained or otherwise received by the applicant during the reporting period. These summary tabulations would consist of lists by body system or by standard organ system classification scheme of all SADR terms and counts of occurrences. The impact of these spontaneous reports on the overall safety evaluation would be discussed briefly. FDA may require applicants to submit to the agency, when appropriate, individual case safety reports (*e.g.*, FDA Form 3500As), within 5 calendar days after receipt of the request, for any or all of the listed SADR with unknown outcome contained within this appendix (*see* section III.H of this document).

III.E.2.k.v. *Class action lawsuits.* This appendix would contain summary tabulations (*e.g.*, serious unlisted SADR, serious listed SADR, nonserious unlisted SADR, nonserious listed SADR) for all SADR obtained or otherwise received during the reporting period by the applicant from class action lawsuits. These summary tabulations would consist of lists by body system or by standard organ system classification scheme of all SADR terms and counts of occurrences. For SADR that are both serious and unlisted, cumulative data would also be provided. The impact of these reports on the overall safety evaluation would be discussed briefly. FDA may require applicants to submit to the agency, when appropriate, individual case safety reports (*e.g.*, FDA Form 3500As), within 5 calendar days after receipt of the request, for any or all of the SADR contained within this appendix (*see* section III.H of this document).

III.E.2.k.vi. *Lack of efficacy reports.* This appendix would contain an assessment of whether it is believed that the frequency of lack of efficacy reports, obtained or otherwise received during the reporting period, is greater than would be predicted by the premarketing clinical trials for the drug or biological product. This assessment would be provided whether a serious SADR, nonserious SADR, or no SADR results from a lack of efficacy of the product.

III.E.2.k.vii. *Information on resistance to antimicrobial drug products.* This appendix would contain information, received or otherwise obtained by the applicant, on resistance to antimicrobial drug products intended to treat infectious diseases. Information would include:

- Changes in U.S. microbial in vitro susceptibility,
- The relationship of changes in U.S. microbial in vitro susceptibility and clinical outcomes,
- Therapeutic failure that may possibly be due to resistance to the antimicrobial drug product, and
- Whether the U.S. labeling should be revised because of the information on antimicrobial resistance learned during the period covered by the report.

III.E.2.k.viii. *Medication errors.* This appendix would contain summary tabulations for all domestic reports of medication errors submitted during the reporting period as an expedited report. For actual medication errors, summary tabulations would be provided for serious SADR, nonserious SADR, and no SADR. For serious SADR, cumulative data (*i.e.*, all cases reported to date) would also be provided. For potential medication errors, the number of reports for specific errors would be provided. If an SADR occurs, the summary tabulations would consist of lists by body system or by standard organ system classification scheme of all SADR terms and counts of occurrences. The impact of these reports on the overall safety evaluation would be discussed briefly.

III.E.2.k.ix. *U.S. patient exposure.* This appendix would contain, for the reporting period, an estimate of the U.S. patient exposure to the drug product(s) or biological product(s) covered by the PSUR (*i.e.*, number of patients, average or median dose received, and average or median length of treatment). The method used to estimate patient exposure would always be described. If the patient exposure is impossible to estimate or is meaningless, an explanation of and justification for such conclusions would be provided. If patient exposure is impossible to estimate, other measures of exposure, such as patient-days, number of prescriptions, or number of dosage units, may be used. If these or other more precise measures are not available and an adequate explanation for the lack of such information is provided, bulk sales may be used.

III.E.2.k.x. *Location of safety records.* This appendix would contain a list of the current address(es) where all safety reports and other safety-related records for the drug product or licensed biological product are maintained. The list of addresses would provide rapid access to safety-related records for FDA inspections and for requests by FDA for additional information concerning safety issues.

III.E.2.k.xi. *Contact person.* The name and telephone number of the licensed

physician or licensed physicians responsible for the content and medical interpretation of the data and information contained within the PSUR would be provided. The fax number and e-mail address of the licensed physician would also be included, if available. This proposal would provide the agency with someone to contact with any questions that may arise during review of a PSUR. FDA is proposing that the contact persons be licensed physicians because of their crucial knowledge of the medical significance of the information provided in a PSUR.

The PSUR excluding appendices, as proposed in this rule, would represent a harmonized core document for worldwide postmarketing periodic safety reporting for marketed drugs and licensed biological products.

III.E.3. Interim Periodic Safety Reports (IPSRs)

Proposed §§ 314.80(c)(3)(iii) and 600.80(c)(3)(iii) would amend FDA's postmarketing periodic safety reporting regulations by adding another new type of postmarketing periodic safety report. FDA is proposing that this new report be identified as an "interim periodic safety report (IPSR)." An IPSR would contain the same information as a PSUR, except that the following information would not be provided:

- Summary tabulations for individual case safety reports, obtained or otherwise received during the reporting period and brief discussion of the data concerning these reports (*see* section III.E.2.f.ii of this document),
- Any important new information received after the data lock point (*e.g.*, significant new cases) (*see* section III.E.2.h of this document),
- Summary tabulations for spontaneous reports of SADR submitted to the applicant by an individual other than a health care professional (*see* section III.E.2.k.iii of this document),
- Summary tabulations for spontaneous reports of SADR with unknown outcome submitted to the applicant by health care professionals and other individuals (*see* section III.E.2.k.iv of this document),
- Summary tabulations for reports of SADR from class action lawsuits (*see* section III.E.2.k.v of this document),
- Summary tabulations of domestic reports of medication errors (*see* section III.E.2.k.viii of this document).

The IPSR would provide the agency with an overview of the safety profile of a drug product containing a drug substance or biological product without requiring summary information on individual case safety reports.

III.E.4. Semiannual Submission of Individual Case Safety Reports

Currently, postmarketing periodic safety reporting regulations (§§ 314.80(c)(2)(ii)(b) and 600.80(c)(2)(ii)(B)) require applicants to submit to FDA in periodic adverse drug experience reports an FDA Form 3500A (VAERS form for vaccines) for each spontaneously reported adverse drug experience occurring in the United States that has not been submitted to the agency as an expedited report (*i.e.*, serious, expected adverse drug experiences and all nonserious adverse drug experiences, whether unexpected or expected). FDA is proposing to remove this requirement (*see* section III.E.1.b of this document). Instead, under proposed §§ 314.80(c)(3)(v) and 600.80(c)(3)(v), the agency would require applicants to submit semiannually a separate report to FDA consisting of a compilation of FDA Form 3500As (VAERS forms for vaccines, CIOMS I forms, if desired, for foreign SADR) for certain spontaneously reported individual case safety reports as described in the following explanation. This report would be identified as "Individual Case Safety Reports—Semiannual Submission."

The semiannual submission from applicants that submit TPSRs for a drug or licensed biological product would include an individual case safety report for each serious, expected SADR, whether domestic or foreign, and each nonserious, unexpected SADR occurring in the United States that is submitted to the applicant during the reporting period from all spontaneous sources (*i.e.*, health care professionals and other individuals). The semiannual submission for vaccines would also include an individual case safety report for each nonserious, expected SADR and each expected SADR with unknown outcome occurring in the United States that is submitted to the applicant during the reporting period from all spontaneous sources. For drugs and licensed biological products that are not vaccines, nonserious, expected SADR and expected SADR with an unknown outcome would not be submitted as individual case safety reports in a semiannual submission. Instead, they would be reported as part of a summary tabulation in a TPSR (*see* section III.E.1.e of this document).

The semiannual submission from applicants that submit PSURs for a drug product containing a drug substance or licensed biological product would include an individual case safety report for each serious, listed SADR, whether

domestic or foreign, and each nonserious, unlisted SADR occurring in the United States that is submitted to the applicant during the reporting period from all spontaneous sources. The semiannual submission for vaccines would also include an individual case safety report for each nonserious, listed SADR and each listed SADR with unknown outcome occurring in the United States that is submitted to the applicant during the reporting period from all spontaneous sources. For drugs and licensed biological products that are not vaccines, nonserious, listed SADR and listed SADR with an unknown outcome would not be submitted as individual case safety reports in a semiannual submission. Instead, they would be reported as part of a summary tabulation in a PSUR (*see* sections III.E.2.f.ii and III.E.2.k.iii of this document). The semiannual submission should not include individual case safety reports for serious, listed SADR that were previously submitted to FDA as a serious, unexpected SADR in an expedited report (*i.e.*, the agency does not want to receive duplicative reports for the same SADR).

FDA needs to continue to receive information on serious, expected/listed SADR and nonserious SADR, whether unexpected/unlisted or expected/listed, to monitor the safety profile of marketed products to determine if studies need to be undertaken to evaluate a particular issue and/or to take appropriate regulatory action (*e.g.*, labeling change, distribution of Dear Healthcare Professional letter, restriction on distribution of product, withdrawal of product from the market). Reports of serious, expected/listed SADR are used to monitor changes in the frequency of occurrence or severity of a serious, expected/listed SADR (*e.g.*, frequency of serious, expected/listed SADR increases because product interacts with a new approved product that is frequently used concomitantly with the product). The agency's proposal to require submission of spontaneously reported serious, expected/listed SADR from foreign sources would provide FDA with important information that the agency currently does not receive (*e.g.*, reports from foreign countries in which the product is approved for more indications than in the United States or the product results in exposure to certain populations that are limited in the United States).

Reports of nonserious, unexpected/unlisted SADR are used to identify new nonserious SADR that are associated with the use of a product (*e.g.*, sedation, sexual dysfunction, gastrointestinal distress). This information is valuable

for individuals taking the product because, if one of these SADR occurs, the individual might suspect that it was due to the product and not due to the onset of a new disorder. These reports may also serve to signal the emergence of a serious, unexpected/unlisted SADR (e.g., an aggregate of reports of decreased white blood cell counts may be an early indicator of a serious condition such as bone marrow suppressive disorder).

The reports (i.e., individual case safety reports for vaccines or summary tabulations for drugs and licensed biological products that are not vaccines) of nonserious, expected/listed SADRs are used to monitor changes in the frequency of occurrence or severity of a nonserious, expected/listed SADR. Such information could indicate a potential safety problem that is worthy of further investigation (e.g., a new drug or food interaction not previously associated with use of the product).

Proposed changes to FDA's current reporting requirements for these types of SADRs include: (1) Different reporting frequencies for the SADRs, (2) receipt of spontaneously reported serious, expected/listed SADRs from foreign sources and (3) submission of nonserious, expected/listed SADRs in a summary tabulation instead of as individual case safety reports for drugs and licensed biological products that are not vaccines. With regard to different reporting frequencies, some SADRs would be reported less frequently (e.g., semiannually rather than every 3 months) and others would be reported more frequently (e.g., semiannually rather than annually). FDA seeks comment on these proposed changes.

The current approved U.S. labeling would be used as the reference document to determine whether an SADR is unexpected or expected, and the CCSI would be used to determine whether an SADR is unlisted or listed.

As described previously, a minimum data set would be required for all individual case safety reports of an SADR (see section III.C.5 of this document). In addition, a full data set would be required for reports of serious, expected SADRs and serious, listed SADRs. If a full data set is not available for these SADR reports, the information required under proposed §§ 314.80(c)(1)(iv) and 600.80(c)(1)(iv) would be provided. For nonserious SADRs with a minimum data set, the proposal would require that all safety information received or otherwise obtained be submitted. The proposal would not require that information in addition to the minimum data set be acquired. Thus, followup would not be

required for nonserious SADRs that contain a minimum data set.

Followup information on SADRs submitted in an individual case safety report—semiannual submission may be submitted in the next individual case safety report—semiannual submission, unless such information changes the classification of the SADR to a serious, unexpected SADR. In these cases, the followup information would be submitted to FDA as an expedited 15-day followup report (see section III.D.6 of this document).

Applicants should not submit any reports of lack of efficacy in an individual case safety report—semiannual submission. As noted previously, applicants would be required to submit to FDA in an expedited manner information regarding certain lack of efficacy reports for the product (i.e., expedited reports of information sufficient to consider product administration changes) and also to provide in postmarketing periodic safety reports an assessment of all lack of efficacy reports for the product as compared to premarketing clinical trials for the product (see section III.C.7 of this document).

Applicants should not submit SADRs from class action lawsuits to FDA in an individual case safety report—semiannual submission. The agency believes, as noted previously, that SADRs from class action lawsuits would be submitted to FDA from other sources (e.g., spontaneous report) prior to initiation of the class action lawsuit (see section III.D.11 of this document). Summary tabulations of these SADRs would be required to be included in postmarketing periodic safety reports (see sections III.E.1.e and III.E.2.k.v of this document).

Applicants should not submit reports of medication errors in an individual case safety report—semiannual submission. These reports would be submitted, as previously noted, as an expedited report (see section III.D.5 of this document).

III.E.5. Reporting Requirements

III.E.5.a. *Reporting intervals.* Current regulations (§§ 314.80(c)(2)(i) and 600.80(c)(2)(i)) require the submission of postmarketing periodic safety reports at quarterly intervals for 3 years from the date of approval of the application in the United States and then annually thereafter. Quarterly safety reports must be submitted within 30 days of the close of the quarter (the first quarter beginning on the date of U.S. approval of the application); annual safety reports must be submitted within 60 days of the anniversary date of U.S. approval of the

application. FDA is proposing revisions to these reporting requirements. The proposals are consistent with the recommendations of ICH (62 FR 27470 at 27472): "Therefore, it is recommended that the preparation of PSUR's for all regulatory authorities should be based on data sets of 6 months or multiples thereof."

Products approved before January 1, 1998. Proposed §§ 314.80(c)(3)(i) and 600.80(c)(3)(i) would require applicants holding an NDA, ANDA, or BLA that was approved for initial marketing of a drug product containing a drug substance or licensed biological product before January 1, 1998, to submit either a TPSR or a PSUR every 5 years after U.S. approval of the application. The proposed rule would also require these applicants to submit a TPSR or an IPSR 7.5 years and 12.5 years after U.S. approval of the application. Under proposed §§ 314.80(c)(3)(iii) and 600.80(c)(3)(iii), the reporting period for an IPSR would cover the period between the last PSUR or TPSR and the data lock point for the IPSR (e.g., between years 5 and 7.5 for an IPSR with a data lock point at 7.5 years after U.S. approval of the application).

Products approved on or after January 1, 1998. Under proposed §§ 314.80(c)(3)(ii) and 600.80(c)(3)(ii), applicants holding an NDA, ANDA, or BLA that was approved for initial marketing of a drug product containing a drug substance or licensed biological product on or after January 1, 1998, would be required to submit a PSUR to FDA with the following schedule:

- Semiannually (i.e., every 6 months) for 2 years after U.S. approval of the application,
- Annually for the next 3 years, and then
- Every 5 years thereafter.

The proposed rule would also require applicants to submit an IPSR 7.5 years and 12.5 years after U.S. approval of the application.

Products with approved pediatric use supplements. Proposed §§ 314.80(c)(3)(iv) and 600.80(c)(3)(iv) would require applicants holding an approved pediatric use supplement to an approved application (i.e., a supplement for use of the human drug or biological product in the pediatric population) to submit a PSUR to FDA with the following schedule:

- Semiannually (i.e., every 6 months) for 2 years after U.S. approval of the supplement,
- Annually for the next 3 years, and
- Then every 5 years thereafter.

The proposed rule would also require these applicants to submit an IPSR 7.5

years and 12.5 years after U.S. approval of the supplement. These applicants would be required to submit PSURs and IPSRs to FDA even if the pediatric use supplement or original application was approved prior to January 1, 1998. FDA is proposing this action to harmonize acquisition of new safety information regarding pediatric populations for timely review by the agency.

All products. Under proposed §§ 314.80(c)(3)(v) and 600.80(c)(3)(v), applicants holding an NDA, ANDA, or BLA would be required to submit an individual case safety reports—semiannual submission to FDA every 6 months after U.S. approval of an application. The 6-month interval for these reports would coincide with the reporting interval (6-month or multiples of 6 months) for TPSRs, PSURs or IPSRs.

Alternative reporting frequency. Proposed §§ 314.80(c) and 600.80(c) would provide that, when appropriate, FDA may require in writing that applicants submit postmarketing periodic safety reports at time intervals other than prescribed by the regulations (see section III.C.4 of this document). Usually such variations would occur if new safety concerns arose requiring more timely reporting (e.g., approval of a new indication or dosage form for the product, approval for use of the product in a new population, new safety issues in individual case safety reports submitted to FDA for the product). When anticipated, FDA would state the revised reporting interval in the approval letter for the new indication, new population, or new dosage form. In other cases, such revisions to the reporting interval would be conveyed to applicants in a written letter from the director of the responsible review division in FDA with an explanation of why such a new reporting time interval is required.

III.E.5.b. *Submission date.* Proposed §§ 314.80(c)(3) and 600.80(c)(3) would require that the data lock point for postmarketing periodic safety reports be the month and day of the international birth date of the drug product (proposed §§ 314.80(c)(3)(i) and 314.80(c)(3)(v)), drug substance (proposed §§ 314.80(c)(3)(ii), 314.80(c)(3)(iii), and 314.80(c)(3)(iv)) or licensed biological product (proposed §§ 600.80(c)(3)(i) through 600.80(c)(3)(v)) or any other month and day agreed on by the applicant and FDA. For example, applicants that are submitting PSURs on an every 5 year basis may, in agreement with FDA, change the data lock point to facilitate international reporting so long as there is never a time period of greater than 5 years in which FDA has not

received a PSUR. Or, the applicant and FDA may agree to change the data lock point to the month and day of U.S. approval of the application if this date would result in better use of the applicant's resources.

Proposed §§ 314.80(c)(3) and 600.80(c)(3) would require that all postmarketing periodic safety reports be submitted to FDA within 60 calendar days after the data lock point for the report. As noted previously, the data lock point (i.e., month and day) for postmarketing periodic safety reports would be based on the month and day of the international birth date for the product and the frequency for submission of these reports would be based on the product's date (i.e., year) of U.S. approval (see section III.A.10 of this document).

III.E.5.c. *Cover letter.* Proposed §§ 314.80(c)(3) and 600.80(c)(3) would require that applicants include a cover letter with all postmarketing periodic safety reports (i.e., TPSRs, PSURs, IPSRs, individual case safety reports—semiannual submissions). This cover letter would contain a list of the NDA and/or ANDA numbers for the human drug products or BLA numbers for the human biological products covered by the report.

III.E.5.d. *International birth date for combination products.* Proposed §§ 314.80(c)(3) and 600.80(c)(3) would also state that the international birth date for combination products would be the international birth date of the human drug product containing the drug substance or licensed biological product that was most recently approved for marketing. For combination products that are also marketed individually, applicants may submit either a separate PSUR for the combination product or include information for the combination product as a separate presentation in the PSUR for one of the individual components.

III.F. Reporting Format

Current postmarketing safety reporting regulations at §§ 310.305(d)(1), 314.80(f)(1), and 600.80(f)(1) require persons subject to these requirements to submit an FDA Form 3500A (VAERS form for vaccines) for each report of an adverse drug experience. Foreign SADR, including those associated with the use of vaccines, may be submitted on an FDA Form 3500A or, if preferred, on a CIOMS I form.

III.F.1. Forms Versus Narrative Format

Proposed §§ 310.305(d)(1), 314.80(c)(4)(i), and 600.80(c)(4)(i) would amend the current postmarketing safety reporting format regulations by

reorganizing these regulations and by adding new information. Proposed §§ 310.305(d)(1)(i) would prescribe, except as provided in the regulations, that:

* * * the manufacturer must complete an FDA Form 3500A for each individual case safety report of an SADR. Reports based on information about individual cases or case series in the scientific literature must be submitted on an FDA Form 3500A(s).

Proposed §§ 314.80(c)(4)(i)(A) and 600.80(c)(4)(i)(A) would prescribe the same requirements for submission of postmarketing individual case safety reports by applicants. Proposed § 600.80(c)(4)(i)(A) would also describe requirements for use of the VAERS form for vaccines. Proposed §§ 310.305(d)(1)(ii), 314.80(c)(4)(i)(B) and 600.80(c)(4)(i)(B) would prescribe that:

Foreign SADR may be submitted either on an FDA Form 3500A or, if preferred, on a CIOMS I form (foreign SARs for vaccines, may be submitted either on a VAERS form, or, if preferred, on a CIOMS I form, for proposed § 600.80(c)(4)(i)(B)).

Proposed §§ 310.305(d)(1)(iii), 314.80(c)(4)(i)(C) and 600.80(c)(4)(i)(C) would prescribe that:

Each domestic report of an actual or potential medication error must be submitted on an FDA Form 3500A (or, for vaccines, on a VAERS form for proposed § 600.80(c)(4)(i)(C)).

Proposed §§ 310.305(d)(1)(iv), 314.80(c)(4)(i)(D) and 600.80(c)(4)(i)(D) would prescribe that:

Reports of overall findings or data in the aggregate from published and unpublished in vitro, animal, epidemiological, or clinical studies must be submitted in a narrative format.

These proposed amendments would clarify the reporting format that would be required for individual case safety reports or other safety information (i.e., overall findings or data in the aggregate). Reports of actual and potential medication errors would be required to be submitted on an FDA Form 3500A (or VAERS form, as appropriate) because these reports describe an individual case even if an SADR does not occur or a patient is not identifiable. Reports of overall findings or data in the aggregate would be submitted in a narrative format rather than on FDA Form 3500A because FDA Form 3500A has been designed for reporting of data from an individual case.

III.F.2. Medical Dictionary for Regulatory Activities (MedDRA)

ICH has developed an international medical terminology, MedDRA (the

medical dictionary for regulatory activities), to support the computerization and transmission of information related to many aspects of the regulation of medical products (ICH M1). Use of a single medical terminology internationally would facilitate global communication of safety information for human drug and biological products (see section II.B.1 of this document).

Proposed §§ 310.305(d)(2), 314.80(c)(4)(ii), and 600.80(c)(4)(ii) would require that each SADR in an individual case safety report be coded on the FDA Form 3500A, CIOMS I Form, or VAERS Form using the appropriate "preferred term" in the latest version of MedDRA in use at the time the manufacturer or applicant becomes aware of the individual case safety report. FDA is proposing to require use of MedDRA to be consistent with ICH M1.

Proposed §§ 310.305(d)(2), 314.80(c)(4)(ii), and 600.80(c)(4)(ii) would also require that each individual case safety report of a medication error be coded both as a medication error and, if applicable, with the preferred term for any SADRs associated with the medication error. The proposal clarifies how actual and potential medication errors would be coded.

MedDRA must be licensed for a fee from an international MSSO. TRW was selected as the MSSO by ICH and the International Federation of Pharmaceutical Manufacturers Associations (IFPMA) through a contract process that involved bids from companies globally. FDA was involved in this process. The costs that would be imposed on industry to license MedDRA was a consideration in the selection of the MSSO.

Companies may license the latest version of MedDRA 5.1 by contacting TRW in Reston, VA, toll free number 877-258-8280 (703-345-7799 in Washington, DC area), FAX 703-345-7755, e-mail subscrib@meddramsso.com, Internet at www.meddramsso.com. Updated versions of MedDRA will be provided to subscribers as part of the annual licensing fee.

MedDRA is a hierarchical system composed of various levels of terminology (*i.e.*, system organ class, high level group term, high level term, preferred term, lower level term). The agency is proposing to require use of the preferred term for reporting to FDA because each preferred term represents a unique medical concept accepted internationally, which will aid in the transmission and translation of reports from various parts of the world. The

preferred term provides medically validated representations of colloquial terms, which will result in fewer misrepresentations and misunderstandings of colloquial reports from various parts of the world. The preferred term also provides medically validated representations of noncurrent terms in other previously widely used coding terminologies such as COSTART and WHOART.

FDA believes that use of MedDRA, a standardized medical terminology, will be welcomed by most of industry. However, for some manufacturers and applicants, use of MedDRA may result in a significant economic hardship. Applicants may request, under §§ 314.90 or 600.90, that FDA waive the requirement that each SADR in an individual case safety report be coded using MedDRA. If FDA finds that this requirement is economically burdensome for a small company, the agency intends to grant the company a waiver. A large company may also be granted a waiver if, for instance, it only markets a single product that generates a few safety reports a year. FDA intends to grant all reasonable waiver requests. This determination will be made on a case-by-case basis.

III.F.3. Single Form for Each Identifiable Patient

Current postmarketing safety reporting regulations, at §§ 310.305(d)(2), 314.80(f)(2), and 600.80(f)(2), state that each completed FDA Form 3500A, VAERS Form, or CIOMS I Form should refer only to an individual patient or a single attached publication. Under proposed §§ 310.305(d)(3), 314.80(c)(4)(iii), and 600.80(c)(4)(iii) FDA would remove the phrase "or a single attached publication" and replace the word "patient" with the word "case." This proposed amendment would clarify that an FDA Form 3500A should be completed for each identifiable patient described in a scientific article (*e.g.*, six FDA Form 3500As should be completed for an article describing six patients experiencing a particular SADR). This would also clarify that an FDA Form 3500A would be used to describe a potential medication error that does not involve a patient.

III.F.4. Contact Person

Proposed §§ 310.305(d)(4), 314.80(c)(4)(iv), and 600.80(c)(4)(iv) would state:

Each completed FDA Form 3500A (VAERS Form for proposed § 600.80(c)(4)(iv)) or CIOMS I Form must include the name and telephone number (and fax number and e-mail address, if available) for the licensed

physician responsible for the content and medical interpretation of the data contained within the form (*i.e.*, contact person for the company).

This information should be provided on FDA Form 3500A under the "contact office" box (box G1 on FDA Form 3500A). This proposed revision would provide FDA with a person to contact with any questions that may arise during review of an individual case safety report. The agency believes that the potential medical significance of these safety reports warrants oversight by a licensed physician.

III.F.5. Computer-Generated Facsimile of FDA Form 3500A or Vaccine Adverse Event Reporting System (VAERS) Form

Current §§ 310.305(d)(3), 314.80(f)(3), and 600.80(f)(3) state that instead of using an FDA Form 3500A, manufacturers and applicants may use a computer-generated FDA Form 3500A or other alternative format provided that the content of the alternative format is equivalent in all elements to those specified in FDA Form 3500A and the format is agreed to in advance by MedWatch: The FDA Medical Products Reporting Program. Alternative formats to the Center for Biologics Evaluation and Research's VAERS Form must be approved by the Division of Biostatistics and Epidemiology (§ 600.80(f)(3)).

Proposed §§ 310.305(d)(5), 314.80(c)(4)(v), and 600.80(c)(4)(v) would remove the use of alternative formats to FDA Form 3500A and the requirement to obtain preapproval by MedWatch for use of a computer-generated FDA Form 3500A. Proposed § 600.80(c)(4)(v) would also remove the use of alternative formats to the VAERS Form and the requirement to obtain preapproval by the Division of Biostatistics and Epidemiology for use of a computer-generated VAERS Form. Instead, the proposed rule would permit manufacturers and applicants to use a computer-generated facsimile of FDA Form 3500A (or VAERS Form for vaccines) provided that it is readable, includes appropriate identifying information and contains all the elements (*i.e.*, format, sections, blocks, titles, descriptors within blocks, text for disclaimer) of FDA Form 3500A (or the VAERS Form for vaccines) in the identical enumerated sequence of the form. The proposed rule would also permit use of a one-page FDA Form 3500A for individual case safety reports in which no suspect medical device is involved. For one-page reports, the box, Section D. *Suspect Medical Device*, on the front page of FDA Form 3500A would be replaced with the box, Section

G. *All Manufacturers*, located on the back page of the form.

To be considered “readable” by FDA, the computer-generated facsimile should be formatted as follows.

- The facsimile should have at least a ¼ inch margin around the entire form so that information is not lost during scanning, copying, or faxing of the document. The left-hand margin may be increased up to ½ inch to permit binding (*e.g.*, hole-punching) of the form; all other margins should continue to be at least ¼ inch.

- The data and text that is contained within the boxes should be in a font size of not less than 10 point.

- The data and text that is contained within the boxes should be in a font type that is easy to read (*e.g.*, CG Times, Arial) and not condensed, because the form may be copied or faxed multiple times. For visual contrast, the font type that is used for the data and text should, if possible, be different than the font type used to create the FDA Form 3500A or VAERS Form.

- All data and text should be contained within each of the boxes, *e.g.*, an “x” mark should be centered within the box, and narratives should include margins so that letters of the text are not obscured or made ambiguous by lines defining a box.

FDA would consider “appropriate identifying information” to include:

- The name of the company centered on the top of the front page;

- In the lower left hand corner of the front page, the phrase “3500A Facsimile” instead of the phrase “FDA Form 3500A (date of form [*e.g.*, 6/93])” or the phrase “VAERS facsimile” instead of the phrase “Form VAERS-1”;

- The phrase “continued” at the end of each field that has additional information continued onto another page; and

- On each continuation page containing additional information, the page number identified as Page ___ of ___, the manufacturer report number in the upper right corner, the name of the company in the upper right corner, and the section and block number (*e.g.*, Block B5) for each narrative entry.

This information is included in the draft guidance of 2001. Any revisions to these parameters would be included in updated versions of the guidance.

III.F.6. Other Revisions

The proposed rule would remove §§ 310.305(d)(4), 314.80(f)(4), and 600.80(f)(4). These paragraphs provide manufacturers and applicants with addresses for obtaining copies of FDA Form 3500A and instructions for

completing the form. FDA is proposing to remove these paragraphs because the addresses are provided in the draft guidance of 2001.

The proposed rule would also remove §§ 314.80(e)(2) and 600.80(e)(2). These paragraphs state that persons subject to the postmarketing safety reporting regulations must separate and clearly mark reports of adverse drug experiences that occur during a postmarketing study as being distinct from those experiences that are being reported spontaneously to the person. FDA is proposing this revision because this information would be submitted to the agency in a completed FDA Form 3500A under the box for “Report source” (box G3 on FDA Form 3500A).

III.G. Patient Privacy

Current postmarketing safety reporting regulations at §§ 310.305(e), 314.80(h), and 600.80(h) state that persons subject to these requirements should not include the names and addresses of individual patients in reports and, instead, should assign a unique code number to each report, preferably not more than eight characters in length. Proposed §§ 310.305(e), 314.80(e), and 600.80(e) would amend these regulations by removing the word “number.” This proposed amendment would clarify that the code selected to identify a patient need not be limited to numbers (*i.e.*, it could contain letters or a mixture of letters and numbers).

III.H. Recordkeeping

Current postmarketing safety recordkeeping regulations at § 314.80(i) require applicants to maintain for a period of 10 years records of all adverse drug experiences known to the applicant, including raw data and any correspondence relating to the adverse drug experiences. Under proposed § 314.80(f), FDA would amend these regulations to read:

The applicant must maintain for a period of 10 years records of all safety information pertaining to its drug product, received or otherwise obtained, including raw data, any correspondence relating to the safety information, and any reports of SADR or medication errors not submitted to FDA or only provided to FDA in a summary tabulation. The applicant must also retain for a period of 10 years any records required to be maintained under this section. When appropriate, FDA may require an applicant to submit any or all of these records to the agency within 5 calendar days after receipt of the request.

This proposed revision clarifies the type of safety records that applicants would be required to maintain for its drug products. With regard to a request for

these records by FDA, the agency would usually make such a request either in response to a suspected safety problem associated with the use of a drug or to determine a company’s compliance with the postmarketing safety reporting requirements. Under proposed § 600.80(f), the agency is proposing similar revisions to the recordkeeping requirements for licensed biological products at § 600.80(i). FDA is proposing these revisions to clarify what types of postmarketing safety reporting records must be maintained.

Current § 310.305(f)(1) requires manufacturers, packers, and distributors to maintain for a period of 10 years records of all adverse drug experiences required under § 310.305, including raw data, any correspondence relating to adverse drug experiences, and the records required to be maintained under § 310.305. FDA is proposing to amend these regulations to be consistent with the postmarketing safety recordkeeping regulations at proposed §§ 314.80(f) and 600.80(f).

III.I. Abbreviated New Drug Application (ANDA) Products

Current § 314.98 requires applicants holding an approved ANDA to comply with the postmarketing safety reporting requirements under § 314.80. The proposed amendments to § 314.80 in this rule would apply to applicants holding an approved ANDA. For postmarketing periodic safety reporting purposes, proposed § 314.98(a) would require applicants holding an approved ANDA to determine the data lock point (*i.e.*, month and day of the international birth date or any other month and day agreed by the applicant and FDA) for their periodic safety reports based on the data lock point of postmarketing periodic safety reports for other drug products containing the same drug substance (*i.e.*, innovator NDA product that is the same drug product as the ANDA product or other ANDA products with the same drug substance if the innovator NDA product is no longer on the market). Thus, postmarketing periodic safety reports from different applicants for drug products containing the same drug substance would be submitted to FDA at the same time. Applicants holding an approved ANDA may contact FDA, if necessary, for assistance in determining the data lock point for postmarketing periodic safety reports.

Proposed § 314.98(a) would also state that applicants holding an approved ANDA would determine the type of postmarketing periodic safety report that would be required to be submitted to FDA (*i.e.*, TPSR, PSUR, or IPSR)

based on the U.S. approval date of the application for the innovator NDA product. If the innovator NDA product (even if no longer on the market) was approved for marketing before January 1, 1998, applicants holding an approved ANDA for the drug product would have the option of submitting either TPSRs or PSURs and IPSRs to FDA. In these cases, an applicant holding an approved ANDA may choose to submit TPSRs to FDA even though other applicants with approved applications for the drug product submit PSURs and IPSRs. If the innovator NDA product was approved for marketing on or after January 1, 1998, applicants holding an approved ANDA for the drug product would be required to submit PSURs and IPSRs to FDA.

Proposed § 314.98(a) also provides that applicants holding an approved ANDA would determine the frequency of submission for postmarketing periodic safety reports based on the U.S. approval date of the application for the innovator NDA product. For example, if the innovator NDA product is the first human drug product containing the drug substance approved in the world and the application is approved for marketing on June 15, 1980, applicants of the innovator NDA product and all ANDA products with the same drug product would either submit a TPSR or PSUR to FDA every 5 years based on the U.S. approval date of the innovator NDA product (e.g., data lock point of June 15, 2000, June 15, 2005). In this case, an applicant with an ANDA approved on January 1, 1999, would have a data lock point of June 15, 2000, even though the reporting period for the drug product is less than 5 years; the next reporting period for the drug product would cover a 5-year period (i.e., June 16, 2000 through June 15, 2005). If the first human drug product containing the drug substance was approved for marketing in Europe on February 1, 1980, and the same drug product was approved in the United States on June 15, 1980, applicants of this drug product and all ANDA products with the same drug product would either submit a TPSR or PSUR to FDA with a 5-year frequency based on the U.S. approval date and with a date lock point based on the European approval date (e.g., February 1, 2000, February 1, 2005).

All applicants holding an approved NDA or ANDA would be required to submit postmarketing individual case safety reports—semiannual submissions to FDA every 6 months (see section III.E.4 in this document). Thus, even though the agency would not be receiving TPSRs, PSURs, and IPSRs for drug products with approved ANDAs

frequently after approval of the product, FDA would receive in a timely manner individual case safety reports for the product (i.e., expedited reports, individual case safety reports—semiannual submission) that would identify any potential problems associated with the formulation of the product. It is not necessary to receive TPSRs, PSURs, or IPSRs for drugs with approved ANDAs more frequently because the innovator NDA product has been evaluated for a number of years.

III.J. Postmarketing Approved New Drug Application (NDA) and Biologics License Application (BLA) Annual Reports

Current § 314.81(b)(2) requires applicants of marketed drug products subject to an NDA to submit an annual report to FDA within 60 days of the anniversary date of U.S. approval of the application. This annual report must contain a brief summary of significant new information from the previous year that might affect the safety, effectiveness, or labeling of the drug product and a description of actions the applicant has taken or intends to take as a result of new information, such as submitting a labeling supplement, adding a warning to the labeling, or initiating a new study (§ 314.81(b)(2)(i)). This summary section must also contain, in accordance with the 1998 pediatric final rule, a statement of whether labeling supplements for pediatric use were submitted and whether new studies in the pediatric population to support appropriate labeling for the pediatric population were initiated. The 1998 pediatric final rule also requires that the summary section include, where possible, an estimate of the patient exposure to the drug product, with special reference to the pediatric population (neonates, infants, children, and adolescents), including dosage form. The annual report also must contain a section on nonclinical laboratory studies that includes copies of unpublished reports and summaries of published reports of new toxicological findings in animal studies and in vitro studies (e.g., mutagenicity) conducted by, or otherwise obtained by, the applicant concerning the ingredients in the drug product (§ 314.81(b)(2)(v)). The applicant must submit a copy of a published report if requested by FDA. The annual report also must contain a section on clinical data that includes, among other data, published clinical trials on safety of the drug (or abstracts of them) and reports of clinical experience pertinent to safety (for example, epidemiological studies or

analyses of experience in a monitored series of patients) conducted by or otherwise obtained by the applicant (§ 314.81(b)(2)(vi)). The clinical data section also must contain, in accordance with the 1998 pediatric final rule, an analysis of available safety and efficacy data in the pediatric population, changes proposed in the labeling based on this information, and an assessment of data needed to ensure appropriate labeling for the pediatric population.

Current § 601.28 requires applicants of licensed biological products to submit an annual report to FDA within 60 days of the anniversary date of U.S. approval of the application. This annual report must contain, among other information, a brief summary stating whether labeling supplements for pediatric use were submitted and whether new studies in the pediatric population to support appropriate labeling for the pediatric population were initiated (§ 601.28(a)). This summary section also must contain, where possible, an estimate of the patient exposure to the product, with special reference to the pediatric population (neonates, infants, children, and adolescents), including dosage form. The annual report also must contain a section on clinical data that includes an analysis of available safety and efficacy data in the pediatric population and changes proposed in the labeling based on this information (§ 601.28(b)). This clinical data section also must contain an assessment of data needed to ensure appropriate labeling for the pediatric population.

As noted in section I of this document, FDA received comments on the October 1994 proposal that noted that the proposed amendments to the agency's postmarketing safety reporting requirements would duplicate certain information required in postmarketing approved NDA annual reports. In light of these comments, FDA is proposing to revoke the requirement for safety-related information in postmarketing approved NDA and BLA annual reports to eliminate duplicative reporting.

FDA is proposing to remove the requirement in § 314.81(b)(2)(i) to report safety information or safety-related labeling changes in the summary section of approved NDA annual reports. FDA is also proposing to remove the requirement in §§ 314.81(b)(2)(i) and 601.28(a) to submit an estimate of patient exposure to the drug product with special reference to the pediatric population. FDA is also proposing to remove the requirement in § 314.81(b)(2)(v) to include the section on nonclinical laboratory studies in approved NDA annual reports. FDA is

also proposing to remove the requirement in §§ 314.81(b)(2)(vi) and 601.28(b) to submit safety-related information in the clinical data section of approved NDA and BLA annual reports. FDA is proposing these changes because this safety-related information for a drug or licensed biological product would be provided to the agency in postmarketing safety reports (*i.e.*, expedited reports, TPSRs, PSURs, IPSRs, individual case safety reports—semiannual submissions). For example, proposed §§ 314.80(c)(2)(ii) and 600.80(c)(2)(ii) would require postmarketing expedited reports for certain information that would be sufficient, based on appropriate medical judgment, to consider changes in product administration (*e.g.*, any significant unanticipated safety finding or data in the aggregate from an *in vitro*, animal, epidemiological, or clinical study, whether or not conducted under an IND, that suggests a significant human risk such as reports of mutagenicity, teratogenicity, or carcinogenicity, or reports of a lack of efficacy with a drug or biological product used in treating a life-threatening or serious disease). Under proposed §§ 314.80(c)(3)(ii)(E), 314.80(c)(3)(iii)(E), 600.80(c)(3)(ii)(E), and 600.80(c)(3)(iii)(E), PSURs and IPSRs would contain a section on worldwide patient exposure that includes, when possible, data broken down by gender and age (especially pediatric versus adult). Under proposed §§ 314.80(c)(3)(ii)(G), 314.80(c)(3)(iii)(F), 600.80(c)(3)(ii)(G) and 600.80(c)(3)(iii)(F), PSURs and IPSRs would include a section on safety studies that would contain a discussion of nonclinical, clinical, and epidemiological studies that contain important safety information. This safety studies section would include all applicant-sponsored studies newly analyzed during the reporting period; new studies specifically planned, initiated, or continuing during the reporting period; and published safety studies in the scientific and medical literature.

III.K. Safety Reporting for *In Vivo* Bioavailability and Bioequivalence Studies

FDA's existing *in vivo* bioavailability and bioequivalence study regulations, under § 320.31(a), require submission of an IND, as prescribed under part 312, for certain studies in humans (*i.e.*, studies that involve a new chemical entity, a radioactively labeled drug product, or a cytotoxic drug product). Section 320.31(b) requires an IND for certain studies in humans using a drug

product that contains an already approved, non-new chemical entity (*i.e.*, a single-dose study where either the maximum single or total daily dose exceeds that specified in the approved labeling for the drug product, a multiple-dose study where either the single or total daily dose exceeds that specified in the approved labeling of the drug product, a multiple-dose study on a controlled release product on which no single-dose study has been completed). Section 320.31(d) exempts all other *in vivo* bioavailability and bioequivalence studies in humans from the requirements of part 312 if certain conditions are satisfied (*i.e.*, samples of any test article and reference standard are reserved by the person conducting the study and released to FDA upon request, studies are conducted in compliance with the requirements for institutional review set forth in 21 CFR part 56 and informed consent set forth in 21 CFR part 50).

FDA believes that drug products that are being investigated in human bioavailability and bioequivalence studies that are not subject to an IND are, in general, safe. However, as noted in section II.B.4 of this document, FDA receives some safety information periodically regarding drugs in these studies, thus making the agency uncertain whether it is receiving all necessary safety information regarding the specificity and severity of SADR related to these drugs or any new SADR that may be related to them. FDA has determined that a more comprehensive and orderly system for collecting safety information for these studies is needed. For this purpose, the agency is proposing to require persons conducting human bioavailability and bioequivalence studies that are not subject to an IND to submit expedited safety reports to FDA to alert the agency to potential safety problems quickly. The proposed rule would not require these persons to submit an IND to FDA for the studies.

FDA believes that this new proposed safety reporting requirement will result in submission of minimal reports to the agency (~ 200/year; *see* table 13 for estimate). FDA seeks comment on the reasonableness of this estimate and requests that comments provide information to support any alternative estimates.

The act provides authority to FDA to require safety reports for human bioavailability and bioequivalence studies that are not subject to an IND. Section 505(i) of the act provides broad authority for FDA to issue regulations governing the clinical investigation of new drugs to protect the rights, safety,

and welfare of human subjects and otherwise to protect the public health. In addition, section 701 of the act (21 U.S.C. 371) provides that the agency has authority to issue regulations for the efficient enforcement of the act.

FDA is proposing to amend its regulations at § 320.31(d) to require persons conducting human bioequivalence and bioavailability studies that are not subject to an IND to submit safety reports to FDA as prescribed under § 312.32 for drug products subject to an IND. Under proposed § 312.32(c)(1), a written safety report must be submitted within 15 calendar days to FDA and all participating investigators for any SADR that, based on the opinion of the investigator or sponsor, is both serious and unexpected and for information that, based upon appropriate medical judgment, might materially influence the benefit-risk assessment of an investigational drug, or that would be sufficient to consider changes in either product administration or in the overall conduct of a clinical investigation. Examples of reportable information would include any significant unanticipated safety finding or data in the aggregate from an *in vitro*, animal, epidemiological, or clinical study, whether or not conducted under an IND, that suggests a significant human risk, such as reports of mutagenicity, teratogenicity, or carcinogenicity, or reports of a lack of efficacy with a drug or biological product used in treating a life-threatening or serious disease. In addition, under proposed § 312.32(c)(2), a telephone or facsimile transmission safety report must be submitted within 7 calendar days to FDA for any unexpected fatal or life-threatening SADR.

Proposed § 320.31(d)(3) would require that these safety reports be transmitted to all participating investigators and the appropriate FDA division in the Center for Drug Evaluation and Research. Thus, safety reports for the reference listed drug would be sent to the new drug review division responsible for that drug; safety reports for the investigational drug product would be sent to the Director, Division of Bioequivalence, Office of Generic Drugs. The proposed rule would also require that each written notification bear prominent identification of its contents, *i.e.*, "Bioavailability/Bioequivalence Safety Report." Each report should clearly identify the sponsor of the bioavailability or bioequivalence study and the contract research organization, if applicable. In each written Bioavailability/Bioequivalence Safety Report, the sponsor would be required

to identify all safety reports previously filed for the bioavailability or bioequivalence study concerning a similar SADR and to analyze the SADR in light of previous similar reports, as required under proposed

§ 312.32(c)(1)(i) for IND safety reports.

An unexpected adverse drug experience is currently defined, under § 312.32(a), as:

Any adverse drug experience, the specificity or severity of which is not consistent with the current investigator brochure; or, if an investigator brochure is not required or available, the specificity or severity of which is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended. * * *

For reporting purposes under proposed § 320.31(d), an unexpected SADR would be any SADR, the specificity or severity of which is not consistent with the U.S. labeling for the reference listed drug. FDA is proposing use of the U.S. labeling for the reference listed drug for this purpose because studies that are not subject to an IND are unlikely to have an investigator brochure for use as a reference document.

Under proposed § 312.32(c)(4), a sponsor of a clinical study under an IND for a drug marketed in the United States is only required to submit IND safety reports to FDA (review division that has responsibility for the IND) for SADRs that occur during the clinical study itself, whether from domestic or foreign study sites of the IND. Proposed § 312.32(c)(4) would apply to human bioavailability and bioequivalence studies that are the subject of proposed § 320.31(d). In these cases, the reference listed drug would be the marketed drug and persons conducting human bioequivalence and bioavailability studies that are not subject to an IND would only be required to submit safety reports to FDA from their studies.

III.L. Proposed Implementation Scheme

FDA proposes that any final rule that may be issued regarding the proposal to require that SADRs in individual case safety reports be coded using MedDRA become effective 1 year after its date of publication in the **Federal Register**. FDA proposes that any final rule that may be issued based on all other proposals become effective 180 days after its date of publication in the **Federal Register**.

IV. Environmental Impact

The agency has determined under 21 CFR 25.30(h) that this action is of a type that does not individually or cumulatively have a significant effect on

the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

V. Analysis of Impacts

V.A. Background and Summary

FDA has examined the impacts of the proposed rule under Executive Order 12866, the Regulatory Flexibility Act (5 U.S.C. 601–612), and the Unfunded Mandates Reform Act of 1995 (2 U.S.C. 1501 *et seq.*). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). Under the Regulatory Flexibility Act, if a rule has a significant impact on a substantial number of small entities, an agency must analyze regulatory options that would minimize any significant impact of the rule on small entities. Title II of the Unfunded Mandates Reform Act of 1995 requires that agencies prepare a written assessment of anticipated costs and benefits before proposing any rule that may result in an expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of \$100 million in any one year (adjusted annually for inflation). Section 205 of the Unfunded Mandates Reform Act also requires that the agency identify and consider a reasonable number of regulatory alternatives and from those alternatives select the least costly, most cost-effective, or least burdensome alternative that achieves the objective of the rule.

The following analysis, in conjunction with the remainder of this document, demonstrates that this proposed rule is consistent with the regulatory philosophy and principles identified in Executive Order 12866 and in the other two statutes. The proposed rule would amend current safety reporting requirements for human drug and biological products. Based on the analysis below, as summarized in table 11, FDA projects that the annual benefits would exceed the costs if this proposed rule resulted in a 2 percent reduction in hospital-related SADRs. The agency believes that a reduction in hospital related SADRs of at least 2 percent is a reasonable and likely outcome of this rule. The agency has determined that the proposed rule is an economically significant rule as described in the Executive Order. As required by the Regulatory Flexibility

Act, the agency's Initial Regulatory Flexibility Analysis is included in this section. Because the rule may impose a mandate on the private sector that will result in a 1-year expenditure of \$110 million or more (the current inflation adjusted threshold), FDA has conducted a cost-benefit analysis according to the Unfunded Mandates Reform Act. The relationship of this proposed rule with other agency rulemaking is described in the background section (*e.g.*, reproposal of postmarketing periodic safety reporting requirements) (*see* section I of this document).

The proposed rule covers a small part of a broader based set of international initiatives (ICH and CIOMS) that, taken collectively, have the potential to generate substantial benefits, savings, and efficiencies for consumers, manufacturers, and regulators. The full benefits of this proposed rule will accrue when international regulatory inconsistencies are addressed, safety reporting submission requirements are harmonized internationally, and electronic information exchange is uniform and compatible for the major participants involved in monitoring drug safety. A primary objective of the proposed rule is the harmonization of FDA's safety reporting requirements with international initiatives. The proposed rule would also improve the quality of information contained in postmarketing individual case safety reports for human drug and biological products. By providing more complete information for individual case safety reports, the revised reports would enhance the ability of the drug and biologics manufacturers and the agency to identify, monitor, and communicate the risks and benefits of marketed drug and biological products. Monitoring these risks and benefits is especially critical for newly approved products introduced to large and diverse patient populations.

Specifically, the proposed rule would clarify and codify the agency's expectations for timely acquisition, evaluation, and submission of relevant safety information for marketed human drug and biological products. The proposed rule would expand postmarketing expedited safety reporting to include unexpected SADRs that cannot be classified as either serious or nonserious, information that is sufficient to consider changes in product administration, certain medically significant SADRs, and actual and potential medication errors as specified in the proposal. The proposed rule would require that each SADR in postmarketing individual case safety reports be coded using a single medical

dictionary, MedDRA. The proposed rule would also require applicants to conduct a more thorough review and analysis of the safety profile of marketed drug and biological products. Finally, the proposed rule would codify current best practices in postmarketing safety reporting.

The proposed rule would also amend FDA's regulation on postmarketing annual reports for human drugs and licensed biological products to revoke the requirement for submission of safety-related information. The agency would also require the submission of expedited safety reports for certain bioavailability and bioequivalence studies that are exempt from submission of an IND.

The summary of the costs and benefits of this proposed rule are presented in table 11. The total one-time costs of \$144.2 million are primarily for adopting MedDRA and include

planning for implementation of the MedDRA requirements, purchasing materials, and converting existing systems to the new dictionary. Firms would also incur annual operating costs of about \$106.6 million for complying with the revised safety reporting and recordkeeping requirements and \$28.5 million for maintaining the new MedDRA system. Total annualized costs are \$155.6 million (assuming a 10-year regulatory period and a 7 percent discount rate). A 10-year regulatory period for annualizing the costs and benefits of this proposed rule was selected as a reasonable time frame to adjust for investments, returns and savings given the potential for unforeseen advances in both medical and information technology. In addition, by the fourth year savings and costs remain constant.

The expected health benefits of the rule would result from the improved

timeliness and quality of the safety reports and analyses. Submission of more complete safety information would reduce the number and duration of hospitalizations due to SADRs. If the proposed rule reduced the incidence of SADR-related hospitalizations by 2 percent, these annual savings could be \$368.5 million (see table 11). A 1 percent reduction in hospital related events would save \$184 million annually; a 3 percent reduction would save \$553 million annually. In addition, industry will experience economic benefits due to the more efficient allocation of resources permitted by the international harmonization of the safety reporting requirements. The annualized present value of these savings is \$28.5 million assuming a 7 percent discount over 10 years (see table 11). The agency believes this represents only a partial estimate of future industry savings.

TABLE 11.—SUMMARY OF THE COSTS AND BENEFITS
[\$ million]

Benefits assuming a 2 percent reduction in hospital related SADRs		Annual		
Reducing hospital costs				368.5
More efficient use of resources				128.5
Total benefits				397.0

¹ This is the annualized present value of the estimated savings assuming a 7 percent discount over 10 years.

Costs	One-Time	Annual	Annualized
Safety Reporting and Recordkeeping:			
Expedited reports (Except medication errors)		29.0	29.0
Expedited reports—medication errors		68.0	68.0
Periodic/other reports		9.6	9.6
Implementing MedDRA	144.2	28.5	49.0
Total	144.2	135.1	155.6

V.B. Market Failure

The host of international requirements and procedures that currently govern safety reporting for drugs and biologics creates substantial economic inefficiencies for firms. Manufacturers of drug and biological products operating in global markets must meet the regulatory safety reporting requirements of each country in which the product is marketed. In many cases, these safety reporting requirements, in particular submission timeframes for SADR reports, vary substantially among countries. Thus, drug and biologics manufacturers must devote considerable resources to reformatting the data and information pertaining to each SADR according to specific national requirements. Also, because the timing of report submissions is typically determined by

product approval dates for each country, manufacturers must submit reports to different countries at different intervals. Such activities impose substantial costs on both industry and regulatory authorities. Moreover, product safety can be compromised due to the difficulty of analyzing SADR reports based on the inconsistent use of terms derived from multiple dictionaries.

Despite the general recognition that manufacturers could realize substantial gains if safety reporting and terminologies were standardized globally, companies currently have limited incentives to invest capital and resources in standardized reporting systems (e.g., MedDRA) unless the standards are required by regulation. This shortfall in industry incentives occurs because the economic gains of harmonization cannot be attained by individual firms acting alone. Although

most regulatory authorities have agreed in principal to implement international standardized reporting procedures, formal procedures have not yet been established. A few companies have voluntarily invested in the standardized process, but in the absence of global standards, these firms are uncertain of potential gains. FDA believes that the proposed rule is a necessary step toward achieving the desired international standardization and its corresponding economic and health benefits.

Industry would benefit from FDA action to reduce uncertainties associated with investments in harmonization and from the ability to more efficiently allocate resources associated with safety reporting. Society would benefit from the improved quality of adverse event information that is a critical component to reducing health care costs associated with avoidable SADRs. More timely and

improved information on SADRs is needed to ensure the safe use of products and to monitor early warnings and unexpected risks associated with drugs, drug-drug interactions, drug-food interactions, and risks to certain patient populations.

V.C. Benefits

The benefits of the proposed rule would result both from the public health gains attributable to the improved scope, uniformity, and quality of information and analyses submitted in safety reports and the economic savings attributable to the more efficient use of industry and regulatory resources.

This proposed rule would require improved factual and analytic data underlying safety reporting and analysis, provide for more timely safety information for certain serious SADRs, and would require a common medical dictionary, MedDRA.

The timely identification of SADRs is critical to managing risk information and to the safe prescribing and use of new drugs. Accurate and timely risk information is especially significant in the early months after product launch to develop appropriate prescribing and use behaviors as health care practitioners and consumers are learning about the product safety and use. Newly approved product use can quickly grow from a few thousand patients (the population in clinical trials) to many thousands or millions. Rare but serious SADRs are detected only after exposure to very large patient populations. Forty percent of SADR reports are for drugs approved within the last 3 years. Compounding this need for timely serious SADR information, U.S. patients are increasingly the first in the world to have access to new medications (49 percent of new drugs were first approved in the United States between 1996 and 1998, compared with 31 percent in 1991–1995).

More timely and improved factual information would also enhance the identification of other important factors associated with the risks of SADRs. These factors include subpopulations that may differ from clinical trial participants, patients taking multiple medications or medications that require therapeutic monitoring, and patients with concurrent comorbidities.

This rule would require affected entities to complete either a minimum or full set of data in safety reports, reflecting levels of risk. That is, more detail is required for higher risk events and reduced reporting for lower risk events. This rule would also require the use of MedDRA, a medical dictionary

developed by the ICH, in coding SADR terms. MedDRA will provide a uniform, consistent and specific presentation of medical terms. By eliminating the use of multiple dictionaries, MedDRA would facilitate the retrieval, presentation, and summarization of SADR data and enhance the global communication and acceptance of safety information and reports. The use of a single dictionary will substantially upgrade the quality of safety analysis by incorporating uniformity of terms. MedDRA will aid in more expeditious and broader international drug use comparisons within a class, and prescribing and use decisions. Providing more complete information and more timely safety assessments would enhance the ability of the manufacturers to more quickly identify, monitor, and communicate the potential risks and benefits of marketed drugs and biologics.

It is well recognized that drug safety information is a critical element in the risk management of marketed drugs and biologics. In addition, the medical literature provides substantial documentation of avoidable hospitalizations associated with SADRs. Improving the quality and timeliness of safety information and accelerating the communication of risk information will enable health care practitioners and consumers to take appropriate corrective actions (in the case of medication errors) and to make more informed decisions about treatments. Moreover, the management of risk information is an essential component of risk-based decisions that determine the continued marketing or withdrawal of effective products with newly identified serious SADRs. We discuss benefits more fully below and show that a small reduction in the number of hospitalizations due to SADRs (as low as 0.85 percent), due to improved prescribing and use decisions, would result in the annual benefits outweighing the total costs.

V.C.1. Expanded Safety Information

New drug approval decisions are based on safety and testing information derived from clinical trials that typically include several thousands of patients. However, the number of individuals tested in preapproval trials is not sufficiently large to reliably detect rare, serious SADRs. Patient exposure can quickly grow from thousands to millions after product launch. Thus, especially in the first few years after product launch, postmarketing surveillance is a critical component of the overall continuing review and assessment of drug safety (Ref. 1). Recent studies have identified common

factors associated with increased risks of SADRs. These factors include subpopulations who differ from the clinical trial participants, e.g., the elderly, patients taking multiple medications or medications that require therapeutic monitoring, and patients with concurrent comorbidities (Refs. 2 through 5). The proposed rule would require companies to collect proactively more complete safety information, improving the factual and analytical data underlying the safety analyses. This expanded risk information would enable health care practitioners and consumers to take appropriate corrective actions (in cases of avoidable medication errors) and to make more informed decisions about treatments.

V.C.2. Improved Uniformity and Quality of Safety Information

For years, numerous health care organizations, teaching hospitals, health care professionals, and educators have recognized the importance to public health of monitoring SADRs. Substantial evidence demonstrates that effective monitoring and analyzing of SADRs facilitate the identification of trends and warning signals that result in improved medication use and patient care (Refs. 6 through 10). Yet, the current drug and biologics safety reporting system, encompassing raw material suppliers, manufacturers, health care providers, and consumers, is fragmented with respect to its oversight and lacks common reporting procedures and tools for evaluating SADRs. For example, FDA oversees mandatory safety reporting by manufacturers of drug and biological products and voluntary reporting from health care providers and consumers. Health care facilities, on the other hand, may be subject to safety reporting oversight by individual state regulatory programs, although not all states have oversight systems. The Joint Commission on Accreditation of Health Care Organizations (JCAHO), which accredits health care facilities, has had standards for establishing SADR reporting systems for hospitalized patients for many years. Hospitals may establish their own systems independently and almost all conform to the JCAHO standards (Ref. 11). Despite growing evidence that avoidable SADRs and serious SADRs are important public health problems and widespread acknowledgment that monitoring SADRs provides public health benefits, FDA continues to receive reports of only a small percentage of the serious and avoidable SADRs that occur in health care facilities (Ref. 12). This proposed rule would improve safety reporting by drug

and biologics manufacturers, which may serve to provide a national framework for improved data collection and analysis of safety reports from a variety of sources.

The proposed rule would also require the use of MedDRA, a single, medical terminology developed by ICH that can be used for the coding of SADR terms. MedDRA is a broad-based dictionary, developed for international use, that combines both SADR and morbidity terminology to provide a uniform, consistent, and specific presentation of medical terms. By eliminating the use of multiple dictionaries, MedDRA would facilitate the retrieval, presentation, and summarization of SADR data and enhance the global communication and acceptance of safety information and reports. In addition, the use of a single comprehensive medical dictionary by drug safety reporters and reviewers would substantially upgrade the quality of safety analysis by incorporating uniformity of terms. Standardizing the terms and improving the quality of the roughly 250,000 safety reports submitted annually to FDA would lead to better and more timely safety assessments and to improved communication of risk information. The widespread use and acceptance of standardized SADR information by regulators would ultimately enhance drug comparisons within a class and drug prescribing and use decisions.

V.C.3. Potential Savings From Reduced SADR-Related Hospitalizations

Improved timeliness and analysis of SADR data would lead to a better understanding and a more rapid communication of the risks of SADRs. By providing such improvements, the proposed rule would reduce the incidence of SADRs. An agency estimate of the potential economic benefits of the rule is presented below and reflects the value of the expected hospital cost savings and the avoided lost wages that might result from reduced numbers of SADRs.

V.C.3.a. *Reduced rate of SADR-related hospitalizations.* Numerous studies have documented drug-related hospitalizations (60 FR 44182 at 44232, August 24, 1995). A comprehensive review of 36 articles focused specifically on SADRs as the primary cause of hospitalization. This study counted the number of reactions attributed to unintended consequences of drug therapy, excluding admissions due to overdose, intentional poisoning, attempted suicides, drug abuse, or intoxication. The percentage of hospitalizations due to SADRs ranged from 0.2 to 22 percent, with a mean of

5.5 percent. FDA adjusted this figure to 5 percent to remove over-the-counter drugs (Ref. 13). Based on 27.8 million hospital admissions reported in 1997, excluding obstetrical admissions (Ref. 14), the agency estimates the annual number of SADR-related hospitalizations at about 1.4 million (5 percent \times 27.8 million). Absent available data, the agency assumes the costs associated with SADR-related hospitalizations are similar to the average cost of a hospital stay, but requests comments and supporting data on this assumption. Therefore, applying an estimated cost of \$9,177 for an average hospital stay (Ref. 15) implies total annual SADR-related hospital admission costs of about \$12 billion ($\$9,177 \times 1.4$ million).

If the improved reporting and analyses of SADRs led to the avoidance of only 2 percent of these hospitalizations, the economic savings would amount to \$252.2 million annually.

V.C.3.b. *Reduced rate of in-hospital SADRs.* Bates et al. conducted a random sample of nonobstetrical admissions to two large tertiary care hospitals in Massachusetts over a 6-month period (Ref. 16). His prospective investigation of SADRs included interviews with medical staff and daily reviews of all medical charts. He estimated the incidence of all SADRs, including medical errors, at 6.5 percent with an average increase in hospital costs of \$2,595 per case. Extrapolating these findings, FDA estimated the annual number of in-hospital SADRs at 1.8 million and the total additional hospital cost at \$4.7 billion annually. If this proposed rule led to a 2 percent reduction, the economic benefits would be \$93.6 million annually.

In a comprehensive review of studies that estimated the incidence of SADRs and/or the magnitude of hospital costs due to SADRs, the U.S. General Accounting Office cited substantial variation in estimates (Ref. 17). These differences may be due to inconsistent definitions of SADRs, different study methodologies (active prospective investigation versus retrospective review of patient records), representativeness of the samples, and particular methods used to extrapolate study findings to a national level. For example, Lazarou et al. and Classen et al. estimated the incidence of serious SADRs using the WHO definition of SADR and excluding other factors such as poisonings, intentional overdoses, and therapeutic failure (Refs. 18 and 19). These two studies had findings similar to Bates et al. On the other hand, Thomas et al. reviewed randomly

selected hospital discharge records in two states and found a lower incidence of "drug injury". However, he used a particularly restrictive definition of SADR, one that resulted in prolonged hospitalization or disability at discharge (Ref. 20). Despite the uncertainties of estimating the incidence and cost of hospital related SADRs, FDA believes that the \$4.7 billion estimate for in-hospital SADRs derived above provides a plausible estimate.

V.C.3.c. *Indirect benefits of reducing the hospital costs of SADRs.* The indirect benefits of reduced drug-related illnesses are derived from estimates of the costs of missed work or reduced productivity. Several studies on SADR-related hospital admissions stratified findings by patient age. Roughly 58 percent of SADR admissions were for patients aged 20 to 59. The remaining 42 percent were for patients under 20 years (less than 10 percent) and over 59 years old (Refs. 21 through 23). To calculate productivity losses, the agency assumed 56 hours per admission for patients aged 20 to 59 years (40 hours of lost work per hospitalization plus 16 additional hours for recovery and followup doctor visits)² and 14 hours for the remaining groups (to account for lost volunteer time or for time away from work for the care givers of dependent patients). The wage rates used are the average hourly production workers earnings of \$15.96 for patients aged 20 to 59 (\$12.28 plus 30 percent for benefits), and \$12.28 for the remaining patients or their care givers (Ref. 14). The estimated value of this lost productivity is \$812 million.

To estimate similar indirect benefits for in-hospital SADRs, the agency assumed the same distribution of patient ages. Related productivity losses are assumed to be 16 and 6 additional hours respectively, for patients aged 20 to 59, and for the remaining groups. The estimated value of this lost productivity is \$323 million.

A 2 percent reduction in costs of SADR-related hospitalizations and prolonged hospitalizations would yield indirect benefit savings of \$22.7 million. These estimates may somewhat overstate the value of lost productivity for the 20 to 59 age group because all patients are assumed to be employed. On the other hand, indirect benefits for the remaining age groups are understated because many of these patients are in the workforce and for those who are not, data are inadequate to measure their contribution to society.

² The agency used 40 hours to estimate work productivity losses. This estimate is consistent with current hospital discharge data and with the length of stay for drug-related hospitalizations (Ref. 21).

V.C.3.d. *Sum of SADR-related costs.* Summing these estimates, the total annual direct and indirect benefits of reducing avoidable SADR-related hospitalizations and longer hospital stays by 2 percent would lead to economic benefits of \$368.5 million per year. Varying the assumption of a 2 percent reduction in hospital costs with a 1, 3, and 5 percent reduction, would yield annual benefits of \$184 million, \$553 million, and \$921 million, respectively. A reduction of only 0.85 percent in the hospital costs associated with SADRs would be needed to outweigh the annualized industry costs of \$155 million. Furthermore, under any of these scenarios, the total SADR-related hospital savings would outweigh the costs of this rule. With a 2 percent or greater reduction, the annual benefits would outweigh the costs beginning in the first year. Nonetheless, the agency seeks comment on our estimates of expected reductions in hospital-related costs, including the potential for reducing the incidence and length of stay of hospital-related SADRs.

In contrast to focusing only on hospital costs of SADRs, one study estimated the direct costs of drug-related morbidity and mortality for the ambulatory population at \$76.6 billion annually, with the largest component \$47.4 billion for drug-related hospitalizations (Ref. 24). The remaining cost components included: \$14.4 billion for long-term care, \$7.5 billion for physician visits, \$5.3 billion for emergency department visits, and \$1.9 billion for additional prescriptions. Again, assuming a 2 percent reduction, savings are approximately \$948 million annually.

V.C.4. Cost Savings and More Efficient Use of Resources

The proposed rule is intended to complement and formalize international efforts by industry representatives and major international regulatory bodies to achieve a more uniform and global approach to safety reporting. The content, analyses, and timing of SADR report submissions would closely align with international initiatives and recommendations. To the extent that U.S. requirements become harmonized within a global context, companies that compete internationally would benefit from this proposed rule. Multiple international due dates for safety report submissions and reformatting of the same information to meet different regulatory requirements represent opportunity costs that could be allocated elsewhere. Companies would accrue savings through a substantial reduction or elimination of the

reformatting of postmarketing periodic safety report information to meet varying international requirements and by synchronizing report frequencies and due dates internationally. Thus, as the international community harmonizes, companies would achieve efficiencies, eliminate duplicative processes, and reallocate those resources more efficiently.

The agency contracted with the Eastern Research Group, Inc. (ERG), an economics consulting firm, to estimate the potential benefits that would accrue to drug and biologics companies in the long run, as international harmonization efforts align and generate cost savings. These savings include more efficient regulatory safety reporting, more efficient sharing of safety information, and a common medical terminology. ERG estimated the following specific categories of benefits: More efficient management of drug safety data, more efficient intercompany agreements, and international harmonization of the postmarketing periodic safety report format (*i.e.*, use of PSUR format). ERG applied estimates of savings by category and firm size to the number of affected firms within each affected industry. The methodologies and procedures for deriving these estimates are fully presented in ERG's final report (Ref. 25).

V.C.4.a. *Savings related to maintaining and building data bases of SADRs and intercompany transfers of drug safety data.*

Drug and biologics companies maintain safety data bases of all domestic and foreign SADRs involving their products. The management of these data bases can be quite complex depending on the individual circumstances of manufacturing and marketing. Companies may have foreign subsidiaries, domestic and foreign manufacturing sites, and varied licensing agreements with other companies for marketing products. Foreign subsidiaries and licensees generally submit SADR reports to U.S. companies by fax. U.S. companies then reenter the reports into their own databases. Use of standardized safety report formats and content internationally will lend itself to electronic transmission of safety information. In these cases, intercompany and intracompany sharing of safety information will be substantially facilitated. ERG estimated these benefits at \$3.1 million annually.

V.C.4.b. *Savings related to greater ease in entering into intercompany agreements.* As requirements for drug and biologics safety reporting become harmonized, drug and biologics companies will find it easier to

coordinate safety reporting efforts when entering into various agreements with other manufacturers or sales organizations. In the current organizational structure of the industry, companies are frequently negotiating licensing agreements, mergers, joint ventures, and other contractual matters with other companies. For these arrangements, companies must develop, share, and merge drug safety reports from around the world. At present, negotiation of drug safety data sharing is often complicated by reporting formats and requirements that differ between regions. ERG estimated the potential savings that would accrue from simplified negotiation of licensing agreements due to standardized reporting formats and requirements at \$4.2 million annually.

V.C.4.c. *Savings related to eventual international harmonization to the PSUR format.* ERG estimated the potential savings to industry of preparing a single PSUR that would be accepted by regulatory authorities internationally on the same date. Currently, companies are faced with many inconsistent requirements and must meet the individual requirements and timeframes of each country. ERG estimated these savings at \$24.3 million annually.

V.C.4.d. *Potential savings in clinical trial management.* Some companies noted that they would convert medical terms from clinical trials to MedDRA whether or not it was required by FDA. Assuming that this transition will gradually apply to future clinical trials, a single medical terminology, internationally developed, accepted, and applied, would allow companies to more easily transmit, integrate, and analyze clinical trial data from global sites. Subsequent reductions in time and resources would contribute to reduced costs during drug development. Based on input from industry, ERG developed a narrow focus of savings associated with clinical trial data management valued at \$7.2 million annually.

V.C.4.e. *Leveraging specialized knowledge.* This proposed rule also provides the groundwork for establishing focused centers of technical information on drug safety. Global companies and regulatory agencies will have the opportunity to create economies of expertise by concentrating specialized knowledge of global drug use and product risks and benefits in centralized locations. To the extent that safety information is better managed, understood, and shared with interested parties, substantial benefits will accrue. Neither ERG nor FDA could quantify these benefits.

V.C.4.f. *Total benefits.* ERG estimated the total industry savings from more efficient use of resources to be \$38.8 million annually. This estimate, however, accounts for only a modest portion of the potential benefits of the broader set of initiatives that enhance electronic submissions and global harmonization of safety reporting. Table

12 summarizes the estimated annual benefits of this proposed rule. The agency recognizes, however, that the industry savings component will not be fully realized until safety reporting requirements are harmonized internationally. The agency believes that these benefits could be achieved in a relatively short period after this rule

becomes final. The agency is ready to accept PSUR formats and the use of MedDRA for coding of individual case safety reports at the present time (see draft guidance of 2001). In addition, the European Union and Japan currently accept PSUR formats and the use of MedDRA.

TABLE 12.—SUMMARY OF THE ANNUAL BENEFITS

Savings category	\$ Million (annually)
Public health benefits for a 2 percent reduction in SADR-related hospital costs:	
Reduced SADR-related hospital admissions	252.2
Reduced in-hospital SADRs	93.6
Indirect benefits from reduced hospitalizations	22.7
Total hospital-related savings	368.5
Expanded safety information on product approvals	(²)
Improved risk communication and product selection	(²)
Future Industry Savings:	
Efficiencies in database maintenance	3.1
Facilitation of PSUR submissions	24.3
Facilitation of intercompany negotiations	4.2
Clinical trial management	7.2
Total Industry Savings	138.8
Economies of Managing Drug Expertise	(²)

¹ Assuming 1/3 of these savings begin in year 2 (\$11.6 million), 2/3 in year 3 (\$23.3 million), and \$38.8 million in years 4 through 10, the annualized present value is \$28.5 million, discounted at 7 percent over 10 years. The 10-year time horizon allows a reasonable projection of current information given the unforeseen progress and impacts of medical and computer technology.

² Not estimated.

V.D. *Costs of Compliance*

This section presents the estimated compliance costs of the proposed requirements. As explained in the following paragraphs, the proposed rule clarifies and expands existing requirements for submitting premarketing expedited reports, postmarketing expedited initial and followup reports, and postmarketing periodic safety reports to FDA. Drug and biologics manufacturers would be required to use direct verbal contact to collect information sufficient to determine the nature, severity, and outcome of SADRs and to evaluate and describe the safety profile or changes in the safety profile of marketed drugs. The proposed regulation also specifies criteria for reporting individual case safety reports and designates data elements that must be completed as a condition for initial and followup reporting. Each SADR in a postmarketing individual case safety report for human drugs and biologics must be coded using the appropriate “preferred term” in the latest version of MedDRA. The proposal also requires a physician to review the postmarketing expedited and periodic safety reports. The proposed rule would codify the data elements, analyses, and report format of the required postmarketing

periodic safety report submissions and harmonize many of these requirements with ICH initiatives. Applicants holding an approved marketing application would be required to submit semiannual individual case safety reports and more detailed postmarketing periodic safety reports that contain cumulative and comprehensive data, analyses, tabulations, summaries, and other information. The proposed rule also includes revisions to IND safety reporting requirements and bioavailability and bioequivalence study requirements.

V.D.1. *Costs of New Recordkeeping and Reporting Requirements*

V.D.1.a. *Number of reports.* In 1998, manufacturers and applicants of human drug and biological products submitted approximately 230,000 individual case safety reports of SADRs to FDA. Data from about 130,000 of these individual case safety reports in the agency’s Adverse Event Reporting System (AERS) were analyzed to estimate the annual number of future SADR reports expected to be included as revised expedited and new semiannual submissions. However, not enough data exists to predict the number of new expedited reports the agency may expect each year. For this analysis,

estimates of new expedited reports for human drugs and biological products were based on counts of similar reports received by the agency during 1998. The estimated number of expedited reports for blood products is derived from published studies (Refs. 26 and 27).

The agency does not know how many TPSRs, and PSURs and IPSRs would be submitted annually, because applicants with pre-1998 drug approvals can submit either format. In addition, applicants with ANDAs approved on or after January 1, 1998, may choose to submit a TPSR rather than a PSUR or IPSR if the innovator NDA was approved before January 1, 1998. Despite this uncertainty, this analysis estimates the number of new filings of postmarketing periodic safety reports based on average counts of pre- and post-1998 drug approvals.

The number of affected reports for prescription drugs marketed for human use without an approved application, IND safety reports, bioavailability/ bioequivalence safety reports, and other reports were projected from counts of similar reports received by FDA. Estimates for the total number of reports affected by the proposed rule are shown in table 13.

TABLE 13.—NUMBER OF AFFECTED REPORTS BY REGULATORY STATUS

Type of report	Drugs marketed without an approved application	NDA/AND	Biologics	Blood products	IND	Bioavailability and bioequivalence	Total
Expedited:							
Serious and unexpected SADRs	350	50,000	3,000	0	0	0	53,350
Always expedited report	50	1,500	100	0	0	0	1,650
Unexpected SADR with unknown outcome	46	912	25	0	0	0	983
Information sufficient to consider product administration changes ..	5	300	4	0	0	0	309
Medication errors	1,000	100,000	10,000	0	0	0	111,000
30-day followup	340	43,000	3,000	0	0	0	46,340
Serious SARs—blood products	0	0	0	7,000	0	0	7,000
IND Safety							
Information sufficient to consider product administration changes ..	0	0	0	0	600	0	600
Bioavailability/bioequivalence safety report	0	0	0	0	0	200	200
Periodic:							
TPSR	0	1,400	35	0	0	0	1,435
PSUR	0	2,500	35	0	0	0	2,535
ISUR	0	350	3	0	0	0	353
Individual case safety reports—semiannual submission	0	4,726	480	0	0	0	5,206
Other:							
Reports to manufacturer or applicant	4	4,548	100	0	0	0	4,652
Submit safety records to FDA upon request	2	15	4	0	0	0	21
Annual reports	0	2,363	69	0	0	0	2,432

V.D.1.b. *New time burden.* The proposed rule requires manufacturers and applicants to use active query to acquire the outcome (*i.e.*, whether an SADR is serious or nonserious) and required data set for any spontaneously reported individual case safety report that they receive pertaining to their marketed human drug or biological product. Furthermore, the proposed rule requires that every individual case safety report submitted to the agency be assigned an appropriate MedDRA code. Although individual case safety reports are currently submitted for most SADRs, depending on the type of SADR, the proposed rule may impose an additional burden on health professional personnel if active query is not already used routinely by a manufacturer or applicant. Regulatory affairs personnel working with the health professional may spend additional time assigning the MedDRA code and documenting the active query. The agency seeks comment on the reasonableness of the estimates of the time burden and the type of employee anticipated to fulfill the new requirements detailed in the following paragraphs.

V.D.1.b.i. *Expedited reports.* The nature of the SADR (*i.e.*, whether the SADR is expected or unexpected) and whether the outcome is known (*i.e.*,

SADR is serious or nonserious) will determine the data needed and when and if an individual case safety report should be submitted to FDA. At present, individual case safety reports of SADRs that are both serious and unexpected are submitted as 15-day alert reports.

The proposed rule adds conditions for determining expedited reports (*e.g.*, minimum data set required). In addition, it specifies that an expedited report for an individual case safety report must contain a full data set, including MedDRA codes, and that supporting documentation such as hospital discharge records, autopsy reports, or death certificates must be submitted, if available. This aspect of the proposal may impose a new burden estimated at 1 hour each for health professionals and regulatory affairs personnel (see table 14).

The proposal defines new criteria for determining when expedited reports should be submitted. Certain medically significant SADRs as listed in the proposal, whether unexpected or expected, and all domestic reports of actual and potential medication errors would be required to be submitted to FDA in an expedited manner.

Furthermore, when the outcome of a spontaneous, unexpected SADR cannot be determined, an expedited report must be submitted to the agency. In

these circumstances, manufacturers and applicants are assumed to allocate from 16 to 24 hours more time for health professionals and regulatory affairs and clerical personnel to prepare and submit these new reports. Table 14 lists the additional hours each type of employee may spend complying with these new requirements.

In addition to individual case safety reports, manufacturers and applicants may receive safety information from domestic or foreign studies that is judged to be sufficient to consider a change in product administration. In this case, the proposed rule requires that a narrative report of these findings be submitted to the agency as an expedited report. Preparing and submitting this new report may take up to 8 hours of time from health professionals and regulatory affairs and clerical personnel as shown in table 14.

V.D.1.b.ii. *Followup reports.* The proposed rule establishes timeframes and data elements required for submission of expedited individual case safety reports. If required data elements were not submitted with the initial filing of an expedited report of a serious SADR or a medication error report, then the applicant must continue to use active query to obtain the additional information. This information must be submitted to FDA in a followup report

within 30 calendar days of the previous filing. If the full data set is still not obtainable, the 30-day followup report must include all safety information obtained, highlighting new information and stating the reasons for the inability to obtain complete information. The agency estimates that 8 additional hours, as shown in table 14, are needed for these followup reports.

Applicants must also submit any new safety information to FDA for any other expedited or followup report within 15 days of receipt of the new information. This provision is currently required; therefore, no additional hours are allocated to this provision.

V.D.1.b.iii. *Blood products.* Collection and transfusing facilities are currently required to investigate, prepare, and maintain written reports of complaints of SARs arising as a result of blood collection or transfusion. Furthermore, if a fatality occurs as a complication of blood collection or transfusion, facilities must notify FDA as soon as possible and follow up with a written report within 7 calendar days after the fatality occurs. The proposed rule will require that all written reports submitted to the agency use the individual case safety report format. This change in reporting format is not expected to increase the time needed to prepare and submit reports of fatalities. In addition, the proposed rule will require that any serious nonfatal SAR related to collection or transfusion of blood and blood components be submitted as a expedited report within 45 calendar days. As shown in table 14, blood facilities may spend up to 16 hours more preparing and submitting each of these expedited reports.

V.D.1.b.iv. *IND and bioavailability/bioequivalence safety reports.* Sponsors of an IND are currently required to submit written and telephone safety reports. The proposed rule will add some conditions for reporting and require that reportable SADR include the minimum data set. Sponsors of INDs will be required to submit written safety reports to FDA and all participating investigators of: (1) Any SADR that, based on the opinion of either the sponsor or investigator, is both serious and unexpected and (2) any information that might materially influence the

benefit-risk assessment of an investigational drug or that would be sufficient to consider a change in either product administration or in the overall conduct of a clinical investigation. The agency is also expanding the current requirement for telephone and facsimile transmission of safety reports of unexpected death or life-threatening SADRs to include those that meet these criteria based on the opinion of either the sponsor or investigator. In addition, the agency is making minor changes to align current IND safety reporting requirements with the proposed changes to postmarketing safety reporting.

The agency anticipates that very few investigator-initiated reports would be submitted under the proposed rule. Because the number of new reports (*i.e.*, approximately 10 per year) would represent less than 0.2 percent of all individual IND safety reports submitted to the agency in a year, no additional burden is estimated. However, up to 4 hours may be needed for sponsors to accommodate the new requirements for written safety reports for information sufficient to consider a change in product administration (see table 14).

In addition, the agency would require submission of expedited safety reports for certain bioavailability and bioequivalence studies that are exempt from submission of an IND. The agency estimates 14 hours per report are needed to comply (see table 14).

V.D.1.b.v. *Semiannual submissions of postmarketing individual case safety reports.* The current regulations require that postmarketing individual case safety reports from domestic marketing experience for serious expected adverse drug experiences, nonserious unexpected adverse drug experiences, and nonserious expected adverse drug experiences be submitted to the agency in postmarketing periodic safety reports. Under the proposed rule, most individual case safety reports not submitted to FDA as an expedited report would be submitted as a separate report twice a year. All reports of actual or potential medication errors, whether or not an SADR occurs, would be submitted as expedited reports and not submitted semiannually. Individual case safety reports of nonserious SADRs

that are expected or listed would no longer be submitted to the agency. Exceptions, for vaccines, would be reports of nonserious, expected SARs and expected SARs with an unknown outcome, which would be submitted semiannually. Nevertheless, applicants would be expected to maintain these reports and include them in tabular summaries provided in the postmarketing periodic safety reports (*e.g.*, PSURs).

Whereas the current postmarketing periodic safety reporting regulations do not apply to foreign reports of SADRs, the proposed rule would require that foreign individual case safety reports of serious and expected or listed SADRS be submitted semiannually. The agency is unable to predict how many foreign reports may be submitted. For the purpose of this analysis, therefore, the number of nonserious and expected or listed individual case safety reports is assumed to be equal to the number of serious and expected or listed foreign reports, and the overall number of individual case safety reports submitted in a year would remain unchanged.

Although the number of individual case safety reports submitted annually as a postmarketing periodic safety report is expected to remain stable, the timing of these submissions may change. Reports will be submitted less frequently (semiannually rather than quarterly) for products that have been on the market for less than 3 years and more frequently (semiannually rather than annually) for products that have been on the market for more than 3 years. Furthermore, additional time may be needed for an active query to obtain a full data set for reports of serious and expected or listed SADRs and a minimum data set for all SADRs. Based on reports to AERS in 1998, the agency estimates that, on average, approximately 35 individual case safety reports may be submitted semiannually for each drug product. Regulatory affairs personnel and health professionals might spend up to 10 additional hours each to obtain and process information for each semiannual submission (see table 14).

TABLE 14.—ESTIMATED NEW BURDEN FOR EXPEDITED AND SEMIANNUAL REPORTS

Type of report	New or revised	New burden (hours)			
		Health professional	Regulatory affairs	Clerical	Total
<i>Expedited:</i>					
Serious and unexpected SADR	Revised	1	1	0	2
Always expedited report	New	2	12	2	16
Unexpected SADR with unknown outcome	New	3	18	3	24

TABLE 14.—ESTIMATED NEW BURDEN FOR EXPEDITED AND SEMIANNUAL REPORTS—Continued

Type of report	New or revised	New burden (hours)			
		Health professional	Regulatory affairs	Clerical	Total
Information sufficient to consider product administration changes.	New	3	3	2	8
Medication errors	New	2	12	2	16
30-day followup	New	3	4	1	8
Serious SARs—blood products	Revised	2	12	2	16
<i>IND Safety:</i>					
Information sufficient to consider product administration changes.	Revised	1	2	1	4
<i>Bioavailability/bioequivalence safety report</i>	New	1	11	2	14
<i>Individual case safety reports—semiannual submission.</i>	Revised	10	10	0	20

V.D.1.b.vi. *Postmarketing periodic safety reports (TPSR, PSUR, and IPSR).* Current agency regulations require applicants to submit postmarketing periodic safety reports at specified intervals. Each periodic safety report must contain a narrative summary and analysis of adverse drug experiences received since the last periodic report. The proposed regulation would require applicants to provide more thorough

review and analysis of the safety profile for certain drugs. For all applications approved on or after January 1, 1998, these reports would be in the PSUR format (with some variation) that is currently accepted by other regulatory authorities. These applications would be submitted semiannually for 2 years after the U.S. approval date, annually for the next 3 years, and every 5 years thereafter. In contrast to current regulations,

postmarketing periodic safety reports would have to contain a more comprehensive analysis of the product's safety record. Specifically, applicants would be required to submit, as described in chart 1, summary tabulations of SADRs (*i.e.*, all SADR terms and counts of occurrences) received since the last periodic report categorized by body system or standard organ system classification scheme.

CHART 1.—REQUIRED SUMMARY TABULATIONS OF SADRS FOR PSURS

Source	Outcome
Spontaneous submissions from health care professionals	All serious and nonserious.
Studies or individual patient INDs	All serious.
Scientific literature	All serious; all nonserious unlisted.
Regulatory authorities	All serious.
Other (<i>e.g.</i> poison control centers, epidemiological data bases)	All serious.

In addition, applicants would have to submit cumulative summary tabulations for SADRs that are both serious and unlisted. Applicants would be required to include a discussion of these data including the medical significance or mechanism.

Applicants would be required to submit a discussion of safety information from applicant-sponsored studies (either planned or initiated) and published safety studies and abstracts. Furthermore, applicants would be required to include a discussion of certain lack of efficacy reports and important new information received after the data lock point. In addition to analysis of individual case safety reports and studies, applicants would be required to submit a comprehensive analysis of other safety information specified in the proposal, such as increased frequencies of listed SADRs, specific populations, and drug interactions.

Applicants would also be required to provide other relevant safety and baseline information as specified in the proposal. This information would include worldwide marketing status, changes to the CCSI, actions taken for safety reasons, and worldwide patient exposure. Appendices would include additional safety information as specified in the proposal including information related to the current (or proposed changes) in the U.S. labeling and safe use of the product, summary tabulations of spontaneous individual case safety reports from individuals other than a health care professional, summary tabulations of individual case safety reports of SADRs with unknown outcome and medication errors, summary tabulations of SADRs from class action lawsuits, U.S. patient exposure, assessments of lack of efficacy reports and new information on resistance to antimicrobial drug products. In addition, the name and

telephone number of the licensed physicians responsible for the content and medical interpretation of the information in the PSUR and the addresses where all safety reports and other safety related records are maintained would be included.

The proposal also requires IPSRs for approvals on or after January 1, 1998. While following a similar format as the PSUR, the IPSR is less comprehensive than the PSUR (*i.e.*, does not require submission of summary tabulation information). This report would be submitted 7.5 and 12.5 years after the U.S. approval date.

Under the proposed regulation, TPSRs would be required for applications approved before January 1, 1998. Although less comprehensive than the PSUR, the TPSR would have to contain product safety information, including summary tabulations and a narrative summary and analysis of individual case safety reports, and a history of safety-related actions taken during the

reporting period. The timing for these report submissions would be at 5, 7.5, 10, 12.5, and 15 years after U.S. approval of the product and then every 5 years thereafter. Applicants would have the option to file using the PSUR and IPSR formats.

The additional times required to complete the proposed changes to postmarketing periodic safety report submissions are shown in table 15. The agency estimates that the new burdens would be 16 hours for TPSRs, 40 hours

for PSURs, and 30 hours for IPSRs. These times represent estimates of the average time per report, recognizing that preparation times for each postmarketing periodic safety reports may take as little as a day for products with few or no SADRs or as much as several months for other products that are more complex or associated with many SADRs. Based on reports received by the agency, a few products account for the majority of the reports of SADRs. For example, 1998 AERS data showed

that approximately 75 percent of the postmarketing periodic safety reports for drug products included 10 or fewer individual case safety reports, accounting for only about 5 percent of all of those reports submitted with postmarketing periodic safety reports. The other 25 percent of postmarketing periodic safety reports included the remaining 95 percent of individual case safety reports submitted in 1998.

TABLE 15.—ESTIMATED NEW BURDEN FOR PERIODIC SAFETY REPORTS AND OTHER REPORTS

Type of report	New or revised	New burden (hours)			
		Health professional	Regulatory affairs	Clerical	Total
<i>Periodic:</i>					
TPSR—application approved before 1/1/95	Revised	3	9	4	16
PSUR—application approved on or after 1/1/95	New	8	24	8	40
IPSR—application approved on or after 1/1/95	New	6	18	6	30
<i>Other:</i>					
Reports of nonserious SADRs and certain medication errors to manufacturer or applicant.	New	0	1	0	1
Submit safety records to FDA upon request	New	0	4	4	8
Annual reports	Revised	¹ (3)	(7.5)	(3)	(14)

¹ Values in parentheses represent an estimate of the decrease in burden.

V.D.1.b.vii. *Other reports.* Currently, persons submitting postmarketing safety reports may elect to submit reports of serious adverse drug experiences to the manufacturer or applicant rather than submitting serious unexpected adverse drug experiences directly to FDA. The proposed rule would require submission of all safety reports (*i.e.*, serious and nonserious SADRs and medication errors) to the manufacturer or applicant within 5 calendar days of initial receipt of the information. Contractors may need to allocate up to 1 additional hour to prepare and submit each report of a nonserious SADR or medication error that does not result in an SADR (see table 15).

Persons maintaining records of SADRs may be asked to submit any or all records to FDA within 5 calendar

days. The agency estimates that 21 such requests for SADR records would be made in a given year. This new reporting requirement may take regulatory affairs and clerical personnel up to 4 hours each to fulfill each request (see table 15).

FDA will no longer require that applicants subject to an NDA or BLA submit certain safety related information with annual reports. This reduction in reporting requirements will decrease the burden on these applicants. To prepare and submit each annual report, applicants may save an estimated 13.5 hours annually (see table 15).

V.D.1.c. *Annual cost of the reporting and recordkeeping provisions.* Hourly compensation estimates for personnel implicated in the proposed changes to

safety reports are shown in table 16. The additional cost of the proposed changes for each type of affected report and the total annual cost of the proposed rule are summarized in table 17. However, because the annual costs depend on the actual number and type of reports submitted to FDA, these costs are uncertain and may fluctuate from year to year. For example, if there are 50 percent fewer reports than estimated, annual costs would be approximately \$52.2 million instead of \$106.6 million. If the number of reports submitted is 50 percent more than shown in table 17, the annual costs would be about \$159.9 million. The agency seeks comments on the reasonableness of its estimates of number of reports, burden hours, and costs.

TABLE 16.—HOURLY COMPENSATION

Health Practitioner ¹	Regulatory Affairs ^{2,3}	Clerical ²
\$67.31	\$36.92	\$17.39

¹ Hourly compensation derived from the annual salary range for clinical research physicians in the pharmaceutical industry from <http://careers.yahoo.com>. Hourly compensation includes benefits equal to 40 percent of hourly wage.

² U.S. Department of Labor, BLS, "Employer Costs for Employee Compensation, Table 12," March 1999.

³ Includes biostatisticians.

TABLE 17.—TOTAL ANNUAL COST OF NEW REPORTING BURDEN

Type of report	Number of affected reports	Per report cost of new burden	Annual cost (\$ mil)
<i>Expedited:</i>			
Serious and unexpected SADR	53,350	\$104.23	\$5.6
Always expedited reports	1,650	612.44	1.0
Unexpected SADR with unknown outcome	983	918.65	0.9
Information sufficient to consider product administration changes	309	\$347.46	0.1
Medication errors	111,000	612.44	68.0
30-day followup	46,340	366.99	17.0
Serious SARs—blood products	7,000	612.44	4.3
<i>IND Safety:</i>			
Information sufficient to consider product administration changes	600	158.54	0.1
Bioavailability/bioequivalence safety report	200	508.21	0.1
<i>Periodic:</i>			
TPSR	1,435	603.76	0.9
PSUR	2,535	1,563.66	4.0
IPSR	353	1,172.75	0.4
Individual case safety reports—semiannual submission	5,206	1,042.28	5.4
<i>Other:</i>			
Reports of nonserious SADR and certain medication errors to manufacturer or applicant	4,652	36.92	0.2
Submit safety records to FDA upon request	21	217.24	0.0
Annual reports	2,432	¹ (530.99)	(1.3)
Total Annual Cost of New Reporting Burden			\$106.60

¹ Values in parentheses represent an estimate of cost savings.

V.D.2. Costs of MedDRA

FDA contracted with ERG to estimate the industry cost of using MedDRA terms to code individual case safety reports. In the fall of 1999, ERG and FDA staff visited three drug companies and conducted telephone interviews with several more companies and industry consultants. The purpose of the interviews was to collect information to assist in estimating the major cost components of implementing MedDRA. ERG's complete report is on file with the hearing clerk (Ref. 25).

Companies were asked to describe costs incurred or projected based on company experiences. Companies identified major cost elements that include one-time implementation costs such as planning and coordination of the conversion, converting existing data and information systems, and training. Recurring costs include MedDRA subscription and maintenance costs.

ERG applied estimates of cost by category and firm size to the number of affected firms within each industry. Estimates of affected drug and biologic product manufacturers are derived by applying data from 1998 FDA Adverse Drug Event Reports and Vaccine Adverse Event Reports to aggregate firm data from the Small Business Administration, Census of Manufactures and the National Science Foundation. Estimates of affected blood facilities are derived from the FDA Center for Biologics Evaluation and Research database of licensed and/or registered

establishments, the National Blood Data Research Center and the Census Bureau.

Limitations on ERG cost estimation include the complexities associated with firms' abilities to separate incremental costs from factors that substantially influence expenditures, such as integrating operations of one or more newly merged corporations, isolating U.S. corporate policies and operations from global corporate policies and operations, and reaching consensus on the extent and timing of the conversion of historical SADR and data.

V.D.2.a. One-time costs

V.D.2.a.i. *Planning and coordination.* Companies will need to allocate time to plan and coordinate the conversion of MedDRA across their affected operations. Planning costs are affected by the extent of decentralization of coding and pharmacovigilance work within the corporate structure. Managers for drug and biologics firms are expected to spend from 240 hours for very small firms to 1,400 hours for very large firms (greater than 750 or 500 employees respectively for drug and biologics firms) for planning and coordination. Costs per company ranged from \$10,800 to \$64,500 for drug and biologics firms. In contrast to drug and biologics firms, blood facilities have a limited range of products, do not need to convert legacy data, and typically operate only in the United States. Therefore, ERG judged that compliance

costs for blood facilities would be 4 to 5 percent of equivalent-sized drug and biologics firms. Estimated costs per firm range from \$450 to \$2,260 for very small and very large firms, respectively.

V.D.2.a.ii. *Development of information technology support structure.* Companies reported that information technology (IT) personnel will need to modify existing database systems to:

- Accommodate adding a new medical dictionary,
- Allow for MedDRA's complex hierarchical structure and wider field widths,
- Reconcile the comparability of existing dictionaries with MedDRA (in the short term),
- Integrate a Web browser, and
- Install or modify an autoencoder system.

IT personnel are estimated to need from 720 hours for very small firms to 1,920 hours for very large firms to develop and validate computer data systems that will accommodate MedDRA. Costs are estimated to range from \$25,850 to \$68,900 for drug and biologics firms. No costs were forecast for blood facilities.

V.D.2.a.iii. *Purchase or development of an autoencoder.* Companies reported that they currently use an existing database such as COSTART or WHOART and supplement these dictionaries with their own medical vocabulary. Autoencoders assist with the automated conversion of existing medical terms to MedDRA. Companies

may purchase autoencoders, adapt existing in-house versions, or use outside contractors. Converting existing terms to MedDRA is estimated to cost from \$20,000 to \$100,000 for drug and biologics firms. Costs are not applicable to blood facilities.

V.D.2.a.iv. *Conversion of legacy safety data.* Some companies reported that they would convert virtually all of their legacy data into MedDRA terms even though it is not required by this proposed rule. Some companies maintain that this conversion includes information from clinical trials. Nonetheless, some companies may not convert their legacy drug safety data into MedDRA or may convert only some of their products, based on criteria associated with experience and history of the drug. ERG estimated that 75 percent of companies would incur conversion costs to allow for the range of company responses. The number of terms that are converted automatically (with autoencoders) or manually will affect conversion costs. Estimated costs per company for converting existing legacy data range from about \$16,500 (for converting 15,000 terms) for very small firms to \$275,000 (for converting roughly 250,000 terms) for very large drug firms. Costs for biologics firms of corresponding size range from \$3,300 (for 3,000 terms) to \$55,000 (for about 50,000 terms). Costs are not applicable to blood facilities.

V.D.2.a.v. *Training of personnel.* Companies reported that staff most likely to receive MedDRA training include medical coders, biostatisticians, and pharmacovigilance, IT, and regulatory affairs personnel. In addition to formal training, medical data coders will require several months of experience before they become

proficient with coding in MedDRA. Training costs are dependent on the number of employees that must be trained in MedDRA and the level of training needed for their relevant duties. Training costs were estimated to range from \$9,300 to \$330,300 for very small to very large drug manufacturers and from \$9,300 to \$90,600 for biologics firms of corresponding size. ERG estimated training costs from \$1,300 to \$4,300 for very small to very large blood facilities.

V.D.2.a.vi. *Revision of standard operating procedures (SOPs).* Companies will revise a substantial group of SOPs in implementing MedDRA. Affected procedures include dictionary/coding, IT, and drug safety/pharmacovigilance. Drug and biologics firms are expected to need from 130 to 1,300 hours for very small to very large firms to revise their SOPs for MedDRA, with costs ranging from \$5,900 to \$59,200. ERG allocated 8 to 50 hours for developing or revising SOPs for blood facilities. Per firm costs for SOPs are estimated to range from \$370 to \$2,260 for very small to very large blood facilities.

V.D.2.b. Recurring costs

V.D.2.b.i. *MedDRA core subscription.* Companies must pay subscription costs on an annual basis to the MedDRA MSSO. Core subscription costs vary with the size of the company and with the level of services. Estimates of costs range from \$5,000 to \$40,000 for drug and biologics firms. ERG judged that blood facilities would incur only modest annual costs associated with MedDRA subscription and updates because of the limited range of terminology describing medical outcomes. ERG assumed that blood

facilities would either work through industry associations to negotiate lower per firm subscription costs or, alternatively, contract with contract research organizations to obtain the necessary MedDRA codes.

V.D.2.b.ii. *MedDRA versions and quarterly updates.* Currently the MSSO intends to provide quarterly updates as well as periodic new versions of MedDRA. Companies did not have a sufficient history with incorporating MedDRA changes to estimate the costs of updates. Cost components would include senior level reviews of each update, communicating the changes to affected personnel, and IT support to upload and reconcile new versions. Costs are estimated to range from \$5,700 to \$43,000 for drug and biologics firms. No costs were assigned to blood facilities.

V.D.2.b.iii. *Maintenance of existing dictionaries.* Companies reported that they may need to maintain their existing dictionaries for an indeterminate time. Conditions that could influence whether and for how long a company would need to maintain its existing dictionaries are: (1) The company uses different dictionaries for its postmarketing safety and clinical study data bases; (2) the company has products in late-stage clinical trials; and (3) the company has marketed products near the end of their useful life. ERG estimates the maintenance costs for existing dictionaries are expected to range from \$4,300 to \$136,400 annually for drug manufacturers and from \$4,300 to \$43,400 annually for biologics manufacturers. No costs were assigned to blood facilities.

Table 18 presents the estimated costs to industry of implementing MedDRA for each cost category.

TABLE 18.—TOTAL COMPLIANCE COSTS OF MEDDRA BY COST CATEGORY

Drugs and biologics	Total cost ¹ (\$ million)	Percent of total ¹
First-Time Costs:		
Planning and coordination	16.3	9
Purchase or development of auto-encoder	20.5	12
Personnel training	46.0	27
Development of IT structure	14.7	9
Legacy safety data conversion	31.9	18
Revision of SOPs	14.8	9
Total First-time	144.2	83
Recurring Costs:		
Annual MedDRA core subscription	6.6	4
MedDRA versioning	6.9	4
Maintenance of additional medical dictionary	15.0	9
Total recurring	28.5	16
Total first year costs (First-time + recurring)	172.8	100

¹ Totals may not add due to rounding.

V.E. Small Business Analysis

The following analysis along with other sections of this preamble constitute the agency's regulatory flexibility analysis as required under the Regulatory Flexibility Act.

V.E.1. Need for and Objectives of the Rule

A primary objective of this proposed rule is the harmonization of FDA's safety reporting requirements with international initiatives. The proposed rule would also improve the quality of information contained in postmarketing safety reports for marketed human drug and biological products. By providing more complete information for individual case safety reports, the revised reports would enhance the ability of manufacturers, applicants, and the agency to identify, monitor, and communicate the risks and benefits of marketed drug and biological products. Monitoring these risks and benefits is especially critical for recently approved products introduced to large and diverse patient populations following market approval.

V.E.2. Description and Estimate of Small Entities

The proposed rule applies to manufacturers, applicants, and contractors of drug and biological products, and persons involved in blood collection and transfusion. The Small Business Administration (SBA) defines a small business in Standard Industrial Classification (SIC) 2834 (or North American Industry Classification System (NAICS) code 325412) as one employing fewer than 750 employees and in SIC 2836 (or NAICS code

325414) as one employing fewer than 500 employees. According to 1996 U.S. Bureau of the Census statistics, almost 90 percent of the firms under these SIC codes are considered small businesses. A review of 1998 AERS data, which contain postmarketing 15-day and periodic safety reports from manufacturers and applicants of marketed drug and biological products, found that about 200 firms submitted at least one individual case safety report for a trade name product and that the majority of these firms were considered large under the SBA definitions. However, the number of firms submitting reports vary from year to year. Therefore, using the 1998 AERS data, estimates of the percentages of reporting firms by size were distributed to the number of firms in each SIC, suggesting that about 230 drug and 72 biologics firms would be affected by the proposed rule, of which 190, or about 60 percent, would be considered small.

FDA estimates that about 3,200 blood facilities would be affected by the proposed regulation. Approximately 3,000 are hospitals with blood collection and/or compatibility testing operations, classified in SIC 8062 (or NAICS code 62211), and 200 are blood banks or non-hospital blood and plasmapheresis centers, classified in SIC 8099 (or NAICS code 621991). The SBA defines businesses in SIC 8062 and 8099 with annual revenues of \$25 million and \$7.5 million or less, respectively, as small. ERG estimated the number of small businesses affected in SIC's 8062 and 8099 at 1,786 and 188, respectively. This is approximately 60 and 94 percent of the blood facilities in SICs 8062 and 8099, respectively, that will be

implementing the MedDRA requirements.

V.E.3. Projected Reporting, Recordkeeping, and Other Compliance Requirements

V.E.3.a. Reporting and recordkeeping requirements. The proposed rule may impose an additional burden on manufacturers of human drug products for which SADR are reported. In any year, SADR may be reported for about half of the products marketed in the United States. AERS data from 1998 suggest that small firms manufactured less than 12 percent of the products for which SADR were reported. Moreover, during this same year, only about 2 percent of the postmarketing 15-day alert reports submitted to the agency were from small firms. Nevertheless, the proposed changes to the postmarketing safety reporting requirements may impose a substantial burden on a significant number of small firms, especially small startup firms with only one product on the market. The extent of the impact will depend on the time that has elapsed since the drug was approved and the number and types of individual case safety reports received in a reporting period.

To illustrate the impact of the safety reporting and recordkeeping requirements of the proposed rule, table 19 shows the hypothetical first-year burden for a drug approved 6 months prior to the effective date of the final rule. Under this scenario, the first-year burden incurred for a newly approved product might be as much as \$19,600, assuming 26 expedited and 6 followup reports, two semiannual reports, and two PSURs had been submitted.

TABLE 19.—HYPOTHETICAL FIRST-YEAR REPORTING AND RECORDKEEPING BURDEN FOR NEWLY APPROVED DRUG PRODUCT

	Expedited (serious, unexpected SADR)	Expedited (medication errors)	Expedited (unexpected SADR with unknown outcome)	Always expedited report	30-day follow-up	Individual case safety report—semi-annual submission	PSUR	Total
Per report new burden ¹	\$104	\$612	\$919	\$612	\$367	\$1,042	\$1,564	
Number of reports	8	16	1	1	6	2	2	36
Totals ²	\$834	\$9,799	\$919	\$612	\$2,202	\$2,084	\$3,128	\$19,578

¹ Only whole dollar values are shown.

² Values rounded to the nearest whole number.

V.E.3.b. Implementing MedDRA. Implementing MedDRA would impose additional significant one-time and recurring costs on drug and biological product manufacturers. Costs would vary among individual firms depending

on circumstances, including the number of products manufactured, the frequency of SADR, and the extent of legacy data converted. Table 20 displays ERG's estimates per firm of revenues, annualized compliance costs and costs

as a percent of revenues. Costs for small entities are 0.15 percent and 0.28 percent of revenues for drug and biological product manufacturers, respectively. Similarly, average compliance costs for small entities are

0.01 percent and 0.03 percent of revenue for SICs 8062 and 8099, respectively.

TABLE 20.—COMPLIANCE COSTS AS A PERCENT OF ESTIMATED REVENUES FOR SMALL ENTITIES

Industry classification	Number of employees	Number of affected firms	Per firm estimated revenues (\$000)	Per firm annualized compliance costs (\$000)	Compliance cost as a percent of estimated revenues
SIC 2834 Pharmaceutical preparations	< 750	146	44,265	66.9	0.15
SIC 2836 Biological products	< 500	44	15,752	44.4	0.28
SIC 8062 General medical and surgical hospitals	< 500	1,786	13,366	0.6	0.01
SIC 8099 Blood banks (Health and allied services, NEC) ..	< 500	188	1,320	0.3	0.03

The reporting, coding, and analysis of SADR are standard procedures that manufacturers routinely conduct under current regulations. No additional professional skills would be necessary to comply with this rule. However, current safety reviewers, analysts, and IT personnel would need training to implement MedDRA.

V.E.4. Alternatives and Steps To Minimize the Impact on Small Entities

The major objectives of this proposed rule are to harmonize FDA’s safety reporting requirements with international initiatives and to improve the quality of safety reports. With these objectives in mind, the agency considered alternatives to this proposed rule.

V.E.4.a. *Do nothing.* The agency considered but rejected the option of not proposing this rule. The proposed rule would align FDA’s safety report terms, formats and requirements for human drugs and biological products with the recommendations of ICH. With regard to use of a medical dictionary for safety reporting purposes, at the present time, major problems exist with comparing safety data globally because multiple medical dictionaries are being used internationally for coding of SADR (see section III.F.2 of this document). In this rule, the agency proposes to require the use of MedDRA, the medical dictionary developed by ICH. FDA believes that “to do nothing” would be inconsistent with the agency’s efforts to harmonize safety reporting with international initiatives.

Another objective of this proposed rule is to improve the quality of safety reports. In this preamble, the agency cited a substantial number of studies that estimate the number of SADR that have resulted in a hospitalization or that occur in a hospital and the hospital costs related to SADR. Safety reports that are complete are critical and necessary to reduce SADR, medication errors, and hospital costs. This proposed rule would improve the agency’s ability to monitor the safety of human drugs

and biological products. In light of this information, “to do nothing” would be inconsistent with the agency’s mission of protecting public health.

V.E.4.b. *Do not require a medical dictionary.* The agency considered but rejected the alternative of not requiring the use of MedDRA terms in individual case safety reports. MedDRA is an integral part of the postmarket safety reporting system that was developed jointly with international stakeholders. Requiring MedDRA terms in safety reports will enhance the analysis of drug safety information. Moreover, MedDRA is a medical dictionary designed to translate terms in multiple languages, thus aiding in more expeditious and broader international drug use comparisons and analysis. Not requiring MedDRA would compromise the agency objective of improving drug safety reporting and analysis. In addition, continued use of multiple medical dictionaries to code SADR will perpetuate the major problems with comparing safety data globally that currently exist.

V.E.4.c. *Do not require medication errors as expedited reports.* The agency considered but rejected the alternative of not requiring medication errors as expedited reports. Requiring expedited reports of medication errors would allow the agency to review critical information and take appropriate and more timely action on SADR that are preventable. Not requiring expedited reports of medication errors would ignore a key step in reducing medical errors.

V.E.4.d. *Do not require blood establishments to submit reports for all serious SADR associated with blood collection and transfusion.* The agency considered but rejected the alternative of not requiring blood establishments to submit reports for all serious SADR associated with blood collection and transfusion, in addition to the current requirement to submit reports of fatalities. Because these establishments are currently required to conduct

investigations and prepare and maintain reports of serious SADR, this proposal would impose minimal costs. However, only some serious SADR must be reported in a timely manner. The agency believes it is critical that we receive all such reports. This would improve the agency’s ability to take appropriate action to protect the blood supply more consistently, to enhance donor safety and to ensure the safety, purity and potency of blood and blood components for administration to patients.

V.E.4.e. *Do not require certain bioavailability and bioequivalence reports as expedited reports.* The agency considered but rejected the alternative of not requiring expedited reports of SADR for bioavailability and bioequivalence studies not subject to an IND. This requirement would allow the agency quicker access to information and would facilitate appropriate action to protect those enrolled in clinical trials.

V.E.4.f. *Waivers for economic hardship.* The agency recognizes that requiring individual case safety reports to be coded using MedDRA will likely impose significant costs on some small firms (see section III.F.2 of this document). One alternative would be to consider the option of allowing companies to request a waiver from MedDRA coding, based on economic hardship. The agency is seeking comment on ways to reduce economic hardships of implementing MedDRA while maintaining adequate procedures to monitor and assess the safety of products.

V.E.4.g. *Small business outreach, training, and assistance.* The agency has received both written and verbal input from interested parties, including small businesses, on the recommendations of ICH regarding safety reporting for human drugs and biological products (e.g., the ICH E2A guidance, the ICH E2C guidance, and ICH M1). These public comments addressed published draft versions of the ICH guidances as well as numerous agency presentations

at public workshops and forums (e.g., sponsored by the Drug Information Association (DIA) or the Pharmaceutical Education and Research Institute (PERI)). The agency has considered these comments in development of this proposed rule.

Once this proposed rule is finalized, the agency will provide the public with an overview of the provisions in the rule at workshops and forums (e.g., DIA meetings, PERI workshops). All firms, including small firms, would have an opportunity to attend these presentations.

Firms can access AERS-related information on the Internet at <http://www.fda.gov/cder/aers/index.htm>. The AERS site includes a "Reporting Regulations and Guidances" page that provides a summary of the rulemaking (proposed rules, final rules) and guidances regarding the agency's safety reporting requirements for human drugs and biological products. This site is updated as changes to the safety reporting requirements are made.

V.F. Unfunded Mandates Reform Act of 1995

On the basis of the preceding discussion, under the Unfunded Mandates Reform Act, FDA concludes that if only .85 percent of the estimated SADR are prevented, then the benefits of this proposed rule will exceed the annualized compliance costs that it imposes on the U.S. economy. In addition, the agency has considered other alternatives as discussed in section V.E.4 of this document and determined that the proposed rule is the best alternative that would meet the objectives of this rule.

V.G. References

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

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16. Bates, David W. *et al.*, "The Costs of Adverse Drug Events in Hospitalized Patients," *Journal of the American Medical Association*, 277:307-311, 1997.
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19. Classen, David C. *et al.*, "Adverse Drug Events in Hospitalized Patients Excess Length of Stay, Extra Costs and Attributable Mortality," *Journal of the American Medical Association*, 277:301-306, 1997.
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VI. Paperwork Reduction Act of 1995

This proposed rule contains collections of information which are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501-3520). "Collection of information" is defined in 44 U.S.C. 3502(3) and 5 CFR 1320.3(c) and includes agency requests or requirements that members of the public obtain, maintain, retain, or report information to the agency, or disclose information to a third party or to the public. The title, description, and respondent description of the information collection are shown below with an estimate of the annual reporting burden. Included in the estimate is the time for reviewing instructions, gathering and maintaining the data needed, and completing and reviewing the collection of information.

FDA invites comments on: (1) Whether the proposed collection of information is necessary for proper performance of FDA's functions, including whether the information will have practical utility; (2) the accuracy of FDA's estimate of the burden of the proposed collection of information, including the validity of the methodology and assumptions used; (3) ways to enhance the quality, utility, and clarity of the information to be collected; and (4) ways to minimize the burden of the collection of information

on respondents, including through the use of automated collection techniques, when appropriate, and other forms of information technology.

Title: Safety Reporting Requirements for Human Drug and Biological Products

Description: The proposed rule would amend FDA's safety reporting regulations for human drug and biological products to implement definitions, and reporting formats and standards as recommended by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and by the World Health Organization's Council for International Organizations of Medical Sciences (CIOMS); 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 safety reporting requirements; and make other minor revisions. The proposed rule would also amend FDA's postmarketing annual reports regulations for human drugs and licensed biological products by revising the content for these reports. These changes would 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. The estimates provided in this section are not only attributed to the new proposed requirements in this rulemaking but also include burdens associated with our current safety reporting requirements.

VI.A. Expedited Safety Reporting

Proposed §§ 310.305(c)(2)(i), 314.80(c)(2)(i), and 600.80(c)(2)(i) would require manufacturers and applicants to submit a report to FDA for each SADR, received or otherwise obtained, that is both serious and unexpected, whether foreign or domestic, as soon as possible, but in no case later than 15 calendar days after receipt by the manufacturer or applicant of the minimum data set for the serious, unexpected SADR. Based on data concerning the number of expedited reports currently received by the agency, FDA estimates that approximately 350 expedited reports of serious and unexpected SADRs will be submitted annually under proposed § 310.305(c)(2)(i); approximately 50,000 reports will be submitted annually under proposed § 314.80(c)(2)(i); and

approximately 3,000 reports will be submitted annually under proposed § 600.80(c)(2)(i). FDA estimates that approximately 14 manufacturers under proposed § 310.305(c)(2)(i) will submit these reports; approximately 282 applicants under proposed § 314.80(c)(2)(i) will submit these reports; and approximately 69 applicants under proposed § 600.80(c)(2)(i) will submit these reports. Based on the agency's familiarity with the content of expedited reports for serious and unexpected SADRs, FDA estimates that it will take an average of 16 hours for manufacturers and applicants to prepare and submit one of these reports to FDA. Preparation of an expedited report for a serious and unexpected SADR would include gathering information (proposed §§ 310.305(b) and (c)(1), 314.80(b) and (c)(1), and 600.80(b) and (c)(1)), providing attachments, if applicable (proposed §§ 310.305(c)(2)(ix) and (c)(2)(x), 314.80(c)(2)(ix), and 600.80(c)(2)(ix)), and formatting information (proposed §§ 310.305(c)(2)(xii), (d), and (e), 314.80(c)(2)(xi), (c)(4), and (e), and 600.80(c)(2)(xi), (c)(4), and (e)).

Proposed §§ 310.305(c)(2)(ii), 314.80(c)(2)(ii), and 600.80(c)(2)(ii) would require manufacturers and applicants to submit a report to FDA concerning information, received or otherwise obtained, whether foreign or domestic, that would be sufficient, based upon appropriate medical judgment, to consider product administration changes (*e.g.*, any significant unanticipated safety finding or data in the aggregate from an *in vitro*, animal, epidemiological, or clinical study, whether or not conducted under an IND, that suggests a significant human risk, such as reports of mutagenicity, teratogenicity, or carcinogenicity, or reports of a lack of efficacy with a drug or biological product used in treating a life-threatening or serious disease). Manufacturers and applicants would be required to submit this information to FDA as soon as possible, but in no case later than 15 calendar days after determination by the manufacturer or applicant that the information qualifies for expedited reporting. Expedited reports containing information that would be sufficient to consider changes in product administration are a new type of safety report. Based on data concerning voluntary reporting of this type of information to the agency, FDA estimates that approximately 5 expedited reports concerning information sufficient to consider

product administration changes will be submitted annually under proposed § 310.305(c)(2)(ii); approximately 300 reports will be submitted annually under proposed § 314.80(c)(2)(ii); and approximately 4 reports will be submitted annually under proposed § 600.80(c)(2)(ii). FDA estimates that approximately 5 manufacturers under proposed § 310.305(c)(2)(ii) will submit these expedited reports; approximately 50 applicants under proposed § 314.80(c)(2)(ii) will submit these expedited reports; and approximately 4 applicants under proposed § 600.80(c)(2)(ii) will submit these expedited reports. Based on the content of the voluntary reports submitted to the agency, FDA estimates that it will take an average of 8 hours for manufacturers and applicants to prepare and submit an expedited report to FDA concerning information sufficient to consider product administration changes. Preparation of these expedited reports would include gathering information (proposed §§ 310.305(b) and (c)(1), 314.80(b) and (c)(1), and 600.80(b) and (c)(1)), providing attachments, if applicable (proposed §§ 310.305(c)(2)(ix) and (c)(2)(x), 314.80(c)(2)(ix), and 600.80(c)(2)(ix)), and formatting information (proposed §§ 310.305(c)(2)(xii), (d), and (e), 314.80(c)(2)(xi), (c)(4), and (e), and 600.80(c)(2)(xi), (c)(4), and (e)).

Proposed §§ 310.305(c)(2)(iii), 314.80(c)(2)(iii), and 600.80(c)(2)(iii) would require manufacturers and applicants to submit a report to FDA for each SADR that is unexpected and for which the determination of an outcome is unattainable (*i.e.*, SADR with unknown outcome) within 45 calendar days after initial receipt by the manufacturer or applicant of the minimum data set for an unexpected SADR. Expedited reports of unexpected SADRs with an unknown outcome are a new type of safety report. Based on data concerning the number of unexpected SADR reports with an unknown outcome currently received by the agency, FDA estimates that approximately 46 expedited reports of an unexpected SADR with an unknown outcome will be submitted annually under proposed § 310.305(c)(2)(iii); approximately 912 reports will be submitted annually under proposed § 314.80(c)(2)(iii); and approximately 25 reports will be submitted annually under proposed § 600.80(c)(2)(iii). FDA estimates that approximately 10 manufacturers under proposed § 310.305(c)(2)(iii) will submit these expedited reports; approximately 109 applicants under proposed

§ 314.80(c)(2)(iii) will submit these expedited reports; and approximately 12 applicants under proposed § 600.80(c)(2)(iii) will submit these expedited reports. Based on the agency's familiarity with the content of expedited reports for serious and unexpected SADRs, FDA estimates that it will take an average of 24 hours for manufacturers and applicants to prepare and submit an expedited report for an unexpected SADR with an unknown outcome to FDA. Preparation of expedited reports for unexpected SADRs with an unknown outcome would include gathering information (proposed §§ 310.305(b) and (c)(1), 314.80(b) and (c)(1), and 600.80(b) and (c)(1)), providing attachments, if applicable (proposed §§ 310.305(c)(2)(ix) and (c)(2)(x), 314.80(c)(2)(ix), and 600.80(c)(2)(ix)), and formatting information (proposed §§ 310.305(c)(2)(xii), (d), and (e), 314.80(c)(2)(xi), (c)(4), and (e), and 600.80(c)(2)(xi), (c)(4), and (e)).

Proposed §§ 310.305(c)(2)(iv), 314.80(c)(2)(iv), and 600.80(c)(2)(iv) would require manufacturers and applicants to submit to FDA each SADR, received or otherwise obtained, whether foreign or domestic, that is the subject of an always expedited report. Certain medically significant SADRs (*e.g.*, ventricular fibrillation, liver necrosis, confirmed or suspected transmission of an infectious agent by a marketed drug or biological product) which may jeopardize the patient or subject and/or require medical or surgical intervention to treat the patient or subject would be subject to an always expedited report. These SADRs would be submitted to FDA whether unexpected or expected and whether or not the SADR leads to a serious outcome. Always expedited reports would be submitted to the agency within 15 calendar days after initial receipt by the manufacturer or applicant of the minimum data set for the report. Always expedited reports are a new type of safety report. Based on data concerning the number of safety reports currently received by the agency for the SADRs specified under proposed §§ 310.305(c)(2)(iv), 314.80(c)(2)(iv), and 600.80(c)(2)(iv), FDA estimates that approximately 50 always expedited reports will be submitted annually under proposed § 310.305(c)(2)(iv); approximately 1,500 reports will be submitted annually under proposed § 314.80(c)(2)(iv); and approximately 100 reports will be submitted annually under proposed § 600.80(c)(2)(iv). FDA estimates that approximately 10 manufacturers under proposed § 310.305(c)(2)(iv) will submit these

expedited reports; approximately 100 applicants under proposed § 314.80(c)(2)(iv) will submit these expedited reports; and approximately 10 applicants under proposed § 600.80(c)(2)(iv) will submit these expedited reports. Based on the agency's familiarity with the content of expedited reports for serious and unexpected SADRs, FDA estimates that it will take an average of 16 hours for manufacturers and applicants to prepare and submit an always expedited report to the agency. Preparation of always expedited reports would include gathering information (proposed §§ 310.305(b) and (c)(1), 314.80(b) and (c)(1), and 600.80(b) and (c)(1)), providing attachments, if applicable (proposed §§ 310.305(c)(2)(ix) and (c)(2)(x), 314.80(c)(2)(ix), and 600.80(c)(2)(ix)), and formatting information (proposed §§ 310.305(c)(2)(xii), (d), and (e), 314.80(c)(2)(xi), (c)(4), and (e), and 600.80(c)(2)(xi), (c)(4), and (e)).

Proposed §§ 310.305(c)(2)(v), 314.80(c)(2)(v), and 600.80(c)(2)(v) would require manufacturers and applicants to submit all domestic reports of medication errors, whether actual or potential. Expedited reports of medication errors are a new type of safety report. Based on data concerning the number of domestic reports of medication errors voluntarily submitted to the agency, FDA estimates that approximately 1,000 reports of medication errors will be submitted annually under proposed § 310.305(c)(2)(v); approximately 100,000 reports will be submitted annually under proposed § 314.80(c)(2)(v); and approximately 10,000 reports will be submitted annually under proposed § 600.80(c)(2)(v). FDA estimates that approximately 10 manufacturers under proposed § 310.305(c)(2)(v) will submit these expedited reports; approximately 150 applicants under proposed § 314.80(c)(2)(v) will submit these expedited reports; and approximately 30 applicants under proposed § 600.80(c)(2)(v) will submit these expedited reports. Based on the agency's familiarity with the content of expedited reports for serious and unexpected SADRs, FDA estimates that it will take an average of 16 hours for manufacturers and applicants to prepare and submit an expedited report of a medication error to the agency. Preparation of medication error reports would include gathering information (proposed §§ 310.305(b) and (c)(1), 314.80(b) and (c)(1), and 600.80(b) and (c)(1)), providing attachments, if

applicable (proposed §§ 310.305(c)(2)(ix) and (c)(2)(x), 314.80(c)(2)(ix), and 600.80(c)(2)(ix)), and formatting information (proposed §§ 310.305(c)(2)(xii), (d), and (e), 314.80(c)(2)(xi), (c)(4), and (e), and 600.80(c)(2)(xi), (c)(4), and (e)).

Proposed §§ 310.305(c)(2)(vi), 314.80(c)(2)(vi), and 600.80(c)(2)(vi) would require manufacturers and applicants to submit a 30-day followup report to FDA for any expedited report under proposed §§ 310.305(c)(2)(i), (c)(2)(iv), (c)(2)(v), 314.80(c)(2)(i), (c)(2)(iv), (c)(2)(v), 600.80(c)(2)(i), (c)(2)(iv), and (c)(2)(v) that does not contain a full data set. These 30-day followup reports would be submitted within 30 calendar days after submission of the expedited report. Thirty-day followup reports are a new type of safety report. Based on data concerning the number of followup reports received by the agency, FDA estimates that approximately 340 30-day followup reports will be submitted annually under proposed § 310.305(c)(2)(vi); approximately 43,000 30-day followup reports will be submitted annually under proposed § 314.80(c)(2)(vi); and approximately 3,000 30-day followup reports will be submitted annually under proposed § 600.80(c)(2)(vi). FDA estimates that approximately 7 manufacturers under proposed § 310.305(c)(2)(vi) will submit 30-day follow up reports; approximately 140 applicants under proposed § 314.80(c)(2)(vi) will submit 30-day follow up reports; and approximately 69 applicants under proposed § 600.80(c)(2)(vi) will submit 30-day followup reports. Based on the agency's familiarity with the content of followup reports for serious and unexpected SADRs, FDA estimates that it will take an average of 8 hours for manufacturers and applicants to prepare and submit a 30-day follow up report to the agency. Preparation of 30-day follow up reports would include gathering information (proposed §§ 310.305(b) and (c)(1), 314.80(b) and (c)(1), and 600.80(b) and (c)(1)), providing attachments, if applicable (proposed §§ 310.305(c)(2)(ix) and (c)(2)(x), 314.80(c)(2)(ix), and 600.80(c)(2)(ix)), and formatting information (proposed §§ 310.305(c)(2)(xii), (d), and (e), 314.80(c)(2)(xi), (c)(4), and (e), and 600.80(c)(2)(xi), (c)(4), and (e)).

Proposed §§ 310.305(c)(2)(vii), 314.80(c)(2)(vii), and 600.80(c)(2)(vii) would require manufacturers and applicants to submit a 15-day followup report to FDA concerning any new information, received or otherwise obtained, after any initial expedited report or any followup report, except for

expedited reports which are subject to the 30-day followup reporting requirement under proposed §§ 310.305(c)(2)(vi), 314.80(c)(2)(vi), and 600.80(c)(2)(vi). Proposed §§ 310.305(b)(2), 314.80(b)(2), and 600.80(b)(2) would also require manufacturers and applicants to submit 15-day followup reports to FDA with any new information concerning an individual case safety report forwarded to the manufacturer or applicant by FDA. Proposed §§ 310.305(c)(2)(viii)(A), 314.80(c)(2)(viii)(A), and 600.80(c)(2)(viii)(A) would also require manufacturers and applicants to submit to FDA as 15-day followup reports any documents required under these paragraphs that become available after submission of an expedited report. These 15-day followup reports would be submitted within 15 calendar days of initial receipt of the new information by the manufacturer or applicant. Based on data concerning the number of followup reports currently received by the agency, FDA estimates that approximately 55 15-day followup reports will be submitted annually under proposed § 310.305(b)(2), (c)(2)(vii), and (c)(2)(viii)(A); approximately 10,000 15-day followup reports will be submitted annually under proposed § 314.80(b)(2), (c)(2)(vii), and (c)(2)(viii)(A); and approximately 1,000 15-day followup reports will be submitted annually under proposed § 600.80(b)(2), (c)(2)(vii), and (c)(2)(viii)(A). FDA estimates that approximately 10 manufacturers under proposed § 310.305 will submit 15-day followup reports; approximately 184 applicants under proposed § 314.80 will submit 15-day followup reports; and approximately 69 applicants under proposed § 600.80 will submit 15-day followup reports. Based on the agency's familiarity with the content of followup reports for serious and unexpected SADRs, FDA estimates that it will take an average of 4 hours for manufacturers and applicants to prepare and submit a 15-day followup report to FDA. Preparation of 15-day followup reports would include gathering information (proposed §§ 310.305(b) and (c)(1), 314.80(b) and (c)(1), and 600.80(b) and (c)(1)), providing attachments, if applicable (proposed §§ 310.305(c)(2)(ix) and (c)(2)(x), 314.80(c)(2)(ix), and 600.80(c)(2)(ix)), and formatting information (proposed §§ 310.305(c)(2)(xii), (d), and (e), 314.80(c)(2)(xi), (c)(4), and (e), and 600.80(c)(2)(xi), (c)(4), and (e)).

Proposed §§ 310.305(c)(2)(xi), 314.80(c)(2)(x), and 600.80(c)(2)(x)

would require contractors and shared manufacturers to submit safety reports of any SADRs or medication errors for the product to the manufacturer (proposed §§ 310.305(c)(2)(xi) or applicant (proposed §§ 314.80(c)(2)(x) and 600.80(c)(2)(x)) within 5 calendar days of its receipt by the contractor or shared manufacturer. Based on information included in individual case safety reports currently submitted to the agency, FDA estimates that approximately 10 safety reports will be submitted to manufacturers annually under proposed § 310.305(c)(2)(xi); approximately 11,370 safety reports will be submitted to applicants annually under proposed § 314.80(c)(2)(x); and approximately 250 safety reports will be submitted to applicants annually under proposed § 600.80(c)(2)(x). FDA estimates that approximately 5 contractors under proposed § 310.305 will submit safety reports to the manufacturer; approximately 100 contractors under proposed § 314.80 will submit safety reports to the applicant; and approximately 20 contractors and shared manufacturers under proposed § 600.80 will submit safety reports to the applicant. Based on the agency's familiarity with the content of individual case safety reports, FDA estimates that it will take an average of 2 hours for contractors and shared manufacturers to prepare and submit a safety report to a manufacturer or applicant.

Proposed § 312.32(c)(1)(i) would require sponsors to notify FDA and all participating investigators in a written IND safety report of any SADR, based on the opinion of the investigator or sponsor, that 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. The sponsor would identify all safety reports previously filed with the IND concerning a similar SADR and would analyze the significance of the SADR in light of previous, similar reports. Based on data concerning the number of written IND safety reports currently received by the agency, FDA estimates that approximately 4,860 written IND safety reports of serious and unexpected SADRs will be submitted annually under proposed § 312.32(c)(1)(i) for human drugs, and approximately 2,980 written IND safety reports will be submitted annually under proposed § 312.32(c)(1)(i) for human biological products. FDA estimates that approximately 457 sponsors will submit written IND safety reports for human drugs, and

approximately 602 sponsors will submit written IND safety reports for human biological products. Based on the agency's familiarity with the content of written IND safety reports for serious and unexpected SADRs, FDA estimates that it will take an average of 16 hours for sponsors to prepare and submit one of these reports to FDA. Preparation of a written IND safety report for a serious and unexpected SADR would include gathering information (proposed § 312.32(b)) and formatting information (proposed § 312.32(c)(1)(iii)).

Proposed § 312.32(c)(1)(ii) would require sponsors to notify FDA and all participating investigators in a written IND safety report of information, based on appropriate medical judgment, that might materially influence the benefit-risk assessment of an investigational drug, or would be sufficient to consider changes in either product administration or in the overall conduct of a clinical investigation (e.g., any significant unanticipated safety finding or data in the aggregate from an in vitro, animal, epidemiological, or clinical study, whether or not conducted under an IND, that suggests a significant human risk, such as reports of mutagenicity, teratogenicity, or carcinogenicity, or reports of a lack of efficacy with a drug or biological product used in treating a life-threatening or serious disease). This information would be submitted as soon as possible, but in no case later than 15 calendar days after determination by the sponsor that the information qualifies for expedited reporting. Based on information contained in written IND safety reports that the agency has received in the past, FDA estimates that approximately 300 written IND safety reports concerning information that might materially influence the benefit-risk assessment of an investigational drug, or that would be sufficient to consider changes in either product administration or in the overall conduct of a clinical investigation will be submitted annually under proposed § 312.32(c)(1)(ii) for human drugs, and approximately 300 reports will be submitted annually under proposed § 312.32(c)(1)(ii) for human biological products. FDA estimates that approximately 100 sponsors will submit these written IND safety reports for human drugs, and approximately 100 sponsors will submit these reports for human biological products. Based on the agency's familiarity with the content of written IND safety reports, FDA estimates that it will take an average of 8 hours for sponsors to prepare and submit this type of written IND safety

report to FDA. Preparation of these written IND safety reports would include gathering information (proposed § 312.32(b)) and formatting information (proposed § 312.32(c)(1)(iii)).

Proposed § 312.32(c)(2) would require sponsors to notify FDA by telephone or by facsimile transmission of any unexpected fatal or life-threatening SADR based on the opinion of the investigator or sponsor as soon as possible but in no case later than 7 calendar days after receipt by the sponsor of the minimum data set for an unexpected fatal or life-threatening SADR. Based on data concerning the number of telephone IND safety reports currently received by the agency, FDA estimates that approximately 490 telephone and facsimile IND safety reports will be submitted annually under proposed § 312.32(c)(2) for human drugs, and approximately 290 reports will be submitted annually under proposed § 312.32(c)(2) for human biological products. FDA estimates that approximately 135 sponsors will submit these reports for human drugs, and approximately 180 sponsors will submit these reports for human biological products. Based on the agency's familiarity with telephone and facsimile IND safety reports, FDA estimates that it will take an average of 4 hours for sponsors to prepare and submit one of these reports to FDA. Preparation of a telephone or facsimile IND safety report would include gathering information (proposed § 312.32(b)).

Proposed § 312.64(b) would require an investigator to notify the sponsor of any serious SADR immediately and any other SADR promptly unless the protocol or investigator's brochure specifies a different timetable for reporting the SADR. Based on data concerning the number of sponsors currently conducting clinical investigations under an IND and the number of written IND safety reports currently received by the agency, FDA estimates that approximately 100,000 investigator safety reports will be submitted to sponsors annually under proposed § 312.64(b) for human drugs, and approximately 60,000 investigator safety reports will be submitted to sponsors annually under proposed § 312.64(b) for human biological products. FDA estimates that approximately 10,000 investigators will submit safety reports to sponsors for human drugs, and approximately 6,000 investigators will submit safety reports to sponsors for human biological products. Based on the agency's familiarity with the content of IND safety reports, FDA estimates that it will

take an average of 2 hours for an investigator to prepare and submit one of these reports to the sponsor.

Proposed § 320.31(d)(3) would require persons conducting human bioavailability and bioequivalence studies that are not subject to an IND to submit to FDA written safety reports as prescribed under proposed § 312.32(c)(1) and telephone and facsimile safety reports as prescribed under proposed § 312.32(c)(2). These persons would submit these safety reports to all participating investigators and the appropriate FDA division in the Center for Drug Evaluation and Research (*i.e.*, safety reports for the reference listed drug would be forwarded to the new drug review division that has responsibility for that drug; safety reports for the investigational drug product would be forwarded to the Director, Division of Bioequivalence, Office of Generic Drugs). These persons would be required to identify all safety reports previously filed for the bioavailability or bioequivalence study concerning a similar SADR, and analyze the SADR in light of previous similar reports, as required under proposed § 312.32(c)(1)(i). Written, telephone, and facsimile safety reports for bioavailability and bioequivalence studies not subject to an IND are a new type of safety report. Based on data concerning voluntary reporting to the agency of safety information for these bioavailability and bioequivalence studies, FDA estimates that approximately 200 safety reports will be submitted annually under proposed § 320.31(d)(3). FDA estimates that approximately 10 sponsors will submit these safety reports. Based on the agency's familiarity with the content of IND safety reports, FDA estimates that it will take an average of 14 hours for sponsors to prepare and submit a safety report to FDA.

Proposed § 606.170(b) would require blood establishments to notify FDA in a written report of any serious SAR, except a fatality, within 45 calendar days after determination of a serious SAR. These written reports would be submitted to FDA using the reporting format provided in proposed § 600.80(c)(4). Based on data from the scientific literature and reports voluntarily received by the agency, FDA estimates that approximately 7,000 written reports will be submitted annually under proposed § 606.170(b). FDA estimates that approximately 3,062 blood establishments will submit these written reports. Based on the agency's familiarity with the content of expedited reports for serious and unexpected SADRs, FDA estimates that it will take

an average of 16 hours to prepare and submit each of these written reports to FDA.

Proposed § 606.170(c) would require blood establishments to notify FDA by telephone, facsimile, express mail, or electronically transmitted mail as soon as possible of an SAR that results in a fatality. Proposed § 606.170(c) would also require these facilities to submit a written report to FDA within 7 calendar days after the fatality. The written reports would be submitted using the reporting format provided in proposed § 600.80(c)(4). Based on data concerning the number of reports for fatalities associated with blood collection and transfusion currently received by the agency, FDA estimates that approximately 75 reports will be submitted annually under proposed § 606.170(c). FDA estimates that approximately 75 blood establishments will submit these reports. Based on the agency's familiarity with the content of written reports for a fatality, FDA estimates that it will take an average of 20 hours to prepare and submit each of these reports to FDA.

VI.B. Periodic Safety Reports

Proposed §§ 314.80(c)(3)(i) and 600.80(c)(3)(i) would require persons holding an application (*i.e.*, NDA, ANDA, BLA) approved before January 1, 1998, to submit a TPSR every 5 years after U.S. approval of the application. These persons would also be required to submit a TPSR at 7.5 and 12.5 years after U.S. approval of the application. Based on data concerning postmarketing periodic safety reports currently received by the agency, FDA estimates that approximately 1,400 TPSRs will be submitted annually under proposed § 314.80(c)(3)(i); approximately 35 TPSRs will be submitted annually under proposed § 600.80(c)(3)(i). FDA estimates that approximately 80 applicants under proposed § 314.80(c)(3)(i) will submit TPSRs, and approximately 20 applicants under proposed § 600.80(c)(3)(i) will submit TPSRs. Based on the agency's familiarity with the content of postmarketing periodic safety reports, FDA estimates that it will take an average of 20 hours for applicants to prepare and submit a TPSR to FDA. Preparation of a TPSR would include gathering information (proposed §§ 314.80(b) and 600.80(b)), and providing attachments (proposed §§ 314.80(c)(3) and 600.80(c)(3)).

Proposed §§ 314.80(c)(3)(ii) and 600.80(c)(3)(ii) would require persons holding an application (*i.e.*, NDA, ANDA, BLA) approved on or after January 1, 1998, to submit a PSUR to

FDA according to the following schedule: Semiannually for 2 years after U.S. approval of the application, annually for the next 3 years, and then every 5 years thereafter. Proposed §§ 314.80(c)(3)(i) and 600.80(c)(3)(i) would permit persons holding an application (*i.e.*, NDA, ANDA, BLA) approved before January 1, 1998, to submit a PSUR, in lieu of a TPSR, every 5 years after U.S. approval of the application. Proposed §§ 314.80(c)(3)(iv) and 600.80(c)(3)(iv) would require persons holding an approved supplement to an approved application for use of the human drug or biological product in the pediatric population to submit a PSUR (even if the supplement or application was approved prior to January 1, 1998) to FDA according to the following schedule: Semiannually for 2 years after U.S. approval of the supplement, annually for the next 3 years, and then every 5 years thereafter. Based on data concerning postmarketing periodic safety reports currently received by the agency, FDA estimates that approximately 2,500 PSURs will be submitted annually under proposed § 314.80(c)(3)(i), (c)(3)(ii), and (c)(3)(iv), and approximately 35 PSURs will be submitted annually under proposed § 600.80(c)(3)(i), (c)(3)(ii), and (c)(3)(iv). FDA estimates that approximately 200 applicants under proposed § 314.80(c)(3) will submit PSURs, and approximately 20 applicants under proposed § 600.80(c)(3) will submit PSURs. Based on the agency's familiarity with the content of PSURs voluntarily submitted to the agency, FDA estimates that it will take an average of 40 hours for applicants to prepare and submit a PSUR to the agency. Preparation of a PSUR would include gathering information (proposed §§ 314.80(b) and 600.80(b)) and providing attachments (proposed §§ 314.80(c)(3) and 600.80(c)(3)).

Proposed §§ 314.80(c)(3)(iii) and 600.80(c)(3)(iii) would require persons holding an application (*i.e.*, NDA, ANDA, BLA) approved on or after January 1, 1998, to submit an IPSR to FDA 7.5 years and 12.5 years after U.S. approval of the application. Proposed §§ 314.80(c)(3)(i) and 600.80(c)(3)(i) would permit persons holding an application (*i.e.*, NDA, ANDA, BLA) approved before January 1, 1998, to submit an IPSR at 7.5 and 12.5 years after U.S. approval of the application. Proposed §§ 314.80(c)(3)(iv) and 600.80(c)(3)(iv) would require persons holding an approved supplement to an approved application for use of the human drug or biological product in the pediatric population to submit an IPSR

(even if the supplement or application was approved prior to January 1, 1998) to FDA at 7.5 and 12.5 years after U.S. approval of the supplement. Based on data concerning postmarketing periodic safety reports currently received by the agency, FDA estimates that approximately 350 IPSRs will be submitted annually under proposed § 314.80(c)(3)(i), (c)(3)(iii), and (c)(3)(iv), and approximately 3 IPSRs will be submitted annually under proposed § 600.80(c)(3)(i), (c)(3)(iii), and (c)(3)(iv). FDA estimates that approximately 40 applicants under proposed § 314.80(c)(3) will submit IPSRs, and approximately 3 applicants under proposed § 600.80(c)(3) will submit IPSRs. Based on the agency's familiarity with the content of PSURs voluntarily submitted to the agency, FDA estimates that it will take an average of 30 hours for applicants to prepare and submit an IPSR to FDA. Preparation of an IPSR would include gathering information (proposed §§ 314.80(b) and 600.80(b)) and providing attachments (proposed §§ 314.80(c)(3) and 600.80(c)(3)).

Proposed §§ 314.80(c)(3)(v) and 600.80(c)(3)(v) would require persons holding an application (*i.e.*, NDA, ANDA, BLA) to submit to FDA every 6 months after U.S. approval of the application a report that consists of individual case safety reports (*i.e.*, FDA Form 3500As, VAERS forms for vaccines, CIOMS I forms, if desired, for foreign SADR) for certain spontaneously reported SADR for marketed human drug and biological products. Applicants that submit TPSRs to FDA would submit a report consisting of individual case safety reports for each spontaneously reported serious, expected SADR, whether domestic or foreign, and each spontaneously reported nonserious, unexpected SADR occurring in the United States during the reporting period. Reports for vaccines would include a VAERS form for each spontaneously reported nonserious, expected SAR and each expected SAR with unknown outcome occurring in the United States during the reporting period. Applicants that submit PSURs or IPSRs to FDA would submit a report consisting of individual case safety reports for each spontaneously reported serious, listed SADR, whether domestic or foreign, and each spontaneously reported nonserious, unlisted SADR occurring in the United States during the reporting period. Reports for vaccines would include a VAERS form for each spontaneously reported nonserious, listed SAR and each listed SAR with unknown outcome occurring

in the United States during the reporting period. If a full data set is not available for a report of a serious SADR, the reason(s) for the lack of such information would be provided. Based on data concerning postmarketing periodic safety reports currently received by the agency, FDA estimates that approximately 4,726 of these reports will be submitted annually under proposed § 314.80(c)(3)(v), and approximately 480 of these reports will be submitted annually under proposed § 600.80(c)(3)(v). FDA estimates that approximately 285 applicants under proposed § 314.80(c)(3) will submit these reports, and approximately 69 applicants under proposed § 600.80(c)(3) will submit reports. Based on the agency's familiarity with the content of postmarketing periodic safety reports, FDA estimates that it will take an average of 120 hours for applicants to prepare and submit a report under proposed §§ 314.80(c)(3)(v) and 600.80(c)(3)(v) to the agency. Preparation of a report under proposed §§ 314.80(c)(3)(v) and 600.80(c)(3)(v) would include gathering information (proposed §§ 314.80(b) and (c)(1), and 600.80(b) and (c)(1)), providing attachments, if applicable (proposed §§ 314.80(c)(2)(ix) and (c)(3), and 600.80(c)(2)(ix) and (c)(3)), and formatting information (proposed §§ 314.80(c)(4) and (e), and 600.80(c)(4) and (e)).

VI.C. Other Reports

Proposed §§ 310.305(f)(1), 314.80(f), and 600.80(f) would require manufacturers, applicants, contractors, and shared manufacturers to submit to FDA, when appropriate, any or all records required to be maintained by these persons. These records would be required to be submitted within 5 calendar days after receipt of the request by the person. Records of all safety information pertaining to the person's product, received or otherwise obtained, including raw data, any correspondence relating to the safety information, and any reports of SADR or medication errors not submitted to FDA or only provided to FDA in a summary tabulation would be included, as well as records required to be maintained under proposed § 310.305 (310.305(c)(1)(ii), (c)(1)(iii)(A), (c)(2)(ii), (c)(2)(viii)(A), and (c)(2)(xi)(C)), proposed § 314.80 (314.80(c)(1)(ii), (c)(1)(iii)(A), (c)(2)(ii), (c)(2)(viii)(A), and (c)(2)(x)(C)), and proposed § 600.80 (600.80(c)(1)(ii), (c)(1)(iii)(A), (c)(2)(ii), (c)(2)(viii)(A), and (c)(2)(x)(C)). Submission of SADR records to FDA represents a new reporting requirement. Based on the agency's requests for voluntary

submission of safety records, FDA estimates that approximately 2 requests for submission of records will be fulfilled annually under proposed § 310.305(f)(1), approximately 15 requests for submission of records will be fulfilled annually under proposed § 314.80(f), and approximately 4 requests for submission of records will be fulfilled annually under proposed § 600.80(f). FDA estimates that approximately 2 manufacturers and contractors under proposed § 310.305 will submit these records, approximately 15 applicants and contractors under proposed § 314.80 will submit these records, and approximately 4 applicants, contractors and shared manufacturers under proposed § 600.80 will submit these records. Based on the volume of safety information voluntarily submitted to FDA in response to an agency request for such information, FDA estimates that it will take an average of 8 hours for manufacturers, applicants, contractors, and shared manufacturers to fulfill each request for submission of records to the agency.

Proposed § 314.81(b)(2) would require applicants of marketed drug products subject to an NDA to submit an annual report to FDA within 60 days of the anniversary date of U.S. approval of the application. This report would contain summary information; distribution data; chemistry, manufacturing, and controls changes; clinical data; and a status report of any postmarketing studies performed by, or on behalf of, the applicant. Based on data concerning the number of approved NDA annual reports received by the agency, FDA estimates that approximately 2,363 reports will be submitted under proposed § 314.81(b)(2). FDA estimates that approximately 286 applicants will submit these reports. Based on the agency's familiarity with the content of approved NDA annual reports, FDA estimates that it will take an average of 35.5 hours for applicants to prepare and submit one of these annual reports to FDA.

Proposed § 601.28 would require applicants of licensed biological products to submit an annual report of postmarketing pediatric studies to FDA within 60 days of the anniversary date of approval of the application. This report would contain summary information, clinical data in the pediatric population, and a status report of any postmarketing studies in the pediatric population. Based on data concerning the number of approved BLA annual reports received by the agency, FDA estimates that approximately 69 reports will be

submitted under proposed § 601.28. FDA estimates that approximately 69 applicants will submit these reports. Based on the agency's familiarity with the content of approved BLA annual reports, FDA estimates that it will take an average of 25 hours for applicants to prepare and submit an annual report to the agency.

VI.D. Recordkeeping

Proposed §§ 310.305(c)(2)(xi)(B), 314.80(c)(2)(x)(B), and 600.80(c)(2)(x)(B) would require that contracts between manufacturers and contractors (proposed § 310.305(c)(2)(xi)(B)) and applicants and contractors (proposed §§ 314.80(c)(2)(x)(B) and 600.80(c)(2)(x)(B)) specify the safety reporting responsibilities of the contractor. For purposes of this section, a record represents a contract. Based on information contained in individual case safety reports submitted to the agency in the past (*i.e.*, report source), FDA estimates that approximately 4 records will be maintained annually under proposed § 310.305(c)(2)(xi)(B), approximately 480 records will be maintained annually under proposed § 314.80(c)(2)(x)(B), and approximately 2 records will be maintained annually under proposed § 600.80(c)(2)(x)(B). FDA estimates that approximately 2 manufacturers under proposed § 310.305 will maintain these records, approximately 160 applicants under proposed § 314.80 will maintain these records, and approximately 2 applicants under proposed § 600.80 will maintain these records. Based on the agency's familiarity with recordkeeping processes, FDA estimates that it will take an average of 1 hour for manufacturers and applicants to maintain each record annually under proposed §§ 310.305(c)(2)(xi)(B), 314.80(c)(2)(x)(B), and 600.80(c)(2)(x)(B).

Proposed §§ 310.305(f), 314.80(f), and 600.80(f) would require manufacturers, applicants, contractors, and shared manufacturers to maintain for a period of 10 years records of all safety information, received or otherwise obtained, including raw data; any correspondence relating to the safety information; and any reports of SADR or medication errors not submitted to FDA or only provided to FDA in a summary tabulation. These persons would also be required to retain for a period of 10 years any records required to be maintained under proposed § 310.305 (§ 310.305(c)(1)(ii), (c)(1)(iii)(A), (c)(2)(ii), (c)(2)(viii)(A), and (c)(2)(xi)(C)), proposed § 314.80 (§ 314.80(c)(1)(ii), (c)(1)(iii)(A), (c)(2)(ii), (c)(2)(viii)(A), and (c)(2)(x)(C)), and

proposed § 600.80 (§ 600.80(c)(1)(ii), (c)(1)(iii)(A), (c)(2)(ii), (c)(2)(viii)(A), and (c)(2)(x)(C)). For the purposes of this section, a record includes any and all documentation regarding an individual SADR or medication error. Based on data concerning the number of SADRs currently reported to the agency, FDA estimates that approximately 500 records will be maintained annually under proposed § 310.305(f), approximately 220,000 records will be maintained annually under proposed § 314.80(f), and approximately 20,000 records will be maintained annually under proposed § 600.80(f). FDA estimates that approximately 25 manufacturers and contractors under proposed § 310.305 will maintain these records, approximately 700 applicants and contractors under proposed § 314.80 will maintain these records, and approximately 69 applicants, contractors, and shared manufacturers under proposed § 600.80 will maintain these records. Based on the agency's familiarity with recordkeeping processes, FDA estimates that it will take an average of 5 hours for manufacturers, applicants, contractors, and shared manufacturers to maintain each record annually under proposed §§ 310.305, 314.80, and 600.80.

Proposed §§ 310.305(g), 314.80(g), and 600.80(g) would require manufacturers, applicants, contractors, and shared manufacturers to maintain written procedures for the surveillance, receipt, evaluation, and reporting of safety information to FDA. Based on the number of persons subject to the postmarketing safety reporting regulations, FDA estimates that approximately 25 records will be maintained annually under proposed § 310.305(g), approximately 700 records will be maintained annually under proposed § 314.80(g), and approximately 69 records will be maintained annually under proposed § 600.80(g). FDA estimates that approximately 25 manufacturers and contractors under proposed § 310.305 will maintain these records, approximately 700 applicants and contractors under proposed § 314.80 will maintain these records, and approximately 69 applicants, contractors, and shared manufacturers under proposed § 600.80 will maintain these records. Based on the agency's familiarity with recordkeeping processes, FDA estimates that it will take an average of 1 hour for manufacturers, applicants, contractors, and shared manufacturers to maintain a record of the written procedures

annually under proposed §§ 310.305(g), 314.80(g), and 600.80(g).

Proposed § 312.32(c) would require sponsors to maintain records for reports of SADRs that do not contain a minimum data set. This would include any information received or otherwise obtained for the SADR along with a record of their efforts to obtain a minimum data set for the report. For the purposes of this section, a record includes any and all documentation regarding an individual SADR. Maintaining records of SADRs that do not contain a minimum data set represents a new recordkeeping requirement. Based on information contained in IND safety reports, FDA estimates that approximately 200 records will be maintained annually under proposed § 312.32(c) for human drugs; approximately 240 records will be maintained annually under proposed § 312.32(c) for human biological products. FDA estimates that

approximately 50 sponsors will maintain these records for human drugs and approximately 60 sponsors will maintain these records for human biological products. Based on the agency's familiarity with recordkeeping processes, FDA estimates that it will take an average of 1 hour for sponsors to maintain each record annually under proposed § 312.32(c).

Proposed § 606.170(a) would require blood collection and transfusing facilities to maintain records for complaints of SARs regarding each unit of blood or blood product. These facilities must prepare a written report of the investigation of SARs, including followup and conclusions. Based on data for records currently maintained by blood collection and transfusing facilities, FDA estimates that approximately 4,512 records will be maintained annually under proposed § 606.170(a). FDA estimates that approximately 376 facilities will

maintain these records. Based on the agency's familiarity with recordkeeping processes, FDA estimates that it will take an average of 12 hours for facilities to maintain each record annually under proposed § 606.170(a).

Description of Respondents: Business or other for-profit organizations.

In compliance with section 3507(d) of the Paperwork Reduction Act of 1995 (44 U.S.C. 3507(d)), the agency has submitted a copy of this proposed rule to OMB for its review and approval of these information collections. Interested persons are requested to send comments regarding this information collection, including suggestions for reducing this burden, to the Office of Information and Regulatory Affairs, OMB, New Executive Office Bldg., 725 17th St. NW., rm. 10235, Washington, DC 20503, OMB, Attn: Stuart Shapiro, Desk Officer for FDA, FAX: 202-395-6974. Submit written comments on the information collection by April 14, 2003.

TABLE 21.—ESTIMATED ANNUAL REPORTING BURDEN ¹

21 CFR section	Number of respondents	Number of responses per respondent	Total annual responses	Hours per response	Total hours
310.305(c)(2)(i) ²	14	25	350	16	5,600
310.305(c)(2)(ii)	5	1	5	8	40
310.305(c)(2)(iii)	10	4.6	46	24	1,104
310.305(c)(2)(iv)	10	5	50	16	800
310.305(c)(2)(v)	10	100	1,000	16	16,000
310.305(c)(2)(vi)	7	48.6	340	8	2,720
310.305(b)(2), (c)(2)(vii), and (c)(2)(viii)(A)	10	5.5	55	4	220
310.305(c)(2)(xi)	5	2	10	2	20
310.305(f)(1)	2	1	2	8	16
312.32(c)(1)(i) ³ —human drugs	457	10.6	4,860	16	77,760
312.32(c)(1)(ii)—human drugs	100	3	300	8	2,400
312.32(c)(2)—human drugs	135	3.6	490	4	1,960
312.32(c)(1)(i)—human biological products	602	4.9	2,980	16	47,680
312.32(c)(1)(ii)—human biological products	100	3	300	8	2,400
312.32(c)(2)—human biological products	180	1.6	290	4	1,160
312.64(b)—human drugs	10,000	10	100,000	2	200,000
312.64(b)—human biological products	6,000	10	60,000	2	120,000
314.80(c)(2)(i) ⁴	282	177.3	50,000	16	800,000
314.80(c)(2)(ii)	50	6	300	8	2,400
314.80(c)(2)(iii)	109	8.4	912	24	21,888
314.80(c)(2)(iv)	100	15	1,500	16	24,000
314.80(c)(2)(v)	150	666.7	100,000	16	1,600,000
314.80(c)(2)(vi)	140	307.1	43,000	8	344,000
314.80(b)(2), (c)(2)(vii), and (c)(2)(viii)(A)	184	54.3	10,000	4	40,000
314.80(c)(2)(x)	100	113.7	11,370	2	22,740
314.80(c)(3)(i)	80	17.5	1,400	20	28,000
314.80(c)(3)(i), (c)(3)(ii), and (c)(3)(iv)	200	12.5	2,500	40	100,000
314.80(c)(3)(i), (c)(3)(iii), and (c)(3)(iv)	40	8.7	350	30	10,500
314.80(c)(3)(v)	285	16.6	4,726	120	567,120
314.80(f)	15	1	15	8	120
314.81(b)(2)	286	8.3	2,363	35.5	83,886
320.31(d)(3)	10	20	200	14	2,800
600.80(c)(2)(i) ⁵	69	43.5	3,000	16	48,000
600.80(c)(2)(ii)	4	1	4	8	32
600.80(c)(2)(iii)	12	2.1	25	24	600
600.80(c)(2)(iv)	10	10	100	16	1,600
600.80(c)(2)(v)	30	333.3	10,000	16	160,000
600.80(c)(2)(vi)	69	43.5	3,000	8	24,000
600.80(b)(2), (c)(2)(vii), and (c)(2)(viii)(A)	69	14.5	1,000	4	4,000
600.80(c)(2)(x)	20	12.5	250	2	500
600.80(c)(3)(i)	20	1.8	35	20	700
600.80(c)(3)(i), (c)(3)(ii), and (c)(3)(iv)	20	1.8	35	40	1,400

TABLE 21.—ESTIMATED ANNUAL REPORTING BURDEN ¹—Continued

21 CFR section	Number of respondents	Number of responses per respondent	Total annual responses	Hours per response	Total hours
600.80(c)(3)(i), (c)(3)(iii), and (c)(3)(iv)	3	1	3	30	90
600.80(c)(3)(v)	69	6.9	480	120	57,600
600.80(f)	4	1	4	8	32
601.28	69	1	69	25	1,725
606.170(b)	3,062	2.3	7,000	16	112,000
606.170(c)	75	1	75	20	1,500
Total	23,283	2,149.7	424,794	896.5	4,541,113

¹ The estimates provided in this table are not only attributed to the new proposed requirements in this rulemaking but also include burdens associated with our current safety reporting requirements. There are no capital costs or operating and maintenance costs associated with this collection of information.

² The paragraphs of § 310.305 cited in the table include burdens associated with gathering information under § 310.305(b) and (c)(1), providing attachments, if applicable, under § 310.305(c)(2)(ix) and (c)(2)(x), and formatting information under § 310.305(c)(2)(xii), (d), and (e).

³ The paragraphs of § 312.32 cited in the table include burdens associated with gathering information under § 312.32(b) and formatting information under § 312.32(c)(1)(iii).

⁴ The paragraphs of § 314.80 cited in the table include burdens associated with gathering information under § 314.80(b) and (c)(1), providing attachments, if applicable, under § 314.80(c)(2)(ix) and (c)(3), and formatting information under § 314.80(c)(2)(xi), (c)(4), and (e).

⁵ The paragraphs of § 600.80 cited in the table include burdens associated with gathering information under § 600.80(b) and (c)(1), providing attachments, if applicable, under § 600.80(c)(2)(ix) and (c)(3), and formatting information under § 600.80(c)(2)(xi), (c)(4), and (e).

TABLE 22.—ESTIMATED ANNUAL RECORDKEEPING BURDEN ¹

21 CFR section	Number of recordkeepers	Annual frequency of recordkeeping	Total annual records	Hours per record	Total hours
310.305(c)(2)(xi)(B)	2	2	4	1	4
310.305(f) ²	25	20	500	5	2,500
310.305(g)	25	1	25	1	25
312.32(c)—human drugs	50	4	200	1	200
312.32(c)—human biological products	60	4	240	1	240
314.80(c)(2)(x)(B)	160	3	480	1	480
314.80(f) ³	700	314.3	220,000	5	1,100,000
314.80(g)	700	1	700	1	700
600.80(c)(2)(x)(B)	2	1	2	1	2
600.80(f) ⁴	69	289.8	20,000	5	100,000
600.80(g)	69	1	69	1	69
606.170(a)	376	12	4,512	12	54,144
Total	2,238	653.1	246,732	35	1,258,364

¹ The estimates provided in this table are not only attributed to the new proposed requirements in this rulemaking but also include burdens associated with our current safety reporting requirements. There are no capital costs or operating costs associated with this collection of information. There are maintenance costs of \$2,025 annually per recordkeeper (\$2,000 annually per recordkeeper for existing recordkeeping requirements (see 67 FR 47821) and \$25 annually per recordkeeper for new proposed requirements in this rulemaking).

² Includes records required to be maintained under § 310.305(c)(1)(ii), (c)(1)(iii)(A), (c)(2)(ii), (c)(2)(viii)(A), and (c)(2)(xi)(C).

³ Includes records required to be maintained under § 314.80(c)(1)(ii), (c)(1)(iii)(A), (c)(2)(ii), (c)(2)(viii)(A), and (c)(2)(x)(C).

⁴ Includes records required to be maintained under § 600.80(c)(1)(ii), (c)(1)(iii)(A), (c)(2)(ii), (c)(2)(viii)(A), and (c)(2)(x)(C).

VII. Executive Order 13132: Federalism

Executive Order 13132 requires Federal agencies to carefully examine regulatory actions to determine if they would have a significant impact on federalism. Using the criteria and principles set forth in the Executive order, the agency has considered the impact of this proposed rule on the States, on their relationship with the Federal Government, and on the distribution of power and responsibilities among the various levels of government.

FDA is publishing this proposed rule to revise its regulations governing the format, content, and submission of safety reports to the agency for human drugs and biological products. The proposal would revise current

regulations to implement definitions and reporting formats and standards recommended by ICH and CIOMS. The proposal would codify the agency's expectations for timely acquisition, evaluation, and submission of relevant safety information for marketed drugs and biological products. The proposal would require that postmarketing individual case safety reports of unexpected SADRs that cannot be classified as either serious or nonserious be submitted to the agency in an expedited manner. The proposal would also require that certain medically significant SADRs always be submitted to FDA in an expedited manner whether the SADR is unexpected or expected. The proposal would also require that all domestic reports of medication errors,

whether actual or potential, be submitted to FDA in an expedited manner. The proposal would clarify certain safety reporting requirements and make other minor revisions. The proposal would also amend the agency's postmarketing annual reports regulations for applicants of human drugs and licensed biological products to revise the content for these reports. The proposal would also amend the agency's bioavailability and bioequivalence study regulations for sponsors of human drugs to require expedited safety reports for certain studies which are exempt from submission of an IND. Because enforcement of these safety reporting requirements would be a Federal responsibility, there would be little, if

any, impact on the States from this rule if finalized.

FDA has analyzed this proposed rule in accordance with the principles set forth in Executive Order 13132. FDA has determined that the rule does not contain policies that have substantial direct effects on the States, on the relationship between National Government and the States, or on the distribution of power and responsibilities among the various levels of government. Accordingly, the agency has concluded that the rule does not contain policies that have federalism implications as defined in the Executive order and, consequently, a federalism summary impact statement is not required.

List of Subjects

21 CFR Part 310

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

21 CFR Part 312

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

21 CFR Part 314

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

21 CFR Part 320

Drugs, Reporting and recordkeeping requirements.

21 CFR Part 600

Biologics, Reporting and recordkeeping requirements.

21 CFR Part 601

Administrative practice and procedure, Biologics, Confidential business information.

21 CFR Part 606

Blood, Labeling, Laboratories, Reporting and recordkeeping requirements.

Therefore, under the Federal Food, Drug, and Cosmetic Act, the Public Health Service Act, and under authority delegated to the Commissioner of Food and Drugs, it is proposed that 21 CFR parts 310, 312, 314, 320, 600, 601, and 606 be amended as follows:

PART 310—NEW DRUGS

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

Authority: 21 U.S.C. 321, 331, 351, 352, 353, 355, 360b–360f, 360j, 361(a), 371, 374,

375, 379e; 42 U.S.C. 216, 241, 242(a), 262, 263b–263n.

2. Section 310.305 is revised to read as follows:

§ 310.305 Safety reporting and recordkeeping for manufacturers of prescription drugs marketed for human use without an approved application.

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

Active query means direct verbal contact (*i.e.*, in person or by telephone or other interactive means such as a video conference) with the initial reporter of a suspected adverse drug reaction (SADR) or a medication error by a health care professional (*e.g.*, physician, physician assistant, pharmacist, dentist, nurse, any individual with some form of health care training) representing the manufacturer. For SADR, active query entails, at a minimum, a focused line of questioning designed to capture clinically relevant information associated with the drug product and the SADR, including, but not limited to, information such as baseline data, patient history, physical exam, diagnostic results, and supportive lab results.

Actual medication error means 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.

Contractor means 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 SADRs or medication errors.

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

Full data set means completion of all the applicable elements on FDA Form 3500A (or on a Council for International Organizations of Medical Sciences (CIOMS) I form for reports of foreign SADRs), 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).

Life-threatening SADR means any SADR that, in the view of the initial reporter, places the patient at *immediate* risk of death from the SADR as it occurred. It does not include an SADR

that, had it occurred in a more severe form, might have caused death.

Medication error means 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.

Minimum data set means the report includes an identifiable patient, an identifiable reporter, a suspect drug product, and an SADR.

Nonserious SADR means any SADR that is determined not to be a serious SADR.

Potential medication error means an individual case safety report of information or complaint about product name, labeling, or packaging similarities that does not involve a patient.

SADR with unknown outcome means an SADR that cannot be classified, after active query, as either serious or nonserious.

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

Spontaneous report means 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, 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.

Suspected adverse drug reaction (SADR) means a noxious and unintended response to any dose of a drug 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.

Unexpected SADR means any SADR that is not included in the current U.S. labeling for the drug product. Reactions that may be symptomatically and pathophysiologically related to a reaction included in the U.S. labeling, but differ from the labeled reaction because of greater severity or specificity, would be unexpected. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the U.S. labeling only referred to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the U.S. labeling only included cerebral vascular accidents. "Unexpected," as used in this definition, refers to an SADR that has not been previously observed (*i.e.*, included in the U.S. labeling); it does not refer to an SADR that might be anticipated from the pharmacological properties of the drug product. SADRs that are mentioned in the U.S. labeling as occurring with a class of drugs but not specifically mentioned as occurring with the particular drug are considered unexpected.

(b) *Review of safety information.* (1) Each manufacturer of a prescription drug product marketed for human use without an approved application must promptly review all safety information pertaining to its product obtained or otherwise received by the manufacturer from any source, foreign or domestic, including information derived from commercial marketing experience, postmarketing clinical investigations, postmarketing epidemiology/surveillance studies, animal or in vitro studies, electronic communications with manufacturers via the Internet (*e.g.*, e-mail), reports in the scientific literature, and unpublished scientific papers, as well as reports from foreign regulatory authorities that have not been previously reported to the Food and Drug Administration (FDA) by the manufacturer.

(2) Individual case safety reports that are forwarded to the manufacturer by FDA must not be resubmitted to the agency by the manufacturer; however,

manufacturers must submit to FDA all followup information for these reports.

(c) *Reporting requirements.* The manufacturer must submit to FDA one copy of each expedited report (described under paragraphs (c)(2)(i) through (c)(2)(vii) of this section) pertaining to its drug product. Upon written notice, FDA may require, when appropriate, that the manufacturer submit reports under this section to FDA at times other than those stated.

(1) *Determination of outcome, minimum data set, and full data set—*

(i)(A) *Initial determinations.* Upon initial receipt of an SADR report, the manufacturer must immediately determine, the outcome for the SADR (whether the SADR is serious or nonserious) and at least the minimum data set for the individual case safety report. For reports of actual medication errors that do not result in an SADR and potential medication errors, the manufacturer must immediately determine the minimum information for the individual case safety report (minimum information described under paragraphs (c)(1)(iii)(B) and (c)(1)(iii)(C) of this section). If the manufacturer is not able to immediately determine the information in this paragraph, active query must be used to obtain it as soon as possible.

(B) *Spontaneous reports.* For spontaneous reports, the manufacturer must always assume, for safety reporting purposes under this section, that there is at least a reasonable possibility, in the opinion of the initial reporter, that the drug product caused the spontaneously reported event.

(C) *Clinical trials.* For a clinical trial, the possibility that the drug product caused the SADR or that a medication error has occurred must be assumed if either the investigator or the manufacturer believes that such a reasonable possibility exists.

(ii) *SADRs with unknown outcome.* For an SADR with unknown outcome that cannot be immediately determined, the manufacturer must continue to use active query to attempt to determine the outcome of the SADR within 30 calendar days after initial receipt of the SADR report by the manufacturer. The manufacturer must maintain a record of its efforts to determine the outcome for an SADR with unknown outcome.

(iii)(A) *Minimum data set for SADR reports.* The manufacturer must not submit an individual case safety report for an SADR to FDA if the report does not contain a minimum data set; instead, the manufacturer must 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.

(B) *Minimum information for reports of actual medication errors that do not result in an SADR.* For reports of actual medication errors that do not result in an SADR, an individual case safety report must be submitted to FDA even though the report does not contain a minimum data set (*i.e.*, does not have an SADR). These reports must contain at least an identifiable patient, an identifiable reporter, and a suspect drug product.

(C) *Minimum information for potential medication error reports.* For reports of potential medication errors, an individual case safety report must be submitted to FDA even though the report does not contain a minimum data set (*i.e.*, does not have an identifiable patient or an SADR). These reports must contain at least an identifiable reporter and a suspect drug product.

(iv) *Full data set.* For reports of serious SADRs, always expedited reports (see paragraph (c)(2)(iv) of this section), and medication error reports (see paragraph (c)(2)(v) of this section), the manufacturer must submit a full data set. If a full data set is not available for the report, the manufacturer must use active query to obtain this information. If a full data set is not obtainable, after active query, the manufacturer must:

(A) Submit all safety information, received or otherwise obtained, for the report;

(B) Indicate the reason(s) for its inability to acquire a full data set; and

(C) Document its efforts to obtain a full data set (*i.e.*, description of unsuccessful steps taken to obtain this information).

(v) *Serious SADRs not initially reported by health care professional.* For a serious SADR that was not initially reported to the manufacturer by a health care professional (*e.g.*, report from a consumer), the manufacturer must contact the health care professional associated with the care of the patient using active query to gather further medical perspective on the case and to acquire a full data set for the report. If the manufacturer is unable to contact the health care professional, it must include in the report for the serious SADR:

(A) The reason(s) for its inability to contact the health care professional; and

(B) A description of its efforts to contact the health care professional.

(2) *Postmarketing "expedited reports"—*(i) *Serious and unexpected SADR.* The manufacturer must report to FDA each SADR, received or otherwise obtained, that is both serious and

unexpected, whether foreign or domestic, as soon as possible, but in no case later than 15 calendar days after receipt by the manufacturer of the minimum data set for the serious, unexpected SADR. If a full data set is not available for the serious and unexpected SADR report at the time of initial submission of the report to FDA, the manufacturer must submit the information required under paragraph (c)(1)(iv) of this section and also submit a 30-day followup report as required by paragraph (c)(2)(vi) of this section.

(ii) *Information sufficient to consider product administration changes.* The manufacturer must also report to FDA information, received or otherwise obtained, whether foreign or domestic, that would be sufficient, based upon appropriate medical judgment, to consider changes in product administration. The manufacturer must submit this information to FDA, as soon as possible, but in no case later than 15 calendar days after determination by the manufacturer that the information qualifies for expedited reporting. Examples of such information include any significant unanticipated safety finding or data in the aggregate from an in vitro, animal, epidemiological, or clinical study, whether or not conducted under an investigational new drug application (IND), that suggests a significant human risk, such as reports of mutagenicity, teratogenicity, or carcinogenicity, or reports of a lack of efficacy with a drug product used in treating a life-threatening or serious disease. The manufacturer must maintain a record of its efforts to determine whether the information required to be reported under this paragraph qualifies for expedited reporting.

(iii) *Unexpected SADR with unknown outcome.* The manufacturer must also report to FDA each SADR that is unexpected and for which the determination of an outcome is unattainable (*i.e.*, SADR with unknown outcome) within 45 calendar days after initial receipt by the manufacturer of the minimum data set for the unexpected SADR. The manufacturer must document in the expedited report the reason(s) for the inability to determine the outcome.

(iv) *Always expedited report.* (A) The manufacturer must also report to FDA each SADR, received or otherwise obtained, whether foreign or domestic, that is the subject of an always expedited report. These reports must be submitted to FDA as soon as possible, but in no case later than 15 calendar days after receipt by the manufacturer of the minimum data set for the report.

The following medically significant SADRs, which may jeopardize the patient or subject and/or require medical or surgical intervention to treat the patient or subject, are subject to an always expedited report:

- (1) Congenital anomalies,
- (2) Acute respiratory failure,
- (3) Ventricular fibrillation,
- (4) Torsades de pointe,
- (5) Malignant hypertension,
- (6) Seizure,
- (7) Agranulocytosis,
- (8) Aplastic anemia,
- (9) Toxic epidermal necrolysis,
- (10) Liver necrosis,
- (11) Acute liver failure,
- (12) Anaphylaxis,
- (13) Acute renal failure,
- (14) Sclerosing syndromes,
- (15) Pulmonary hypertension,
- (16) Pulmonary fibrosis,
- (17) Confirmed or suspected

transmission of an infectious agent by a marketed drug or biological product,

- (18) Confirmed or suspected endotoxin shock, and
- (19) Any other medically significant SADR that FDA determines to be the subject of an always expedited report (*i.e.*, may jeopardize the patient or subject and/or require medical or surgical intervention to treat the patient or subject).

(B) SADRs that are the subject of an always expedited report must be submitted to FDA whether unexpected or expected and whether or not the SADR leads to a serious outcome. If a full data set is not available for an always expedited report at the time of initial submission of the report to FDA, the manufacturer must submit the information required under paragraph (c)(1)(iv) of this section and also submit a 30-day followup report as required by paragraph (c)(2)(vi) of this section.

(v) *Medication errors*—(A) *Actual medication error.* The manufacturer must also submit to FDA each domestic report of an actual medication error, received or otherwise obtained, as soon as possible, but in no case later than 15 calendar days after receipt by the manufacturer of the minimum data set for a report of an SADR or, if an SADR does not occur, the minimum information described under paragraph (c)(1)(iii)(B) of this section (*i.e.*, identifiable patient, identifiable reporter, and suspect drug product).

(B) *Potential medication error.* The manufacturer must also submit to FDA each domestic report of a potential medication error, received or otherwise obtained, as soon as possible, but in no case later than 15 calendar days after receipt by the manufacturer of the minimum information described under

paragraph (c)(1)(iii)(C) of this section (*i.e.*, identifiable reporter and suspect drug product).

(C) *Full data set.* If a full data set is not available for an actual or potential medication error report at the time of initial submission of the report to FDA, the manufacturer must submit the information required under paragraph (c)(1)(iv) of this section and also submit a 30-day followup report as required by paragraph (c)(2)(vi) of this section.

(vi) *The 30-day followup report.* The manufacturer must use active query to obtain additional information for any expedited report under paragraphs (c)(2)(i), (c)(2)(iv), and (c)(2)(v) of this section that does not contain a full data set and must submit a followup report to FDA within 30 calendar days after initial submission of the expedited report to FDA by the manufacturer. If a full data set is still not obtainable, the 30-day followup report must contain the information required under paragraph (c)(1)(iv) of this section. Any new safety information in the 30-day followup report must be highlighted. Any new information, received or otherwise obtained, after submission of a 30-day followup report must be submitted to FDA as a 15-day followup report under paragraph (c)(2)(vii) of this section.

(vii) *The 15-day followup report.* The manufacturer must report to FDA any new information, received or otherwise obtained, for any expedited or followup report (except for initial expedited reports under paragraphs (c)(2)(i), (c)(2)(iv), and (c)(2)(v) of this section that do not contain a full data set) within 15 calendar days of initial receipt of the new information by the manufacturer. Expedited reports under paragraphs (c)(2)(i), (c)(2)(iv), and (c)(2)(v) of this section that do not contain a full data set at the time of initial submission of the report to FDA are subject to the 30-day followup reporting requirements under paragraph (c)(2)(vi) of this section rather than the 15-day followup reporting requirements under this paragraph.

(viii) *Supporting documentation.* (A) If the patient dies, the manufacturer must submit a copy of the autopsy report to FDA, if it is available. If an autopsy report is not available, the manufacturer must submit a death certificate to FDA. If an autopsy report becomes available after the manufacturer has submitted a death certificate to the agency, the autopsy report must be submitted to FDA. If the patient was hospitalized, the manufacturer must submit a copy of the hospital discharge summary to FDA, if it is available. If any of these documents is not in English, the document must be

accompanied by an English translation. Manufacturers must use active query to obtain these documents. These documents must be submitted to FDA as 15-day followup reports (see paragraph (c)(2)(vii) in this section) within 15 calendar days of initial receipt of the document by the manufacturer. If these documents are not submitted to FDA in a 15-day followup report within 3 months after submission of the initial expedited report for the death or hospitalization, the agency will assume that active query by the manufacturer has not resulted in access to these documents. In this case, a record of the reason(s) for the lack of such documentation and the effort that was made to obtain the documentation must be maintained by the manufacturer.

(B) Each expedited report must contain in the narrative a list of other relevant documents (e.g., medical records, laboratory results, data from studies) for the report that are maintained by the manufacturer. When appropriate, FDA may require a manufacturer to submit copies of one or more of these documents to the agency within 5 calendar days after receipt of the request.

(ix) *Scientific literature.* An expedited report based on information from the scientific literature applies only to reports found in scientific and medical journals. These expedited reports must be accompanied by a copy of the published article.

(x) *Attachments.* Each expedited report must be accompanied by a copy of the current U.S. labeling for the drug product and a list of current addresses where all safety reports and other safety-related records for the drug product are maintained by manufacturers and contractors.

(xi) *Submission of safety reports by contractors.* (A) Contractors must submit to the manufacturer safety reports of any SADR or medication errors for the manufacturer's drug product, obtained or otherwise received, within 5 calendar days of initial receipt of the report by the contractor. The contractor must submit a safety report for an SADR to the manufacturer even if the report does not contain a minimum data set. Upon receipt of the safety report from a contractor, the manufacturer must comply with the postmarketing safety reporting requirements of this section.

(B) A contract between the manufacturer and a contractor must specify the postmarketing safety reporting responsibilities of the contractor. The manufacturer is responsible for ensuring that the contractors of its drug products comply

with these postmarketing safety reporting responsibilities.

(C) The contractor must maintain a record of each submission to the manufacturer under paragraph (c)(2)(xi)(A) of this section that includes:

- (1) A copy of each safety report;
- (2) The date the report was initially received by the contractor;
- (3) The date the report was submitted to the manufacturer; and
- (4) The name and address of the manufacturer.

(D) The recordkeeping, written procedures, and disclaimer provisions under paragraphs (f) through (h) of this section apply to contractors.

(xii) *Report identification.* Each expedited report submitted to FDA under paragraphs (c)(2)(i) through (c)(2)(vii) of this section must bear prominent identification as to its contents, e.g., "expedited report—§ 310.305—serious and unexpected SADR," "expedited report—§ 310.305—30-day followup report." Each type of report (e.g., serious and unexpected SADR reports, 30-day followup reports) must be submitted to FDA under separate cover. Reports of medication errors must indicate whether the error is actual or potential and if actual, whether a serious SADR, nonserious SADR, or no SADR occurred, e.g., "expedited report—§ 310.305—actual medication error—nonserious SADR," "expedited report—§ 310.305—potential medication error."

(d) *Reporting format.* (1)(i) Except as provided in paragraphs (d)(1)(ii), (d)(1)(iv), and (d)(5) of this section, the manufacturer must complete an FDA Form 3500A for each individual case safety report of an SADR. Reports based on information about individual cases or case series in the scientific literature must be submitted on an FDA Form 3500A(s).

(ii) Foreign SADRs may be submitted either on an FDA Form 3500A or, if preferred, on a CIOMS I form.

(iii) Each domestic report of an actual or potential medication error must be submitted on an FDA Form 3500A.

(iv) Reports of overall findings or data in the aggregate from published and unpublished in vitro, animal, epidemiological, or clinical studies must be submitted in a narrative format.

(2) Each SADR in an individual case safety report must be coded on the FDA Form 3500A or CIOMS I form using the appropriate "preferred term" in the latest version of MedDRA (the medical dictionary for regulatory activities) in use at the time the manufacturer becomes aware of the individual case safety report. For individual case safety reports of medication errors, the report

must be coded both as a medication error and, if applicable, with the preferred term for any SADRs associated with the medication error.

(3) Each completed FDA Form 3500A or CIOMS I form should refer only to an individual case.

(4) Each completed FDA Form 3500A or CIOMS I form must include the name and telephone number (and fax number and e-mail address, if available) for the licensed physician responsible for the content and medical interpretation of the data contained within the form (i.e., contact person for the company).

(5) Instead of using FDA Form 3500A, the manufacturer may use a computer-generated facsimile of FDA Form 3500A provided that it is readable, includes appropriate identifying information, and contains all the elements (i.e., format, sections, blocks, titles, descriptors within blocks, text for disclaimer) of FDA Form 3500A in the identical enumerated sequence of the form. For individual case safety reports in which no suspect medical device is involved, a one-page FDA Form 3500A is acceptable.

(e) *Patient privacy.* The names and addresses of individual patients should not be included in reports under this section; instead, the manufacturer and its contractors should assign a unique code to each report, preferably not more than eight characters (i.e., numbers/letters) in length. The name of the reporter from whom the information was received should be included. Names of patients, individual reporters, health care professionals, hospitals, and geographic identifiers in safety reports are not releasable to the public under FDA's public information regulations in part 20 of this chapter.

(f) *Recordkeeping.* (1) Each manufacturer must maintain for a period of 10 years records of all safety information pertaining to its drug product, received or otherwise obtained, including raw data, any correspondence relating to the safety information, and any reports of SADRs or medication errors not submitted to FDA. The manufacturer must also retain for a period of 10 years any records required to be maintained under this section. When appropriate, FDA may require a manufacturer to submit any or all of these records to the agency within 5 calendar days after receipt of the request.

(2) Manufacturers and packers may retain the records required in paragraph (f)(1) of this section as part of its complaint files maintained under § 211.198 of this chapter.

(3) Manufacturers must permit any authorized FDA employee, at all

reasonable times, to have access to and copy and verify the records established and maintained under this section.

(g) *Written procedures.* Each manufacturer must develop and maintain written procedures for the surveillance, receipt, evaluation, and reporting of postmarketing safety information to FDA.

(h) *Disclaimer.* A report or information submitted by a manufacturer under this section (and any release by FDA of that report or information) does not necessarily reflect a conclusion by the manufacturer or by FDA, that the report or information constitutes an admission that the drug caused or contributed to an SADR. The manufacturer 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 SADR.

PART 312—INVESTIGATIONAL NEW DRUG APPLICATION

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

Authority: 21 U.S.C. 321, 331, 351, 352, 353, 355, 371; 42 U.S.C. 262.

4. Section 312.32 is amended by revising paragraphs (a), (b), the introductory text of paragraph (c), paragraphs (c)(1) and (c)(4), and the first sentence of paragraph (c)(2); in paragraph (d)(3) by removing the phrase “adverse drug experience” and by adding in its place the abbreviation “SADR” and by removing the phrase “such experience” and by adding in its place the phrase “such reaction”; and in paragraph (e) by removing the phrase “adverse experience” both times it appears and by adding in its place the abbreviation “SADR” to read as follows:

§ 312.32 IND safety reports.

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

Disability means a substantial disruption of a person’s ability to conduct normal life functions.

Life-threatening suspected adverse drug reaction (SADR) means any SADR that, in the view of the investigator or sponsor, places the patient or subject at immediate risk of death from the SADR as it occurred. It does not include an SADR that, had it occurred in a more severe form, might have caused death.

Minimum data set means the report includes an identifiable patient, an identifiable reporter, a suspect drug product, and an SADR.

Serious SADR means any SADR that results in any of the following outcomes: Death, a life-threatening

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

Suspected adverse drug reaction (SADR) means a noxious and unintended response to any dose of a drug 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.

Unexpected SADR means any SADR, the specificity or severity of which is not consistent with the current investigator brochure; or, if an investigator brochure is not required or available, the specificity or severity of which is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the investigator brochure only referred to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the investigator brochure only included cerebral vascular accidents. “Unexpected,” as used in this definition, refers to an SADR that has not been previously observed (e.g., included in the investigator brochure); it does not refer to an SADR that might be anticipated from the pharmacological properties of the drug product. SADRs that are mentioned in the investigator’s brochure as occurring with a class of drugs but not specifically mentioned as occurring with the particular drug are considered unexpected.

(b) *Review of safety information.* The sponsor must promptly review all information relevant to the safety of the drug obtained or otherwise received by the sponsor from any source, foreign or domestic, including information derived from any clinical or epidemiological

investigations, animal or in vitro studies, reports in the scientific literature, and unpublished scientific papers, as well as reports from foreign regulatory authorities that have not been previously reported to FDA by the sponsor and reports of foreign commercial marketing experience for drugs that are not marketed in the United States.

(c) *IND safety reports.* The sponsor must not submit an individual case safety report for an SADR to FDA if the report does not contain a minimum data set; instead, the sponsor must 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.

(1) *Written reports—(i) Serious and unexpected SADR.* The sponsor must notify FDA and all participating investigators in a written IND safety report of 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. The sponsor must identify all safety reports previously filed with the IND concerning a similar SADR, and must analyze the significance of the SADR in light of previous, similar reports.

(ii) *Information sufficient to consider product administration changes.* The sponsor must also notify FDA and all participating investigators in a written IND safety report of information that, based upon appropriate medical judgment, might materially influence the benefit-risk assessment of an investigational drug or that would be sufficient to consider changes in either product administration or in the overall conduct of a clinical investigation. The sponsor must submit this information to FDA and all participating investigators as soon as possible, but in no case later than 15 calendar days after the determination by the sponsor that the information qualifies for reporting under this paragraph. Examples of such information include any significant unanticipated safety finding or data in the aggregate from an in vitro, animal, epidemiological, or clinical study, whether or not conducted under an IND, that suggests a significant human risk, such as reports of mutagenicity, teratogenicity, or carcinogenicity or reports of a lack of efficacy with a drug product used in treating a life-threatening or serious disease.

(iii) *Submission of written reports.* Each written report may be submitted on an FDA Form 3500A or in a narrative format. Foreign SADRs may be

submitted either on an FDA Form 3500A or, if preferred, on a Council for International Organizations of Medical Sciences (CIOMS) I form. Reports of overall findings or data in the aggregate from published and unpublished in vitro, animal, epidemiological, or clinical studies must be submitted in a narrative format. Each written notice must bear prominent identification of its contents, *i.e.*, "IND safety report." Each written notification to FDA must be transmitted to the FDA review division that has responsibility for the review of the IND. If FDA determines that additional data are needed, the agency may require further data to be submitted.

(2) *Telephone and facsimile transmission safety reports.* The sponsor must also notify FDA by telephone or by facsimile transmission of any unexpected fatal or life-threatening SADR based on the opinion of the investigator or sponsor as soon as possible but in no case later than 7 calendar days after receipt by the sponsor of the minimum data set for the unexpected fatal or life-threatening SADR. * * *

(4) *Investigations of marketed drugs.* A sponsor of a clinical study under an IND for a drug marketed in the United States is only required to submit IND safety reports to FDA (review division that has responsibility for the IND) for SADRs from the clinical study itself, whether from domestic or foreign study sites of the IND. The sponsor must also submit to FDA safety information from these clinical studies as prescribed by the postmarketing safety reporting requirements under §§ 310.305, 314.80, and 600.80 of this chapter. * * *

5. Section 312.64 is amended by revising paragraph (b) to read as follows:

§ 312.64 Investigator reports.

* * * * *

(b) *Safety reports.* An investigator must report to the sponsor any serious SADR (as defined in § 312.32(a)) immediately and any other SADR (as defined in § 312.32(a)) promptly unless the protocol or investigator's brochure specifies a different timetable for reporting the SADR. * * *

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

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

Authority: 21 U.S.C. 321, 331, 351, 352, 353, 355, 355a, 356, 356a, 356b, 356c, 371, 374, 379e.

7. Section 314.80 is revised to read as follows:

§ 314.80 Postmarketing safety reporting and recordkeeping.

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

Active query means direct verbal contact (*i.e.*, in person or by telephone or other interactive means such as a video conference) 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, any individual with some form of health care training) representing the applicant. For SADRs, active query entails, at a minimum, a focused line of questioning designed to capture clinically relevant information associated with the drug product and the SADR, including, but not limited to, information such as baseline data, patient history, physical exam, diagnostic results, and supportive lab results.

Actual medication error means 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.

Company core data sheet means 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. The only purpose of this document is to provide the company core safety information (CCSI) for periodic safety update reports (PSURs), interim periodic safety reports (IPSRs), and certain individual case safety reports—semiannual submissions (*i.e.*, if PSURs are submitted for the product).

Company core safety information (CCSI) means 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. It is the reference information by which an SADR is determined to be "listed" or "unlisted" for PSURs, IPSRs, and certain individual case safety reports—semiannual submissions (*i.e.*, if PSURs are submitted for the product).

Contractor means any person (*e.g.*, manufacturer, packer or distributor) whether its name appears on the label of the product; licensee; contract

research organization) that has entered into a contract with the applicant to manufacture, pack, sell, distribute, or develop the drug or to maintain, create, or submit records regarding SADRs or medication errors.

Data lock point means the date designated as the cut-off date for data to be included in a postmarketing periodic safety report.

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

Full data set means completion of all the applicable elements on FDA Form 3500A (or on a Council for International Organizations of Medical Sciences (CIOMS) I form for reports of foreign SADRs), 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).

International birth date means the date the first regulatory authority in the world approved the first marketing application for a human drug product containing the drug substance.

Life-threatening SADR means any SADR that, in the view of the initial reporter, places the patient at immediate risk of death from the SADR as it occurred. It does not include an SADR that, had it occurred in a more severe form, might have caused death.

Listed SADR means an SADR whose nature, specificity, severity, and outcome are consistent with the information in the CCSI.

Medication error means 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.

Minimum data set means the report includes an identifiable patient, an identifiable reporter, a suspect drug product, and an SADR.

Nonserious SADR means any SADR that is determined not to be a serious SADR.

Potential medication error means an individual case safety report of information or complaint about product name, labeling, or packaging similarities that does not involve a patient.

SADR with unknown outcome means an SADR that cannot be classified, after active query, as either serious or nonserious.

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

Spontaneous report means 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 applicant or contractor, 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.

Suspected adverse drug reaction (SADR) means a noxious and unintended response to any dose of a drug 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.

Unexpected SADR means any SADR that is not included in the current U.S. labeling for the drug product. Reactions that may be symptomatically and pathophysiologically related to a reaction included in the U.S. labeling, but differ from the labeled reaction because of greater severity or specificity, would be unexpected. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the U.S. labeling only referred to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the U.S. labeling only included cerebral vascular accidents. "Unexpected," as used in this definition, refers to an SADR that has

not been previously observed (i.e., included in the U.S. labeling); it does not refer to an SADR that might be anticipated from the pharmacological properties of the drug product. SADRs that are mentioned in the U.S. labeling as occurring with a class of drugs but not specifically mentioned as occurring with the particular drug are considered unexpected.

Unlisted SADR means an SADR whose nature, specificity, severity, or outcome is not consistent with the information included in the CCSI.

(b) *Review of safety information.* (1) Each applicant having an approved application for a drug product under section 505(c) of the act must promptly review all safety information pertaining to its product obtained or otherwise received by the applicant from any source, foreign or domestic, including information derived from commercial marketing experience, postmarketing clinical investigations, postmarketing epidemiology/surveillance studies, animal or in vitro studies, electronic communications with applicants via the Internet (e.g., e-mail), reports in the scientific literature, and unpublished scientific papers, as well as reports from foreign regulatory authorities that have not been previously reported to FDA by the applicant.

(2) Individual case safety reports that are forwarded to the applicant by FDA must not be resubmitted to the agency by the applicant; however, applicants must include information from these individual case safety reports in any comprehensive safety analysis subsequently submitted to FDA. In addition, applicants must submit to FDA all followup information for these individual case safety reports.

(c) *Reporting requirements.* The applicant must submit to FDA two copies of each postmarketing expedited report (described under paragraphs (c)(2)(i) through (c)(2)(vii) of this section) and one copy of each postmarketing periodic safety report of an individual case safety reports—semiannual submission (described under paragraph (c)(3)(v) of this section) pertaining to its drug product. The applicant must also submit to FDA one copy of a PSUR, IPSR, or traditional periodic safety report (TPSR) along with one copy for each approved application for a human drug product covered by the report. FDA may waive the requirement for multiple copies in appropriate instances. Upon written notice, FDA may require, when appropriate, that the applicant submit reports under this section to FDA at times other than those stated. An applicant that wishes to submit reports

under this section at different intervals must submit to FDA a request for a waiver under § 314.90.

(1) *Determination of outcome, minimum data set, and full data set—*(i)(A) *Initial determinations.* Upon initial receipt of an SADR report, the applicant must immediately determine the outcome for the SADR (whether the SADR is serious or nonserious) and at least the minimum data set for the individual case safety report. For reports of actual medication errors that do not result in an SADR and potential medication errors the applicant must immediately determine the minimum information for the individual case safety report (minimum information described under paragraphs (c)(1)(iii)(B) and (c)(1)(iii)(C) of this section). If the applicant is not able to immediately determine the information in this paragraph, active query must be used to obtain it as soon as possible.

(B) *Spontaneous reports.* For spontaneous reports, the applicant must always assume, for safety reporting purposes under this section, that there is at least a reasonable possibility, in the opinion of the initial reporter, that the drug product caused the spontaneously reported event.

(C) *Clinical trials.* For a clinical trial, the possibility that the drug product caused the SADR or that a medication error has occurred must be assumed if either the investigator or the applicant believes that such a reasonable possibility exists.

(ii) *SADRs with unknown outcome.* For an SADR with unknown outcome that cannot be immediately determined, the applicant must continue to use active query to attempt to determine the outcome of the SADR within 30 calendar days after initial receipt of the SADR report by the applicant. The applicant must maintain a record of its efforts to determine the outcome for an SADR with unknown outcome.

(iii)(A) *Minimum data set for SADR reports.* The applicant must not submit an individual case safety report for an SADR to FDA if the report does not contain a minimum data set; instead, the applicant must 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.

(B) *Minimum information for reports of actual medication errors that do not result in an SADR.* For reports of actual medication errors that do not result in an SADR, an individual case safety report must be submitted to FDA even though the report does not contain a minimum data set (i.e., does not have an SADR). These reports must contain at

least an identifiable patient, an identifiable reporter, and a suspect drug product.

(C) *Minimum information for potential medication error reports.* For reports of potential medication errors, an individual case safety report must be submitted to FDA even though the report does not contain a minimum data set (*i.e.*, does not have an identifiable patient or an SADR). These reports must contain at least an identifiable reporter and a suspect drug product.

(iv) *Full data set.* For reports of serious SADRs, always expedited reports (see paragraph (c)(2)(iv) of this section), and medication error reports (see paragraph (c)(2)(v) of this section), the applicant must submit a full data set. If a full data set is not available for the report, the applicant must use active query to obtain this information. If a full data set is not obtainable, after active query, the applicant must:

(A) Submit all safety information, received or otherwise obtained, for the report;

(B) Indicate the reason(s) for its inability to acquire a full data set; and

(C) Document its efforts to obtain a full data set (*i.e.*, description of unsuccessful steps taken to obtain this information).

(v) *Serious SADRs not initially reported by a health care professional.* For a serious SADR that was not initially reported to the applicant by a health care professional (*e.g.*, report from a consumer), the applicant must contact the health care professional associated with the care of the patient using active query to gather further medical perspective on the case and to acquire a full data set for the report. If the applicant is unable to contact the health care professional, it must include in the report for the serious SADR:

(A) The reason(s) for its inability to contact the health care professional; and

(B) A description of its efforts to contact the health care professional.

(vi) *Nonserious SADRs.* For reports of nonserious SADRs with a minimum data set, except for those resulting from a medication error, all safety information received or otherwise obtained by the applicant must be submitted to FDA even though information in addition to the minimum data set is not required to be acquired. Reports of nonserious SADRs resulting from a medication error require a full data set under paragraph (c)(1)(iv) of this section.

(2) *Postmarketing "expedited reports"—(i) Serious and unexpected SADR.* The applicant must report to FDA each SADR, received or otherwise obtained, that is both serious and

unexpected, whether foreign or domestic, as soon as possible, but in no case later than 15 calendar days after receipt by the applicant of the minimum data set for the serious unexpected SADR. If a full data set is not available for the serious and unexpected SADR at the time of initial submission of the expedited report to FDA, the applicant must submit the information required under paragraph (c)(1)(iv) of this section and also submit a 30-day followup report as required by paragraph (c)(2)(vi) of this section.

(ii) *Information sufficient to consider product administration changes.* The applicant must also report to FDA information, received or otherwise obtained, whether foreign or domestic, that would be sufficient, based upon appropriate medical judgment, to consider changes in product administration. The applicant must submit this information to FDA as soon as possible, but in no case later than 15 calendar days after determination by the applicant that the information qualifies for expedited reporting. Examples of such information include any significant unanticipated safety finding or data in the aggregate from an *in vitro*, animal, epidemiological, or clinical study, whether or not conducted under an investigational new drug application (IND), that suggests a significant human risk, such as reports of mutagenicity, teratogenicity, or carcinogenicity, or reports of a lack of efficacy with a drug product used in treating a life-threatening or serious disease. The applicant must maintain a record of its efforts to determine whether the information required to be reported under this paragraph qualifies for expedited reporting.

(iii) *Unexpected SADR with unknown outcome.* The applicant must also report to FDA each SADR that is unexpected and for which the determination of an outcome is unattainable (*i.e.*, SADR with unknown outcome) within 45 calendar days after initial receipt by the applicant of the minimum data set for the unexpected SADR. The applicant must document in the expedited report the reason(s) for the inability to determine the outcome.

(iv) *Always expedited report.* (A) The applicant must also report to FDA each SADR, received or otherwise obtained, whether foreign or domestic, that is the subject of an always expedited report. These reports must be submitted to FDA as soon as possible, but in no case later than 15 calendar days after receipt by the applicant of the minimum data set for the report. The following medically significant SADRs, which may jeopardize the patient or subject and/or

require medical or surgical intervention to treat the patient or subject are subject to an always expedited report:

- (1) Congenital anomalies,
- (2) Acute respiratory failure,
- (3) Ventricular fibrillation,
- (4) Torsades de pointe,
- (5) Malignant hypertension,
- (6) Seizure,
- (7) Agranulocytosis,
- (8) Aplastic anemia,
- (9) Toxic epidermal necrolysis,
- (10) Liver necrosis,
- (11) Acute liver failure,
- (12) Anaphylaxis,
- (13) Acute renal failure,
- (14) Sclerosing syndromes,
- (15) Pulmonary hypertension,
- (16) Pulmonary fibrosis,
- (17) Confirmed or suspected transmission of an infectious agent by a marketed drug or biological product,
- (18) Confirmed or suspected endotoxin shock, and
- (19) Any other medically significant SADR that FDA determines to be the subject of an always expedited report (*i.e.*, may jeopardize the patient or subject and/or require medical or surgical intervention to treat the patient or subject).

(B) SADRs that are the subject of an always expedited report must be submitted to FDA whether unexpected or expected and whether the SADR leads to a serious outcome or not. If a full data set is not available for an always expedited report at the time of initial submission of the report to FDA, the applicant must submit the information required under paragraph (c)(1)(iv) of this section and also submit a 30-day followup report as required by paragraph (c)(2)(vi) of this section.

(v) *Medication errors—(A) Actual medication error.* The applicant must also submit to FDA each domestic report of an actual medication error, received or otherwise obtained, as soon as possible, but in no case later than 15 calendar days after receipt by the applicant of the minimum data set for a report of an SADR or, if an SADR does not occur, the minimum information described under paragraph (c)(1)(iii)(B) of this section (*i.e.*, identifiable patient, identifiable reporter, and suspect drug product).

(B) *Potential medication error.* The applicant must also submit to FDA each domestic report of a potential medication error, received or otherwise obtained, as soon as possible, but in no case later than 15 calendar days after receipt by the applicant of the minimum information described under paragraph (c)(1)(iii)(C) of this section (*i.e.*, identifiable reporter and suspect drug product).

(C) *Full data set.* If a full data set is not available for an actual or potential medication error report at the time of initial submission of the report to FDA, the applicant must submit the information required under paragraph (c)(1)(iv) of this section and also submit a 30-day followup report as required by paragraph (c)(2)(vi) of this section.

(vi) *The 30-day followup report.* The applicant must use active query to obtain additional information for any expedited report under paragraphs (c)(2)(i), (c)(2)(iv), and (c)(2)(v) of this section that does not contain a full data set and must submit a followup report to FDA within 30 calendar days after initial submission of the expedited report to FDA by the applicant. If a full data set is still not obtainable, the 30-day followup report must contain the information required under paragraph (c)(1)(iv) of this section. Any new safety information in the 30-day followup report must be highlighted. Any new information, received or otherwise obtained, after submission of a 30-day followup report must be submitted to FDA as a 15-day followup report under paragraph (c)(2)(vii) of this section.

(vii) *The 15-day followup report.* The applicant must report to FDA any new information, received or otherwise obtained, for any expedited or followup report (except for initial expedited reports under paragraphs (c)(2)(i), (c)(2)(iv), and (c)(2)(v) of this section that do not contain a full data set) within 15 calendar days of initial receipt of the new information by the applicant. Expedited reports under paragraphs (c)(2)(i), (c)(2)(iv), and (c)(2)(v) of this section that do not contain a full data set at the time of initial submission of the report to FDA are subject to the 30-day followup reporting requirements under paragraph (c)(2)(vi) of this section rather than the 15-day followup reporting requirements under this paragraph.

(viii) *Supporting documentation.* (A) If the patient dies, the applicant must submit a copy of the autopsy report to FDA, if it is available. If an autopsy report is not available, the applicant must submit a death certificate to FDA. If an autopsy report becomes available after the applicant has submitted a death certificate to the agency, the autopsy report must be submitted to FDA. If the patient was hospitalized, the applicant must submit a copy of the hospital discharge summary to FDA, if it is available. If any of these documents is not in English, the document must be accompanied by an English translation. Applicants must use active query to obtain these documents. These documents must be submitted to FDA as

15-day followup reports (see paragraph (c)(2)(vii) of this section) within 15 calendar days of initial receipt of the document by the applicant. If these documents are not submitted to FDA in a 15-day followup report within 3 months after submission of the initial expedited report for the death or hospitalization, the agency will assume that active query by the applicant has not resulted in access to these documents. In this case, a record of the reason(s) for the lack of such documentation and the effort that was made to obtain the documentation must be maintained by the applicant.

(B) Each expedited report must contain in the narrative a list of other relevant documents (e.g., medical records, laboratory results, data from studies) for the report that are maintained by the applicant. When appropriate, FDA may require an applicant to submit copies of one or more of these documents to the agency within 5 calendar days after receipt of the request.

(ix) *Scientific literature.* An expedited report based on information from the scientific literature applies only to reports found in scientific and medical journals. These expedited reports must be accompanied by a copy of the published article.

(x) *Submission of safety reports by contractors.* (A) Contractors must submit to the applicant safety reports of any SADR or medication errors for the applicant's drug product, obtained or otherwise received, within 5 calendar days of initial receipt of the report by the contractor. The contractor must submit a safety report for an SADR to the applicant even if the report does not contain a minimum data set. Upon receipt of the safety report from the contractor, the applicant must comply with the postmarketing safety reporting requirements of this section.

(B) A contract between the applicant and a contractor must specify the postmarketing safety reporting responsibilities of the contractor. The applicant is responsible for assuring that the contractors of its drug products comply with these postmarketing safety reporting responsibilities.

(C) The contractor must maintain a record of each submission to the applicant under paragraph (c)(2)(x)(A) of this section that includes:

- (1) A copy of each safety report;
- (2) The date the report was initially received by the contractor;
- (3) The date the report was submitted to the applicant; and
- (4) The name and address of the applicant.

(D) The recordkeeping, written procedures and disclaimer provisions under paragraphs (f), (g), and (i) of this section apply to contractors.

(xi) *Report identification.* Each expedited report submitted to FDA under paragraphs (c)(2)(i) through (c)(2)(vii) of this section must bear prominent identification as to its contents, e.g., "expedited report—serious and unexpected SADR," "expedited report—30-day followup." Each type of report (e.g., serious and unexpected SADR reports, 30-day followup reports) must be submitted to FDA under separate cover. Reports of medication errors must indicate whether the error is actual or potential and, if actual, whether a serious SADR, nonserious SADR, or no SADR occurred, e.g., "expedited report—actual medication error—nonserious SADR," "Expedited report—potential medication error."

(3) *Postmarketing periodic safety reports.* The applicant must submit postmarketing periodic safety reports under this section (i.e., TPSRs, PSURs, IPSRs, individual case safety reports—semiannual submission) to FDA within 60 calendar days after the data lock point for the report. The applicant must include a cover letter containing a list of the new drug application number(s) (i.e., NDA number(s)) for the human drug product(s) covered by the postmarketing periodic safety report. The international birth date for combination products is the international birth date of the human drug product containing the drug substance most recently approved for marketing.

(i) *Traditional periodic safety reports (TPSRs).* An applicant holding an application for a human drug product approved under section 505(c) of the act before January 1, 1998, must submit either a PSUR as prescribed under paragraph (c)(3)(ii) of this section or a TPSR as described under this paragraph every 5 years after U.S. approval of the application. In addition, these applicants must submit either an IPSR as described under paragraph (c)(3)(iii) of this section or a TPSR as described under this paragraph 7.5 years and 12.5 years after U.S. approval of the application. The data lock point for the TPSR, PSUR, or IPSR is the month and day of the international birth date of the drug product or any other month and day agreed on by the applicant and FDA. Each TPSR must contain:

(A) *Summary.* This section of the TPSR includes:

- (1) A narrative summary and analysis of serious, expected SADRs and nonserious, unexpected SADRs

occurring in the United States that were submitted to the applicant during the reporting period from all spontaneous sources (*i.e.*, health care professionals and other individuals) (with an index consisting of a line listing of the applicant's manufacturer report number and SADR term(s));

(2) An analysis of the expedited reports submitted during the reporting period under paragraphs (c)(2)(i) through (c)(2)(vii) of this section (all expedited reports must be appropriately referenced by the applicant's manufacturer report number, SADR term(s), if appropriate, and date of submission to FDA);

(3) A discussion of any increased reporting frequency of serious, expected SADRs, including comments on whether it is believed that the data reflect a meaningful change in SADR occurrence, and an assessment of whether it is believed that the frequency of lack of efficacy reports, obtained or otherwise received during the reporting period, is greater than would be predicted by the premarketing clinical trials for the drug product; and

(4) The applicants' conclusion as to what, if any, safety-related actions should be taken based on the analysis of the safety data in the TPSR (*e.g.*, labeling changes, studies initiated);

(B) *Summary tabulations.* This section of the TPSR includes summary tabulations (*i.e.*, lists of all SADR terms and counts of occurrences) presented by body system or by standard organ system classification scheme for:

(1) All serious expected SADRs, nonserious unexpected SADRs, nonserious expected SADRs, and expected SADRs with unknown outcome occurring in the United States that are submitted to the applicant during the reporting period from all spontaneous sources (*i.e.*, health care professionals and other individuals);

(2) All serious unexpected SADRs, unexpected SADRs with unknown outcome, and always expedited reports that were previously submitted to FDA in an expedited report under paragraphs (c)(2)(i), (c)(2)(iii), and (c)(2)(iv) of this section (include cumulative data for serious unexpected SADRs, *i.e.*, all cases reported to date);

(3) All reports of SADRs not previously submitted to FDA by the applicant (*e.g.*, reports submitted to applicants by FDA, reports obtained from FDA from freedom of information requests at the discretion of the applicant, reports from class action lawsuits); and

(4) All domestic reports of medication errors previously submitted to FDA under paragraph (c)(2)(v) of this section.

For actual medication errors, provide summary tabulations of serious SADRs, nonserious SADRs, and no SADRs. For potential medication errors, provide the number of reports for specific errors;

(C) *History of safety-related actions taken.* This section of the TPSR includes a history of safety-related actions taken since the last periodic safety report (*e.g.*, labeling changes, studies initiated);

(D) *Location of safety records.* This section of the TPSR includes a list of the current address(es) where all safety reports and other safety-related records for the drug product are maintained; and

(E) *Contact person.* This section of the TPSR includes the name and telephone number for the licensed physician(s) responsible for the content and medical interpretation of the information contained within the TPSR. Include, if available, the fax number and e-mail address for the licensed physician(s).

(ii) *Periodic safety update report (PSUR).* An applicant holding an application for a human drug product approved under section 505(c) of the act on or after January 1, 1998, must submit a PSUR to FDA according to the following schedule: Semiannually (*i.e.*, every 6 months) for 2 years after U.S. approval of the application, annually for the next 3 years and then every 5 years thereafter. The data lock point for the PSUR is the month and day of the international birth date of the drug substance or any other month and day agreed on by the applicant and FDA. Each PSUR must contain:

(A) *Title page, table of contents, and introduction.* (1) The title page includes, at a minimum, the following information:

(i) Name and international birth date of the drug substance that is the subject of the PSUR,

(ii) Various dosage forms and formulations of the drug substance covered by the PSUR,

(iii) Name and address of the applicant,

(iv) Reporting period covered by the PSUR, and

(v) Date of the PSUR.

(2) The introduction:

(i) Provides a brief description of how the PSUR relates to previous reports and circumstances;

(ii) References relevant drug products or substances reported in other periodic safety reports (*e.g.*, a combination product reported in a separate PSUR); and

(iii) Indicates any data duplication with other PSURs.

(B) *Worldwide marketing status.* This section of the PSUR contains a table of the chronological history of the

worldwide marketing status of the drug product(s) covered by the PSUR from the date the product(s) was first approved (*i.e.*, the international birth date) through its current status (*i.e.*, cumulative information). The table consists of:

(1) Dates of drug approval and renewal;

(2) Safety-related restrictions on product use;

(3) Indications for use and special populations covered by the drug approval;

(4) Lack of approval of the drug substance in any dosage form or for any indication for use by any regulatory authority(ies);

(5) Withdrawal of a pending marketing application for the drug product by the applicant for safety- or efficacy-related reasons;

(6) Dates of market launches; and

(7) Trade name(s).

(C) *Actions taken for safety reasons.*

(1) This section of the PSUR includes details on the following types of regulatory authority-initiated (*e.g.*, by FDA) and/or applicant-initiated actions related to safety that were taken during the period covered by the PSUR and between the data lock point and PSUR submission (*i.e.*, "late-breaking" safety concerns):

(i) Withdrawal or suspension of drug product approval or indication for use approval;

(ii) Failure to obtain a marketing authorization renewal or to obtain an approval for a new indication for use;

(iii) Restrictions on distribution (*e.g.*, products recalled for safety reasons);

(iv) Clinical trial suspension;

(v) Dosage modification;

(vi) Changes in target population or indications; and

(vii) Formulation changes.

(2) This section of the PSUR also contains a narrative identifying the safety-related reasons that led to these actions with relevant documentation appended when appropriate.

(3) Any communication with health care professionals (*e.g.*, Dear Healthcare Professional letters) resulting from such actions must also be described with copies appended.

(D) *Changes to CCSI.* This section of the PSUR describes changes to the CCSI (*e.g.*, new contraindications, precautions, warnings, SADRs, or interactions) made during the period covered by the PSUR. A copy of any modified section of the CCSI must be included. The applicant must use the CCSI in effect at the beginning of the reporting period for the PSUR. The revised CCSI is to be used as the reference document for the next reporting period.

(E) *Worldwide patient exposure.* (1) This section of the PSUR includes, for the reporting period, an estimate of the worldwide patient exposure to the drug product(s) covered by the PSUR (*i.e.*, number of patients, average or median dose received, and average or median length of treatment). The method used to estimate patient exposure must always be described. If the patient exposure is impossible to estimate or is meaningless, an explanation of and justification for such conclusions must be provided. If patient exposure is impossible to estimate, other measures of exposure, such as patient-days, number of prescriptions, or number of dosage units, may be used. If these or other more precise measures are not available and an adequate explanation for the lack of such information is provided, bulk sales may be used.

(2) When possible, data broken down by gender and age (especially pediatric versus adult) must be provided. For the pediatric population, data must be reported, if possible, by age group (*e.g.*, neonates, infants, children, adolescents). If these data are not available, an explanation must be included.

(3) When a pattern of reports indicates a potential problem, details by country (with locally recommended dosage regimens) or other segmentation (*e.g.*, indication, dosage form) must be presented.

(F) *Individual case safety reports.* (1) This section of the PSUR includes summary tabulations of individual case safety reports (*e.g.*, serious unlisted SADRs, serious listed SADRs, nonserious unlisted SADRs, nonserious listed SADRs) for the following SADRs obtained or otherwise received during the reporting period:

(i) All serious and nonserious SADRs from spontaneous sources that were submitted to applicants by a health care professional;

(ii) All serious SADRs from studies, individual patient INDs, or, in foreign countries, from named-patient "compassionate" use;

(iii) All serious SADRs and nonserious unlisted SADRs from the scientific literature;

(iv) All serious SADRs from regulatory authorities; and

(v) Serious SADRs from other sources such as reports created by poison control centers and epidemiological data bases.

(2) The summary tabulations must be made up of lists by body system or by standard organ system classification scheme of all SADR terms and counts of occurrences. For SADRs that are determined to be both serious and

unlisted, include cumulative data (*i.e.*, all cases reported to date).

(3) The applicant must conclude this section with a brief discussion of the data concerning the individual case safety reports in the PSUR (*e.g.*, discussion of medical significance or mechanism).

(G) *Safety studies.* This section of the PSUR contains a discussion of nonclinical, clinical, and epidemiological studies that contain important safety information, as follows:

(1) All applicant-sponsored studies newly analyzed during the reporting period (copies of full reports should be appended only if new safety issues are raised or confirmed; FDA may request copies of other studies, if necessary);

(2) New studies specifically planned, initiated, or continuing during the reporting period that examine a safety issue, whether actual or hypothetical; and

(3) Published safety studies in the scientific and medical literature, including relevant published abstracts from meetings (provide literature citation).

(H) *Other information.* This section of the PSUR includes:

(1) A discussion of medically relevant lack of efficacy reports (*e.g.*, might represent a significant hazard to the treated population) for a product(s) used to treat serious or life-threatening diseases; and

(2) Any important new information received after the data lock point (*e.g.*, significant new cases).

(I) *Overall safety evaluation.* This section of the PSUR contains a concise, yet comprehensive, analysis of all of the safety information provided in the PSUR, including new information provided under paragraph (c)(3)(ii)(H)(2) of this section. In addition, this section of the PSUR includes an assessment by the applicant of the significance of the data collected during the reporting period, as well as from the perspective of cumulative experience.

(1) The applicant must highlight any new information on:

(i) Serious, unlisted SADRs;

(ii) Increased reporting frequencies of listed SADRs, including comments on whether it is believed that the data reflect a meaningful change in SADR occurrence;

(iii) A change in characteristics of listed SADRs (*e.g.*, severity, outcome, target population); and

(iv) Nonserious, unlisted SADRs.

(2) As part of the overall safety evaluation, the applicant must also explicitly address any new safety issue including but not limited to the

following (lack of significant new information for each of the following must be mentioned):

(i) Drug interactions;

(ii) Experience with overdose, whether deliberate or accidental, and its treatment;

(iii) Drug abuse or intentional misuse;

(iv) Positive or negative experiences during pregnancy or lactation;

(v) Effects with long-term treatment; and

(vi) Experience in special patient groups (*e.g.*, pediatric, geriatric, organ impaired). For the pediatric population, data must be evaluated, if possible, by age group (*e.g.*, neonates, infants, children, adolescents).

(J) *Conclusion.* This section of the PSUR:

(1) Indicates new safety information that is not in accord with previous cumulative experience and with the CCSI in use at the beginning of the reporting period (*e.g.*, new evidence that strengthens a possible causal relationship between the drug product and an SADR such as positive rechallenge, an epidemiological association, or new laboratory studies); and

(2) Specifies and justifies any action recommended or initiated, including changes in the CCSI.

(K) *Appendices.* This section of the PSUR includes:

(1) *Company core data sheet.* Provide a copy of the company core data sheet covered by this PSUR (*i.e.*, in effect at the beginning of the period covered by the PSUR) as well as the company core data sheet for the next reporting period. Company core data sheets must be numbered and dated and include the date of last revision.

(2) *U.S. labeling.* Provide a copy of the current approved U.S. labeling. Specify any safety information that is included in the CCSI but not in the U.S. labeling and provide an explanation for the discrepancy. Describe any safety-related changes or proposed changes to the U.S. labeling made during the reporting period (include the supplement number(s) and date(s) of submission for the supplement(s) and any suggested change(s) that should be considered based on the safety analysis in the PSUR).

(3) *Spontaneous reports submitted to the applicant by an individual other than a health care professional.* Provide summary tabulations (*e.g.*, serious unlisted SADRs, serious listed SADRs, nonserious unlisted SADRs, nonserious listed SADRs) for all spontaneously reported serious SADRs, whether domestic or foreign, and all spontaneously reported nonserious

SADRs occurring in the United States, obtained or otherwise received during the reporting period by the applicant from an individual other than a health care professional (e.g., reports from consumers). These summary tabulations must consist of lists by body system or by standard organ system classification scheme of all SADR terms and counts of occurrences. For those SADRs that are determined to be both serious and unlisted, include cumulative data (i.e., all cases reported to date by individuals other than a health care professional). Include a brief discussion of the impact of the spontaneous reports described in this appendix on the overall safety evaluation.

(4) *SADRs with unknown outcome.* Provide summary tabulations for unlisted and listed SADRs with unknown outcome from all spontaneous sources (i.e., health care professionals and other individuals), obtained or otherwise received by the applicant during the reporting period. These summary tabulations must consist of lists by body system or by standard organ system classification scheme of all SADR terms and counts of occurrences. Include a brief discussion of the impact of the spontaneous reports described in this appendix on the overall safety evaluation.

(5) *Class action lawsuits.* Provide summary tabulations (e.g., serious unlisted SADRs, serious listed SADRs, nonserious unlisted SADRs, nonserious listed SADRs) for all SADRs obtained or otherwise received during the reporting period by the applicant from class action lawsuits. These summary tabulations must consist of lists by body system or by standard organ system classification scheme of all SADR terms and counts of occurrences. For those SADRs that are determined to be both serious and unlisted, include cumulative data. Include a brief discussion of the impact of the reports described in this appendix on the overall safety evaluation.

(6) *Lack of efficacy reports.* Provide an assessment of whether it is believed that the frequency of lack of efficacy reports, obtained or otherwise received during the reporting period, is greater than would be predicted by the premarketing clinical trials for the drug product.

(7) *Information on resistance to antimicrobial drug products.* Provide information, received or otherwise obtained by the applicant, on resistance to antimicrobial drug products intended to treat infectious diseases. Include information on changes in U.S. microbial in vitro susceptibility, the relationship of changes in U.S. microbial in vitro susceptibility and

clinical outcomes, therapeutic failure that may possibly be due to resistance to the antimicrobial drug product, and whether the U.S. labeling should be revised because of the information on antimicrobial resistance learned during the period covered by this PSUR.

(8) *Medication errors.* Provide summary tabulations of all domestic reports of medication errors submitted during the reporting period under paragraph (c)(2)(v) of this section. For actual medication errors, provide summary tabulations for serious SADRs, nonserious SADRs, and no SADRs (for serious SADRs include cumulative data, i.e., all cases reported to date). For potential medication errors, provide the number of reports for specific errors. If an SADR occurs, the summary tabulations must consist of lists by body system or by standard organ system classification scheme of all SADR terms and counts of occurrences. Include a brief discussion of the impact on the overall safety evaluation of these reports.

(9) *U.S. patient exposure.* Provide, for the reporting period, an estimate of the U.S. patient exposure to the drug product(s) covered by the PSUR (i.e., number of patients, average or median dose received, and average or median length of treatment). The method used to estimate patient exposure must always be described. If the patient exposure is impossible to estimate or is meaningless, an explanation of and justification for such conclusions must be provided. If patient exposure is impossible to estimate, other measures of exposure, such as patient-days, number of prescriptions, or number of dosage units, may be used. If these or other more precise measures are not available and an adequate explanation for the lack of such information is provided, bulk sales may be used.

(10) *Location of safety records.* Provide a list of the current address(es) where all safety reports and other safety-related records for the drug product(s) are maintained.

(11) *Contact person.* Provide the name and telephone number of the licensed physician(s) responsible for the content and medical interpretation of the data and information contained within the PSUR. Include, if available, the fax number and e-mail address of the licensed physician(s).

(iii) *Interim periodic safety report (IPSR).* An applicant holding an application for a human drug product approved under section 505(c) of the act on or after January 1, 1998, must submit an IPSR to FDA 7.5 years and 12.5 years after U.S. approval of the application. The data lock point for the IPSR is the

month and day of the international birth date of the drug substance or any other month and day agreed on by the applicant and FDA. The reporting period for the IPSR covers the period between the last PSUR or TPSR and the data lock point for the IPSR (e.g., between years 5 and 7.5 for an IPSR with a data lock point 7.5 years after U.S. approval of the application). Each IPSR must contain:

(A) *Title page, table of contents, and introduction.* (1) The title page includes, at a minimum, the following information:

(i) Name and international birth date of the drug substance that is the subject of the IPSR,

(ii) Various dosage forms and formulations of the drug substance covered by the IPSR,

(iii) Name and address of the applicant,

(iv) Reporting period covered by the IPSR, and

(v) Date of the IPSR.

(2) The introduction:

(i) Provides a brief description of how the IPSR relates to previous reports and circumstances,

(ii) References relevant drug products or substances reported in other periodic safety reports (e.g., a combination product reported in a separate IPSR), and

(iii) Indicates any data duplication with other IPSRs.

(B) *Worldwide marketing status.* This section of the IPSR contains a table of the chronological history of the worldwide marketing status of the drug product(s) covered by the IPSR from the date the product(s) was first approved (i.e., the international birth date) through its current status (i.e., cumulative information). The table consists of:

(1) Dates of drug approval and renewal;

(2) Safety-related restrictions on product use;

(3) Indications for use and special populations covered by the drug approval;

(4) Lack of approval of the drug substance in any dosage form or for any indication for use by any regulatory authority(ies);

(5) Withdrawal of a pending marketing application for a drug product by the applicant for safety or efficacy related reasons;

(6) Dates of market launches; and

(7) Trade name(s).

(C) *Actions taken for safety reasons.*

(1) This section of the IPSR includes details on the following types of regulatory authority-initiated (e.g., by FDA) and/or applicant-initiated actions

related to safety that were taken during the period covered by the IPSR and between the data lock point and IPSR submission (*i.e.*, "late-breaking" safety concerns):

(i) Withdrawal or suspension of drug product approval or indication for use approval;

(ii) Failure to obtain a marketing authorization renewal or to obtain an approval for a new indication for use;

(iii) Restrictions on distribution (*e.g.*, products recalled for safety reasons);

(iv) Clinical trial suspension;

(v) Dosage modification;

(vi) Changes in target population or indications; and

(vii) Formulation changes.

(2) This section of the IPSR also contains a narrative identifying the safety-related reasons that led to these actions with relevant documentation appended when appropriate.

(3) Any communication with health care professionals (*e.g.*, Dear Healthcare Professional letters) resulting from such actions must also be described with copies appended.

(D) *Changes to CCSI*. This section of the IPSR describes changes to the CCSI (*e.g.*, new contraindications, precautions, warnings, SADRs, or interactions) made during the period covered by the IPSR. A copy of any modified section of the CCSI must be included. The applicant must use the CCSI in effect at the beginning of the reporting period for the IPSR. The revised CCSI is to be used as the reference document for the next reporting period.

(E) *Worldwide patient exposure*. (1) This section of the IPSR includes, for the reporting period, an estimate of the worldwide patient exposure to the drug product(s) covered by the IPSR (*i.e.*, number of patients, average or median dose received, and average or median length of treatment). The method used to estimate patient exposure must always be described. If the patient exposure is impossible to estimate or is meaningless, an explanation of and justification for such conclusions must be provided. If patient exposure is impossible to estimate, other measures of exposure, such as patient-days, number of prescriptions, or number of dosage units, may be used. If these or other more precise measures are not available and an adequate explanation for the lack of such information is provided, bulk sales may be used.

(2) When possible, data broken down by gender and age (especially pediatric versus adult) must be provided. For the pediatric population, data must be reported, if possible, by age group (*e.g.*, neonates, infants, children,

adolescents). If these data are not available, an explanation must be included.

(3) When a pattern of reports indicates a potential problem, details by country (with locally recommended dosage regimens) or other segmentation (*e.g.*, indication, dosage form) must be presented.

(F) *Safety studies*. This section of the IPSR contains a discussion of nonclinical, clinical, and epidemiological studies that contain important safety information, as follows:

(1) All applicant-sponsored studies newly analyzed during the reporting period (copies of full reports should be appended only if new safety issues are raised or confirmed; FDA may request copies of other studies, if necessary);

(2) New studies specifically planned, initiated, or continuing during the reporting period that examine a safety issue, whether actual or hypothetical; and

(3) Published safety studies in the scientific and medical literature, including relevant published abstracts from meetings (provide literature citation).

(G) *Other information*. This section of the IPSR includes a discussion of medically relevant lack of efficacy reports (*e.g.*, might represent a significant hazard to the treated population) for a product(s) used to treat serious or life-threatening diseases.

(H) *Overall safety evaluation*. This section of the IPSR contains a concise, yet comprehensive, analysis of all of the safety information provided in the IPSR. In addition, this section of the IPSR must include an assessment by the applicant of the significance of the data collected during the reporting period, as well as from the perspective of cumulative experience.

(1) The applicant must highlight any new information on:

(i) Serious, unlisted SADRs;

(ii) Increased reporting frequencies of listed SADRs, including comments on whether it is believed that the data reflect a meaningful change in SADR occurrence;

(iii) A change in characteristics of listed SADRs (*e.g.*, severity, outcome, target population); and

(iv) Nonserious, unlisted SADRs.

(2) As part of the overall safety evaluation, the applicant must also explicitly address any new safety issue including but not limited to the following (lack of significant new information for each of the following must be mentioned):

(i) Drug interactions;

(ii) Experience with overdose, whether deliberate or accidental, and its treatment;

(iii) Drug abuse or intentional misuse;

(iv) Positive or negative experiences during pregnancy or lactation;

(v) Effects with long-term treatment; and

(vi) Experience in special patient groups (*e.g.*, pediatric, geriatric, organ impaired). For the pediatric population, data must be evaluated, if possible, by age group (*e.g.*, neonates, infants, children, adolescents).

(I) *Conclusion*. This section of the IPSR:

(1) Indicates new safety information that is not in accord with previous cumulative experience and with the CCSI in use at the beginning of the reporting period (*e.g.*, new evidence that strengthens a possible causal relationship between the drug product and an SADR such as positive rechallenge, an epidemiological association or new laboratory studies); and

(2) Specifies and justifies any action recommended or initiated, including changes in the CCSI.

(J) *Appendices*. This section of the IPSR includes:

(1) *Company core data sheet*. Provide a copy of the company core data sheet covered by this IPSR (*i.e.*, in effect at the beginning of the period covered by the IPSR), as well as the company core data sheet for the next reporting period. Company core data sheets must be numbered and dated and include the date of last revision.

(2) *U.S. labeling*. Provide a copy of the current approved U.S. labeling. Specify any safety information that is included in the CCSI but not in the U.S. labeling and provide an explanation for the discrepancy. Describe any safety-related changes or proposed changes to the U.S. labeling made during the reporting period (include the supplement number(s) and date(s) of submission for the supplement(s) and any suggested change(s) that should be considered based on the safety analysis in this IPSR.

(3) *Spontaneous reports submitted to the applicant by an individual other than a health care professional*. Provide a brief discussion of the impact on the overall safety evaluation of any spontaneously reported serious SADRs, whether domestic or foreign, and any spontaneously reported nonserious SADRs occurring in the United States, obtained or otherwise received during the reporting period by the applicant from an individual other than a health care professional (*e.g.*, reports from consumers).

(4) *SADRs with unknown outcome.* Provide a brief discussion of the impact on the overall safety evaluation of any spontaneously reported unlisted and listed SADRs with unknown outcome obtained or otherwise received during the reporting period by the applicant from health care professionals and other individuals.

(5) *Class action lawsuits.* Provide a brief discussion of the impact on the overall safety evaluation of any safety information obtained or otherwise received during the reporting period by the applicant from class action lawsuits.

(6) *Lack of efficacy reports.* Provide an assessment of whether it is believed that the frequency of any lack of efficacy reports, obtained or otherwise received during the reporting period, is greater than would be predicted by the premarketing clinical trials for the drug product.

(7) *Information on resistance to antimicrobial drug products.* Provide information, received or otherwise obtained by the applicant, on resistance to antimicrobial drug products intended to treat infectious diseases. Include information on changes in U.S. microbial in vitro susceptibility, the relationship of changes in U.S. microbial in vitro susceptibility and clinical outcomes, therapeutic failure that may possibly be due to resistance to the antimicrobial drug product, and whether the U.S. labeling should be revised because of the information on antimicrobial resistance learned during the period covered by this IPSR.

(8) *Medication errors.* Provide a brief discussion of the impact on the overall safety evaluation of all domestic reports of medication errors submitted during the reporting period under paragraph (c)(2)(v) of this section.

(9) *U.S. patient exposure.* Provide, for the reporting period, an estimate of the U.S. patient exposure to the drug product(s) covered by the IPSR (*i.e.*, number of patients, average or median dose received, and average or median length of treatment). The method used to estimate patient exposure must always be described. If the patient exposure is impossible to estimate or is meaningless, an explanation of and justification for such conclusions must be provided. If patient exposure is impossible to estimate, other measures of exposure, such as patient-days, number of prescriptions, or number of dosage units, may be used. If these or other more precise measures are not available and an adequate explanation for the lack of such information is provided, bulk sales may be used.

(10) *Location of safety records.* Provide a list of the current address(es)

where all safety reports and other safety-related records for the drug product are maintained.

(11) *Contact person.* Provide the name and telephone number for the licensed physician(s) responsible for the content and medical interpretation of the information contained within the IPSR. Include, if available, the fax number and e-mail address for the licensed physician(s).

(iv) *Pediatric use supplements.* After approval of a pediatric use supplement to an approved application (*i.e.*, a supplement for use of the human drug product in the pediatric population), the applicant must submit PSURs to FDA as prescribed under paragraph (c)(3)(ii) of this section according to the following schedule: Semiannually for 2 years after U.S. approval of the supplement, annually for the next 3 years, and then every 5 years thereafter. These applicants must also submit IPSRs to FDA as prescribed under paragraph (c)(3)(iii) of this section at 7.5 years and 12.5 years after U.S. approval of the supplement. The data lock point for the PSUR and IPSR is the month and day of the international birth date of the drug substance or any other month and day agreed on by the applicant and FDA.

(v) *Semiannual submission of individual case safety reports.* (A) An applicant holding an application for a human drug product approved under section 505(c) of the act must submit to FDA semiannually (*i.e.*, every 6 months) after U.S. approval of the application a separate report that consists of individual case safety reports for certain spontaneously reported SADRs for the human drug product. The individual case safety reports must be submitted to FDA on the form designated by the agency under paragraph (c)(4) of this section. The data lock point for the report is the month and day of the international birth date of the drug product or any other month and day agreed on by the applicant and FDA. This report must be identified as "individual case safety reports—semiannual submission."

(B) Applicants that submit TPSRs to FDA for the drug product must submit an individual case safety report for each serious, expected SADR, whether domestic or foreign, and each nonserious, unexpected SADR occurring in the United States that is submitted to the applicant during the reporting period from all spontaneous sources (*i.e.*, health care professionals and other individuals). Applicants that submit PSURs to FDA for the drug product must submit an individual case safety report for each serious, listed SADR, whether domestic or foreign, and each

nonserious, unlisted SADR occurring in the United States that is submitted to the applicant during the reporting period from all spontaneous sources. If a full data set is not available for a serious SADR, the applicant must submit the information required under paragraph (c)(1)(iv) of this section.

(C) Followup information on SADRs submitted in an individual case safety report—semiannual submission may be submitted in the next individual case safety report—semiannual submission unless such information changes the classification of the SADR to a serious, unexpected SADR. In these cases, the followup information must be submitted to FDA as a 15-day followup report (see paragraph (c)(2)(vii) of this section).

(4) *Reporting format.* (i)(A) Except as provided in paragraphs (c)(4)(i)(B), (c)(4)(i)(D), and (c)(4)(v) of this section, the applicant must complete an FDA Form 3500A for each individual case safety report of an SADR. Reports based on information about individual cases or case series in the scientific literature must be submitted on an FDA Form 3500A(s).

(B) Foreign SADRs may be submitted either on an FDA Form 3500A or, if preferred, on a CIOMS I form.

(C) Each domestic report of an actual or potential medication error must be submitted on an FDA Form 3500A.

(D) Reports of overall findings or data in the aggregate from published and unpublished in vitro, animal, epidemiological, or clinical studies must be submitted in a narrative format.

(ii) Each SADR in an individual case safety report must be coded on the FDA Form 3500A or CIOMS I form using the appropriate "preferred term" in the latest version of MedDRA (the medical dictionary for regulatory activities) in use at the time the applicant becomes aware of the individual case safety report. For individual case safety reports of medication errors, the report must be coded both as a medication error and, if applicable, with the preferred term for any SADRs associated with the medication error.

(iii) Each completed FDA Form 3500A or CIOMS I form should refer only to an individual case.

(iv) Each completed FDA Form 3500A or CIOMS I form must include the name and telephone number (and fax number and e-mail address, if available) for the licensed physician responsible for the content and medical interpretation of the data contained within the form (*i.e.*, contact person for the company).

(v) Instead of using FDA Form 3500A, the applicant may use a computer-generated facsimile of FDA Form 3500A provided that it is readable, includes

appropriate identifying information, and contains all the elements (i.e., format, sections, blocks, titles, descriptors within blocks, text for disclaimer) of FDA Form 3500A in the identical enumerated sequence of the form. For individual case safety reports in which no suspect medical device is involved, a one-page FDA Form 3500A is acceptable.

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

(e) *Patient privacy.* The names and addresses of individual patients should not be included in reports under this section; instead, the applicant and its contractors should assign a unique code to each report, preferably not more than eight characters (i.e., numbers and/or letters) in length. The name of the reporter from whom the information was received should be included. Names of patients, individual reporters, health care professionals, hospitals, and geographic identifiers in safety reports are not releasable to the public under FDA's public information regulations in part 20 of this chapter.

(f) *Recordkeeping.* Each applicant must maintain for a period of 10 years records of all safety information pertaining to its drug product, received or otherwise obtained, including raw data, any correspondence relating to the safety information, and any reports of SADRs or medication errors not submitted to FDA or only provided to FDA in a summary tabulation. Each applicant must also retain for a period of 10 years any records required to be maintained under this section. When appropriate, FDA may require an applicant to submit any or all of these records to the agency within 5 calendar days after receipt of the request.

(g) *Written procedures.* Each applicant must develop and maintain written procedures for the surveillance, receipt, evaluation, and reporting of postmarketing safety information to FDA.

(h) *Withdrawal of approval.* If an applicant fails to establish and maintain records and make reports required under this section, FDA may withdraw approval of the application and, thus,

prohibit continued marketing of the drug product that is the subject of the application.

(i) *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 SADR. 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 SADR.

8. Section 314.81 is amended by removing paragraph (b)(2)(v), by redesignating paragraphs (b)(2)(vi) through (b)(2)(ix) as paragraphs (b)(2)(v) through (b)(2)(viii), respectively, and by revising paragraph (b)(2)(i) and newly redesignated paragraph (b)(2)(v) to read as follows:

§ 314.81 Other postmarketing reports.

- * * * *
- (b) * * *
- (2) * * *

(i) *Summary.* A brief summary of significant new information from the previous year that might affect the effectiveness of the drug product or the sections of the drug product labeling that are not related to safety. The report must also contain a brief description of actions the applicant has taken or intends to take as a result of this new information, for example, submit an efficacy labeling supplement or initiate a new study. The summary must briefly state whether supplements for pediatric use have been submitted and whether new studies in the pediatric population to support appropriate labeling for the pediatric population have been initiated.

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(v) *Clinical data.* (A) Published clinical trials of the drug (or abstracts of them), including clinical trials on effectiveness; clinical trials on new uses; and biopharmaceutic, pharmacokinetic, and clinical pharmacology studies conducted by or otherwise obtained by the applicant. Review articles, papers describing safety related information or the use of the drug product in medical practice, papers and abstracts in which the drug is used as a research tool, promotional articles, press clippings, and papers that do not contain tabulations or summaries of original data should not be reported.

(B) Summaries of completed unpublished clinical trials, or prepublication manuscripts if available, conducted by, or otherwise obtained by,

the applicant. Supporting information should not be reported. (A study is considered completed 1 year after it is concluded.)

(C) Analysis of available efficacy data in the pediatric population and changes proposed in the labeling based on this information. An assessment of data needed to ensure appropriate labeling for the pediatric population must be included.

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9. Section 314.98 is amended in paragraph (a) by adding the abbreviation "(ANDA)" after the phrase "abbreviated new drug application", by removing the citation "§ 314.94" and by adding in its place the phrase "section 505(j) of the Act", by removing the phrase "adverse drug experiences" and by adding in its place the phrase "suspected adverse drug reactions", and by adding two sentences to the end of the paragraph; and in paragraph (b) by removing the phrase "Division of Epidemiology and Surveillance (HFD-730), Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857" and by adding in its place the word "FDA" to read as follows:

§ 314.98 Postmarketing reports.

(a) * * * For purposes of postmarketing periodic safety reporting, applicants must determine the data lock point (i.e., month and day of the international birth date or any other month and day agreed by the applicant and FDA) for their periodic safety reports based on the data lock point of postmarketing periodic safety reports for other drug products containing the same drug substance (i.e., innovator new drug application (NDA) product that is the same drug product as the ANDA product, or other ANDA products with the same drug substance if the innovator NDA product is no longer on the market). Applicants must determine the type of postmarketing periodic safety report required to be submitted to FDA (i.e., traditional periodic safety report (TPSR), periodic safety update report (PSUR) or interim periodic safety report (IPSR)) and the frequency of submission for these reports based on the U.S. approval date of the application for the innovator NDA product.

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PART 320—BIOAVAILABILITY AND BIOEQUIVALENCE REQUIREMENTS

10. The authority citation for 21 CFR part 320 continues to read as follows:

Authority: 21 U.S.C. 321, 351, 352, 355, 371.

11. Section 320.31 is amended by revising paragraph (d) to read as follows:

§ 320.31 Applicability of requirements regarding an “Investigational New Drug Application.”

* * * * *

(d) A bioavailability or bioequivalence study in humans other than one described in paragraphs (a) through (c) of this section is exempt from the requirements of part 312 of this chapter, except for the safety reporting requirements under § 312.32 of this chapter, if the following conditions are satisfied:

(1) If the study is one described under § 320.38(b) or § 320.63, the person conducting the study, including any contract research organization, must retain reserve samples of any test article and reference standard used in the study and release the reserve samples to FDA upon request in accordance with and for the period specified in § 320.38;

(2) An in vivo bioavailability or bioequivalence study in humans must be conducted in compliance with the requirements for institutional review set forth in part 56 of this chapter and informed consent set forth in part 50 of this chapter; and

(3) Safety reports as prescribed under § 312.32 of this chapter must be transmitted to all participating investigators and the appropriate FDA division in the Center for Drug Evaluation and Research (*i.e.*, safety reports for the reference listed drug must be sent to the new drug review division that has responsibility for that drug, safety reports for the investigational drug product must be sent to the Director, Division of Bioequivalence, Office of Generic Drugs). Each written notification under this paragraph must bear prominent identification of its contents, *i.e.*, “bioavailability/bioequivalence safety report.” For reporting purposes under this paragraph, an unexpected suspected adverse drug reaction (SADR) is any SADR, the specificity or severity of which is not consistent with the U.S. labeling for the reference listed drug.

PART 600—BIOLOGICAL PRODUCTS: GENERAL

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

Authority: 21 U.S.C. 321, 351, 352, 353, 355, 360, 360i, 371, 374; 42 U.S.C. 216, 262, 263, 263a, 264, 300aa–25.

13. Section 600.80 is revised to read as follows:

§ 600.80 Postmarketing reporting of suspected adverse reactions.

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

Active query means direct verbal contact (*i.e.*, in person or by telephone or other interactive means such as a video conference) with the initial reporter of a suspected adverse reaction (SAR) or medication error by a health care professional (*e.g.*, physician, physician assistant, pharmacist, dentist, nurse, any individual with some form of health care training) representing the applicant. For SARs, active query entails, at a minimum, a focused line of questioning designed to capture clinically relevant information associated with the licensed biological product and the SAR, including, but not limited to, information such as baseline data, patient history, physical exam, diagnostic results, and supportive lab results.

Actual medication error means 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 SAR, nonserious SAR, or no SAR.

Blood component means as defined in § 606.3(c) of this chapter.

Company core data sheet means a document prepared by the applicant containing, in addition to safety information, material relating to indications, dosing, pharmacology, and other information concerning the biological product. The only purpose of this document is to provide the company core safety information (CCSI) for periodic safety update reports (PSURs), interim periodic safety reports (IPSRs), and certain individual case safety reports—semiannual submissions (*i.e.*, if PSURs are submitted for the product).

Company core safety information (CCSI) means 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 biological product. It is the reference information by which an SAR is determined to be “listed” or “unlisted” for PSURs, IPSRs, and certain individual case safety reports—semiannual submissions (*i.e.*, if PSURs are submitted for the product).

Contractor means any person (*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 has entered into a

contract with the applicant (includes participants involved in divided manufacturing) to manufacture, pack, sell, distribute, or develop the licensed biological product or to maintain, create, or submit records regarding SARs or medication errors.

Data lock point means the date designated as the cut-off date for data to be included in a postmarketing periodic safety report.

Disability means a substantial disruption of a person’s ability to conduct normal life functions.

Full data set means completion of all the applicable elements on FDA Form 3500A or the vaccine adverse event reporting system (VAERS) form (or on a Council for International Organizations of Medical Sciences (CIOMS) I form for reports of foreign SARs), including a concise medical narrative of the case (*i.e.*, an accurate summary of the relevant data and information pertaining to an SAR or medication error).

International birth date means the date the first regulatory authority in the world approved the first marketing application for a human biological product.

Life-threatening SAR means any SAR that, in the view of the initial reporter, places the patient at *immediate* risk of death from the SAR as it occurred. It does not include an SAR that, had it occurred in a more severe form, might have caused death.

Listed SAR means an SAR whose nature, specificity, severity, and outcome are consistent with the information in the CCSI.

Medication error means 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.

Minimum data set means the report includes an identifiable patient, an identifiable reporter, a suspect biological product, and an SAR.

Nonserious SAR means any SAR that is determined not to be a serious SAR.

Potential medication error means an individual case safety report of information or complaint about product name, labeling, or packaging similarities that does not involve a patient.

SAR with unknown outcome means an SAR that cannot be classified, after

active query, as either serious or nonserious.

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

Spontaneous report means a communication from an individual (e.g., health care professional, consumer) to a company or regulatory authority that describes an SAR or medication error. It does not include cases identified from information solicited by the applicant, shared manufacturer, or contractor, 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.

Suspected adverse reaction (SAR) means a noxious and unintended response to any dose of a biological 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.

Unexpected SAR means any SAR that is not included in the current U.S. labeling for the licensed biological product. Reactions that may be symptomatically and pathophysiologically related to a reaction included in the U.S. labeling, but differ from the labeled reaction because of greater severity or specificity, would be unexpected. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the U.S. labeling only referred to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the U.S.

labeling only included cerebral vascular accidents. "Unexpected," as used in this definition, refers to an SAR that has not been previously observed (i.e., included in the U.S. labeling); it does not refer to an SAR that might be anticipated from the pharmacological properties of the licensed biological product. SARs that are mentioned in the U.S. labeling as occurring with a class of products but not specifically mentioned as occurring with the particular product are considered unexpected.

Unlisted SAR means an SAR whose nature, specificity, severity, or outcome is not consistent with the information included in the CCSI.

(b) *Review of safety information.* (1) Any person having a biologics license under § 601.20 of this chapter must promptly review all safety information pertaining to its product obtained or otherwise received by the applicant from any source, foreign or domestic, including information derived from commercial marketing experience, postmarketing clinical investigations, postmarketing epidemiology/surveillance studies, animal or in vitro studies, electronic communications with applicants via the Internet (e.g., e-mail), reports in the scientific literature, and unpublished scientific papers, as well as reports from foreign regulatory authorities that have not been previously reported to the Food and Drug Administration (FDA) by the applicant.

(2) Individual case safety reports that are forwarded to the applicant by FDA must not be resubmitted to the agency by the applicant; however, applicants must include information from these individual case safety reports in any comprehensive safety analysis subsequently submitted to FDA. In addition, applicants must submit to FDA all followup information for these individual case safety reports.

(c) *Reporting requirements.* For nonvaccine biological products, the applicant must submit to FDA two copies of each postmarketing expedited report (described under paragraphs (c)(2)(i) through (c)(2)(vii) of this section) and each postmarketing periodic safety report of an individual case safety reports—semiannual submission (described under paragraph (c)(3)(v) of this section) pertaining to its product. For nonvaccine biological products, the applicant must also submit to FDA one copy of a PSUR, IPSR, or traditional periodic safety report (TPSR) along with one copy for each approved application for a human licensed biological product covered by the report. For vaccines, the applicant must submit to VAERS two copies of

each safety report pertaining to its product and required under this section. FDA may waive the requirement for multiple copies in appropriate instances. Upon written notice, FDA may require, when appropriate, that the applicant submit reports under this section to the agency at times other than those stated. An applicant that wishes to submit reports under this section at different intervals must submit to FDA a request for a waiver under § 600.90.

(1) *Determination of outcome, minimum data set, and full data set—*(i)(A) *Initial determinations.* Upon initial receipt of an SAR report, the applicant must immediately determine the outcome for the SAR (whether the SAR is serious or nonserious) and at least the minimum data set for the individual case safety report. For reports of actual medication errors that do not result in an SAR and potential medication errors, the applicant must immediately determine the minimum information for the individual case safety report (minimum information described under paragraphs (c)(1)(iii)(B) and (c)(1)(iii)(C) of this section). If the applicant is not able to immediately determine the information in this paragraph, active query must be used to obtain it as soon as possible.

(B) *Spontaneous reports.* For spontaneous reports, the applicant must always assume, for safety reporting purposes under this section, that there is at least a reasonable possibility, in the opinion of the initial reporter, that the biological product caused the spontaneously reported event.

(C) *Clinical trials.* For a clinical trial, the possibility that the biological product caused the SAR or that a medication error has occurred must be assumed if either the investigator or the applicant believes that such a reasonable possibility exists.

(ii) *SARs with unknown outcome.* For an SAR with unknown outcome that cannot be immediately determined, the applicant must continue to use active query to attempt to determine the outcome of the SAR within 30 calendar days after initial receipt of the SAR report by the applicant. The applicant must maintain a record of its efforts to determine the outcome for an SAR with unknown outcome.

(iii) (A) *Minimum data set for SAR reports.* The applicant must not submit an individual case safety report for an SAR to FDA if the report does not contain a minimum data set; instead, the applicant must maintain records of any information received or otherwise obtained for the SAR along with a record of its efforts to obtain a minimum data set.

(B) *Minimum information for reports of actual medication errors that do not result in an SAR.* For reports of actual medication errors that do not result in an SAR, an individual case safety report must be submitted to FDA even though the report does not contain a minimum data set (*i.e.*, does not have an SAR). These reports must contain at least an identifiable patient, an identifiable reporter, and a suspect biological product.

(C) *Minimum information for potential medication error reports.* For reports of potential medication errors, an individual case safety report must be submitted to FDA even though the report does not contain a minimum data set (*i.e.*, does not have an identifiable patient or an SAR). These reports must contain at least an identifiable reporter and a suspect biological product.

(iv) *Full data set.* For reports of serious SARs, always expedited reports (see paragraph (c)(2)(iv) of this section), and medication error reports (see paragraph (c)(2)(v) of this section), the applicant must submit a full data set. If a full data set is not available for the report, the applicant must use active query to obtain this information. If a full data set is not obtainable after active query, the applicant must:

(A) Submit all safety information, received or otherwise obtained, for the report;

(B) Indicate the reason(s) for its inability to acquire a full data set; and

(C) Document its efforts to obtain a full data set (*i.e.*, description of unsuccessful steps taken to obtain this information).

(v) *Serious SARs not initially reported by a health care professional.* For a serious SAR that was not initially reported to the applicant by a health care professional (*e.g.*, report from a consumer), the applicant must contact the health care professional associated with the care of the patient using active query to gather further medical perspective on the case and to acquire a full data set for the report. If the applicant is unable to contact the health care professional, it must include in the report for the serious SAR:

(A) The reason(s) for its inability to contact the health care professional; and

(B) A description of its efforts to contact the health care professional.

(vi) *Nonserious SARs.* For reports of nonserious SARs with a minimum data set, except for those resulting from a medication error, all safety information received or otherwise obtained by the applicant must be submitted to FDA even though information in addition to the minimum data set is not required to be acquired. Reports of nonserious SARs

resulting from a medication error require a full data set under paragraph (c)(1)(iv) of this section.

(2) *Postmarketing "expedited reports"*—(i) *Serious and unexpected SAR.* The applicant must report to FDA each SAR, received or otherwise obtained, that is both serious and unexpected, whether foreign or domestic, as soon as possible, but in no case later than 15 calendar days after receipt by the applicant of the minimum data set for the serious, unexpected SAR. If a full data set is not available for the serious and unexpected SAR report at the time of initial submission of the report to FDA, the applicant must submit the information required under paragraph (c)(1)(iv) of this section and also submit a 30-day followup report as required by paragraph (c)(2)(vi) of this section.

(ii) *Information sufficient to consider product administration changes.* The applicant must also report to FDA information, received or otherwise obtained, whether foreign or domestic, that would be sufficient, based upon appropriate medical judgment, to consider changes in product administration. The applicant must submit this information to FDA as soon as possible, but in no case later than 15 calendar days after determination by the applicant that the information qualifies for expedited reporting. Examples of such information include any significant unanticipated safety finding or data in the aggregate from an *in vitro*, animal, epidemiological, or clinical study, whether or not conducted under an investigational new drug application (IND), that suggests a significant human risk, such as reports of mutagenicity, teratogenicity, or carcinogenicity, or reports of a lack of efficacy with a biological product used in treating a life-threatening or serious disease. The applicant must maintain a record of its efforts to determine whether the information required to be reported under this paragraph qualifies for expedited reporting.

(iii) *Unexpected SAR with unknown outcome.* The applicant must also report to FDA each SAR that is unexpected and for which the determination of an outcome is unattainable (*i.e.*, SAR with unknown outcome) within 45 calendar days after initial receipt by the applicant of the minimum data set for the unexpected SAR. The applicant must document in the expedited report the reason(s) for the inability to determine the outcome.

(iv) *Always expedited report.* (A) The applicant must also report to FDA each SAR, received or otherwise obtained, whether foreign or domestic, that is the

subject of an always expedited report. These reports must be submitted to FDA as soon as possible, but in no case later than 15 calendar days after receipt by the applicant of the minimum data set for the report. The following medically significant SARs, which may jeopardize the patient or subject and/or require medical or surgical intervention to treat the patient or subject, are subject to an always expedited report:

- (1) Congenital anomalies,
- (2) Acute respiratory failure,
- (3) Ventricular fibrillation,
- (4) Torsades de pointe,
- (5) Malignant hypertension,
- (6) Seizure,
- (7) Agranulocytosis,
- (8) Aplastic anemia,
- (9) Toxic epidermal necrolysis,
- (10) Liver necrosis,
- (11) Acute liver failure,
- (12) Anaphylaxis,
- (13) Acute renal failure,
- (14) Sclerosing syndromes,
- (15) Pulmonary hypertension,
- (16) Pulmonary fibrosis,
- (17) Confirmed or suspected

transmission of an infectious agent by a marketed drug or biological product,

(18) Confirmed or suspected endotoxin shock, and

(19) Any other medically significant SAR that FDA determines to be the subject of an always expedited report (*i.e.*, may jeopardize the patient or subject and/or require medical or surgical intervention to treat the patient or subject).

(B) SARs that are the subject of an always expedited report must be submitted to FDA whether unexpected or expected and whether or not the SAR leads to a serious outcome. If a full data set is not available for an always expedited report at the time of initial submission of the report to FDA, the applicant must submit the information required under paragraph (c)(1)(iv) of this section and also submit a 30-day followup report as required by paragraph (c)(2)(vi) of this section.

(v) *Medication error*—(A) *Actual medication error.* The applicant must also submit to FDA each domestic report of an actual medication error, received or otherwise obtained, as soon as possible, but in no case later than 15 calendar days after receipt by the applicant of the minimum data set for a report of an SAR or, if an SAR does not occur, the minimum information described under paragraph (c)(1)(iii)(B) of this section (*i.e.*, identifiable patient, identifiable reporter, and suspect biological product).

(B) *Potential medication error.* The applicant must also submit to FDA each domestic report of a potential

medication error, received or otherwise obtained, as soon as possible, but in no case later than 15 calendar days after receipt by the applicant of the minimum information described under paragraph (c)(1)(iii)(C) of this section (*i.e.*, identifiable reporter and suspect biological product).

(C) *Full data set.* If a full data set is not available for an actual or potential medication error report at the time of initial submission of the report to FDA, the applicant must submit the information required under paragraph (c)(1)(iv) of this section and also submit a 30-day followup report as required by paragraph (c)(2)(vi) of this section.

(vi) *The 30-day followup report.* The applicant must use active query to obtain additional information for any expedited report under paragraphs (c)(2)(i), (c)(2)(iv), and (c)(2)(v) of this section that does not contain a full data set and must submit a followup report to FDA within 30 calendar days after initial submission of the expedited report to FDA by the applicant. If a full data set is still not obtainable, the 30-day followup report must contain the information required under paragraph (c)(1)(iv) of this section. Any new safety information in the 30-day followup report must be highlighted. Any new information received or otherwise obtained after submission of a 30-day followup report must be submitted to FDA as a 15-day followup report under paragraph (c)(2)(vii) of this section.

(vii) *The 15-day followup report.* The applicant must report to FDA any new information, received or otherwise obtained, for any expedited or followup report (except for initial expedited reports under paragraphs (c)(2)(i), (c)(2)(iv), and (c)(2)(v) of this section that do not contain a full data set) within 15 calendar days of initial receipt of the new information by the applicant. Expedited reports under paragraphs (c)(2)(i), (c)(2)(iv), and (c)(2)(v) of this section that do not contain a full data set at the time of initial submission of the report to FDA are subject to the 30-day followup reporting requirements under paragraph (c)(2)(vi) of this section rather than the 15-day followup reporting requirements under this paragraph.

(viii) *Supporting documentation.* (A) If the patient dies, the applicant must submit a copy of the autopsy report to FDA, if it is available. If an autopsy report is not available, the applicant must submit a death certificate to FDA. If an autopsy report becomes available after the applicant has submitted a death certificate to the agency, the autopsy report must be submitted to FDA. If the patient was hospitalized, the

applicant must submit a copy of the hospital discharge summary to FDA, if it is available. If any of these documents is not in English, the document must be accompanied by an English translation. Applicants must use active query to obtain these documents. These documents must be submitted to FDA as 15-day followup reports (see paragraph (c)(2)(vii) of this section) within 15 calendar days of initial receipt of the document by the applicant. If these documents are not submitted to FDA in a 15-day followup report within 3 months after submission of the initial expedited report for the death or hospitalization, the agency will assume that active query by the applicant has not resulted in access to these documents. In this case, a record of the reason(s) for the lack of such documentation and the effort that was made to obtain the documentation must be maintained by the applicant.

(B) Each expedited report must contain in the narrative a list of other relevant documents (*e.g.*, medical records, laboratory results, data from studies) for the report that are maintained by the applicant. When appropriate, FDA may require an applicant to submit copies of one or more of these documents to the agency within 5 calendar days after receipt of the request.

(ix) *Scientific literature.* An expedited report based on information from the scientific literature applies only to reports found in scientific and medical journals. These expedited reports must be accompanied by a copy of the published article.

(x) *Submission of safety reports by contractors and shared manufacturers.*

(A) Contractors and shared manufacturers must submit to the applicant (includes participants involved in divided manufacturing) safety reports of any SARs or medication errors for the applicant's biological product, obtained or otherwise received, within 5 calendar days of initial receipt of the report by the contractor or shared manufacturer. The contractor and shared manufacturer must submit a safety report for an SAR to the applicant even if the report does not contain a minimum data set. Upon receipt of the safety report from a contractor or shared manufacturer, the applicant must comply with the postmarketing safety reporting requirements of this section.

(B) A contract between the applicant and a contractor must specify the postmarketing safety reporting responsibilities of the contractor. The applicant is responsible for ensuring that the contractors and shared

manufacturers of its licensed biological products comply with these postmarketing safety reporting responsibilities.

(C) The contractor and shared manufacturer must maintain a record of each submission to the applicant under paragraph (c)(2)(x)(A) of this section that includes:

- (1) A copy of each safety report;
- (2) The date the report was initially received by the contractor or shared manufacturer;
- (3) The date the report was submitted to the applicant; and
- (4) The name and address of the applicant.

(D) The recordkeeping, written procedures, and disclaimer provisions under paragraphs (f), (g), and (j) of this section apply to contractors and shared manufacturers.

(xi) *Report identification.* Each expedited report submitted to FDA under paragraphs (c)(2)(i) through (c)(2)(vii) of this section must bear prominent identification as to its contents, *e.g.*, "expedited report—serious and unexpected SAR," "expedited report—30-day followup report." Each type of report (*e.g.*, serious and unexpected SAR reports, 30-day followup reports) must be submitted to FDA under separate cover. Reports of medication errors must indicate whether the error is actual or potential and if actual, whether a serious SAR, nonserious SAR, or no SAR occurred, *e.g.*, "expedited report—actual medication error—nonserious SAR," "expedited report—potential medication error."

(3) *Postmarketing periodic safety reports.* The applicant must submit postmarketing periodic safety reports under this section (*i.e.*, TPSRs, PSURs, IPSRs, individual case safety reports—semiannual submission) to FDA within 60 calendar days after the data lock point for the report. The applicant must include a cover letter containing a list of the biologics license application number(s) (*i.e.*, BLA number(s)) for the human biological product(s) covered by the postmarketing periodic safety report. The international birth date for combination products is the international birth date of the human licensed biological product most recently approved for marketing.

(i) *Traditional periodic safety reports (TPSRs).* Each applicant holding a biologics license under § 601.20 of this chapter for a human biological product approved before January 1, 1998, must submit either a PSUR as prescribed under paragraph (c)(3)(ii) of this section or a TPSR as described under this paragraph every 5 years after U.S.

approval of the application. In addition, these applicants must submit either an IPSR as described under paragraph (c)(3)(iii) of this section or a TPSR as described under this paragraph 7.5 years and 12.5 years after U.S. approval of the application. The data lock point for the TPSR, PSUR, or IPSR is the month and day of the international birth date of the licensed biological product or any other month and day agreed on by the applicant and FDA. Each TPSR must contain:

(A) *Summary*. This section of the TPSR includes:

(1) A narrative summary and analysis of serious, expected SARs and nonserious, unexpected SARs occurring in the United States that were submitted to the applicant during the reporting period from all spontaneous sources (*i.e.*, health care professionals and other individuals) (with an index consisting of a line listing of the applicant's manufacturer report number and SAR term(s));

(2) An analysis of the expedited reports submitted during the reporting period under paragraphs (c)(2)(i) through (c)(2)(vii) of this section (all expedited reports must be appropriately referenced by the applicant's manufacturer report number, SAR term(s), if appropriate, and date of submission to FDA);

(3) A discussion of any increased reporting frequency of serious, expected SARs, including comments on whether it is believed that the data reflect a meaningful change in SAR occurrence, and an assessment of whether it is believed that the frequency of lack of efficacy reports is greater than would be predicted by the premarketing clinical trials for the biological product; and

(4) The applicant's conclusion as to what, if any, safety-related actions should be taken based on the analysis of the safety data in the TPSR (*e.g.*, labeling changes, studies initiated).

(B) *Summary tabulations*. This section of the TPSR includes summary tabulations (*i.e.*, lists of all SAR terms and counts of occurrences) presented by body system or by standard organ system classification scheme for:

(1) All serious expected SARs, nonserious unexpected SARs, nonserious expected SARs, and expected SARs with unknown outcome occurring in the United States that are submitted to the applicant during the reporting period from all spontaneous sources (*i.e.*, health care professionals and other individuals);

(2) All serious unexpected SARs, unexpected SARs with unknown outcome, and always expedited reports that were previously submitted to FDA

in an expedited report under paragraphs (c)(2)(i), (c)(2)(iii), and (c)(2)(iv) of this section (include cumulative data for serious unexpected SARs, *i.e.*, all cases reported to date);

(3) All reports of SARs not previously submitted to FDA by the applicant (*e.g.*, reports submitted to applicants by FDA, reports obtained from FDA from freedom of information requests at the discretion of the applicant, reports from class action lawsuits); and

(4) All domestic reports of medication errors previously submitted to FDA under paragraph (c)(2)(v) of this section. For actual medication errors, provide summary tabulations of serious SARs, nonserious SARs, and no SARs. For potential medication errors, provide the number of reports for specific errors;

(C) *History of safety-related actions taken*. This section of the TPSR includes a history of safety-related actions taken since the last periodic safety report (*e.g.*, labeling changes, studies initiated);

(D) *Location of safety records*. This section of the TPSR includes a list of the current address(es) where all safety reports and other safety-related records for the licensed biological product(s) are maintained; and

(E) *Contact person*. This section of the TPSR includes the name and telephone number for the licensed physician(s) responsible for the content and medical interpretation of the information contained within the TPSR. Include, if available, the fax number and e-mail address for the licensed physician(s).

(ii) *Periodic safety update report (PSUR)*. An applicant holding a biologics license under § 601.20 of this chapter for a human biological product approved on or after January 1, 1998, must submit a PSUR to FDA according to the following schedule: Semiannually (*i.e.*, every 6 months) for 2 years after U.S. approval of the application, annually for the next 3 years, and then every 5 years thereafter. The data lock point for the PSUR is the month and day of the international birth date of the licensed biological product or any other month and day agreed on by the applicant and FDA. Each PSUR must contain:

(A) *Title page, table of contents, and introduction*. (1) The title page includes, at a minimum, the following information:

(i) Name and international birth date of the licensed biological product(s) that is the subject of the PSUR,

(ii) Various dosage forms and formulations of the biological product(s) covered by the PSUR,

(iii) Name and address of the applicant,

(iv) Reporting period covered by the PSUR, and

(v) Date of the PSUR.

(2) The introduction:

(i) Provides a brief description of how the PSUR relates to previous reports and circumstances;

(ii) References relevant biological products reported in other periodic safety reports (*e.g.*, a combination product reported in a separate PSUR); and

(iii) Indicates any data duplication with other PSURs.

(B) *Worldwide marketing status*. This section of the PSUR contains a table of the chronological history of the worldwide marketing status of the biological product(s) covered by the PSUR from the date the product(s) was first approved (*i.e.*, the international birth date) through its current status (*i.e.*, cumulative information). This table consists of:

(1) Dates of biological product approval and renewal;

(2) Safety-related restrictions on product use;

(3) Indications for use and special populations covered by the biological product approval;

(4) Lack of approval of the biological product in any dosage form or for any indication for use by any regulatory authority(ies);

(5) Withdrawal of a pending marketing application for the biological product by the applicant for safety- or efficacy-related reasons;

(6) Dates of market launches; and

(7) Trade name(s).

(C) *Actions taken for safety reasons*.

(1) This section of the PSUR includes details on the following types of regulatory authority-initiated (*e.g.*, by FDA) and/or applicant-initiated actions related to safety that were taken during the period covered by the PSUR and between the data lock point and PSUR submission (*i.e.*, "late-breaking" safety concerns):

(i) Withdrawal or suspension of biological product approval or indication for use approval;

(ii) Failure to obtain a marketing authorization renewal or to obtain an approval for a new indication for use;

(iii) Restrictions on distribution (products recalled for safety reasons);

(iv) Clinical trial suspension;

(v) Dosage modification;

(vi) Changes in target population or indications; and

(vii) Formulation changes.

(2) This section of the PSUR also contains a narrative identifying the safety-related reasons that led to these actions with relevant documentation appended when appropriate.

(3) Any communication with health care professionals (e.g., Dear Healthcare Professional letters) resulting from such actions must also be described with copies appended.

(D) *Changes to CCSI*. This section of the PSUR describes changes to the CCSI (e.g., new contraindications, precautions, warnings, SARs, or interactions) made during the period covered by the PSUR. A copy of any modified section of the CCSI must be included. The applicant must use the CCSI in effect at the beginning of the reporting period for the PSUR. The revised CCSI is to be used as the reference document for the next reporting period.

(E) *Worldwide patient exposure*. (1) This section of the PSUR includes, for the reporting period, an estimate of the worldwide patient exposure to the biological product(s) covered by the PSUR (i.e., number of patients, average or median dose received, and average or median length of treatment). The method used to estimate patient exposure must always be described. If the patient exposure is impossible to estimate or is meaningless, an explanation of and justification for such conclusions must be provided. If patient exposure is impossible to estimate, other measures of exposure, such as patient-days, number of prescriptions, or number of dosage units, may be used. If these or other more precise measures are not available and an adequate explanation for the lack of such information is provided, bulk sales may be used.

(2) When possible, data broken down by gender and age (especially pediatric versus adult) must be provided. For the pediatric population, data must be reported, if possible, by age group (e.g., neonates, infants, children, adolescents). If these data are not available, an explanation must be included.

(3) When a pattern of reports indicates a potential problem, details by country (with locally recommended dosage regimens) or other segmentation (e.g., indication, dosage form) must be presented.

(F) *Individual case safety reports*. (1) This section of the PSUR includes summary tabulations of individual case safety reports (e.g., serious unlisted SARs, serious listed SARs, nonserious unlisted SARs, nonserious listed SARs) for the following SARs obtained or otherwise received during the reporting period:

(i) All serious and nonserious SARs from spontaneous sources that were submitted to applicants by a health care professional,

(ii) All serious SARs from studies, individual patient INDs, or, in foreign countries, from named-patient

“compassionate” use,

(iii) All serious SARs and nonserious unlisted SARs from the scientific literature,

(iv) All serious SARs from regulatory authorities, and

(v) Serious SARs from other sources such as reports created by poison control centers and epidemiological data bases.

(2) The summary tabulations must be made up of lists by body system or by standard organ system classification scheme of all SAR terms and counts of occurrences. For SARs that are determined to be both serious and unlisted, include cumulative data (i.e., all cases reported to date).

(3) The applicant must conclude this section with a brief discussion of the data concerning the individual case safety reports in the PSUR (e.g., discussion of medical significance or mechanism).

(G) *Safety studies*. This section of the PSUR contains a discussion of nonclinical, clinical, and epidemiological studies that contain important safety information, as follows:

(1) All applicant-sponsored studies newly analyzed during the reporting period (copies of full reports should be appended only if new safety issues are raised or confirmed; FDA may request copies of other studies, if necessary);

(2) New studies specifically planned, initiated, or continuing during the reporting period that examine a safety issue, whether actual or hypothetical; and

(3) Published safety studies in the scientific and medical literature, including relevant published abstracts from meetings (provide literature citation).

(H) *Other information*. This section of the PSUR includes:

(1) A discussion of medically relevant lack of efficacy reports (e.g., might represent a significant hazard to the treated population) for a product(s) used to treat serious or life-threatening diseases; and

(2) Any important new information received after the data lock point (e.g., significant new cases).

(I) *Overall safety evaluation*. This section of the PSUR contains a concise, yet comprehensive, analysis of all of the safety information provided in the PSUR, including new information provided under paragraph

(c)(3)(ii)(H)(2) of this section. In addition, this section of the PSUR includes an assessment by the applicant of the significance of the data collected

during the reporting period, as well as from the perspective of cumulative experience.

(1) The applicant must highlight any new information on:

(i) Serious, unlisted SARs;

(ii) Increased reporting frequencies of listed SARs, including comments on whether it is believed that the data reflect a meaningful change in SAR occurrence;

(iii) A change in characteristics of listed SARs (e.g., severity, outcome, target population); and

(iv) Nonserious, unlisted SARs.

(2) As part of the overall safety evaluation, the applicant must also explicitly address any new safety issue including but not limited to the following (lack of significant new information for each of the following must be mentioned):

(i) Drug interactions;

(ii) Experience with overdose, whether deliberate or accidental, and its treatment;

(iii) Drug abuse or intentional misuse;

(iv) Positive or negative experiences during pregnancy or lactation;

(v) Effects with long-term treatment; and

(vi) Experience in special patient groups (e.g., pediatric, geriatric, organ impaired). For the pediatric population, data must be evaluated, if possible, by age group (e.g., neonates, infants, children, adolescents).

(J) *Conclusion*. This section of the PSUR:

(1) Indicates new safety information that is not in accord with previous cumulative experience and with the CCSI in use at the beginning of the reporting period (e.g., new evidence that strengthens a possible causal relationship between the biological product and an SAR, such as positive rechallenge, an epidemiological association, or new laboratory studies); and

(2) Specifies and justifies any action recommended or initiated, including changes in the CCSI.

(K) *Appendices*. This section of the PSUR includes:

(1) *Company core data sheet*. Provide a copy of the company core data sheet covered by this PSUR (i.e., in effect at the beginning of the period covered by the PSUR), as well as the company core data sheet for the next reporting period. Company core data sheets must be numbered and dated and include the date of last revision.

(2) *U.S. labeling*. Provide a copy of the current approved U.S. labeling. Specify any safety information that is included in the CCSI but not in the U.S. labeling, and provide an explanation for the

discrepancy. Describe any safety-related changes or proposed changes to the U.S. labeling made during the reporting period (include the supplement number(s) and date(s) of submission for the supplement(s)) and any suggested change(s) that should be considered based on the safety analysis in this PSUR.

(3) *Spontaneous reports submitted to the applicant by an individual other than a health care professional.* Provide summary tabulations (e.g., serious unlisted SARs, serious listed SARs, nonserious unlisted SARs, nonserious listed SARs) for all spontaneously reported serious SARs, whether domestic or foreign, and all spontaneously reported nonserious SARs occurring in the United States, obtained or otherwise received during the reporting period by the applicant from an individual other than a health care professional (e.g., reports from consumers). These summary tabulations must consist of lists by body system or by standard organ system classification scheme of all SAR terms and counts of occurrences. For those SARs that are determined to be both serious and unlisted, include cumulative data (i.e., all cases reported to date by individuals other than a health care professional). Include a brief discussion of the impact of the spontaneous reports described in this appendix on the overall safety evaluation.

(4) *SARs with unknown outcome.* Provide summary tabulations for unlisted and listed SARs with unknown outcome from all spontaneous sources (i.e., health care professionals and other individuals), obtained or otherwise received by the applicant during the reporting period. These summary tabulations must consist of lists by body system or by standard organ system classification scheme of all SAR terms and counts of occurrences. Include a brief discussion of the impact of the spontaneous reports described in this appendix on the overall safety evaluation.

(5) *Class action lawsuits.* Provide summary tabulations (e.g., serious unlisted SARs, serious listed SARs, nonserious unlisted SARs, nonserious listed SARs) for all SARs obtained or otherwise received during the reporting period by the applicant from class action lawsuits. These summary tabulations must consist of lists by body system or by standard organ system classification scheme of all SAR terms and counts of occurrences. For those SARs that are determined to be both serious and unlisted, include cumulative data. Include a brief discussion of the impact of the reports

described in this appendix on the overall safety evaluation.

(6) *Lack of efficacy reports.* Provide an assessment of whether it is believed that the frequency of lack of efficacy reports, obtained or otherwise received during the reporting period, is greater than would be predicted by the premarketing clinical trials for the biological product.

(7) *Medication errors.* Provide summary tabulations of all domestic reports of medication errors submitted during the reporting period under paragraph (c)(2)(v) of this section. For actual medication errors, provide summary tabulations of serious SARs, nonserious SARs, and no SARs (for serious SARs, include cumulative data, i.e., all cases reported to date). For potential medication errors, provide the number of reports for specific errors. If an SAR occurs, the summary tabulations must consist of lists by body system or by standard organ system classification scheme of all SAR terms and counts of occurrences. Include a brief discussion of the impact on the overall safety evaluation of these reports.

(8) *U.S. patient exposure.* Provide, for the reporting period, an estimate of the U.S. patient exposure to the biological product(s) covered by the PSUR (i.e., number of patients, average or median dose received, and average or median length of treatment). The method used to estimate patient exposure must always be described. If the patient exposure is impossible to estimate or is meaningless, an explanation of and justification for such conclusions must be provided. If patient exposure is impossible to estimate, other measures of exposure, such as patient-days, number of prescriptions, or number of dosage units, may be used. If these or other more precise measures are not available and an adequate explanation for the lack of such information is provided, bulk sales may be used.

(9) *Location of safety records.* Provide a list of the current address(es) where all safety reports and other safety-related records for the licensed biological product(s) are maintained.

(10) *Contact person.* Provide the name and telephone number for the licensed physician(s) responsible for the content and medical interpretation of the data and information contained within the PSUR. Include, if available, the fax number and e-mail address for the licensed physician(s).

(iii) *Interim periodic safety report (IPSR).* An applicant holding a biologics license under § 601.20 of this chapter for a human biological product approved on or after January 1, 1998, must submit an IPSR to FDA 7.5 years and 12.5 years after U.S. approval of the

application. The data lock point for the IPSR is the month and day of the international birth date of the licensed biological product or any other month and day agreed on by the applicant and FDA. The reporting period for the IPSR covers the period between the last PSUR or TPSR and the data lock point for the IPSR (e.g., between years 5 and 7.5 for an IPSR with a data lock point 7.5 years after U.S. approval of the application). Each IPSR must contain:

(A) *Title page, table of contents, and introduction.* (1) The title page includes, at a minimum, the following information:

(i) Name and international birth date of the licensed biological product(s) that is the subject of the IPSR,

(ii) Various dosage forms and formulations of the biological product(s) covered by the IPSR,

(iii) Name and address of the applicant,

(iv) Reporting period covered by the IPSR, and

(v) Date of the IPSR.

(2) The introduction: (i) Provides a brief description of how the IPSR relates to previous reports and circumstances,

(ii) References relevant biological products reported in other periodic safety reports (e.g., a combination product reported in a separate IPSR), and

(iii) Indicates any data duplication with other IPSRs.

(B) *Worldwide marketing status.* This section of the IPSR contains a table of the chronological history of the worldwide marketing status of the biological product(s) covered by the IPSR from the date the product(s) was first approved (i.e., the international birth date) through its current status (i.e., cumulative information). This table consists of:

(1) Dates of biological product approval and renewal;

(2) Safety-related restrictions on product use;

(3) Indications for use and special populations covered by the biological approval;

(4) Lack of approval of the biological product in any dosage form or for any indication for use by any regulatory authority(ies);

(5) Withdrawal of a pending marketing application for the biological product by the applicant for safety- or efficacy-related reasons;

(6) Dates of market launches; and

(7) Trade name(s).

(C) *Actions taken for safety reasons.*

(1) This section of the IPSR includes details on the following types of regulatory authority-initiated (e.g., by FDA) and/or applicant-initiated actions

related to safety that were taken during the period covered by the IPSR and between the data lock point and IPSR submission (*i.e.*, "late-breaking" safety concerns):

- (i) Withdrawal or suspension of biological product approval or indication for use approval;
- (ii) Failure to obtain a marketing authorization renewal or to obtain an approval for a new indication for use;
- (iii) Restrictions on distribution (products recalled for safety reasons);
- (iv) Clinical trial suspension;
- (v) Dosage modification;
- (vi) Changes in target population or indications; and
- (vii) Formulation changes.

(2) This section of the IPSR also contains a narrative identifying the safety-related reasons that led to these actions with relevant documentation appended when appropriate.

(3) Any communication with health care professionals (*e.g.*, Dear Healthcare Professional letters) resulting from such actions must also be described with copies appended.

(D) *Changes to CCSI*. This section of the IPSR describes changes to the CCSI (*e.g.*, new contraindications, precautions, warnings, SARs, or interactions) made during the period covered by the IPSR. A copy of any modified section of the CCSI must be included. The applicant must use the CCSI in effect at the beginning of the reporting period for the IPSR. The revised CCSI is to be used as the reference document for the next reporting period.

(E) *Worldwide patient exposure*. (1) This section of the IPSR includes, for the reporting period, an estimate of the worldwide patient exposure to the biological product(s) covered by the IPSR (*i.e.*, number of patients, average or median dose received, and average or median length of treatment). The method used to estimate patient exposure must always be described. If the patient exposure is impossible to estimate or is meaningless, an explanation of and justification for such conclusions must be provided. If patient exposure is impossible to estimate, other measures of exposure, such as patient-days, number of prescriptions, or number of dosage units, may be used. If these or other more precise measures are not available and an adequate explanation for the lack of such information is provided, bulk sales may be used.

(2) When possible, data broken down by gender and age (especially pediatric versus adult) must be provided. For the pediatric population, data must be reported, if possible, by age group (*e.g.*,

neonates, infants, children, adolescents). If these data are not available, an explanation must be included.

(3) When a pattern of reports indicates a potential problem, details by country (with locally recommended dosage regimens) or other segmentation (*e.g.*, indication, dosage form) must be presented.

(F) *Safety studies*. This section of the IPSR contains a discussion of nonclinical, clinical, and epidemiological studies that contain important safety information, as follows:

(1) All applicant-sponsored studies newly analyzed during the reporting period (copies of full reports should be appended only if new safety issues are raised or confirmed; FDA may request copies of other studies, if necessary);

(2) New studies specifically planned, initiated, or continuing during the reporting period that examine a safety issue, whether actual or hypothetical; and

(3) Published safety studies in the scientific and medical literature, including relevant published abstracts from meetings (provide literature citation).

(G) *Other information*. This section of the IPSR includes a discussion of medically relevant lack of efficacy reports (*e.g.*, might represent a significant hazard to the treated population) for a product(s) used to treat serious or life-threatening diseases.

(H) *Overall safety evaluation*. This section of the IPSR contains a concise, yet comprehensive, analysis of all of the safety information provided in the IPSR. In addition, this section of the IPSR includes an assessment by the applicant of the significance of the data collected during the reporting period, as well as from the perspective of cumulative experience.

(1) The applicant must highlight any new information on:

- (i) Serious, unlisted SARs;
- (ii) Increased reporting frequencies of listed SARs, including comments on whether it is believed that the data reflect a meaningful change in SAR occurrence;
- (iii) A change in characteristics of listed SARs (*e.g.*, severity, outcome, target population); and
- (iv) Nonserious, unlisted SARs.

(2) As part of the overall safety evaluation, the applicant must also explicitly address any new safety issue including but not limited to the following (lack of significant new information for each of the following must be mentioned):

- (i) Drug interactions;

(ii) Experience with overdose, whether deliberate or accidental, and its treatment;

(iii) Drug abuse or intentional misuse;

(iv) Positive or negative experiences during pregnancy or lactation;

(v) Effects with long-term treatment; and

(vi) Experience in special patient groups (*e.g.*, pediatric, geriatric, organ impaired). For the pediatric population, data must be evaluated, if possible, by age group (*e.g.*, neonates, infants, children, adolescents).

(I) *Conclusion*. This section of the IPSR:

(1) Indicates new safety information that is not in accord with previous cumulative experience and with the CCSI in use at the beginning of the reporting period (*e.g.*, new evidence that strengthens a possible causal relationship between the biological product and an SAR, such as positive rechallenge, an epidemiological association or new laboratory studies); and

(2) Specifies and justifies any action recommended or initiated, including changes in the CCSI.

(J) *Appendices*. This section of the IPSR includes:

(1) *Company core data sheet*. Provide a copy of the company core data sheet covered by this IPSR (*i.e.*, in effect at the beginning of the period covered by the IPSR), as well as the company core data sheet for the next reporting period. Company core data sheets must be numbered and dated and include the date of last revision.

(2) *U.S. labeling*. Provide a copy of the current approved U.S. labeling. Specify any safety information that is included in the CCSI but not in the U.S. labeling and provide an explanation for the discrepancy. Describe any safety-related changes or proposed changes to the U.S. labeling made during the reporting period (include the supplement number(s) and date(s) of submission for the supplement(s) and any suggested change(s) that should be considered based on the safety analysis in this IPSR.

(3) *Spontaneous reports submitted to the applicant by an individual other than a health care professional*. Provide a brief discussion of the impact on the overall safety evaluation of any spontaneously reported serious SARs, whether domestic or foreign, and any spontaneously reported nonserious SARs occurring in the United States, obtained or otherwise received during the reporting period by the applicant from an individual other than a health care professional (*e.g.*, reports from consumers).

(4) *SARs with unknown outcome.* Provide a brief discussion of the impact on the overall safety evaluation of any spontaneously reported unlisted and listed SARs with unknown outcome obtained or otherwise received during the reporting period by the applicant from health care professionals and other individuals.

(5) *Class action lawsuits.* Provide a brief discussion of the impact on the overall safety evaluation of any safety information obtained or otherwise received during the reporting period by the applicant from class action lawsuits.

(6) *Lack of efficacy reports.* Provide an assessment of whether it is believed that the frequency of any lack of efficacy reports, obtained or otherwise received during the reporting period, is greater than would be predicted by the premarketing clinical trials for the biological product.

(7) *Medication errors.* Provide a brief discussion of the impact on the overall safety evaluation of all domestic reports of medication errors submitted during the reporting period under paragraph (c)(2)(v) of this section.

(8) *U.S. patient exposure.* Provide, for the reporting period, an estimate of the U.S. patient exposure to the biological product(s) covered by the IPSR (*i.e.*, number of patients, average or median dose received, and average or median length of treatment). The method used to estimate patient exposure must always be described. If the patient exposure is impossible to estimate or is meaningless, an explanation of and justification for such conclusions must be provided. If patient exposure is impossible to estimate, other measures of exposure, such as patient-days, number of prescriptions, or number of dosage units, may be used. If these or other more precise measures are not available and an adequate explanation for the lack of such information is provided, bulk sales may be used.

(9) *Location of safety records.* Provide a list of the current address(es) where all safety reports and other safety-related records for the licensed biological product(s) are maintained.

(10) *Contact person.* Provide the name and telephone number for the licensed physician(s) responsible for the content and medical interpretation of the information contained within the IPSR. Include, if available, the fax number and e-mail address for the licensed physician(s).

(iv) *Pediatric use supplements.* After approval of a pediatric use supplement to an approved application (*i.e.*, a supplement for use of the human biological product in the pediatric population), the applicant must submit

PSURs to FDA as prescribed under paragraph (c)(3)(ii) of this section according to the following schedule: Semiannually for 2 years after U.S. approval of the supplement, annually for the next 3 years, and then every 5 years thereafter. These applicants must also submit IPSRs to FDA as prescribed under paragraph (c)(3)(iii) of this section at 7.5 years and 12.5 years after U.S. approval of the supplement. The data lock point for the PSUR and IPSR is the month and day of the international birth date of the licensed biological product or any other month and day agreed on by the applicant and FDA.

(v) *Semiannual submission of individual case safety reports.* (A) An applicant holding a biologics license under § 601.20 of this chapter for a human biological product must submit to FDA semiannually (*i.e.*, every 6 months) after U.S. approval of the application a separate report that consists of individual case safety reports for certain spontaneously reported SARs for the biological product. The individual case safety reports must be submitted on the form designated by the agency under paragraph (c)(4) of this section. The data lock point for the report is the month and day of the international birth date of the licensed biological product or any other month and day agreed on by the applicant and FDA. This report must be identified as “individual case safety reports—semiannual submission.”

(B) Applicants that submit TPSRs to FDA for the licensed biological product must submit an individual case safety report for each serious, expected SAR, whether domestic or foreign, and each nonserious, unexpected SAR occurring in the United States that is submitted to the applicant during the reporting period from all spontaneous sources (*i.e.*, health care professionals and other individuals). Reports for vaccines must include an individual case safety report for each nonserious, expected SAR and each expected SAR with unknown outcome occurring in the United States that is submitted to the applicant during the reporting period from all spontaneous sources. Applicants that submit PSURs to FDA for the licensed biological product must submit an individual case safety report for each serious, listed SAR, whether domestic or foreign, and each nonserious, unlisted SAR occurring in the United States that is submitted to the applicant during the reporting period from all spontaneous sources. Reports for vaccines must include an individual case safety report for each nonserious, listed SAR and each listed SAR with unknown outcome occurring in the

United States that is submitted to the applicant during the reporting period from all spontaneous sources. If a full data set is not available for a report of a serious SAR, the applicant must submit the information required under paragraph (c)(1)(iv) of this section.

(C) Followup information to SARs submitted in an individual case safety report—semiannual submission may be submitted in the next individual case safety report—semiannual submission unless such information changes the classification of the SAR to a serious, unexpected SAR. In these cases, the followup information must be submitted to FDA as a 15-day followup report (see paragraph (c)(2)(vii) of this section).

(4) *Reporting format.* (i)(A) Except as provided in paragraphs (c)(4)(i)(B), (c)(4)(i)(D), and (c)(4)(v) of this section, the applicant must complete the reporting form designated by FDA for each individual case safety report of an SAR (FDA Form 3500A or, for vaccines, a VAERS form). Reports based on information about individual cases or case series in the scientific literature must be submitted on an FDA Form 3500A(s) or, for vaccines, on a VAERS form(s).

(B) Foreign SARs may be submitted either on an FDA Form 3500A or, if preferred, on a CIOMS I form; foreign SARs for vaccines may be submitted either on a VAERS form or, if preferred, on a CIOMS I form.

(C) Each domestic report of an actual or potential medication error must be submitted on an FDA Form 3500A, or, for vaccines, on a VAERS form.

(D) Reports of overall findings or data in the aggregate from published and unpublished *in vitro*, animal, epidemiological, or clinical studies must be submitted in a narrative format.

(ii) Each SAR in an individual case safety report must be coded on the FDA Form 3500A, VAERS form, or CIOMS I form using the appropriate “preferred term” in the latest version of MedDRA (the medical dictionary for regulatory activities) in use at the time the applicant becomes aware of the individual case safety report. For individual case safety reports of medication errors, the report must be coded both as a medication error and, if applicable, with the preferred term for any SARs associated with the medication error.

(iii) Each completed FDA Form 3500A, VAERS form, or CIOMS I form should refer only to an individual case.

(iv) Each completed FDA Form 3500A, VAERS form or CIOMS I form must include the name and telephone number (and fax number and e-mail address, if available) for the licensed

physician responsible for the content and medical interpretation of the data contained within the form (*i.e.*, contact person for the company).

(v) Instead of using FDA Form 3500A (or a VAERS form for vaccines), the applicant may use a computer-generated facsimile of FDA Form 3500A (or the VAERS form for vaccines) provided that it is readable, includes appropriate identifying information, and contains all the elements (*i.e.*, format, sections, blocks, titles, descriptors within blocks, text for disclaimer) of FDA Form 3500A (or the VAERS form for vaccines) in the identical enumerated sequence of the form. For individual case safety reports in which no suspect medical device is involved, a one-page FDA Form 3500A is acceptable.

(d) *Multiple reports.* An applicant should not include in reports under this section any SARs that occurred in clinical trials if they were previously submitted as part of the license application. If a report refers to more than one biological product marketed by an applicant, the applicant should submit the report to the license for the product listed first in the report.

(e) *Patient privacy.* For nonvaccine biological products, the names and addresses of individual patients should not be included in reports under this section; instead, the applicant, shared manufacturer and contractors should assign a unique code to each report, preferably not more than eight characters (*i.e.*, numbers and/or letters) in length. The name of the reporter from whom the information was received should be included. Names of patients, individual reporters, health care professionals, hospitals, and geographic identifiers in safety reports are not releasable to the public under FDA's public information regulations in part 20 of this chapter. For vaccine SAR reports, these data will become part of the CDC Privacy Act System 09-20-0136, "Epidemiologic Studies and Surveillance of Disease Problems." Information identifying the person who received the vaccine or that person's legal representative will not be made available to the public, but may be available to the vaccinee or legal representative.

(f) *Recordkeeping.* Each applicant must maintain for a period of 10 years records of all safety information pertaining to its product, received or otherwise obtained, including raw data, any correspondence relating to the safety information, and any reports of SARs or medication errors not submitted to FDA or only provided to FDA in a summary tabulation. Each applicant must also retain for a period

of 10 years any records required to be maintained under this section. When appropriate, FDA may require an applicant to submit any or all of these records to the agency within 5 calendar days after receipt of the request.

(g) *Written procedures.* Each applicant must develop and maintain written procedures for the surveillance, receipt, evaluation, and reporting of safety information to FDA.

(h) *Revocation of license.* If an applicant fails to establish and maintain records and make reports required under this section with respect to a licensed biological product, FDA may revoke the license for such a product in accordance with the procedures of § 601.5 of this chapter.

(i) *Exemptions.* Manufacturers of the following listed products are not required to submit safety reports under this section:

(1) Whole blood or components of whole blood. These products are subject to the reporting requirements for blood and blood components in § 606.170 of this chapter.

(2) In vitro diagnostic products, including assay systems for the detection of antibodies or antigens to retroviruses. These products are subject to the reporting requirements for devices.

(j) *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 biological product caused or contributed to an SAR. An applicant need not admit, and may deny, that the report or information submitted under this section constitutes an admission that the biological product caused or contributed to an SAR.

PART 601—LICENSING

14. The authority citation for 21 CFR part 601 continues to read as follows:

Authority: 15 U.S.C. 1451–1561; 21 U.S.C. 321, 351, 352, 353, 355, 356b, 360, 360c–360f, 360h–360j, 371, 374, 379e, 381; 42 U.S.C. 216, 241, 262, 263, 264; sec. 122, Pub. L. 105–115, 111 Stat. 2322 (21 U.S.C. 355 note).

§ 601.28 [AMENDED]

15. Section 601.28 *Annual reports of postmarketing pediatric studies* is amended by removing the second sentence in paragraph (a) and the phrase "safety and" in the first sentence in paragraph (b).

PART 606—CURRENT GOOD MANUFACTURING PRACTICE FOR BLOOD AND BLOOD COMPONENTS

16. The authority citation for 21 CFR part 606 continues to read as follows:

Authority: 21 U.S.C. 321, 331, 351, 352, 355, 360, 360j, 371, 374; 42 U.S.C. 216, 262, 263a, 264.

17. Section 606.170 is revised to read as follows:

§ 606.170 Suspected adverse reaction investigation and reporting.

(a) Any reports of complaints of suspected adverse reactions (SARs), as defined in § 600.80(a) of this chapter, regarding each unit of blood or blood product arising as a result of blood collection or transfusion must be investigated promptly and thoroughly. Records of the complaint and investigation must be maintained. The collection or transfusing facility must prepare and maintain a written report of the investigation of SARs, including followup and conclusions, as part of the record for that lot or unit of final product. If it is determined that there was an SAR related to transfusion or possibly related to the collection procedure, then copies of all such reports must be forwarded to and maintained by the manufacturer or collection facility.

(b) For any serious SAR, as defined in § 600.80(a) of this chapter, except for a fatality, the facility performing the compatibility testing (if the SAR is related to transfusion) or the collecting facility (if the SAR is related to the blood collection procedure), must submit a written report to the Center for Biologics Evaluation and Research (CBER), at FDA within 45 calendar days after determination of the serious SAR. The written report must be submitted using the reporting format provided in § 600.80(c)(4) of this chapter.

(c) For an SAR that results in a fatality, the Director, Office of Compliance and Biologics Quality, at CBBER must be notified by telephone, facsimile, express mail, or electronically transmitted mail as soon as possible. Within 7 calendar days after the fatality, the collection facility (if the fatality is related to blood collection) or the facility performing the compatibility tests (if the fatality is related to transfusion) must submit a written report to CBBER, FDA, using the reporting format provided in § 600.80(c)(4) of this chapter.

(Information collection requirements approved by the Office of Management and Budget under control number 0910–0116)

Dated: December 13, 2002.

Mark B. McClellan,

Commissioner of Food and Drugs.

Dated: January 29, 2003.

Tommy G. Thompson,

Secretary of Health and Human Services.

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