

Proposed Rules

Federal Register

Vol. 74, No. 161

Friday, August 21, 2009

This section of the FEDERAL REGISTER contains notices to the public of the proposed issuance of rules and regulations. The purpose of these notices is to give interested persons an opportunity to participate in the rule making prior to the adoption of the final rules.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 310, 314, and 600

[Docket No. FDA-2008-N-0334]

RIN 0910-AF96

Postmarketing Safety Reports for Human Drug and Biological Products; Electronic Submission Requirements

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is proposing to amend its postmarketing safety reporting regulations for human drug and biological products to require that persons subject to mandatory reporting requirements submit safety reports in an electronic format that FDA can process, review, and archive. FDA is taking this action to improve the agency's systems for collecting and analyzing postmarketing safety reports. The proposed change would help the agency to more rapidly review postmarketing safety reports, identify emerging safety problems, and disseminate safety information in support of FDA's public health mission. In addition, the proposed amendments would be a key element in harmonizing FDA's postmarketing safety reporting regulations with international standards for the electronic submission of safety information.

DATES: Submit written or electronic comments on the proposed rule by November 19, 2009. Submit comments on information collection issues under the Paperwork Reduction Act of 1995 by September 21, 2009, (see section "VII. Paperwork Reduction Act of 1995" of this document). See section III.G of this document for the proposed effective date of a final rule based on this proposed rule.

ADDRESSES: You may submit comments, identified by Docket No. FDA-2008-N-

0334 and/or RIN number 0910-AF96, by any of the following methods, except that comments on information collection issues under the Paperwork Reduction Act of 1995 must be submitted to the Office of Regulatory Affairs, Office of Management and Budget (OMB) (see the "Paperwork Reduction Act of 1995" section of this document).

Electronic Submissions

Submit electronic comments in the following way:

- Federal eRulemaking Portal: <http://www.regulations.gov>. Follow the instructions for submitting comments.

Written Submissions

Submit written submissions in the following ways:

- FAX: 301-827-6870.
- Mail/Hand delivery/Courier [For paper, disk, or CD-ROM submissions]: Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

To ensure more timely processing of comments, FDA is no longer accepting comments submitted to the agency by e-mail. FDA encourages you to continue to submit electronic comments by using the Federal eRulemaking Portal, as described previously, in the **ADDRESSES** portion of this document under *Electronic Submissions*.

Instructions: All submissions received must include the agency name and Docket No. and Regulatory Information Number (RIN) for this rulemaking. All comments received may be posted without change to <http://www.regulations.gov>, including any personal information provided. For additional information on submitting comments, see the "Comments" heading of the **SUPPLEMENTARY INFORMATION** section of this document.

Docket: For access to the docket to read background documents or comments received, go to <http://www.regulations.gov> and insert the docket number(s), found in brackets in the heading of this document, into the "Search" box and follow the prompts and/or go to the Division of Dockets Management, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

The information collection provisions of this proposed rule have been submitted to OMB for review. Interested persons are requested to fax comments regarding information collection by

September 21, 2009, to the Office of Information and Regulatory Affairs, OMB. To ensure that comments on information collection are received, OMB recommends that written comments be faxed to the Office of Information and Regulatory Affairs, OMB, Attn: FDA Desk Officer, FAX: 202-395-7285, or e-mailed to oir_submission@omb.eop.gov.

FOR FURTHER INFORMATION CONTACT:

For information concerning human drug products: Roger Goetsch, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 22, Silver Spring, MD, 20993-0002, 301-770-9299, or

For information concerning human biological products: Stephen Ripley, Center for Biologics Evaluation and Research (HFM-17), Food and Drug Administration, 1401 Rockville Pike, suite 200N, Rockville, MD, 20852-1448, 301-827-6210.

SUPPLEMENTARY INFORMATION:

Table of Contents

- I. Introduction
- II. Background
 - A. Current Postmarketing Safety Reporting Requirements
 1. Description and Timing of Safety Reports
 2. Current Format for the Submission of Postmarketing Safety Reports
 - B. Previously Proposed Revisions to the Postmarketing Safety Reporting Requirements
 - C. Rationale for Requiring Electronic Submission of Postmarketing Safety Reports
 1. Expedited Identification of Emerging Safety Problems
 2. Improved Speed and Efficiency of Industry and Agency Operations
 3. International Harmonization of Safety Reporting
 - D. Electronic Format Submission Initiatives
 1. Electronic Submission of Postmarketing Safety Reports
 2. Comments on the Advance Notice of Proposed Rulemaking (ANPRM) for Mandatory Electronic Submission of Postmarketing Safety Reports to FDA
- III. Description of the Proposed Rule
 - A. Electronic Submission of Postmarketing Safety Reports

- B. Safety Reports Not Covered by the Proposed Rule
- C. Waivers
- D. Individual Case Safety Report (ICSR)—Definition and Required Information
- E. Removal of Paper Format Provisions
- F. Miscellaneous Changes
- G. Proposed Implementation Timeframe
- IV. Legal Authority
- V. Environmental Impact
- VI. Analysis of Impacts
 - A. Benefits
 - B. Costs
 - C. Summary of Benefits and Costs
 - D. Alternatives Considered
 - E. Small Business Impact
- VII. Paperwork Reduction Act of 1995
 - A. Reporting Cost
 - B. Capital Costs
- VIII. Federalism
- IX. Request for Comments

I. Introduction

When a drug or biological product is approved and enters the market, the product is introduced to a larger patient population in settings different from clinical trials. New information generated during the postmarketing period offers further insight into the benefits and risks of the product, and evaluation of this information is important to ensure the safe use of these products.

FDA receives information regarding postmarketing adverse drug experiences¹ from safety reports submitted to the agency. For nearly 35 years, FDA has received these postmarketing safety reports on paper. In recent years, many companies have voluntarily submitted these reports to the agency in electronic format.

Data from both electronic and paper reports are entered into FDA's Adverse Event Reporting System (AERS) database. AERS is a computerized information database designed to support FDA's postmarketing safety surveillance program for drug and biological products. The AERS database is used to store and analyze data received in postmarketing safety reports. Safety reporting data submitted on paper must first be converted into an electronic format before being entered into AERS.²

FDA is proposing to require use of an electronic format for the submission of postmarketing safety reports (see section

II of this document), which would be an important step toward improving the agency's systems for collecting and analyzing these reports. The proposal would:

- Eliminate the time and costs associated with submitting paper reports (for industry) and converting data from paper reports into electronic format for review and analysis (for the agency),
- Expedite the agency's access to safety information and provide data to the agency in a format that would support more efficient and comprehensive reviews, and
- Enhance our ability to rapidly communicate information about suspected problems to health care providers, consumers, applicants, and sponsors within the United States and internationally in support of FDA's public health mission.

The proposed rule would require that postmarketing safety reports be submitted to us in an electronic format that we can process, review, and archive. Consistent with FDA's current practice for firms that already submit these reports in electronic format voluntarily, technical specifications referenced in FDA guidance documents will describe how to submit such reports to the agency.³ As necessary, the agency will revise the technical specifications referenced in FDA guidance documents to address changing technical specifications or any additional specifications that may be needed for mandatory electronic safety reporting. Using guidance documents to communicate these technical specifications will permit FDA to be more responsive to rapidly occurring changes in the technological environment.

Currently, the technical specifications referenced in guidance documents rely upon and adopt certain safety reporting and transmission standards recommended by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). ICH was formed to facilitate the harmonization of technical requirements for the registration of

pharmaceutical products among the three ICH regions: The European Union, Japan, and the United States. In this proposed rule, we reaffirm our intention to continue to rely on these ICH-recommended standards, in addition to providing other options (see section II.D.1 of this document). We believe the continued use of ICH standards will promote harmonization of safety reporting among regulatory agencies and facilitate the international exchange of postmarketing safety information. Accordingly, this proposed rule is consistent with ongoing agency initiatives to encourage the widest possible use of electronic technology and to promote international harmonization of safety reporting for human drug and biological products through reliance on ICH standards. (See section II.C.3 of this document for additional discussion of ICH.)

In this document, we provide background information on the current status of FDA's postmarketing safety reporting requirements (current regulations and previously proposed revisions) (sections II.A and II.B of this document). We also discuss the rationale for proposing this rule (section II.C of this document). Additionally, we describe electronic postmarketing safety reporting initiatives (section II.D of this document), including an advanced notice of proposed rulemaking (ANPRM) that we issued in 1998. Finally, we describe the proposed rule (section III of this document).

II. Background

A. Current Postmarketing Safety Reporting Requirements

The current postmarketing safety reporting requirements for drug and biological products are summarized below. The proposed electronic reporting amendments would leave the substantive aspects of these requirements largely unchanged.

1. Description and Timing of Safety Reports

Under existing regulations in part 310, 314, and 600 (21 CFR part 310, 314, and 600), specifically §§ 310.305, 314.80, 314.98, and 600.80, manufacturers, packers, distributors,⁴

⁴For § 600.80, "distributor" also includes shared manufacturers, joint manufacturers, or any other participant involved in divided manufacturing.

⁵In this document, the term "applicant" is used instead of the term "licensed manufacturer" for persons with approved BLAs.

⁶ICSR attachments include published articles that must accompany ICSRs based on scientific literature (§§ 314.80(d) and 600.80(d)), as well as other supporting information such as relevant

¹For purposes of this preamble, the term *adverse drug experience* includes an *adverse experience* associated with use of a biological product.

²Additional information regarding the AERS database may be found at: <http://www.fda.gov/cder/aers/default.htm>.

³The most current information on submitting postmarketing safety reports in electronic format can be found in the draft guidance on "Providing Regulatory Submissions in Electronic Format—Postmarketing Individual Case Safety Reports" (73 FR 33436, June 12, 2008) and the "Periodic safety update reports" section of the guidance on "Providing Regulatory Submissions in Electronic Format—Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications" (Revision 2, June 2008). We intend to finalize the draft guidance document in the near future.

and applicants⁵ with approved new drug applications (NDAs), abbreviated new drug applications (ANDAs), and biological license applications (BLAs) and those that market prescription drugs for human use without an approved application are required to submit postmarketing safety reports of adverse drug experiences to FDA. These safety reports include individual case safety reports (ICSRs), and other related documents (ICSR attachments⁶) for each adverse drug experience. An ICSR is a description of the adverse drug experience that includes the basic elements, or facts, of each reportable event for an individual patient or subject. Under the current regulations, persons who submit safety reports on paper must use the approved reporting form for ICSRs—either the FDA Form 3500A or an equivalent form as discussed below. Although current regulations do not use the term ICSR, the term is used in FDA and ICH guidances to refer to the adverse drug experience information supplied on the FDA Form 3500A or other approved forms, including those currently submitted in electronic format.⁷ Accordingly, we will refer throughout this document to the description of each adverse drug experience related to an individual patient or subject using human drug or biological products as an ICSR. As discussed in section III.E of this document, consistent with the proposed change to a mandatory electronic format for safety reports, we propose to delete most references to the paper forms (e.g., FDA Form 3500A) from FDA postmarketing safety reporting regulations and to add: (1) A definition of ICSR for drugs and biologics and (2) a statement of the information required to be reported in an ICSR.

a. 15-day Alert reports. FDA regulations require manufacturers, packers, distributors, and applicants to submit an ICSR on FDA Form 3500A, or its equivalent, for each postmarketing adverse drug experience that is both serious and unexpected to the agency within 15 calendar days of initial receipt of information about the adverse drug experience (15-day “Alert reports”). An unexpected adverse drug experience is any adverse drug experience that is not listed in the current labeling for the product (§§ 310.305(b), 314.80(a), and 600.80(a)).

Followup reports are required to be submitted within 15 calendar days of receipt of new information or as requested by FDA, and are also submitted on an FDA Form 3500A or on an equivalent form. In addition to the ICSR, 15-day Alert reports frequently include related documents, such as medical records, hospital discharge summaries, or other documentation related to the event (ICSR attachments).

To avoid duplication of reports, nonapplicant manufacturers, packers, and distributors of drug and biological products having an approved application may, under §§ 314.80 and 600.80, submit all reports of serious adverse drug experiences to the applicant within 5 calendar days of receipt of the report instead of to FDA. Similarly, packers and distributors of prescription drug products marketed without an approved application may meet their postmarketing 15-day safety reporting obligations under § 310.305 by submitting all reports of serious adverse drug experiences to the manufacturer within 5 calendar days of the receipt of the information instead of to FDA. Applicants/manufacturers receiving such data must then, in turn, submit a 15-day Alert report to FDA.

b. Periodic reports. In addition to 15-day Alert reports, applicants are also required to submit postmarketing periodic safety reports to FDA. For each approved application, applicants are required under §§ 314.80 and 600.80 to submit a periodic report quarterly or annually, depending on how long the drug or biological product has been approved. Upon written notice, the agency can require that an applicant submit these reports to FDA at different times than those stated. These reports contain the following information: (1) A narrative summary and analysis of the information in the report, (2) an analysis of all of the 15-day Alert reports submitted during the reporting interval, (3) an ICSR (and ICSR attachments, if applicable) for each adverse drug experience not previously reported (i.e., reports of all serious, expected (labeled) and nonserious events)⁸, and (4) a history of actions taken since the last periodic report because of the reports of adverse drug experiences. The descriptive information portions of a postmarketing periodic safety report

(report summary, analysis of 15-day Alert reports, and history of actions) are submitted to the agency in a narrative format accompanied by the ICSRs and any ICSR attachments for all serious, expected and nonserious adverse drug experiences that occurred during the reporting period. Manufacturers of drugs marketed without an approved application (e.g., NDA, ANDA) are not required to submit postmarketing periodic safety reports to FDA.

c. Distribution reports. In addition to periodic reports, under § 600.81, applicants with approved BLAs are also required to submit distribution reports to the agency every 6 months or at other intervals that the agency may specify with written notice. These reports contain information about the quantity of biological product distributed under the BLA, including the quantity distributed to distributors.

d. Nonprescription human drug products marketed without an approved application. Public Law 109-462, enacted on December 22, 2006, amended the Federal Food, Drug, and Cosmetic Act (the act) to create a new section 760 (21 U.S.C. 379aa), entitled “Serious Adverse Event Reporting for Nonprescription Drugs.” Section 760 of the act requires manufacturers, packers, or distributors whose name appears on the label of nonprescription human drug products marketed without an approved application to report serious adverse events associated with their products. Effective December 22, 2007, section 760 of the act requires these reports to be submitted to FDA within 15 business days. As required by section 2(e)(3) of Public Law 109-462, FDA issued a draft guidance for industry entitled “Postmarketing Adverse Event Reporting for Nonprescription Human Drug Products Marketed without an Approved Application” (72 FR 58316, October 15, 2007). The draft guidance describes the minimum data elements and the relevant policies and procedures for making these reports under section 760 of the act. It provides, among other things, that the reports be submitted on paper on FDA Form 3500A or in the electronic format described in the guidance.

This proposed rule does not contain language that would require that safety reports under section 760 of the act for nonprescription human drug products marketed without an approved application be submitted to FDA in electronic format. However, we are soliciting public comment on whether the final rule should require the use of electronic format for these reports. We expect that any electronic format requirements for these section 760

hospital discharge summaries and autopsy reports/death certificates.

⁷ Health Level Seven (HL7), a technical-standards group accredited by the American National Standards Institute (ANSI), also uses the term ICSR to describe adverse event information supplied for FDA regulated products.

⁸ In some cases, applicants may request a waiver for submission of an ICSR for nonserious, expected adverse drug experiences. See section XI.A of FDA’s draft guidance for industry on “Postmarketing Safety Reporting for Human Drug and Biological Products Including Vaccines” available on the Internet at <http://www.fda.gov/Drugs/Guidance/ComplianceRegulatoryInformation/Guidances/default.htm> under “Procedural.”

reports would be quite similar to the requirements for other categories of drug products addressed by this rule. Any decision whether to include section 760 reports will be informed by the public comments submitted in response to this proposal and the agency's experience since submission of serious adverse event reports for nonprescription human drug products marketed without an approved application became mandatory in December 2007.

Finally, note that nonprescription drugs that are marketed under approved applications (NDAs or ANDAs) are not covered under section 760 of the act. Such products are subject to reporting under current §§ 314.80 and 314.81. Reports submitted to FDA under those sections would be subject to the mandatory electronic format requirements proposed in this rule as described elsewhere in this document.

2. Current Format for the Submission of Postmarketing Safety Reports

a. Drug and biological products. FDA currently accepts all postmarketing ICSRs in either a paper format or an electronic format. Sections 310.305(d), 314.80(f), and 600.80(f) authorize use of a paper FDA Form 3500A for reporting of single cases of adverse drug experiences for human drug and biological products. The regulations also permit use of the form introduced by the World Health Organization's (WHO's) Council for International Organizations of Medical Sciences (CIOMS) Working Group I for reporting single cases of foreign adverse drug experiences that are serious and unexpected (CIOMS I form).

Section 11.2(b)(2) currently provides that regulatory submissions may be voluntarily provided to the agency in electronic form⁹ if the submissions are identified by FDA in its electronic submissions public docket as submissions the agency will accept in electronic form.¹⁰ Postmarketing safety reports for drug and nonvaccine biological products have been identified in the docket as submissions the agency can accept in electronic format. See Memorandums 23 and 28 in FDA's electronic submissions public docket. If the reporter elects to file the safety report in electronic format rather than on paper, current §§ 310.305(d), 314.80(f), and 600.80(f) require that the

ICSRs in the electronic report include the same information as the paper FDA Form 3500A or CIOMS I form.

Accordingly, under current regulations, an ICSR submission can take the form of a paper FDA Form 3500A, a paper CIOMS I form, or comparable information submitted in electronic format. (See section II.D.1 of this document). Each of these is a different method of transmitting to FDA the same basic elements of the ICSR, whether on paper or in electronic format. As described in section II.D.1.a of this document, ICSR attachments and the descriptive information portions of periodic safety reports may also be submitted electronically.

b. Vaccine products. Adverse experience reporting for vaccine products may be submitted to the Vaccine Adverse Event Reporting System (VAERS). VAERS is a computerized information database designed to support the Centers for Disease Control and Prevention's (CDC's) and FDA's postmarketing surveillance program for vaccine products. Postmarketing ICSRs for vaccines can be submitted on a VAERS paper form¹¹ or reported on-line using the VAERS secure web-based system¹². Each of these is a different method of transmitting to CDC/FDA the same basic elements of the ICSR. Currently, VAERS does not have the capability to receive electronic ICSRs submitted through the FDA's electronic submissions gateway. However, developments are underway to implement this submission capability.

B. Previously Proposed Revisions to the Postmarketing Safety Reporting Requirements

In the **Federal Register** of March 14, 2003 (68 FR 12406), FDA published a proposed rule to amend its safety reporting requirements for human drug and biological products (Safety Reporting Proposed Rule). The agency proposed new definitions and reporting formats and standards for pre- and postmarketing safety reporting as recommended by ICH (see section II.C.3 of this document) and by CIOMS. Some of the proposed amendments were based on the recommendations of ICH, while others were proposed by the agency on its own initiative. With regard to coding of postmarketing ICSRs

to standardize safety reports for comparison and analysis, the agency proposed use of the Medical Dictionary for Regulatory Activities (MedDRA) terminology developed by ICH¹³. The agency also proposed to require the submission of new types of postmarketing safety reports to FDA. FDA is currently considering the comments that it has received on the Safety Reporting Proposed Rule. Any new postmarketing safety reports that are required by a safety reporting final rule would be required to be submitted electronically in accordance with this rulemaking, if adopted as final.

C. Rationale for Requiring Electronic Submission of Postmarketing Safety Report

As explained more below, the agency proposes to require that all postmarketing safety reports for human drugs and biological products be submitted in electronic format. By requiring submission of these reports in electronic format, FDA would expedite access to safety information and facilitate international harmonization and exchange of this information. This, in turn, would lead to more efficient reviews of safety data and enhance our ability to rapidly disseminate safety information to health care providers, consumers, applicants, sponsors, and other regulatory authorities in support of FDA's public health mission. In addition, the agency would recognize a significant cost savings by converting the safety reporting system from a paper submission process to an all electronic system that would increase the accuracy of information and reduce the need for manual data entry.

1. Expedited Identification of Emerging Safety Problems

Establishment and maintenance of efficient risk management programs (where appropriate) is an agency priority (see FDA's January 2007 response to the Institute of Medicine (IOM) report on drug safety entitled "The Future of Drug Safety: Promoting and Protecting the Health of the Public,"

¹³ MedDRA is a medically validated medical terminology created by ICH as a cooperative effort between the pharmaceutical industry and regulators from the United States, Europe, and Japan for sharing regulatory information for human medical products and activities (see www.ich.org/cache/compo/276-254-1.html). MedDRA establishes a terminology database for use in the regulatory process for medical products and has become the accepted standard for regulatory activities involving adverse drug experiences. Use of MedDRA would serve the public health by facilitating the collection, presentation, and analysis of adverse drug experience information from medical products during clinical and scientific reviews and marketing.

⁹ The content of labeling for NDAs, certain BLAs, ANDAs, annual reports, and supplements is currently the only regulatory submission required to be submitted to the agency electronically (68 FR 69009, December 11, 2003).

¹⁰ Docket No. FDA-1992-S-0039 (formerly Docket No. 1992S-0251) can be accessed on the Internet at <http://www.regulations.gov>.

¹¹ The VAERS form can be accessed on the Internet at <http://secure.vaers.org/vaersdata/entryintro.htm>. FDA has verified the Web site addresses throughout this document, but FDA is not responsible for any subsequent changes to the Web sites after this document publishes in the **Federal Register**.

¹² Report on-line at <https://secure.vaers.org>.

FDA's March 2005 guidance for industry entitled "Development and Use of Risk Minimization Action Plans," and FDA's 2007 Strategic Action Plan).¹⁴ The changes proposed in this rule, if adopted, would improve the agency's management of risks from human drug and biological products by expediting the postmarketing identification and communication of emerging safety information for these products.

Requiring that postmarketing ICSRs be submitted in electronic format would result in reducing the time required for FDA to enter information from a paper safety report into a database for evaluation and analysis. Currently, approximately 60 percent of all ICSRs (i.e., 15-day Alert reports and ICSRs associated with periodic reports¹⁵) are submitted to FDA on paper for input into the AERS database (approximately 30,000/month). With regard to 15-day Alert reports, approximately one-third are submitted on paper (approximately 8,000/month) to FDA. Fifteen-day Alert reports that are submitted on paper generally reach FDA's data entry contractor within the required 15 days following the adverse drug experience, but then the ICSRs must be manually entered into the AERS database. These ICSRs are entered into the FDA AERS database on a priority basis because they may indicate a new, previously unidentified risk. The time required for data entry, validation, and quality control processes, however, adds an additional 2 weeks before the ICSRs are actually available for assessment by FDA's safety evaluators. With regard to periodic ICSRs, approximately 80 percent are submitted on paper (approximately 22,000/month).¹⁶ Periodic ICSRs, which are submitted on paper, may not be available for review by safety evaluators for up to 2 months after submission to the agency because of their volume and because ICSRs in

15-day Alert reports must take first priority.

In contrast, the ICSRs in both 15-day Alert and periodic reports submitted in electronic format are processed and available for safety evaluator review much more quickly because there is no need for data entry and the associated quality control and validation processes are faster. Instead of 2 months for periodic ICSRs or 2 weeks for 15-day Alert ICSRs that are submitted in a paper format, ICSRs submitted in electronic format are, generally, available to reviewers within 2 days of their receipt by FDA. The requirement for electronic safety reports is expected to result in faster processing and this will permit FDA to more quickly identify emerging safety issues and rapidly disseminate significant safety information to the medical community and the public with corresponding benefits to the public health.

2. Improved Speed and Efficiency of Industry and Agency Operations

The proposed electronic formatting requirements for postmarketing safety reports would enhance operations for both industry and FDA. Electronic reporting can benefit industry by eliminating the costs associated with collating, copying, storing, retrieving, and mailing paper copies. In addition, FDA would benefit from the elimination of data entry processes and significant reduction in physical storage requirements. When data are provided only on paper, the information must be converted manually into an electronic form to review and analyze. This process is time consuming, costly, and creates an opportunity for data entry error to occur.

FDA expects to provide two options for submitting electronically formatted ICSRs. Reporters would be able to submit ICSRs by using either an ICH-compatible electronic transmission system, or a Web-based form similar to those used for commercial transactions, such as retail purchases, on the Internet. (These options, as well as those for submission of ICSR attachments in electronic form, are discussed in more detail in section II.D.1 of this document.) For companies that submit large numbers of ICSRs, use of the ICH-compatible system for electronic transmission would be cost effective because the information from the ICSRs will be transmitted directly from the company's database to FDA without needing additional administrative support for manual entry of the information. For companies that submit a small number of ICSRs, use of the Web-based form may be more cost

effective than using the ICH-compatible system.

FDA has worked with industry on electronic submission of postmarketing ICSRs since 1998. In 2001, FDA announced through public docket number 92S-0251 that the agency would accept voluntary electronic submissions of ICSRs for 15-day Alert and periodic safety reports in lieu of a paper submission (see section II.A.2 of this document). Currently, over 40 pharmaceutical companies are voluntarily using electronic format to submit to FDA ICSRs for both 15-day Alert and periodic reports for human drug and biologics, with more than 500,000 ICSRs submitted to date. This experience has shown that electronic data submissions to the AERS database reduce the cost of data entry and facilitate the review process. It currently costs FDA approximately \$35 to process a report submitted on paper. In comparison, a report submitted in an electronic format costs approximately \$12 to process.

3. International Harmonization of Safety Reporting

In developing this proposal, FDA considered the international standards developed by ICH for the submission of safety information. The other ICH regions (the European Union (EU) and Japan) are also implementing the standards recommended by ICH for the electronic submission of safety reports. The procedures for the electronic submission of postmarketing safety reports in this proposed rule would, therefore, reduce costs to industry associated with maintaining multiple electronic systems designed to meet the needs of different regulatory authorities. The proposed electronic safety reporting regulations would also encourage better communication between FDA and the industry, as well as with other regulators, nationally and abroad, while reducing the costs associated with reporting. Moreover, the industry would be able to rely on one form of electronic reporting, which would reduce the administrative costs of compliance.

a. *Status of electronic submissions in the EU.* The European Commission drafted guidance on adverse event reporting, including Volume 9 of "The Rules Governing Medicinal Products in the European Union" (the EU rules), which contains a specific emphasis on pharmacovigilance. The EU rules require the electronic submission of adverse event reports (effective November 2005) and incorporate international guidelines reached within the framework of the ICH. The EU rules specify that the electronic transmission

¹⁴ These resources are available on the Internet at (IOM response) <http://www.fda.gov/downloads/drugs/drugsafety/postmarketingdrugsafetyinformationforpatientsandproviders/UCM171627.pdf>, (strategic plan) <http://www.fda.gov/ope/stratplan07/stratplan07.htm>, and (guidance) [http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm#under "Clinical/Medical."](http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm#under%20Clinical/Medical)

¹⁵ See section II.A.1.b of this preamble for a description of periodic ICSRs.

¹⁶ Postmarketing periodic reports are required to be submitted to the FDA for each approved NDA, ANDA, and BLA and are due quarterly for the first 3 years after U.S. approval of the application and annually thereafter. An ICSR in a periodic safety report includes the same elements in the same format as an ICSR in a 15-day Alert report, but describes an adverse drug experience that is not both serious and unexpected (i.e., all nonserious adverse drug experiences or serious, expected adverse drug experiences).

and management of safety reports will be carried out according to the guidelines and specifications contained in ICH guidance on safety reporting and electronic standards.

b. *Status of electronic submissions in Japan.* On October 27, 2003, the Japanese Ministry of Health, Labour, and Welfare mandated that ICH guidance E2BM¹⁷ compliant ICSRs be submitted in electronic format either by the Internet or by physical media.

c. *Global impact of a standard electronic submission.* FDA collaborates with many international regulatory counterparts on drug safety issues. Frequently, FDA sends to and receives from other regulators paper copies of ICSRs for further clinical analysis of specific drug safety issues. FDA envisions that regulatory partners participating in ICH, and other regulators that choose to implement the same standards, will be able to electronically exchange specific ICSRs in real time as safety issues emerge. As a result, regulatory partners would be assured that they are making regulatory decisions based on a full complement of available information.

D. Electronic Format Submission Initiatives

1. Electronic Submission of Postmarketing Safety Reports

a. *Voluntary electronic submissions.* In the **Federal Register** of March 20, 1997 (62 FR 13430), FDA published a regulation on electronic records and electronic signatures (21 CFR part 11). In August 2003, FDA issued guidance for industry entitled "Part 11, Electronic Records; Electronic Signatures—Scope and Application," describing the agency's thinking regarding part 11. Part 11 generally provides that in instances where records are submitted to the agency, such records may be submitted in electronic format instead of paper format, provided that FDA has identified the submission in FDA's electronic submissions public docket as the type of submission that FDA can accept in electronic format.

¹⁷ ICH first issued guidance on "E2B Data Elements for Transmission of Individual Case Safety Reports" in July 1997 (ICH E2B). ICH E2B was revised in 2000 to include adjustments based on successful pilot projects conducted in the three ICH regions (ICH E2BM). ICH is currently revising its E2B guidance again to provide additional information and clarification and has released ICH E2B(R) in draft. The term "ICH E2B guidance" used in this document includes all ICH guidance on the E2B topic of data elements for the transmission of ICSRs. The guidances are available on the Internet at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm> under the ICH—Efficacy category or <http://www.fda.gov/cber/guidelines.htm> under the ICH guidance documents category.

Postmarketing safety reports have been identified in FDA's electronic submissions public docket as submissions that FDA may accept in electronic format¹⁸.

Presently, FDA allows applicants, manufacturers, packers, and distributors to submit postmarketing safety reports (both 15-day Alert and periodic reports) in electronic format by sending the reports to FDA either: (1) Through FDA's Electronic Submission Gateway (ESG) or (2) on physical media, e.g., CD-ROM, digital tape, or floppy disk (sent by mail).¹⁹ These electronic submissions may include ICSRs, any ICSR attachments, and descriptive information. The data elements and electronic transport formats that FDA can accept for electronic ICSRs are described in technical specifications referenced in FDA guidance documents.²⁰ Currently, FDA can accept attachments to ICSRs and the descriptive information of periodic reports in an electronic form as portable document format (PDF) files, which may be sent through the FDA's ESG or mailed to FDA on physical media.²¹ To send these reports by FDA's ESG, a manufacturer/applicant must initially contact FDA's AERS electronic submission coordinator²² to establish an ESG connection with FDA's network.

b. *ICH standards.* FDA codes and analyzes electronic submissions of safety information received via the ESG or on physical media based on ICH standards.²³ ICH has developed international standards for the electronic submission of safety information that include: (1)

¹⁸ Docket No. FDA-1992-S-0039 (formerly Docket No. 1992S-0251) can be accessed on the Internet at <http://www.regulations.gov>.

¹⁹ FDA expects that, in the future, all electronic submissions to the agency will be sent through the ESG and that use of physical media for such submissions will, eventually, be phased-out.

²⁰ FDA is currently accepting electronic submissions using either the ICH E2B or ICH E2BM data elements; ICH E2B and ICH E2BM are available on the Internet at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm> under the ICH—Efficacy category or <http://www.fda.gov/cber/guidelines.htm> under the ICH guidance documents category.

²¹ See footnote number 19 in this document.

²² FDA's AERS electronic submission coordinator may be contacted at aersesub@fda.hhs.gov.

²³ See www.ich.org/cache/compo/276-254-1.html.

²⁴ ICH M2 provides electronic standards for the transfer of regulatory information (ESTRI). The M2 ESTRI recommendations facilitate international electronic communication in the three ICH regions. The ICH M2 working group developed a specification for the implementation of E2B data elements that allows for the transmission of all types of ICSRs, regardless of source and destination. ICH M2 recommendations are revised periodically to reflect the evolving nature of the technology. More information on M2 ESTRI is available on the Internet at <http://estri.ich.org>.

Standardized common data elements for transmission of ICSRs (ICH E2B guidance), and (2) electronic standard transmission procedures (ICH M2²⁴). ICH E2B guidance provides standardized common data elements for the transmission of ICSRs by identifying and defining the data elements for the transmission of all types of ICSRs, regardless of source and destination. The ICH format for ICSRs includes provisions for transmitting all the relevant data elements useful to assess an individual adverse drug reaction or adverse event report. The common data elements are sufficiently comprehensive to cover complex reports from most sources, different data sets, and different transmission requirements.

c. *FDA Web-based submission portal.* In addition to submission of ICSRs through the ESG, FDA is developing a Web-based electronic submission portal to collect and process safety information for all FDA-regulated products that will be consistent with ICH standards and may be used as another method for reporting adverse drug experiences to the agency.²⁵ FDA's Web-based portal will allow for the secure electronic submission of postmarketing ICSRs directly into FDA's AERS database once information is typed into a Web-based electronic form. Users will receive electronic confirmation that their submissions have been received by FDA. Any person who is subject to FDA's postmarketing safety reporting requirements and has Internet access will be able to use the Web-based form to submit ICSRs to the agency. The Web-based submission function will assist entities that submit a small number of safety reports by creating a simpler and more efficient mechanism for reporting that does not require them to have an internal database that is compatible with the ICH-based system. However, because some administrative support would be needed to manually enter the information for the ICSRs onto a form on the Web, this Web-based electronic reporting format will be less cost effective than direct submission through the ESG (or submitting the information on physical media) for companies with large numbers of safety reports. As soon as FDA can accept submissions using this Web-based form, information in docket 92S-0251, and the guidance documents described in this section will be updated to reflect this option.

²⁵ The Web-based reporting portal is based on the HL7 Individual Case Safety Report standard accredited by ANSI. This standard is for the exchange of adverse event information between computer systems.

2. Comments on the Advance Notice of Proposed Rulemaking (ANPRM) for Mandatory Electronic Submission of Postmarketing Safety Reports to FDA

In the **Federal Register** of November 5, 1998 (63 FR 59746), FDA issued an ANPRM describing the agency's plans to require electronic submission of all postmarketing expedited and periodic ICSRs. In the ANPRM, the agency indicated that it would propose that international standards be used for electronic safety reporting (i.e., precoding of ICSRs using the ICH M1 international medical terminology, ICH E2B format, and ICH M2 transmission specifications).²⁶ FDA also indicated that it was considering requiring that the textual (descriptive) information contained in a postmarketing periodic safety report be submitted to the agency in an electronic format. FDA received comments on the ANPRM from 11 representatives of pharmaceutical companies and associations and one individual. The agency considered these comments in developing this proposed rule on electronic submission of postmarketing safety reports.

a. *General.* In general, the comments supported FDA's plans to require electronic submission of postmarketing safety reports, while a few comments said that electronic submissions to the agency should remain voluntary. One comment said that FDA's goal of having all safety reports submitted in an electronic format would be realized without being mandated as electronic record collection, retrieval, and reporting becomes the generally-recognized norm throughout the pharmaceutical and biologics industry.

FDA believes that the electronic submission of postmarketing safety reports should be required and not voluntary because, although we have accepted the voluntary submission of postmarketing safety reports in electronic format since 2001, we are only receiving approximately 40 percent of ICSRs in electronic format. To expedite the identification of emerging safety problems and to realize cost savings for industry and the agency, we will need to receive close to 100 percent of ICSRs in electronic format.

b. *Waivers.* Several comments provided suggestions for waivers (exemptions) from the requirement to submit postmarketing safety reports electronically to FDA. The comments described two types of waivers: (1)

Temporary hardship waivers and (2) indefinite waivers.

Two comments requested that FDA grant a temporary hardship waiver for companies that experience unanticipated technical difficulties after implementation of the regulation. In this case, the company would be permitted to submit safety reports in a paper format. One comment said that such temporary waivers must be automatic so that regulatory requirements for timely reporting are fulfilled. The comments said that temporary waivers should be evaluated on an individual basis, taking into account factors such as company size, volume of reports, potential issues with international affiliates, and scope of required technical activities. One comment requested that the waiver be renewable for a 6-month period as long as the company can demonstrate progress towards the ability to submit reports electronically.

With regard to indefinite waivers, four comments said that small businesses should be exempt from the requirement to submit postmarketing safety reports in electronic format. The comments said that a waiver should be based on the number of safety reports that a company submits to FDA. They noted that the number of safety reports can vary significantly among manufacturers based on such attributes as company size and product line. One comment said that generic, or other, drug companies that receive few adverse event reports (e.g., 0–5 adverse drug reactions (ADRs) per week) should be exempt from the requirement. The comment stated that compliance with the requirement would place an undue burden on these drug companies because of the associated costs for human resources, equipment, software requirements, and other costs. The comment further stated that if the agency does not create a waiver for drug companies that have few ADRs per week (e.g., less than 5), then a longer transition period should be permitted, during which the agency would accept either paper or electronic ADRs. The transition period would allow sufficient time for drug companies that currently do not have the appropriate resources to establish electronic safety reporting systems. Another comment said that the criterion for an automatic waiver could be limited to NDAs for products with orphan-designated indications, because of the small number of ADRs submitted for these products. The comment also suggested that drug product sponsors who make less than a particular monetary amount for drug product sales per year (e.g., \$100 million) should be exempt from the rule.

Since these comments on the ANPRM were submitted in 1998, Internet access has become commonplace, reducing or eliminating implementation concerns for smaller firms or firms with very few reports. These firms will be able to use the Web-based form. Accordingly, we are not proposing indefinite waivers from implementation of electronic format submission of safety reports.

With regard to temporary waivers, we believe they should only be necessary in rare cases. Larger companies using the ESG could use submission on physical media (i.e., CD-ROM) or the Web-based system as a back-up if they experience temporary technological problems with their ESG submission system. Similarly, smaller firms regularly reporting on the Web-based system could easily find alternative Internet access in the event of a temporary Internet outage at the firm. Given that it is not possible to anticipate all the various situations that might require a waiver, we are proposing in this rule to provide for a temporary waiver of the electronic format submission requirement for good cause shown (see section III.C of this document). As discussed more below, we are specifically requesting comments in this rule on what would constitute "good cause" for a temporary waiver of the electronic format submission requirements.

c. *Textual materials.* ICSRs are often accompanied by textual materials (ISCR attachments), such as hospital discharge summaries or other medical records, published studies, or autopsy reports. Two comments supported the possibility of submitting textual materials electronically in addition to ICSRs. One of the comments recommended that the electronic transmission of textual materials be accepted using ICH standards so that consistency could be enhanced worldwide.

As recommended in the technical specifications referenced in guidances on submitting postmarketing safety reports in electronic format, textual materials can currently be submitted in a paper format or in an electronic format as a PDF file consistent with ICH guidelines.²⁷ When finalized, this rule would require submission of these textual materials in an electronic format we can process, review, and archive. Future changes to technical specifications for such submissions, such as transmission standards and file formats, would be announced in the technical specifications referenced in FDA guidance documents.

²⁶ The proposal to require coding of ICSRs using MedDRA (ICH M1) is included in a separate rulemaking, the Safety Reporting Proposed Rule, described in section II.B of this document.

²⁷ See footnote number 3 of this document.

d. *Security issues.* Several comments discussed security issues related to the confidentiality of data when safety reports are submitted electronically. Some comments stated that industry and the agency must be prepared to respond promptly to changing technology to ensure secure transmission of data. Another comment requested that the tools used for this purpose be commercially available at a reasonable cost.

The agency requires the secure transmission of all electronic submissions. We currently have certificate authority with standard encryption and will continue to use this security method in the agency's ESG for the electronic submission of postmarketing safety reports. The ESG meets National Institute of Standards and Technology (NIST)-800²⁸ series security certification standards.

III. Description of the Proposed Rule

As noted previously, the changes proposed in this rule would, largely, affect the form in which postmarketing safety reports must be submitted to FDA (i.e., in electronic format instead of a paper format) and, in addition, make minor conforming changes to the regulations.

A. Electronic Submission of Postmarketing Safety Reports

The proposal would revise §§ 310.305, 314.80, 314.98, and 600.80 to require that manufacturers, packers, and distributors, and applicants with approved NDAs, ANDAs, and BLAs and those that market prescription drugs for human use without an approved application submit postmarketing safety reports to the agency in an electronic format that FDA can process, review, and archive. We are proposing to delete the specific references to paper reporting forms in §§ 310.305, 314.80, and 600.80. We also propose to add language to these sections which states that FDA will periodically issue guidance on how to provide the electronic submissions (e.g., method of transmission, media, file formats, preparation and organization of files).

Postmarketing 15-day Alert and periodic reports, including the ICSRs, any ICSR attachments and the descriptive information portion of postmarketing periodic safety reports,

would be submitted to FDA in an electronic format. Information on the agency's ability to process, review, and archive these reports is described in the technical specifications referenced in FDA guidance documents (see section I of this document). The reports would be submitted to FDA in an electronic format only; paper copies would not be accepted unless the agency granted a temporary waiver (see section III.C of this document).

Under the proposed rule, for marketed products with an approved application, manufacturers, packers, or distributors that do not hold the application would continue to have the option of submitting 15-day Alert reports directly to FDA or to the application holder under §§ 314.80(c)(1)(iii) and 600.80(c)(1)(iii). If they opt to submit directly to FDA, they would be required to do so in electronic format. If they choose to report to the applicant, they could submit the report in any acceptable format. The applicant, however, would be required to use electronic reporting when it subsequently reports the information to FDA. Similarly, for marketed drug products without an approved application, initial safety reports made to the manufacturer by packers and distributors under current § 310.305(c)(3) could be made in any form agreeable to the reporter and the manufacturer, but this proposal would require all safety reports made to FDA to be made in electronic format.

This proposal applies to all postmarketing safety reports currently required to be submitted to FDA under §§ 310.305, 314.80, 314.98, and 600.80 (including vaccines) and would apply to any new postmarketing safety reports for drug or biological products that are implemented in the future (e.g., new postmarketing safety reports proposed in the Safety Reporting Proposed Rule described in section II.B of this document). The proposal would also revise § 600.81 by requiring the electronic submission of biological lot distribution reports. As previously described for postmarketing safety reports, FDA will also periodically issue guidance on how to provide the electronic submissions for these reports (e.g., method of transmission, media, file formats, preparation and organization of files).

B. Safety Reports Not Covered by the Proposed Rule

Postmarketing safety reports for drugs, including vaccines, constitute the largest volume of paper safety reports received by the agency and, consequently, require the most

resources to input electronically. This proposed rule would permit more efficient management of these postmarketing safety reports by FDA. This proposed rule would not apply to submission of the following safety reports:

- Investigational new drug application (IND) safety reports (§ 312.32);
- Safety update reports for drugs (§ 314.50(d)(5)(vi)(b));
- Approved NDA and BLA annual reports (§§ 314.81(b)(2) and 601.28 (21 CFR 601.28));
- Biological product deviation reports (BPDRs) (§§ 600.14 and 606.171 (21 CFR 606.171));
- Reports of complications of blood transfusion and collection confirmed to be fatal (21 CFR 606.170(b) and 640.73);
- Adverse reaction reports for human cells, tissues and cellular and tissue-based products (HCT/PS) regulated solely under section 361 of the Public Health Service Act (42 U.S.C. 264) (21 CFR 1271.350(a)); and
- NDA-field alert reports (§ 314.81(b)(1)).

We have not proposed to require that premarketing safety reports be submitted electronically because IND safety reports are submitted directly to the review division with responsibility for the IND, and are not uploaded into the AERS database. Blood transfusion and collection fatality reports are submitted to the agency in lower numbers than the postmarketing safety reports addressed in this rule; therefore, we have not proposed that these reports be subject to the mandatory electronic format requirements proposed in this rule. The agency has not yet received blood transfusion and collection fatality reports as electronic submissions, but does receive BPDRs through a voluntary electronic submission process. We are considering a mandatory electronic submission requirement for BPDRs, and blood transfusion and collection fatality reports in the near future and would like to receive industry comment on this possibility.

C. Waivers

Although this proposed rule would require that all postmarketing safety reports be submitted to FDA in electronic format, we are proposing in §§ 310.305(e)(2), 314.80(g)(2), and 600.80(g)(2) to grant a temporary waiver from the electronic format requirement for "good cause" shown. Procedural details for submitting waiver requests, such as where to send the request and any supporting documentation, would be announced in guidance. When a temporary waiver has been granted, a

²⁸ NIST, a nonregulatory Federal agency in the U.S. Commerce Department's Technology Administration, promotes U.S. innovation and industrial competitiveness by advancing measurement science, standards, and technology, including researching and developing test methods and standards for emerging and rapidly changing information technologies.

paper copy of the safety reports would be required to be submitted in a form that FDA can process, review, and archive.²⁹ FDA anticipates that temporary waivers of the requirement to submit postmarketing safety reports to the agency in electronic format will only be needed in rare circumstances. Companies experiencing technical difficulties with their ESG interface could, as a backup, submit reports on physical media or using the Web-based form during short-term, temporary outage. Moreover, for companies that rely on the Web-based form, submissions could be made from any computer with an Internet connection, providing ample alternatives should the company experience a longer term interruption of Internet service at its offices. Accordingly, we seek comments on what circumstances would constitute “good cause” for granting waivers.

D. Individual Case Safety Report (ICSR)—Definition and Required Information

The term ICSR is used to describe the information contained on either an initial or followup report of an individual adverse drug experience, currently reported on an FDA Form 3500A, CIOMS I form, VAERS form, or in electronic format. Given that this proposed rule would require that all safety reports be submitted in electronic format, we believe describing the safety reporting vehicle generically, rather than by reference to the associated paper form, is appropriate. Accordingly, we are proposing in §§ 310.305(b), 314.80(a), and 600.80(a) (with minor modifications) to define an ICSR as a description of an adverse drug experience related to an individual patient or subject. Because the items of information which should be reported in an ICSR are currently specified on the paper reporting forms that will no longer be used, we are also proposing to add a list of the reportable elements in the regulations. Accordingly, proposed §§ 310.305(d), 314.80(f), and 600.80(f) would provide a detailed list of specific types of information in five broad categories that are to be reported on the ICSR. The proposed categories, and examples of some of the types of information in each category, are as follows:

- Patient information (e.g., patient identification code, age, gender);
- Information about the adverse drug experience (e.g., date and description of the adverse drug experience);
- Information about the drug (e.g., drug name, dose, indication, National Drug Code (NDC) number);
- Information identifying the initial reporter (e.g., name and contact information); and
- Information about the drug’s applicant or manufacturer (e.g., name and contact information).

Other than minor wording differences, this proposed list of information to be reported is the same as that currently reflected on the FDA Form 3500A for postmarketing reporting for drugs and biological products. Codification of the ICSR reporting requirements is not intended to change the existing obligation of manufacturers, packers, or distributors to exercise due diligence for purposes of completing all of the applicable elements of an ICSR. The obligation to provide all applicable information described in proposed §§ 310.305(d), 314.80(f), or 600.80(f) would be the same as the current obligation to complete the FDA Form 3500A.³⁰

E. Removal of Paper Format Provisions

FDA believes that it is no longer necessary to describe procedures for paper format submissions in its regulations because the agency anticipates that a paper format will be used on a very limited basis, if at all. Accordingly, FDA is proposing to remove from its regulations provisions describing the details for submission of safety reports in paper format, such as the number of required paper copies or specific markings or notations required on the paper forms. We are proposing to delete in §§ 310.305(d), 314.80(f) and 600.80(f) the provisions specifically describing paper submissions and replace them with a new paragraph (proposed §§ 310.305(e)(1), 314.80(g)(1) and 600.80(g)(1)), which states that ICSRs and any attachments must be submitted to FDA in an electronic format that we can process, review, and archive. In addition, we are proposing to revise current regulations to remove or modify the following references or provisions that are specific to paper formats:

- References to the number of paper copies required for safety report submissions (§§ 310.305(c), 314.80(c), and 600.80(c));

- The requirement to mark paper reports to identify their contents as “15-day Alert report” or “15-day Alert report-followup,” (§§ 310.305(c)(4), 314.80(c)(1)(iv), 600.80(c)(1)(iv));
- The requirement to use FDA Form 3500A, CIOMS I form, or VAERS form or to determine an appropriate alternative format for *voluntary* submission in electronic format (§§ 310.305(d)(1) and (3); 314.80(f)(1) and (3), and 600.80(f)(1) and (3));
- The reference to FDA Form 3500A or other paper forms designated for adverse drug experience reporting by FDA for ICSRs that are submitted as part of periodic reporting requirements (§§ 314.80(c)(2)(ii)(b) and 600.80(c)(2)(ii)(B)); and
- The requirement for identifying reports of adverse drug experiences that occur in postmarketing studies by separating and marking them (§§ 314.80(e)(2), and 600.80(e)(2)).

As discussed previously in this document, in the future, procedural and formatting details, if applicable to electronic submissions, will be included in guidance, rather than in regulations.

F. Miscellaneous Changes

The proposal would amend §§ 310.305, 314.80, 314.98, and 600.80 by replacing the word “shall” with the word “must” except in the first sentence of §§ 314.80(c)(1)(iii) and 600.80(c)(1)(iii), from which the word “shall” would be removed for editorial reasons. FDA is also proposing to revise in § 314.80(c)(2) the paragraph designations that are currently not in correct format. FDA anticipates that these minor changes will clarify the regulations and make them easier to read. FDA is also proposing to change the term “licensed manufacturer” to “applicant” in §§ 600.80, 600.81 and 600.90.

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 these mailing addresses from its regulations because this information is provided in guidance and it is easier to update guidances when an address changes.

Under current § 310.305(c)(1)(i), each report must be accompanied by a copy of the labeling. We are proposing to revise this section to require the submission of the current content of labeling in electronic format unless it is already on file with FDA.

Currently, ICSRs for all adverse drug experiences other than those reported as 15-day Alert or followup reports (i.e., reports of serious, expected or nonserious adverse drug experiences)

²⁹ FDA’s ability to process, review, and archive postmarketing safety reports submitted to the agency in a paper format is described in FDA’s draft guidance for industry on “Postmarketing Safety Reporting for Human Drug and Biological Products Including Vaccines” available on the Internet at <http://www.fda.gov/Drugs/Guidance/ComplianceRegulatoryInformation/Guidances/default.htm> under “Procedural” or at <http://www.fda.gov/cber/guidelines.htm>.

³⁰ For FDA’s current thinking on “due diligence,” see the guidance described in footnote 29 of this document.

are submitted as a batch as part of the postmarketing periodic safety report for the period during which the events occurred. Although the ICSRs may be generated at any time during the reporting period, they are retained by the applicant during the reporting period and submitted to FDA all at once, along with the other (descriptive) portions of the periodic report. FDA is including language in proposed §§ 314.80(c)(2)(B) and 600.80(c)(2)(B) to give applicants the option of submitting these ICSRs at any time during the reporting period, rather than waiting to submit them in a single batch with the descriptive information. As with current submission procedures, all ICSRs of serious, expected or nonserious adverse drug experiences occurring during the reporting period would still be due to the agency by the time the descriptive information is submitted for that period, but the proposed change would permit them to be filed anytime during the reporting period, rather than all at once with the narrative portion of the periodic report. We understand that many applicants would prefer this added flexibility of submitting the ICSRs on an ongoing basis.

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(f), 314.80(i), and 600.80(i) would remove the eight character limit from the provision and add that the preferred methodology for determining the identification code would be set forth in technical specifications referenced in FDA guidance documents. Specific details of this type are most appropriate in the technical specifications referenced in FDA guidance documents, which can be more easily revised as technological requirements change. In addition, these provisions require that the entity submitting the report to FDA include in the ICSR the name of the reporter from whom the information was received. We are proposing to add an exception so that the name of the reporter need not be disclosed in situations where the reporter is also the patient.

Current §§ 310.305(c)(1), 314.80(c)(1)(i), and 600.80(c)(1)(i) require that 15-day Alert reports be submitted "as soon as possible but in no case later than 15 calendar days of initial receipt of the information" by the person. We propose to revise this

language to state "as soon as possible, but no later than 15 calendar days from initial receipt of the information." FDA does not intend this proposed change to have any substantive effect. It is being made solely to simplify the regulatory language and improve its readability.

G. Proposed Implementation Timeframe

FDA proposes that any final rule that may issue based on the proposal become effective 1 year after its date of publication in the **Federal Register**. FDA believes that 1 year is sufficient because many companies are currently submitting their postmarketing safety reports electronically to the agency using ICH standards and more than 1 year is not needed for companies that would choose to set up this system for their submissions. For companies that choose to use the Web-based system, the transition from paper submissions to electronic submissions will be as simple as filling out forms on the Internet and would, therefore, not necessitate more than 1 year to implement. (See section II.D.1.c of this document for discussion.)

IV. Legal Authority

FDA's legal authority to amend its regulations governing the submission of postmarketing safety reports for human drugs and biological products derives from sections 201, 301, 501, 502, 503, 505, 505A, 506, 506A, 506B, 506C, 510, 701, 704, 705, 760, and 801 of the act (21 U.S.C. 321, 331, 351, 352, 353, 355, 355a, 356, 356a, 356b, 356c, 360, 371, 374, 375, 379aa, and 381); and the Public Health Service Act (42 U.S.C. 241, 262, and 264).

V. Environmental Impact

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

VI. Analysis of Impacts

FDA has examined the impacts of the proposed rule under Executive Order 12866 and the Regulatory Flexibility Act (5 U.S.C. 601–612), and the Unfunded Mandates Reform Act of 1995 (Public Law 104–4). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). The agency

believes that this proposed rule is not a significant regulatory action as defined by the Executive order.

The Regulatory Flexibility Act requires agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. Because the average small entity submits very few safety reports and the agency's proposed Web-based method to submit reports electronically would require little additional cost per report, the agency does not believe that this proposed rule would have a significant economic impact on a substantial number of small entities. FDA requests comment on this issue.

Section 202(a) of the Unfunded Mandates Reform Act of 1995 requires that agencies prepare a written statement, which includes an assessment of anticipated costs and benefits, before proposing "any rule that includes any Federal mandate that may result in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of \$100,000,000 or more (adjusted annually for inflation) in any one year." The current threshold after adjustment for inflation is \$133 million, using the most current (2008) Implicit Price Deflator for the Gross Domestic Product. FDA does not expect this proposed rule to result in any 1-year expenditure that would meet or exceed this amount.

The major benefit of this proposed rule would be to public health and the agency in the form of quicker access to postmarketing safety information and an annual savings of about \$2.4 million, including a savings in the cost of paper. Total one-time costs to industry would be between \$4.5 million to \$5.6 million; most of these costs would be for changing standard operating procedures (SOPs), setting up systems for submissions, and acquiring an electronic certificate. Industry would also incur annual costs of between \$133,320 to \$139,380 for Internet upgrades and to maintain electronic certificates.

The proposed rule would require the submission of all postmarketing safety reports, including periodic reports, to FDA in an electronic format. It would affect all persons required to submit postmarketing safety reports under §§ 310.305, 314.80, 314.98, 600.80, and 600.81. As currently proposed, this rule would not change the content of the postmarketing safety reports or the frequency of the reporting requirements. The proposal is part of the agency's initiative to adopt electronic technologies to improve the quality of our operations and increase our efficiency.

A regulation is necessary because the majority of the benefits from increased effectiveness of FDA use of adverse drug experience reports will accrue to the agency and to public health, while the costs are borne by industry. Many of the firms lack the private incentive to divert resources to develop electronic submission capabilities on their own. In other words, for many firms the present value of the cost savings from eliminating paper reports is less than the cost of switching to electronic reports. Without this regulation, the agency would need to maintain adequate resources to convert paper reports to electronic records until all companies adopt the electronic submission format, possibly years in the future. Although some part of this proposed rule would merely shift costs of adopting the electronic format from FDA to industry, the additional social benefit arises from the increased speed and effectiveness of FDA analyses and action based on adverse drug experience reports. The need for the regulation stems from the benefits to the public health from more rapid identification and action on unanticipated adverse drug experiences.

FDA currently accepts postmarketing safety reports submitted electronically using ICH standards (i.e., ICH M2 transmission standards and ICH E2BM data elements) (see section II.D.1.b of this document). Both the EU and Japan have mandated electronic submissions for postmarketing safety reports using these standards. The proposed rule would make the FDA's system compatible with the systems used in Japan and the EU. The proposed rule may also increase the use of international data and international comparisons, which could contribute to more rapid identification and action on serious and unexpected adverse drug experiences.

A. Benefits

The proposal would reduce FDA's current costs associated with processing postmarketing safety reports that are received via paper format. By receiving these reports electronically, FDA would be able to access the safety information more quickly and also reduce data entry errors that could occur during entry of the information from the paper reports into our electronic system. The major benefits of this proposed rule would be to the agency and public health in terms of quicker access to postmarketing safety information, which in turn would lead to faster identification of safety problems. The proposed rule would also reduce the agency's costs for converting paper records in a variety of formats

into electronic form. Resources that are now used to manually enter the reports into FDA's electronic database could be redirected to monitoring drug safety or other agency initiatives.

Currently, the agency receives more than 445,000 postmarketing ICSRs per year. In fiscal year 2006, approximately 60 percent of ICSRs (15-day Alert and periodic) were submitted in paper form. At this time, it takes from 3 to 14 days before a submitted paper record of a 15-day Alert report is available for analysis in the AERS database. Periodic ICSRs submitted on paper may not be entered into AERS for up to 60 days. With a standardized electronic format, records would become available for analysis in AERS as soon as they were processed by FDA (within 2 days of receipt by the agency).

The agency currently spends about \$5.4 million annually on conversion of paper ICSRs to an electronic format, which includes data entry and quality control.³¹ The proposal would result in reduced costs associated with controlling and ensuring the quality of the data. Assuming that the number of reports remains fairly constant over time, we estimate that we would save about \$2.4 million annually in contracting costs by not having to convert paper copies to an electronic format.

The larger public health benefits—more timely identification of drug safety problems with the potential to reduce subsequent adverse drug experiences—cannot be realized fully until a comprehensive surveillance system and international harmonization of reporting requirements are in place (e.g., implementation of the ICH standards discussed in the Safety Reporting Proposed Rule). Obtaining postmarketing safety reports in an electronic format is an important and necessary step toward attaining the larger public health benefits.

B. Costs

FDA estimates that there are approximately 2,020 firms affected by this rule. Table 1 lists the number of firms affected by type of product marketed. To comply with the proposed rule, firms would incur both one-time and annually recurring costs. One-time costs include modifying SOPs, developing electronic submission capabilities, and training employees on the new procedures. Annually recurring costs would include the cost to maintain an electronic certificate and high-speed Internet access. There would be no

³¹ Cost to convert paper reports to electronic format from FDA AERS data entry contract.

change in the actual time required to research and prepare the report, nor would there be any additional reporting requirements as a result of this proposed rule.

As discussed earlier in this preamble, firms marketing nonprescription drug products without an approved application are now subject to safety reporting requirements as a result of Public Law 109-462 (see section II.A.1.d of this document). Although this rule does not propose to require use of an electronic format for submission of these reports, because we are considering such a requirement for the final rule, this analysis includes an estimate of the incremental cost for firms to comply with the submission of these safety reports in an electronic format. While the mandatory reporting requirements are new, analyzing product complaints, including reports of drug induced adverse drug experiences, is a requirement of the Current Good Manufacturing Practice regulations (21 CFR 211.198).

1. One-time costs

a. *Rewriting standard operating procedures and training personnel.* Almost all companies would have to make some changes to their SOPs to reflect the requirements for electronic submission versus mailing the reports to the agency. Most companies that submit postmarketing safety reports to FDA are small and submit few safety reports to the agency; we estimate that it would require about 10 hours to change their SOPs and to train the appropriate employees. Companies with proprietary computer systems used to generate and store safety reports would require considerably more time to modify their SOPs and train the appropriate personnel. We estimate that these firms would require about 50 hours for this task.

We estimate that about 1,520 firms would require 10 hours and about 100 firms would require 50 hours to modify SOPs and train the appropriate personnel. (The firms primarily marketing nonprescription drug products without an approved application are not included in this estimate.) Assuming an average wage rate including benefits of \$68 per hour, the total one-time incremental cost for this proposed requirement would be about \$1.4 million [(1,520 x 10 hours x \$68) + (100 x 50 hours x \$68)] (see table 1 of this document).³²

³² Wage derived from 2007 Bureau of Labor Statistics Occupation Employment Statistics Survey, standard occupation code 11-3042, training manager for pharmaceutical medicine and

Firms producing primarily nonprescription drug products without an approved application will have to establish SOPs for submitting ICSRs. We estimate that it takes between 24 and 40 hours to write a new SOP and another 5 to 10 hours to train the appropriate personnel, depending on the size of the firm.³³ Assuming an average wage cost of \$68 per hour, and the mid-point of the range of hours the cost would be about \$1.1 million (40 hours x \$68 x 400 firms).

b. *Setting up system for submission.* ICSRs would be submitted through FDA's electronic submission gateway (ESG) using one of two methods: One at a time using a Web-based form or by direct transmission through an ICH compatible system. Attachments to the ICSRs, the descriptive information portion of periodic reports and distribution reports would be submitted as PDF files through the ESG. We assumed that because most firms are small and submit few ICSRs, they would use the Web-based form. To comply using this submission method, firms would need high speed Internet connections and would have to download and install up to two free software programs, validate the installation, and train the appropriate personnel on the new procedures. Firms that have dedicated IT staff would be able to install and validate the installation themselves. Smaller firms would probably choose to hire an outside contractor for the installation and validation. We do not have data on the amount of time required to install and validate the installation of the software or the percentage of firms that might need to contract out the installation. For this analysis, we assumed it would take 8 to 16 hours to install and validate the installation of the Java Runtime Edition software and the Java security policy files for the company's Internet browser.³⁴ This estimate also includes the time required to notify FDA and run a test submission through the FDA ESG and to train the appropriate staff. Based on these assumptions and using the \$68 per hour wage the cost for this requirement would range from \$1.0 million to \$2.1 million (8 hours x \$68 wage x 1,920

firms and 16 hours x \$68 wage x 1,920 firms).

Firms that submit a large number of reports each year may choose to use the ICH compatible method. This method allows for the submission of multiple reports at faster transmission rates. We do not know at what threshold of reporting it becomes cost effective for a firm to submit reports using this method. Currently just over 40 firms voluntarily submit ICSRs using this method and they account for about one-half of all 15-day Alert reports submitted each year. We assume that only firms that have existing infrastructure to support the ICH method of transmission would choose this method to submit reports. At the time of a final rule we estimate that about 50 firms would be voluntarily using this method of submission and about 100 additional firms would comply with the rule by adopting this method of reporting for an estimated cost of \$0.3 million (50 hours x \$68 x 150 firms).

c. *Electronic certificate.* All firms would need an electronic certificate to submit any document to the FDA ESG. The electronic certificate identifies the sender and serves as an electronic signature. Firms that have not submitted any electronic documents to the agency would incur a one-time cost to acquire the certificate and recurring costs to keep the certificate active as a result of this proposed rule. The certificates cost about \$20 and are good for 1 year. We assume that the search and transactions costs involved in the initial acquisition of the certificate double the cost of the certificate to \$40 for the first year, half of which would be set-up costs. We also believe that should this rule become final many firms will already have electronic certificates because they are required for electronic submission of other regulatory documents, such as product applications and supplements. If 60 to 70 percent of the firms needed to acquire an electronic certificate to comply with the proposed requirement, the cost would be between \$48,480 and \$56,560 (\$40 x 1,212 firms and \$40 x 1,414 firms, respectively).

In addition to the costs we have estimated, some firms affected by this proposed rule may have to hire outside expertise to install and validate the software installation to comply with the proposed requirements.

d. *Creation of PDF files.* Some companies still maintain safety information as paper records. Companies that store their submissions in paper format rather than electronically may also incur costs to acquire the ability to convert ICSR

attachments, the descriptive information portion of periodic reports, and distribution reports to an electronic format that the agency can process, review, and archive. Currently, this is the PDF format. We assume all firms would have the software and training necessary to convert existing electronic files to a PDF format.

We lack sufficient data to estimate with any certainty the costs to convert paper documents to electronic files that can be transmitted through our ESG. We do not know how many companies maintain paper versus electronic records. We also do not know how many have optical scanning capabilities that would allow them to convert the paper records to electronic PDF files.

Because optical scanners are relatively inexpensive and easy to use, they are commonplace in businesses today. We believe that all of the large firms in the industry currently have such equipment and would incur little or no additional incremental costs for this capability. Most large firms currently store much of their information electronically now, and they should require no more than 30 minutes to convert ICSR attachments to PDF files and proof them, which would be offset by the time they currently use for photocopying, collating, and mailing files. For documents the applicant has in paper format, the time required to scan a document would also be offset by no longer having to photocopy, collate, and mail the submission to us.

Companies that maintain their records in a paper format may have to purchase an optical scanner and the appropriate optical character recognition (OCR) software to comply with this requirement, or they could pay a service provider, such as a copy center, to transform the documents into an electronic PDF file. A suitable scanner with OCR software should not cost more than \$400. FDA assumes that initial setup and training to use the equipment should require no more than 4 hours. At the wage plus benefits rate of \$68 per hour, the one-time cost for setup and training would be about \$272 (4 hours x \$68). If one-half of the companies affected needed to purchase a scanner and train employees to use it, the total one-time costs would be \$0.7 million (((\$400 + \$272) x 1,010) (see table 1 of this document).

To have a service provider convert a black and white paper document to a PDF file would cost about \$10 per page for the first page and about \$2 per page thereafter. If an applicant wanted the documents saved to a disk, it would cost an additional \$20 per transaction.

manufacturing—mean wage rate \$48.73 + 40 percent for nonwage benefits and rounded to \$68, at www.bls.gov.

³³ Eastern Research Group, "Economic Threshold and Regulatory Flexibility Assessment of Proposed Changes to the Current Good Manufacturing Practice Regulations for Manufacturing, Processing, Packing, or Holding Drugs," submitted to the Office of Planning and Evaluation, March 1995.

³⁴ See <http://www.fda.gov/esg/default.htm#tutorials> and <http://www.fda.gov/esg/account.htm>.

Safety report submissions differ greatly in the number of attachments and number of pages submitted depending on the nature of the adverse drug experience and the drug involved. We do not have an estimate of the number of pages of attachments in an average report. However, if an applicant used a service provider to convert 20 pages of material and had it saved to a disk, it would cost about \$70 (\$10 first page + (\$2 x 19 pages) + \$20 to save to disk).

The total one-time incremental costs of this proposed rule would be between \$4.5 million and \$5.6 million. About \$1.4 million to \$1.7 million of this total would be incurred by the firms that primarily market nonprescription drug products without an approved application. (table 1 of this document).

2. Annual costs

The annual costs of this proposed rule would include the costs of maintaining electronic certificates and the increased cost for some firms to obtain high-speed Internet access.

a. *Maintaining the electronic certificate.* Firms would have an annual cost to renew the electronic certificate that identifies the sender. In addition to having to renew the certificate on a regular basis, firms that seldom submit reports would also have to ensure they are capable of transmitting data to the agency. To add these additional costs to the cost of the certificate itself, we assume that firms incur an additional annually recurring cost equal to one-half the price of the certificate (\$10), for a total annually recurring cost of \$30. Assuming that 60 to 70 percent of the firms would not voluntarily submit any required documents electronically without a regulation, the annual cost to maintain certificates would range from \$36,360 and \$42,420 (\$30 x 1,212 firms or \$30 x 1,414 firms).

b. *High-Speed Internet access.* Firms will need high-speed Internet access to use either of the submission methods. A 2004 study of small businesses sponsored by the Small Business Administration found that essentially all small firms in the United States had Internet access and about 50 percent had high-speed Internet access.³⁵ The average cost of high-speed access was about \$40 per month more than dial-up access. Because of the nature of the drug industry and because the average cost of Internet access has been going down over time, we estimate that by the time this proposed rule would be made final,

about 90 percent of firms would have high speed access. The average annual recurring increase in cost for high speed Internet access for the remaining 10 percent of firms would be \$96,960 (\$40 x 12 months x 202 firms).

Table 2 shows the annual costs of the proposed rule. As with the one-time costs, only firms not already making electronic submission of any kind to the agency when this proposed rule becomes final would incur these costs.

C. Summary of Benefits and Costs

The principal benefit of this proposed rule would be the public health benefits associated with more rapid processing and analysis of the almost 300,000 ICSRs currently submitted on paper. In addition, requiring electronic submission would reduce FDA annual operating costs by \$2.4 million.

The total one-time cost for modifying SOPs and establishing electronic submission capabilities is estimated to range from \$4.5 million to \$5.6 million. Annually recurring costs totaled \$133,320 to \$139,380 and included maintenance of electronic submission capabilities, including renewing the electronic certificate, and for some firms the incremental cost to maintain high-speed Internet access. The total annualized cost of the proposed rule, assuming a 7-percent discount rate over 10 years, would be from \$0.8 million to \$0.9 million (\$0.7 million to \$0.8 million at a 3-percent discount rate). We request comment on the accuracy and completeness of the assumptions used to estimate the costs of this proposed rule, including our choice of a 10 year time horizon.

D. Alternatives Considered

During the development of this proposed rule, we considered a number of alternative approaches. The first was to allow persons to voluntarily submit reports electronically. This option is currently available and our experience has shown that a number of companies would resist changing their procedures for a long time. As a result, we would not attain the benefits of standardized formats and quicker access to adverse drug experience data with voluntary electronic submissions.

Another alternative was to allow small entities a longer period of time to comply with the electronic submission requirements. This alternative would have allowed small entities to delay the expense of compliance. This alternative would delay our receiving the full

benefits of quicker access to these reports. Compliance costs for small entities are estimated to be low, less than \$2,260 in one-time costs (sum of cost for equipment, training, and changing SOPs), which should not impose an economic hardship on the small entities.

We also considered requiring electronic submissions but not specifying a format. This alternative would reduce the costs to firms associated with paper. Because receiving reports in many different formats would continue to require the agency to convert the reports into a standard format for analysis, this alternative would delay the full public health benefits of quicker FDA access to these reports.

E. Small Business Impact

The Small Business Administration defines an entity in the pharmaceutical industry as small if it has fewer than 750 employees and a biologic entity as small if it has fewer than 500 employees. Based on this definition about 90 percent of the drug and biologic entities are small. The impact on each entity will vary depending on their electronic submission capabilities when the rule is made final. Much of the incremental cost and all of the recurring costs of this proposed rule are for acquiring and maintaining electronic submission capability (\$1,236 to \$1,780 in one-time costs and up to \$510 in annually recurring costs per small entity). Only firms that have not made any electronic submissions to the agency when this rule becomes final would incur those costs. The writing of SOPs and employee training are the only costs that are specific to this rule (a one-time cost of about \$680 per small entity).

Because the estimated incremental costs per entity are low, between \$1,916 and \$2,460 in one-time incremental costs and up to \$510 in annually recurring costs, and the majority of those costs would be incurred for any electronic submission across the agency, this proposed rule would probably not have a significant economic impact on a substantial number of small entities. However, because we lack data to fully characterize the small entities and the average submittal, we do not certify that there will be no significant impact at this time. We request comment on the tentative conclusion of no significant impact.

³⁵ Pociask, Steve, "A Survey of Small Businesses' Telecommunications Use and Spending," Small

Business Administration Office of Advocacy

contract number SBA-HQ-02-M-0493, March 2004.

TABLE 1.—ONE-TIME COSTS BY FIRM TYPE¹

Type of Firm	Total number of firms	Establishing e-submission capability				Acquiring e-certificate ¹		PDF files	Total	
		Modifying SOPs	Low	High	ICH Method	Low	High		low	high
Drug and biologic products subject to parts 310, 314, and 600	600	\$680,000	\$272,000	\$544,000	\$340,000	\$7,200	\$8,400	\$201,600	\$1,500,800	\$1,774,000
Nonprescription drug products marketed without an approved application	400	1,088,000	217,000	435,200		4,800	5,600	134,400	1,444,800	1,663,200
Medical Gas	1,020	693,300	554,880	1,109,760		12,240	14,280	342,720	1,603,440	2,160,360
Total	2,020	\$2,461,600	\$1,044,480	\$2,088,960	\$340,000	\$24,240	\$28,280	\$678,720	\$4,549,040	\$5,597,560
Annualized at 3% over 10 years									\$553,286	\$656,205
Annualized at 7% over 10 years									\$647,681	\$796,967

¹This refers to the \$20 one-time cost involved in acquiring the certificate, the actual cost of the certificate is captured in the annual recurring costs (table 2 of this document).

TABLE 2.—ANNUAL RECURRING COSTS

Type of Firm	Electronic Certificate		Internet access	Total	
	Low	High		Low	High
Drug and biologic products subject to parts 310, 314, and 600	\$10,800	\$12,600	\$28,800	\$39,600	\$41,400
Nonprescription drug products marketed without an approved application	7,200	8,400	19,200	26,400	27,600
Medical Gas	18,360	21,420	48,960	67,320	70,380
Total	\$36,360	\$42,420	\$96,960	\$133,320	\$139,380

VII. Paperwork Reduction Act of 1995

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

We invite comments on these topics: (1) Whether the 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: Postmarketing Safety Reports for Human Drug and Biological Products: Electronic Submission Requirements.

Description: The proposed rule would amend FDA's postmarketing safety reporting regulations for human drug and biological products, under parts 310, 314 and 600, to require that persons subject to mandatory reporting requirements submit safety reports in an electronic format that FDA can process, review, and archive. Under §§ 310.305, 314.80, 314.98 and 600.80, manufacturers, packers, and distributors, and applicants with approved NDAs, ANDAs and BLAs and those that market prescription drugs for human use without an approved application must currently submit postmarketing safety reports to the agency. Under § 600.81, applicants with

approved BLAs must currently submit biological lot distribution reports to the agency. In this rule, FDA is proposing to require that these postmarketing reports be submitted to the agency in an electronic format that FDA can process, review and archive. We also propose to add language to these sections which states that FDA will periodically issue guidance on how to provide the electronic submissions (e.g., method of transmission, media, file formats, preparation and organization of files). This rule does not change the content of these postmarketing reports. It only proposes to require that they be submitted in an electronic form. Under §§ 310.305(e)(2), 314.80(g)(2), 600.80(g)(2), and 600.81(b)(2), we are also proposing to permit manufacturers, packers, and distributors, and applicants with approved NDAs, ANDAs and BLAs and those that market prescription drugs for human use without an approved application to request a waiver from the electronic format requirement.

We currently have OMB approval for submission of postmarketing safety reports to FDA under parts 310, 314,

and 600. The information collection for part 310 and part 314 is approved under OMB Control Numbers 0910-0291 (Form 3500A) and 0910-0230. The information collection for part 600 is approved under OMB Control Numbers 0910-0291 (Form 3500A) and 0910-0308. We do not expect that the burdens currently estimated, under parts 310, 314 and 600, for submission of postmarketing safety reports to FDA for human drugs and biological products would change as a result of this proposed rule. This is because: (1) Current burden estimates associated with these regulatory requirements have taken into account voluntary submission of these reports in an electronic format and those applicants, manufacturers, packers, and distributors that already submit these reports in an electronic format would have no new reporting burdens, and (2) new burdens for establishing the means for submitting postmarketing safety reports in electronic form to comply with this proposed rule, including obtaining an electronic certificate, revising SOPs, and familiarity with the system, would be negated by the savings in burden from not having to print out the report and

mail it to FDA. These assumptions also apply to applicants submitting biological lot distribution reports under proposed § 600.81. We invite comment on the number of respondents not currently submitting safety reports in electronic format who would need to convert from paper submission. We also invite comment on the reduction in burden associated with not printing out reports and mailing them to FDA and whether this burden reduction is offset by the cost associated with obtaining an electronic certificate, revising SOPs, and familiarizing firms with the system.

Manufacturers, packers, or distributors whose name appears on the label of nonprescription human drug products marketed without an approved application are now required to submit reports of serious adverse events to FDA (see section II.A.1.d of this document). Even though we are not proposing to require that these reports be submitted to FDA in an electronic form at this time, we are considering including such a requirement in the final rule. OMB has recently approved the burden associated with these submissions under OMB Control Number 0910-0636.

In table 3 of this document, we have estimated the burdens associated with

submission of waivers, under proposed §§ 310.305(e)(2), 314.80(g)(2), 600.80(g)(2), 600.81(b)(2) and 21 U.S.C. 379aa(b) and (c)). We expect very few waiver requests (see section III.C of this document). We estimate that approximately one manufacturer would request a waiver annually under §§ 310.305(e)(2), 600.81(b)(2), and 21 U.S.C. 379aa(b) and (c)), and five manufacturers would request a waiver annually under §§ 314.80(g)(2) and 600.80(g)(2). We estimate that each waiver request would take approximately 1 hour to prepare and submit to us.

Description of Respondents: Manufacturers, packers, and distributors, and applicants with approved NDAs, ANDAs and BLAs and those that market prescription drugs for human use without an approved application.

Burden Estimate: Table 3 of this document provides an estimate of the annual reporting burden for submitting requests under the proposed waiver requirement in this rule.

A. Reporting Cost

TABLE 3.—TOTAL ESTIMATED ANNUAL BURDEN FOR THIS PROPOSED RULE

21 CFR Sections	Number of Respondents	Number of Responses Per Respondent	Total Annual Responses	Hours per Response	Total Hours
Waivers					
310.305(e)(2)	1	1	1	1	1
314.80(g)(2)	5	1	5	1	5
600.80(g)(2)	5	1	5	1	5
600.81(b)(2)	1	1	1	1	1
21 U.S.C. 379aa(b) and (c))	1	1	1	1	1
Total Reporting Burden					13

Based on the average hourly wage as calculated in section VI (Analysis of Impacts) of the proposed rule (\$68), the cost to respondents would be \$884 (13 X \$68).

Tables 4 through 7 of this document provide an estimate of the annual

reporting burden currently covered under existing OMB Control Numbers 0910-0291, 0910-0230, 0910-0308, and 0910-0636. As explained previously, we believe that any burden increases associated with electronic reporting are offset by burden decreases associated

with not printing out reports and mailing them to FDA. Therefore, we believe that the burden estimates for these information collections will not change.

TABLE 4.—OMB CONTROL NUMBER 0910-0291

21 CFR Sections	Number of Respondents	Number of Responses Per Respondent	Total Annual Responses	Hours per Response	Total Hours
Form 3500A (§§ 310.305, 314.80, 314.98, & 600.80)	600	765	459,102	1.1	505, 012

Based on the average hourly wage as calculated in section VI (Analysis of Impacts) of the proposed rule (\$68), the cost to respondents would be \$34,340,816 (505,012 x \$68).

TABLE 5.—OMB CONTROL NUMBER 0910–0230

21 CFR Sections	Number of Respondents	Number of Responses Per Respondent	Total Annual Responses	Hours per Response	Total Hours
310.305(c)(5)	1	1	1	1	1
314.80(c)(2)	642	17.88	11,478	60	688,680
Total					688,681

Based on the average hourly wage as calculated in section VI (Analysis of Impacts) of the proposed rule (\$68), the cost to respondents would be \$46,830,308 (688,681 x \$68).

TABLE 6.—OMB CONTROL NUMBER 0910–0308

21 CFR Sections	Number of Respondents	Number of Responses Per Respondent	Total Annual Responses	Hours per Response	Total Hours
600.80(c)(1) & 600.80(e)	88	270.85	23,835	1	23,835
600.80(c)(2)	88	248.55	21,872	28	612,416
600.81	88	2.03	179	1	179
Total					636,430

Based on the average hourly wage as calculated in section VI (Analysis of Impacts) of the proposed rule (\$68), the cost to respondents would be \$43,277,240 (636,430 x \$68).

TABLE 7.—OMB CONTROL NUMBER 0910–0636

21 CFR Sections	Number of Respondents	Number of Responses Per Respondent	Total Annual Responses	Hours per Response	Total Hours
Reports of serious adverse drug events (21 U.S.C. 379aa(b) and (c))	50	250	12,500	2	25,000
Total					25,000

Based on the average hourly wage as calculated in section VI (Analysis of Impacts) of the proposed rule (\$68), the cost to respondents would be \$1,700,000 (25,000 x \$68).

B. Capital Costs

As explained in section VI (Analysis of Impacts) of this document, total one-time costs to industry under this rule would be between \$4.5 million to \$5.6 million; most of these costs would be for changing SOPs, setting up systems for submissions, and acquiring an electronic certificate. Industry would also incur annual costs of between \$133,320 to \$139,380 for Internet upgrades and to maintain electronic certificates.

The information collection provisions of this proposed rule have been submitted to OMB for review. Interested persons are requested to fax comments regarding information collection by (see **DATES** section of this document), to the Office of Information and Regulatory Affairs, OMB. To ensure that comments on the information collection are received, OMB recommends that written comments be faxed to the Office of Information and Regulatory Affairs, OMB, Attn: FDA Desk Officer, FAX: 202–395–7285, or e-mailed to oir_submission@omb.eop.gov. All comments should reference the title of this rule and include the FDA docket number found in brackets in the heading of this document.

VIII. Federalism

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 the 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.

IX. Request for Comments

Interested persons may submit to the Division of Dockets Management (see ADDRESSES) written or electronic comments regarding this document. Submit a single copy of electronic comments or two paper copies of any mailed comments, except that individuals may submit one paper copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday.

List of Subjects

21 CFR Part 310

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

21 CFR Part 314

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

21 CFR Part 600

Biologics, Reporting and recordkeeping requirements.

Therefore, under the Federal Food, Drug, and Cosmetic Act, the Public Health Service Act, and under authority delegated to the Commissioner of Food and Drugs, it is proposed that 21 CFR parts 310, 314, and 600 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 amended by:

a. Removing the word “shall” each time it appears and by adding in its place the word “must”;

b. Adding alphabetically in paragraph (b) the definition of “Individual case safety report (ICSR)”;

c. Revising paragraph (c) introductory text, paragraph (c)(1)(i), and the second sentence of paragraph (c)(3) introductory text; removing the last sentence in paragraph (c)(2), and removing and reserving paragraph (c)(4);

d. Revising paragraph (d); and

e. Redesignating paragraphs (e) through (g) as paragraphs (f) through (h), adding a new paragraph (e), revising newly redesignated paragraph (f), and in newly redesignated paragraph (g)(1) remove “(c)(4)” and add in its place “(c)(3)” to read as follows:

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

* * * * *

(b) * * *

Individual case safety report (ICSR). A description of an adverse drug experience related to an individual patient or subject.

(c) Reporting requirements. Each person identified in paragraph (c)(1)(i) of this section must submit to FDA adverse drug experience information as described in this section. Except as provided in paragraph (e)(2) of this section, 15-day “Alert reports” and followup reports, including ICSRs and any attachments, must be submitted to the agency in electronic format as described in paragraph (e)(1) of this section.

(1) Postmarketing 15-day “Alert reports”. (i) Any person whose name appears on the label of a marketed prescription drug product as its manufacturer, packer, or distributor must report to FDA each adverse drug experience received or otherwise obtained that is both serious and unexpected as soon as possible, but no later than 15 calendar days from initial receipt of the information by the person whose name appears on the label. Each report must be accompanied by the current content of labeling in electronic format unless it is already on file at FDA.

* * * * *

(3) * * * If a packer or distributor elects to submit these adverse drug experience reports to the manufacturer rather than to FDA, it must submit, by any appropriate means, each report to the manufacturer within 5 calendar days of its receipt by the packer or distributor, and the manufacturer must then comply with the requirements of this section even if its name does not appear on the label of the drug product.

* * *

* * * * *

(4) [Reserved]

* * * * *

(d) Information reported on ICSRs. ICSRs include the following information:

(1) Patient information.

- (i) Patient identification code;
(ii) Patient age at the time of adverse drug experience, or date of birth;
(iii) Patient gender; and
(iv) Patient weight.

(2) Adverse drug experience.

- (i) Outcome attributed to adverse drug experience;
(ii) Date of adverse drug experience;
(iii) Date of report;

- (iv) Description of adverse drug experience;
(v) Description of relevant tests, including dates and laboratory data; and
(vi) Other relevant patient history, including preexisting medical conditions.

(3) Suspect medication(s).

- (i) Name;
(ii) Dose, frequency, and route used;
(iii) Therapy dates;
(iv) Diagnosis for use (indication);
(v) State whether adverse drug experience abated after drug use stopped or dose reduced;
(vi) Lot number;
(vii) Expiration date;
(viii) State whether adverse drug experience reappeared after reintroduction of drug;
(ix) NDC number; and
(x) Concomitant medical products and therapy dates.

(4) Initial reporter information.

- (i) Name, address, and phone number;
(ii) Whether the initial reporter is a health professional;
(iii) Occupation; and
(iv) Whether the initial reporter also sent a copy of the report to FDA.

(5) Manufacturer, packer, or distributor information.

- (i) Manufacturer, packer, or distributor name and contact office address;
(ii) Telephone number;
(iii) Report source(s) (e.g., literature, study);
(iv) Date received by manufacturer, packer, or distributor;
(v) Basis for marketing if nonapplication product;
(vi) Type of report being submitted (e.g., 15-day, periodic, followup);
(vii) Adverse drug experience term(s); and
(viii) Manufacturer report number.

(e) Electronic format for submissions.

(1) Each report required to be submitted to FDA under this section, including the ICSR and any attached documentation, must be submitted in an electronic format that FDA can process, review, and archive. FDA will periodically issue guidance on how to provide the electronic submission (e.g., method of transmission, media, file formats, preparation and organization of files).

(2) Waivers. Each person identified in paragraph (c)(1)(i) of this section may request, in writing, a temporary waiver of the requirements in paragraph (e)(1) of this section. These waivers will be granted on a limited basis for good cause shown. If the agency grants the waiver, the person must submit the reports required under paragraph (c) of this section on paper within the required time periods in a form that

FDA can process, review, and archive. FDA will issue guidance on how to provide the paper submission. Procedures for how to request waivers of this requirement will be set forth in guidance.

(f) *Patient privacy.* Manufacturers, packers, and distributors should not include in reports under this section the names and addresses of individual patients; instead, the manufacturer, packer, and distributor should assign a unique code to each report. The preferred methodology for determining the identification code will be set forth in guidance. The manufacturer, packer, and distributor should include the name of the reporter from whom the information was received, unless the reporter is the patient. The names of patients, individual reporters, health care professionals, hospitals, and geographical identifiers in adverse drug experience reports are not releasable to the public under FDA's public information regulations in part 20 of this chapter.

* * * * *

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

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

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

4. Section 314.80 is amended:

a. By removing the word "shall" each time it appears and by adding in its place the word "must";

b. In paragraph (a) by alphabetically adding the definition for "Individual case safety report (ICSR)";

c. In paragraph (c)(1)(i) by removing the phrase "in no case later than 15 calendar days of" and by adding in its place the phrase "no later than 15 calendar days from";

d. By removing the last sentence of paragraph (c)(1)(ii);

e. By removing paragraph (c)(1)(iv);

f. By revising paragraph (c) introductory text, the first and third sentences of paragraph (c)(1)(iii) introductory text, and paragraph (c)(2)(ii);

g. By removing paragraph (d)(2) and by redesignating paragraph (d)(1) as paragraph (d) and revising the first sentence of paragraph (d);

h. By removing paragraph (e)(2) and by redesignating paragraph (e)(1) as paragraph (e);

i. By revising paragraph (f);

j. By redesignating paragraph (g) through paragraph (k) as paragraph (h) through paragraph (l); and revising newly redesignated (i);

k. By adding new paragraph (g) to read as follows:

§ 314.80 Postmarketing reporting of adverse drug experiences.

(a) * * *

Individual case safety report (ICSR). A description of an adverse drug experience related to an individual patient or subject.

* * * * *

(c) *Reporting requirements.* The applicant must submit to FDA adverse drug experience information as described in this section. Except as provided in paragraph (g)(2) of this section, these reports must be submitted to the agency in electronic format as described in paragraph (g)(1) of this section.

(1) * * *

(iii) *Submission of reports.* The requirements of paragraphs (c)(1)(i) and (c)(1)(ii) of this section, concerning the submission of postmarketing 15-day Alert reports, also apply to any person other than the applicant whose name appears on the label of an approved drug product as a manufacturer, packer, or distributor (nonapplicant). * * * If a nonapplicant elects to submit adverse drug experience reports to the applicant rather than to FDA, the nonapplicant must submit, by any appropriate means, each report to the applicant within 5 calendar days of initial receipt of the information by the nonapplicant, and the applicant must then comply with the requirements of this section. * * *

* * * * *

(2) * * *

(ii) Each periodic report is required to contain:

(A) *Descriptive information.* (1) A narrative summary and analysis of the information in the report;

(2) An analysis of the 15-day Alert reports submitted during the reporting interval (all 15-day Alert reports being appropriately referenced by the applicant's patient identification code, adverse reaction term(s), and date of submission to FDA);

(3) A history of actions taken since the last report because of adverse drug experiences (for example, labeling changes or studies initiated); and

(4) An index consisting of a line listing of the applicant's patient identification code, and adverse reaction term(s) for all ICSRs submitted under paragraph (c)(2)(ii)(B) of this section.

(B) *ICSRs for serious, expected and nonserious adverse drug experiences.*

An ICSR for each adverse drug experience not reported under paragraph (c)(1)(i) of this section (all serious, expected and nonserious

adverse drug experiences). All such ICSRs must be submitted to FDA (either individually or in one or more batches) within the timeframe specified in paragraph (c)(2)(i) of this section. ICSRs must only be submitted to FDA once.

* * * * *

(d) *Scientific literature.* A 15-day Alert report based on information in the scientific literature must be accompanied by a copy of the published article. * * *

* * * * *

(f) *Information reported on ICSRs.*

ICSRs include the following information:

(1) *Patient information.*

(i) Patient identification code;

(ii) Patient age at the time of adverse drug experience, or date of birth;

(iii) Patient gender; and

(iv) Patient weight.

(2) *Adverse drug experience.*

(i) Outcome attributed to adverse drug experience;

(ii) Date of adverse drug experience;

(iii) Date of report;

(iv) Description of adverse drug experience;

(v) Description of relevant tests, including dates and laboratory data; and

(vi) Other relevant patient history, including preexisting medical conditions.

(3) *Suspect medication(s).*

(i) Name;

(ii) Dose, frequency, and route used;

(iii) Therapy dates;

(iv) Diagnosis for use (indication);

(v) State whether adverse drug experience abated after drug use stopped or dose reduced;

(vi) Lot number;

(vii) Expiration date;

(viii) State whether adverse drug experience reappeared after reintroduction of drug;

(ix) NDC number; and

(x) Concomitant medical products and therapy dates.

(4) *Initial reporter information.*

(i) Name, address, and phone number;

(ii) Whether the initial reporter is a health professional;

(iii) Occupation; and

(iv) Whether the initial reporter also sent a copy of the report to FDA.

(5) *Applicant information.*

(i) Applicant name and contact office address;

(ii) Telephone number;

(iii) Report source(s) (e.g., literature, study);

(iv) Date received by applicant;

(v) Application number and type;

(vi) Type of report being submitted (e.g., 15-day, periodic, followup);

(vii) Adverse drug experience term(s); and

(viii) Manufacturer report number.

(g) *Electronic format for submissions.*

(1) *Safety report submissions, including ICSRs.* Any attached documentation, and the descriptive information in periodic reports, must be in an electronic format that FDA can process, review, and archive. FDA will periodically issue guidance on how to provide the electronic submission (e.g., method of transmission, media, file formats, preparation and organization of files).

(2) *Waivers.* An applicant or nonapplicant may request, in writing, a temporary waiver of the requirements in paragraph (g)(1) of this section. These waivers will be granted on a limited basis for good cause shown. If the agency grants the waiver, the applicant or nonapplicant must submit reports required under this section on paper within the required time periods in a form that FDA can process, review, and archive. FDA will issue guidance on how to provide the paper submission. Procedures for how to request waivers of this requirement will be set forth in guidance.

* * * * *

(i) *Patient privacy.* An applicant should not include in reports under this section the names and addresses of individual patients; instead, the applicant should assign a unique code to each report. The preferred methodology for determining the identification code will be set forth in guidance. The applicant should include the name of the reporter from whom the information was received, unless the reporter is the patient. The names of patients, health care professionals, hospitals, and geographical identifiers in adverse drug experience reports are not releasable to the public under FDA's public information regulations in part 20 of this chapter.

* * * * *

5. Section 314.98 is revised to read as follows:

§ 314.98 Postmarketing reports.

(a) Each applicant having an approved abbreviated new drug application under § 314.94 that is effective must comply with the requirements of § 314.80 regarding the reporting and recordkeeping of adverse drug experiences.

(b) Each applicant must make the reports required under § 314.81 and section 505(k) of the act for each of its approved abbreviated applications.

PART 600—BIOLOGICAL PRODUCTS: GENERAL

6. The authority citation for 21 CFR part 600 continues in part 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.

* * * * *

7. Section 600.80 is amended:
a. By removing the word "shall" each time it appears and by adding in its place the word "must";

b. By removing the phrase "licensed manufacturer" each time it appears and by adding in its place the word "applicant";

c. In paragraph (a) by alphabetically adding the definition for "Individual case safety report (ICSR)";

d. In paragraph (c)(1)(i) by removing the phrase "in no case later than 15 calendar days of" and by adding in its place the phrase "no later than 15 calendar days from";

e. In paragraph (c)(1)(ii) by removing the last sentence;

f. By removing paragraph (c)(1)(iv);

g. By revising paragraph (c) introductory text, the first and third sentences of paragraph (c)(1)(iii) introductory text, and paragraph (c)(2)(ii);

h. By removing paragraph (d)(2) and by redesignating paragraph (d)(1) as paragraph (d) and revising the first sentence of paragraph (d);

i. By removing paragraph (e)(2) and by redesignating paragraph (e)(1) as paragraph (e);

j. By revising paragraph (f);

k. By redesignating paragraph (g) through paragraph (l) as paragraph (h) through paragraph (m) and by revising newly redesignated paragraph (i); and

l. By adding new paragraph (g) to read as follows:

§ 600.80 Postmarketing reporting of adverse experiences.

(a) * * *
Individual case safety report (ICSR). A description of an adverse experience related to an individual patient or subject.

* * * * *

(c) *Reporting requirements.* The applicant must submit to FDA postmarketing 15-day Alert reports and periodic safety reports pertaining to its biological product as described in this section. These reports must be submitted to the agency in electronic format as described in paragraph (g)(1) of this section, except as provided in paragraph (g)(2) of this section.

(1) * * *

(iii) *Submission of reports.* The requirements of paragraphs (c)(1)(i) and

(c)(1)(ii) of this section, concerning the submission of postmarketing 15-day Alert reports, also apply to any person whose name appears on the label of a licensed biological product as a manufacturer, packer, distributor, shared manufacturer, joint manufacturer, or any other participant involved in divided manufacturing.

* * * If a person elects to submit adverse experience reports to the applicant rather than to FDA, the person must submit, by any appropriate means, each report to the applicant within 5 calendar days of initial receipt of the information by the person, and the applicant must then comply with the requirements of this section. * * *

* * * * *

(2) * * *

(ii) Each periodic report is required to contain:

(A) *Descriptive information.* (1) A narrative summary and analysis of the information in the report;

(2) An analysis of the 15-day Alert reports submitted during the reporting interval (all 15-day Alert reports being appropriately referenced by the applicant's patient identification code, adverse reaction term(s), and date of submission to FDA);

(3) A history of actions taken since the last report because of adverse experiences (for example, labeling changes or studies initiated);

(4) An index consisting of a line listing of the applicant's patient identification code, and adverse reaction term(s) for all ICSRs submitted under paragraph (c)(2)(ii)(B) of this section; and

(B) *ICSRs for serious, expected and nonserious adverse experiences.* An ICSR for each adverse experience not reported under paragraph (c)(1)(i) of this section (all serious, expected and nonserious adverse experiences). All such ICSRs must be submitted to FDA (either individually or in one or more batches) within the timeframe specified in paragraph (c)(2)(i) of this section. ICSRs must only be submitted to FDA once.

* * * * *

(d) *Scientific literature.* A 15-day Alert report based on information in the scientific literature must be accompanied by a copy of the published article. * * *

* * * * *

(f) *Information to be reported on ICSRs.* ICSRs include the following information:

(1) *Patient information.*

(i) Patient identification code;

(ii) Patient age at the time of adverse experience, or date of birth;

- (iii) Patient gender; and
- (iv) Patient weight.
- (2) *Adverse experience.*
- (i) Outcome attributed to adverse experience;
- (ii) Date of adverse experience;
- (iii) Date of report;
- (iv) Description of adverse experience;
- (v) Description of relevant tests, including dates and laboratory data; and
- (vi) Other relevant patient history, including preexisting medical conditions.
- (3) *Suspect medical product(s).*
- (i) Name;
- (ii) Dose, frequency, and route used;
- (iii) Therapy dates;
- (iv) Diagnosis for use (indication);
- (v) State whether adverse experience abated after product use stopped or dose reduced;
- (vi) Lot number;
- (vii) Expiration date;
- (viii) State whether adverse experience reappeared after reintroduction of the product;
- (ix) NDC number, or other unique identifier; and
- (x) Concomitant medical products and therapy dates.
- (4) *Initial reporter information.*
- (i) Name, address, and phone number;
- (ii) Whether the initial reporter is a health professional;
- (iii) Occupation; and
- (iv) Whether the initial reporter also sent a copy of the report to FDA.
- (5) *Applicant information.*
- (i) Applicant name and contact office address;
- (ii) Telephone number;
- (iii) Report source(s) (e.g., literature, study);
- (iv) Date received by applicant;
- (v) Application number and type;
- (vi) Type of report being submitted (e.g., 15-day, periodic, followup);
- (vii) Adverse experience term(s); and
- (viii) Manufacturer report number.
- (g) *Electronic format for submissions.*

(1) Safety report submissions, including ICSRs and any attached documentation and the descriptive information in periodic reports, must be in an electronic format that FDA can process, review, and archive. FDA will periodically issue guidance on how to provide the electronic submission (e.g., method of transmission, media, file formats, preparation and organization of files).

(2) *Waivers.* Persons subject to the requirements of paragraph (c) of this section may request, in writing, a temporary waiver of the requirements in paragraph (g)(1) of this section. These waivers will be granted on a limited basis for good cause shown. If the agency grants the waiver, the person

must submit reports required under this section on paper within the required time periods in a form that FDA can process, review, and archive. FDA will issue guidance on how to provide the paper submission. Requests for waivers must be submitted in accordance with § 600.90.

* * * * *

(i) *Patient privacy.* For nonvaccine biological products, an applicant should not include in reports under this section the names and addresses of individual patients; instead, the applicant should assign a unique code to each report. The preferred methodology for determining the identification code will be set forth in guidance. The applicant should include the name of the reporter from whom the information was received, unless the reporter is the patient. The names of patients, health care professionals, hospitals, and geographical identifiers in adverse experience reports are not releasable to the public under FDA's public information regulations in part 20 of this chapter. For vaccine adverse experience 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.

* * * * *

8. Section § 600.81 is amended:

a. By removing the phrase "licensed manufacturer" each time it appears and by adding in its place the word "applicant";

b. By designating the existing text as paragraph (a) and by adding a new heading for paragraph (a); and

c. By adding new paragraph (b) to read as follows:

§ 600.81 Distribution reports.

(a) Reporting requirements. * * *

(b)(1) *Electronic format.* Except as provided for in paragraph (b)(2) of this section, the distribution reports required under paragraph (a) of this section must be submitted to the agency in electronic format in a form that FDA can process, review, and archive. FDA will periodically issue guidance on how to provide the electronic submission (e.g., method of transmission, media, file formats, preparation and organization of files).

(2) *Waivers.* An applicant may request, in writing, a temporary waiver of the requirements in paragraph (b)(1) of this section. These waivers will be

granted on a limited basis for good cause shown. If the agency grants the waiver, the applicant must submit reports required under this section on paper within the required time period in a form that FDA can process, review, and archive. FDA will issue guidance on how to provide the paper submission. Requests for waivers must be submitted in accordance with § 600.90.

§ 600.90 [Amended]

9. Section 600.90 is amended by removing the phrase "licensed manufacturer" each time it appears and by adding in its place the word "applicant".

Dated: August 5, 2009.

Jeffrey Shuren,

Associate Commissioner for Policy and Planning.

[FR Doc. E9-19682 Filed 8-20-09; 8:45 am]

BILLING CODE 4160-01-S

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 803

[Docket No. FDA-2008-N-0393]

RIN 0910-AF86

Medical Device Reporting: Electronic Submission Requirements

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is proposing to amend its postmarket medical device reporting regulation to require that manufacturers, importers, and user facilities submit mandatory reports of individual medical device adverse events, also known as medical device reports (MDRs) to the agency in an electronic format that FDA can process, review, and archive. Mandatory electronic reporting would improve the agency's process for collecting and analyzing postmarket medical device adverse event information. The proposed regulatory changes would provide the agency with a more efficient data entry process that would allow for timely access to medical device adverse event information and identification of emerging public health issues. Elsewhere in this issue of the **Federal Register**, FDA is also announcing a draft guidance document that provides recommendations on how to prepare and submit electronic MDRs to FDA in a manner that satisfies the requirements