existing infant formula are limited to changing the type of packaging of an existing infant formula (e.g., changing from metal cans to plastic pouches); or

(2) The manufacturer requests an exemption and provides assurances, as required under § 106.121(h), that demonstrate that the change made by the manufacturer to an existing formula does not affect the bioavailability of the protein.

(3) The manufacturer requests an exemption and provides assurances, as required under § 106.121(i), that demonstrate that an alternative method to the PER that is based on sound scientific principles is available to demonstrate that the formula supports the quality factor for the biological quality of the protein.

* * * * *

■ 9. In § 106.100, revise paragraphs (f)(4), (k)(5)(ii), (m), and (o) to read as follows:

§ 106.100 Records.

* * * * *

(f) * * *

(4) Records, in accordance with § 106.30(f), on equipment cleaning, sanitizing, and maintenance that show the date and time of such cleaning, sanitizing, and maintenance and the production aggregate number of each infant formula processed between equipment startup and shutdown for cleaning, sanitizing, and maintenance. The person performing and checking the cleaning, sanitizing, and maintenance shall date and sign or initial the record indicating that the work was performed.

* * * * *

(k) * * *

(5) * * *

(ii) The production aggregate number;

* * * * *

(m) A manufacturer shall maintain all records required under this part in a manner that ensures that both the manufacturer and the Food and Drug Administration can be provided with access to such records within 24 hours. The manufacturer may maintain the records required under this part as original records, as true copies such as photocopies, microfilm, microfiche, or other accurate reproductions of the original records, or as electronic records. Where reduction techniques, such as microfilming, are used, suitable reader and photocopying equipment shall be readily available. All electronic records maintained under this part shall comply with part 11 of this chapter.

* * * * *

(o) The manufacturer shall maintain quality control records that contain sufficient information to permit a public health evaluation of any production aggregate of infant formula.

* * * * *

■ 10. In § 106.120, add paragraph (b)(7) to read as follows:

§ 106.120 New infant formula submission.

* * * * *

(b) * * *

* * * * *

(7) If the manufacturer is requesting an exemption under § 106.91(b)(1)(ii), the manufacturer shall include the scientific evidence that the manufacturer is relying on to demonstrate that the stability of the new infant formula will likely not differ from the stability of formulas with similar composition, processing, and packaging for which there are extensive stability data.

* * * * *

■ 11. In § 106.121 revise paragraphs (d) and (i) and add paragraph (j) to read as follows:

§ 106.121 Quality factor assurances for infant formulas.

* * * * *

(d) If the manufacturer is requesting an exemption under § 106.96(c)(2)(ii), the manufacturer shall include a detailed description of the change and an explanation of why the change made by the manufacturer to an existing infant formula does not the affect the ability of the formula to support normal physical growth.

* * * * *

(i) If the manufacturer is requesting an exemption under § 106.96(g)(3), the manufacturer shall include a detailed explanation of the alternative method, an explanation of why the method is based on sound scientific principles, and the data that demonstrate that the quality factor for the biological quality of the protein has been met.

(j) A statement certifying that the manufacturer has collected and considered all information and data concerning the ability of the infant formula to meet the requirements for quality factors and that the manufacturer is not aware of any information or data that would show that the formula does not meet the requirements for quality factors.

Dated: June 4, 2014.

Leslie Kux,

Assistant Commissioner for Policy.

[FR Doc. 2014–13384 Filed 6–9–14; 8:45 am]

BILLING CODE 4160–01–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 310, 314, 329, and 600

[Docket No. FDA–2008–N–0334]

RIN 9010–AF96

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

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA or we) is amending 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 change will 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 amendments will be a key element in harmonizing FDA's postmarketing safety reporting regulations with international standards for the electronic submission of safety information.

DATES: This rule is effective June 10, 2015.

FOR FURTHER INFORMATION CONTACT: *For information concerning human drug products:* Jean Chung, Center for Drug Evaluation and Research (CDER), Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 71, Rm. 7268, Silver Spring, MD 20993–0002, 240–402–7911.

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

SUPPLEMENTARY INFORMATION:

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I. Introduction

In the **Federal Register** of August 21, 2009 (74 FR 42184), FDA published a proposed rule to require that persons subject to mandatory postmarketing safety reporting requirements for human drug or biological products submit safety reports in an electronic format that the Agency can process, review, and archive.

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 experiences [1] from safety reports submitted to the Agency. For nearly 35 years, FDA has received these postmarketing safety reports on paper. Since 2001, many companies have voluntarily submitted reports for drug and nonvaccine biological products to the Agency in electronic format. Data from both the electronic and paper reports are entered into the FDA Adverse Event Reporting System (FAERS) database. FAERS is a computerized information database designed to support FDA's postmarketing safety surveillance program for drug and nonvaccine biological products. The FAERS database is used to store and analyze data received in postmarketing safety reports. Safety reporting data submitted on paper is first converted into an electronic format before being entered into FAERS.[2] In September 2012, the FAERS database replaced the previously used Adverse Event Reporting System (AERS) database described in the preamble to the proposed rule (74 FR 42184 at 42185). The transition to the FAERS database has been an important step in improving FDA's postmarketing surveillance capabilities. FAERS supports greater functionality and more sophisticated pharmacovigilance tools that enhance FDA's ability to analyze safety information.

The proposed rule proposed that use of an electronic format be mandatory for the submission of all required postmarketing safety reports for human drug and biological products, including vaccines,[3] a change to improve the Agency's systems for collecting and analyzing these reports.

A. The Proposed Rule

In the preamble to the proposed rule (74 FR 42184 at 42187 to 42189), we set forth in detail the rationale for requiring electronic submission of postmarketing safety reports. Receiving postmarketing safety reports in electronic format will expedite access to safety information and facilitate international harmonization and exchange of this information. This, in turn, will lead to more efficient reviews of safety data and will 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 will recognize a significant cost savings by converting the safety reporting system from a paper submission process to a predominantly all-electronic system that will increase the accuracy of information and reduce the need for manual data entry. We also believe this change will benefit industry by eliminating time and costs associated with submitting paper reports.

In the proposed rule, FDA proposed revising §§ 310.305, 314.80, 314.98, and 600.80 (21 CFR 310.305, 314.80, 314.98, and 600.80) to require that manufacturers, packers, and distributors, and applicants 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, submit postmarketing safety reports (i.e., individual case safety reports (ICSRs) and any ICSR attachments) to the Agency in an electronic format that FDA can process, review, and archive. We stated that the proposal would apply to all postmarketing safety reports 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 implemented in the future. (The preamble to the proposed rule (74 FR 42184 at 42185 to 42186) describes current postmarketing safety reporting requirements.) We also proposed revising § 600.81 (21 CFR 600.81) to require the electronic submission of biological lot distribution reports.

The preamble to the proposed rule (74 FR 42184 at 42186 to 42187) also discussed the Dietary Supplement and Nonprescription Drug Consumer Protection Act (Public Law 109–462), enacted on December 22, 2006, which amended the Federal Food, Drug, and Cosmetic Act (the FD&C Act) to create a new section 760 (21 U.S.C. 379aa), entitled ''Serious Adverse Event Reporting for Nonprescription Drugs.'' As noted in the preamble, section 760 of the FD&C Act requires manufacturers, packers, or distributors whose name appears on the label of nonprescription (over-the-counter or OTC) human drug products marketed *without* an approved application to report to FDA serious adverse events associated with their products. It does not apply to OTC drug products marketed under applications approved under section 505 of the FD&C Act (21 U.S.C. 355), which are subject to the reporting requirements under § 314.80, as are all other drugs marketed under approved NDAs or ANDAs.[4] The requirement went into effect in December 2007, and to assist entities in complying with the requirements, FDA issued a guidance for industry entitled ''Postmarketing Adverse Event Reporting for Nonprescription Human Drug Products Marketed Without an Approved Application'' (available on

[1] For purposes of this preamble, the term ''adverse drug experience'' includes an ''adverse experience'' associated with use of a human drug or biological product.

[2] Additional information regarding the FAERS database may be found at *http://www.fda.gov/cder/aers/default.htm*.

[3] Data from postmarketing safety reports for vaccines is entered into the Vaccine Adverse Event Reporting System (VAERS). The VAERS database is used to store and analyze data received in postmarketing safety reports for vaccines.

[4] Section 760 of the FD&C Act provides for mandatory safety reporting for nonprescription human drug products not subject to NDAs or ANDAs. Accordingly, the requirements apply to all OTC drug products marketed without an approved application, including those marketed under the OTC Drug Monograph Review process (whether or not subject to a final monograph), those marketed outside the monograph system, and including those that have been discontinued from marketing but for which a report of an adverse event was received. These reporting requirements became effective December 22, 2007.

FDA's Web site at *http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm).* In the preamble to the proposed rule, we requested comment on whether to require the electronic submission of postmarketing safety reports required by section 760 of the FD&C Act (referred to in this document as section 760 reports). We noted that our decision would be informed by public comments received and our experience with the submission of these reports to date.

The proposed rule stated that FDA would periodically issue guidance on how to provide the electronic submissions (e.g., method of transmission, media, file formats, preparation, and organization of files). Currently, 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 (EU), Japan, and the United States. The proposal reaffirmed our intention to continue to rely on ICH standards while also providing other options for providing electronic submissions to FDA.

In the preamble to the proposed rule, we explained that applicants, manufacturers, packers, and distributors had been voluntarily submitting postmarketing safety reports for drugs and nonvaccine biological products in electronic format by sending the reports to FDA either through FDA's Electronic Submission Gateway (ESG) or on physical media (e.g., CD–ROM (sent by mail).[5] The ESG is the central transmission point for sending information electronically to FDA. Among other things, the ESG allows ICH-compatible postmarketing safety report submissions to be transmitted directly from the company's database to FDA.[6] The direct database-to-database submissions may include ICSRs, any ICSR attachments, and descriptive information. Once received through the ESG, the ICSRs for drug and nonvaccine biological products are downloaded into the FAERS database. FDA has encouraged electronic submission of ICSRs because it is a cost-effective and efficient alternative to paper-based reporting, particularly for companies submitting large numbers of ICSRs. In addition, electronic submission of ICSRs enhances global pharmacovigilance by facilitating electronic transmission and exchange of appropriate information from ICSRs among regulatory bodies and regulated entities through use of common data elements and transmission standards.

In the preamble to the proposed rule, we also explained that we are developing a ''Web-based submission portal'' to collect and process safety information for FDA-regulated products. We anticipated that the Web-based submission portal would allow the secure electronic submission of postmarketing ICSRs directly into FDA's FAERS database once information was entered into a ''Web-based electronic form.'' We stated that the Web-based submission portal would allow submission of ICSRs consistent with ICH standards and could be used as an alternative method for reporting adverse drug experiences to FDA electronically. We noted that the Web-based system would be particularly useful for entities that submit a small number of safety reports because it would create a simpler and more efficient mechanism for reporting that would not require an internal database that is compatible with the ICH-based direct transmission system. (See section II.A for further discussion of the Web-based submission portal.)

Because in certain rare circumstances electronic submission of safety reports may not be feasible, we proposed (in §§ 310.305(e)(2), 314.80(g)(2), and 600.80(g)(2)) to allow for the submission of requests for a temporary waiver from the electronic format requirement and stated that waivers would be granted on a limited basis for good cause shown. We requested comments on circumstances under which a waiver should be granted. We stated that guidance would be issued describing the procedures for submitting a waiver request. Elsewhere in this issue of the **Federal Register**, we are announcing the availability of a draft guidance entitled ''Providing Submissions in Electronic Format—Postmarketing Safety Reports'' (the postmarketing safety reports guidance) (available on FDA's Web site at *http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm*). It is intended to assist persons required to submit postmarketing safety reports in complying with the final rule. In addition, the draft guidance addresses procedures for submitting waiver requests and other information.

We proposed to delete the specific references to paper reporting forms in §§ 310.305, 314.80, and 600.80. Because the paper reporting forms would no longer be used, we proposed to add a list of the reportable elements to proposed §§ 310.305(d), 314.80(f), and 600.80(f). The list of reportable elements in the proposed rule was derived from the elements included in Form FDA 3500A, the paper reporting form. Moreover, the obligation to provide all applicable information described in the proposed rule would be the same as the obligation to complete Form FDA 3500A and VAERS–1. To facilitate the shift away from the paper reporting forms, we also proposed to adopt a generic term for the safety reporting vehicle: Individual case safety report (ICSR). Proposed §§ 310.305(b) and 314.80(a) define an ICSR as ''a description of an adverse drug experience related to an individual patient or subject.'' Proposed § 600.80(a) defines ICSR as ''a description of an adverse experience related to an individual patient or subject.''

B. Changes to the Proposed Rule

We received seven submissions containing comments on the proposed rule. Several commenters expressed support for requiring electronic submission of postmarketing safety reports, agreeing that it would help FDA to more rapidly review safety reports and identify emerging safety issues. Two commenters also expressed support for requiring the electronic submission of safety reports required by section 760 of the FD&C Act; no commenters opposed this requirement for the section 760 reports. Commenters also requested clarification of certain terms and requirements in the proposed rule. We address all of the comments in greater detail in section III.

After considering the comments and based on our experience with postmarketing safety reporting, we have concluded that certain revisions to the proposed rule are appropriate. However, we note that the provisions applicable to safety reporting under §§ 310.305, 314.80, and 600.80 are largely unchanged from the proposed rule.

We have concluded that the electronic submission requirement should extend to safety reports required by section 760 of the FD&C Act. Therefore, the final rule adds part 329 (21 CFR part 329), entitled ''Nonprescription Human Drug Products Subject to Section 760 of the Federal Food, Drug, and Cosmetic Act'' to chapter 21 of the Code of Federal

[5] FDA expects that, in the future, all electronic submissions to the Agency will be sent through the ESG and that use of physical media (e.g., CD–ROM) for such submissions will be phased out.

[6] ICH data elements for postmarketing safety reports are available at *http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM129399.pdf*.

Regulations to address the safety reporting requirements of section 760 of the FD&C Act described in section I.A. This addition responds to the two comments received on this issue, both of which supported requiring the electronic submission of section 760 reports. It also reflects FDA's determination that the electronic submission requirement should extend to these safety reports in furtherance of FDA's goal to more quickly review postmarketing safety reports and identify emerging safety issues.

The final rule adds new § 329.100 to require the electronic submission of section 760 reports. Section 329.100(a) states that safety reports required by section 760 of the FD&C Act must be submitted to FDA in electronic format. Section 329.100(b) explains that for purposes of safety reporting under section 760, an ICSR constitutes the ''MedWatch Form'' (the common name for Form FDA 3500A) required to be submitted in section 760(d) of the FD&C Act, and sets forth the elements that are reported in an ICSR under section 760. As noted previously in this document and in the preamble to the proposed rule, we have adopted the term ''individual case safety report'' (ICSR) because we will no longer be using the paper reporting forms for mandatory postmarketing safety reporting. New § 329.100(c)(1) states that the submissions must be in an electronic format that FDA can process, review, and archive; § 329.100(c)(2) provides for a good-cause waiver; and § 329.100(d) addresses patient privacy. All of these provisions are analogous to the provisions in this final rule for reports submitted under §§ 310.305, 314.80, and 600.80.

The final rule revises the proposed provisions entitled ''Patient privacy'' (in final §§ 310.305(f), 314.80(i), and 600.80(j)) to state, ''the applicant should assign a unique code for identification of the patient.'' [7] This addresses a comment expressing concern that the proposed rule was confusing because it used two different terms to refer to the code that must be assigned to protect patient privacy. Section 329.100(d) uses the revised language.

On our own initiative, we have made revisions that are described as follows. The final rule adds a definition for the term ''ICSR attachments'' to §§ 310.305(b), 314.80(a), and 600.80(a). In §§ 310.305(b) and 314.80(a), ICSR attachments are defined as ''documents related to the adverse drug experience described in an ICSR, such as medical records, hospital discharge summaries, or other documentation.'' In § 600.80(a), ICSR attachments are defined as ''documents related to the adverse experience described in an ICSR, such as medical records, hospital discharge summaries, or other documentation.''

The final rule revises the proposed provisions addressing waivers in proposed §§ 310.305(e)(2), 314.80(g)(2), and 600.80(g)(2). The final rule deletes the statement that if the Agency grants a waiver, the person who requested the waiver must submit the required reports on paper within the required time periods and that FDA intends to issue guidance on how to provide the paper submission. This statement has been deleted so that the rule does not specify that safety reports that cannot be submitted in electronic format must be submitted on paper. We recognize that alternate formats for safety reports, other than paper, such as email or fax, may be appropriate when a waiver of the electronic submission requirement is granted. We will specify an acceptable alternate format at the time the waiver is granted. The final rule also modifies the language indicating that procedures for how to request waivers will be set forth in guidance. The proposed rule stated, ''Procedures for how to request waivers of this requirement will be set forth in guidance.'' The final rule states, ''FDA will issue guidance on requesting a waiver of the requirements [for electronic submission].'' We have made this change to indicate that the guidance addressing waivers may include information on other aspects of the waiver provision, such as circumstances under which FDA may grant waivers, not just the procedures for how to request waivers. (The waiver provision for biological products has been finalized in § 600.80(h)(2).) Section 329.100(c)(2), applicable to section 760 reports for nonprescription products marketed without an approved application, contains this revised language on waivers. It is important to note that the waiver referred to in the final rule (as in the proposed rule) pertains only to the electronic format requirements. It is not a waiver from the underlying safety reporting requirement.

On our own initiative, we have made additional changes to the provisions addressing patient privacy. The proposed provisions entitled ''Patient privacy'' (in proposed §§ 310.305(f), 314.80(i), and 600.80(i)) state that the preferred methodology for determining the identification code will be set forth in guidance. FDA does not believe that it is necessary to identify specific elements in the final rule for which we will be providing technical guidance or specifications. FDA currently provides and will continue to provide technical guidance and specifications for many different aspects of electronic ICSR submission. Accordingly, we are deleting that language from final §§ 310.305(f), 314.80(i), and 600.80(j). However, for drug and nonvaccine biological products, we recommend that no identifying information, such as initials or birthdate, be used as part of the patient identification code. At the same time, under new § 600.80(g), ICSRs for vaccine products will continue to include the patient's name.

In the patient privacy provisions, we proposed that the name of the reporter not be included when the reporter is also the patient. The proposed provision stated that the submitter should include the name of the reporter from whom the information was received, unless the reporter is the patient. FDA is not finalizing the proposal because we have concluded that those submitting mandatory safety reports should include the name of the reporter (in the reporter section of the ICSR), even when the reporter is the patient. It is important for FDA to have the name of the reporter so that we may contact the reporter, if necessary, to obtain followup information about the adverse event reported. To make clear that the name of the reporter should be provided (in the initial reporter information section of the ICSR), even when the reporter is the patient, we are amending the patient privacy provisions in the final rule to state, ''the [submitter] should include the name of the reporter from whom the information was received as part of the initial reporter information, even when the reporter is the patient'' (§§ 310.305(f), 314.80(i), 329.100(d), and 600.80(j)). FDA regulations prohibit the release of the names of patients, health care professionals, hospitals, and geographical identifiers in adverse event reports to the public, so it is unlikely that the patient's privacy will be compromised if the patient's name is provided in situations where the patient is the reporter.

The final rule modifies the language in proposed § 600.81(b)(1) describing the electronic format requirement for biological product lot distribution reports so that it reflects the language used in analogous provisions (§§ 310.305(e)(1), 314.80(g)(1), 329.100(c)(1), and 600.80(h)(1)).

As described later in this section, the final rule also makes some revisions to the proposed provisions that set forth the reportable elements included in an ICSR. Changes to the language

[7] The revised language in § 600.80(j) applies only to nonvaccine biological products. ICSRs for vaccines should not use a patient identification code but should continue to include the patient's name (§ 600.80(g)).

describing certain elements, including the addition of descriptive phrases, have been made to clarify to what information those elements refer. The final rule also adds a new § 600.80(g) and adds certain elements to proposed §§ 310.305(d), 314.80(f), and 600.80(f) to more accurately describe the information currently reported on the VAERS–1 form and Form FDA 3500A. Accordingly, §§ 310.305(d), 314.80(f), 329.100(b), and 600.80(f) list ICSR elements, derived from Form FDA 3500A, for drug and nonvaccine biological products. Section 600.80(g) in the final rule lists ICSR elements for vaccine products derived from the VAERS–1 form.

The new § 600.80(g) has been added to the final rule to capture the information reported on the VAERS–1 form that was inadvertently omitted from the proposed rule. Section 600.80(f) applies only to nonvaccine biological products. Section 600.80(g) in the final rule lists ICSR elements for vaccines that are derived from the VAERS–1 form. The list of elements in § 600.80(g) (for vaccine products) is largely the same as the list of elements for nonvaccine biological products, but there are some variations, including certain additional elements applicable only to safety reporting for vaccine products. Reporting elements that have been included for vaccine ICSRs that are not applicable to ICSRs for nonvaccine biological products include, among others, patient name (in place of patient identification code), birth weight for children under 5, time of adverse experience, illness at the time of vaccination, anatomical site of vaccination, number of previous vaccine doses, time of vaccination, other vaccine(s) administered in the 4 weeks before the vaccination date, name of the person who administered the vaccine, and name of the responsible physician at the facility where the vaccine was administered. This information is currently reported on the VAERS–1 form and is important for FDA to evaluate adverse experiences associated with the administration of vaccines. In addition, because § 600.80(g) does not include patient identification code as a reporting element, FDA has revised § 600.80(c)(2)(ii)(A)(2) and (A)(4), which describe how to reference and index ICSRs in periodic reports, to note that ICSRs for nonvaccine biological products should be referenced and indexed by patient identification code, whereas ICSRs for vaccines should be referenced and indexed by unique case identification number.

The final rule removes from proposed §§ 310.305(d), 314.80(f), and 600.80(f) the element requiring applicants to report information on whether the initial reporter also sent a copy of the report to FDA. FDA does not often use that information to identify duplicate reports, and including that information is not consistent with international electronic reporting standards. The final rule adds to all sections that contain reporting elements the following elements to be reported: (1) Whether the report is a 15-day ''Alert report'' and (2) whether the ICSR is an initial report or a followup report. These two elements replace the element requiring the type of report (e.g., 15-day, periodic, followup). We believe that it is clearer to represent this information with two separate elements. The final rule adds to §§ 310.305(d), 314.80(f), and 600.80(f) the element requiring information on whether the product is a combination product as defined under § 3.2(e) (21 CFR 3.2(e)).[8] The final rule adds to §§ 310.305(d), 314.80(f), and 600.80(f) the element ''whether the product is a prescription or nonprescription product.'' Section 329.100(b) also lists ''whether the product is a prescription or nonprescription product'' as an element to be included in an ICSR. Even though § 310.305 only applies to prescription products and § 329.100 only applies to nonprescription products, for consistency, we use the same language in all sections to describe the information to be provided. The final rule removes from proposed § 310.305(d), ''Basis for marketing if nonapplication product'' because we are able to obtain that information based on the status of the drug as a prescription product and whether a drug application number is provided. The final rule adds to the ICSR elements for each product type (e.g., drug, nonvaccine biological product, vaccine) ''unique case identification number,'' which must be the same in the initial report and any subsequent followup reports. The unique case identification number is different from the ''unique code [used] for identification of the patient.'' The ''unique case identification number'' replaces the ''Manufacturer Report Number'' used on Form FDA 3500A and VAERS–1. Using a unique case identification number (that is the same in the initial ICSR and any followup reports) allows FDA to link the initial ICSR with any followup reports in the FAERS or VAERS database. This will allow FDA to track an individual case over its life cycle.

[8] For purposes of postmarketing safety reporting, combination product, under § 3.2(e), includes: (1) A product comprised of two or more regulated components, i.e., drug/device, biological product/device, drug/biological product, or drug/device/biological product, that are physically, chemically, or otherwise combined or mixed and produced as a single entity and (2) two or more separate products packaged together in a single package or as a unit and comprised of drug and device products, device and biological products, or biological and drug products.

II. Summary of the Final Rule

A. Electronic Submission of Postmarketing Safety Reports

The final rule revises current §§ 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. As addressed in section I.B of this document, the final rule also adds part 329 to address safety reports required by section 760 of the FD&C Act. Section 329.100 requires that reports required to be submitted to the Agency under section 760 of the FD&C Act be submitted in an electronic format that FDA can process, review, and archive.

Under the final rule, the following reports must be submitted to FDA in an electronic format: Postmarketing 15-day Alert report ICSRs and any ICSR attachments; periodic adverse (drug) experience reports (including the ICSRs, any ICSR attachments, and the descriptive information portion); and section 760 reports. A separate ICSR is to be submitted for each individual patient report of an adverse drug experience, just as separate paper forms have been submitted for each individual patient report of an adverse drug experience. Information on the formats the Agency is able to process, review, and archive is described in FDA guidance and associated technical specifications documents available on FDA's Web site.

For marketed products with an approved application, manufacturers, packers, or distributors that do not hold the application 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 reports directly to FDA, they are required to do so in electronic format. If they choose to report to the applicant, they may submit the report in any format acceptable to the reporter and applicant. The applicant, however, is required to use electronic reporting when it subsequently reports the information to FDA. Similarly, for marketed

prescription drug products without an approved application, initial safety reports submitted to the manufacturer by packers and distributors under § 310.305 may be sent in any format agreeable to the reporter and the manufacturer, but all safety reports submitted to FDA must be in electronic format. Under section 760 of the FD&C Act, a retailer whose name appears on the label of a nonprescription (OTC) drug product marketed in the United States without an approved application, as a distributor, may, by agreement, authorize the manufacturer or packer of the nonprescription drug to submit the required reports to FDA (as long as the retailer directs to the manufacturer or packer all adverse events associated with the drug that are reported to the retailer as specified in section 760). The retailer may direct serious adverse event reports to the manufacturer or packer in any agreed-upon format. However, the manufacturer or packer must then send the required reports to FDA in an electronic format that the Agency can process, review, and archive.

This rule will apply to any new postmarketing safety reports for drug or biological products that are implemented in the future (e.g., once finalized, new postmarketing safety reports in the proposed rule to amend safety reporting requirements published in the **Federal Register** of March 14, 2003, 68 FR 12406). The rule also revises § 600.81, requiring the electronic submission of biological lot distribution reports.[9] The specific references to submission of postmarketing safety reports in paper format in §§ 310.305, 314.80, 600.2, and 600.80 have been deleted, and language has been added to these sections which states that FDA will issue guidance on how to provide the electronic submissions (e.g., method of transmission, media, file formats, preparation, and organization of files).

In the proposed rule, we stated that we were developing a Web-based submission portal (for submission of reports to FAERS) that we believed might be preferred by entities that submit a small number of safety reports. The Safety Reporting Portal (SRP) (available at *http://www.safetyreporting.hhs.gov*) allows the secure electronic submission of ICSRs for drug and nonvaccine biological products directly into the FAERS database once information is typed into the Web-based electronic form. The SRP creates a simple and efficient mechanism for electronic reporting that does not require an internal ICH-compatible database. As described in the preamble to the proposed rule, use of the SRP does however require some administrative support to manually enter information for the ICSRs into a Web-based form.

To assist entities that submit a small number of safety reports for vaccines, FDA has made available an eSubmitter tool. The eSubmitter tool is a stand-alone application that can be downloaded free of charge from FDA's Web site at *http://www.fda.gov/forindustry/fdaesubmitter*. The eSubmitter application appears as a fillable form, and once the appropriate fields are filled in, an ICSR in electronic format is generated that can be transmitted through the ESG into the VAERS database. We believe that the eSubmitter tool generally offers the same benefits as the SRP. As noted in § 600.80(h), FDA will issue guidance providing further information about the electronic submission of vaccine reports.

B. Safety Reports Not Covered by the Final 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. We anticipate that this final rule will permit FDA to manage these postmarketing safety reports more efficiently. The final rule only addresses electronic submission of postmarketing safety reports for drugs and biological products and does not apply to submission of the following reports:

- Investigational new drug application (IND) safety reports (§ 312.32 (21 CFR 312.32));
- Safety update reports for drugs (§ 314.50(d)(5)(vi)(b) (21 CFR 314.50(d)(5)(vi)(b));
- Approved NDA and BLA annual reports (§§ 314.81(b)(2) and 601.28 (21 CFR 314.81(b)(2) and 601.28));
- Biological product deviation reports (BPDRs) (§§ 600.14 and 606.171 (21 CFR 600.14 and 606.171));
- Reports of complications of blood transfusion and collection confirmed to be fatal (§§ 606.170(b) and 640.73 (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 (PHS Act) (42 U.S.C. 264) (§ 1271.350(a) (21 CFR 1271.350(a)); and
- NDA-field alert reports (§ 314.81(b)(1) (21 CFR 314.81(b)(1)).

C. Waivers

Although this final rule requires that all postmarketing safety reports be submitted to FDA in electronic format, new §§ 310.305(e)(2), 314.80(g)(2), 329.100(c)(2), 600.80(h)(2), and 600.81(b)(2) allow for a temporary waiver from the electronic format requirement for ''good cause'' shown.[10] Details for submitting waiver requests, such as where to send the request and any supporting information, are provided in the postmarketing safety reports guidance issued today in conjunction with this final rule. When a temporary waiver has been granted, FDA intends to specify an acceptable alternate format for submitting the safety reports. FDA anticipates that temporary waivers of the requirement to submit postmarketing safety reports to the Agency in electronic format will be needed only in rare circumstances.

Companies experiencing technical difficulties with transmission of their electronic submissions to FDA should consult FDA for technical assistance rather than submitting a waiver request. Companies that normally use the direct database-to-database method to submit reports to FDA could use the SRP as a backup method for FAERS submissions and the eSubmitter tool as a backup method for VAERS submissions during short-term, temporary outages.

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

In this final rule, as in the proposed rule, the term ''individual case safety report'' (ICSR) is used to describe the information contained in either an initial or a followup report of an individual adverse drug experience, reported on a Form FDA 3500A, on a Council for International Organizations of Medical Sciences (CIOMS) I form, on a VAERS–1 form, or in electronic format. Because we are requiring that all postmarketing safety reports be submitted in electronic format, we proposed this term to describe the safety reporting vehicle generically, rather than by reference to the associated paper form. In addition, this term in now commonly used in international electronic reporting standards (e.g., ICH E2B, Health Level 7 (HL7)) in reference to such reports.

Accordingly, as proposed, §§ 310.305(b) and 314.80(a) have been revised to define an ICSR as a description of an adverse drug experience related to an individual

[9] As noted in § 600.81, FDA intends to issue guidance addressing electronic submission of these reports.

[10] Waiver requests under §§ 600.80(h)(2) and 600.81(b)(2) must be submitted in accordance with § 600.90.

patient or subject, and § 600.80(a) has been revised to define an ICSR as a description of an adverse experience related to an individual patient or subject. Because the items of information to be reported were specified on the paper reporting forms that will no longer be used for reports covered under this rule, we have added a list of the reportable elements to the regulations. Accordingly, §§ 310.305(d), 314.80(f), 329.100(b), 600.80(f), and 600.80(g) provide detailed lists of specific elements (in five broad categories for nonvaccine products and seven broad categories for vaccine products) that are to be reported in an ICSR, derived from the associated paper forms. The five categories applicable to all products, including vaccines, and examples of some of the types of information in each category, are as follows:

- Patient information (e.g., age, gender);
- Information about the adverse experience (e.g., date and description of the adverse drug experience);
- Information about the suspect medical product (e.g., drug name, dose, indication, National Drug Code (NDC) number);
- Information about the initial reporter (e.g., name and contact information); and
- Information about the drug's applicant or manufacturer or responsible person (e.g., name and contact information)

In addition, the two categories applicable to vaccine products only are as follows:

- Information about other vaccine(s) administered in the previous 4 weeks; and
- Information on the facility and personnel where the vaccine was administered (e.g., name of person who administered vaccine, name of responsible physician and facility where the vaccine was administered).

Though there are minor wording differences, the list of information to be reported is derived from the information reflected on Form FDA 3500A and VAERS–1 for postmarketing reporting for drugs and biological products. Codification of the ICSR reporting requirements is not intended to change the 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 §§ 310.305(d), 314.80(f), 329.100(b), 600.80(f), or 600.80(g) is the same as the obligation to complete Form FDA 3500A or VAERS–1.

E. Removal of Paper Format Provisions

We believe that it is no longer necessary to describe procedures for paper format submissions in the regulations because we anticipate that a paper format will be used on a limited basis, if at all. Accordingly, as proposed, this final rule removes from the 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 have deleted in §§ 310.305(d), 314.80(f), and 600.80(f) the provisions specifically describing paper submissions and replaced them with a paragraph (§§ 310.305(e)(1), 314.80(g)(1), and 600.80(h)(1)), which states that ICSRs and any ICSR attachments must be submitted to FDA in an electronic format that we can process, review, and archive. Additional revisions to remove or modify references or provisions that are specific to paper formats include the following:

- 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 Form FDA 3500A, CIOMS I form, or VAERS–1 form or to determine an appropriate alternative format for *voluntary* submission in electronic format (§§ 310.305(d)(1) and (d)(3), 314.80(f)(1) and (f)(3), and 600.80(f)(1) and (f)(3));
- The reference to Form FDA 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));
- 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));
- The requirement to submit adverse experience reports by mail to CBER's mailing address (§ 600.2(a)) by deleting the phrase ''adverse experience reports'' from § 600.2(a);
- The requirement to submit adverse experience reports by mail to CDER's mailing address (§ 600.2(b)(2));
- The requirement to submit VAERS reports by mail to the VAERS mailing address (§ 600.2(d)); and
- The requirement to submit distribution reports on biological products by mail (§ 600.81) by deleting ''(see mailing addresses in § 600.2)'' from § 600.81.

As noted previously in this document, procedural and formatting recommendations, if applicable to electronic submissions, will be set forth in guidance.[11]

F. Section 745A of the FD&C Act and Electronic Format for Submissions

Section 745A(a) of the FD&C Act (21 U.S.C. 379k–1), added by section 1136 of the Food and Drug Administration Safety and Innovation Act (Pub. L. 112–144), provides that submissions under section 505(b), (i), or (j) of the FD&C Act or section 351(a) or (k) of the PHS Act shall be submitted in such electronic format as specified by FDA in guidance. In section 745A(a) of the FD&C Act, Congress granted explicit statutory authority to FDA to implement the electronic format for submissions requirement by guidance. This grant of authority, however, does not preclude FDA from implementing such requirements by notice and comment rulemaking (5 U.S.C. 553). At this time, even though we conclude that certain submissions that are addressed in this final rule are also within the scope of section 745A(a) of the FD&C Act, FDA has determined that it is appropriate to amend the current regulations on the submission of postmarketing safety reports to remove references to paper submissions and to specify that such reports be submitted in an electronic format that FDA can process, review, and archive. FDA may consider, at a future date, whether certain electronic submission requirements should be specified in guidance pursuant to section 745A(a) of the FD&C Act.

G. Miscellaneous Changes

As proposed, the final rule amends §§ 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'' has been removed for editorial reasons. The final rule revises in § 314.80(c)(2) the paragraph designations that were not in correct format. We believe that these minor changes clarify the regulations and make them easier to read. The final rule, as proposed, also changes the term ''licensed manufacturer'' to ''applicant'' in §§ 600.80, 600.81, and 600.90.

[11] We are also issuing a draft guidance today in conjunction with this final rule. The draft guidance, when finalized, will represent FDA's current thinking on certain topics pertaining to the electronic submission of postmarketing safety reports in the context of this rulemaking.

The mailing addresses for the submission of postmarketing safety reports have been removed from §§ 310.305(c), 314.80(c), 314.98(b), and 600.80(c) because this information is no longer necessary in light of the requirement to submit safety reports electronically.

Final § 310.305(c)(1)(i) requires the submission of a current copy of the labeling in electronic format unless it is already on file with FDA. Previously, under § 310.305(c)(1)(i), each report was to be accompanied by a copy of the labeling. However, if the Agency already has the current labeling on file, we do not believe it is necessary for a current copy of the labeling to be submitted with each report.[12]

For products with approved applications, currently, reports for all adverse experiences other than those submitted as 15-day Alert reports or followup reports to 15-day Alert reports (i.e., reports of adverse experiences that are both serious and expected or nonserious) are required to be submitted as a batch as part of the postmarketing periodic safety report for the reporting interval during which the applicant received the report. Although the ICSRs may be generated at any time from the beginning of the reporting interval through the date that the periodic report is submitted to FDA, they are currently retained by the applicant during this time period and submitted to FDA in a single batch, along with the other (descriptive) portions of the periodic report. The final rule includes language in §§ 314.80(c)(2)(ii)(B) and 600.80(c)(2)(ii)(B) to give applicants the option of submitting these ICSRs at any time up until the due date of the periodic report, rather than waiting to submit them in a single batch with the descriptive portion. All reports of adverse experiences that are both serious and expected or nonserious that the applicant received during the reporting interval must still be submitted to the Agency by the time the descriptive portion is due for that period, but the final rule permits them to be filed anytime up until the due date of the periodic report, rather than in a single batch with the descriptive portion of the periodic report. We have adopted this change, as proposed, because we understand that many applicants prefer this added flexibility of submitting the ICSRs on an ongoing basis.

To protect patient privacy, names of individual patients are not to be included in the patient identification portion of the ICSRs for drug and nonvaccine biological products. We instead require that a unique code be used for patient identification. As proposed, the final rule removes from the provisions entitled ''patient privacy'' the language specifying an eight character limit on the code. Although we also proposed that the name of the reporter not be included when the reporter is also the patient, we are not finalizing that proposal. FDA has determined that it is important for us to have the name of the reporter, even when the patient is the reporter, because it will allow us to contact the reporter, if necessary, to obtain followup information. 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. These same requirements addressing patient privacy have been included in § 329.100(d), applicable to reports required by section 760 of the FD&C Act.

As proposed, we have revised §§ 310.305(c)(1)(i), 314.80(c)(1)(i), and 600.80(c)(1)(i) to state that 15-day Alert reports must be submitted as soon as possible, but no later than 15 calendar days from initial receipt of the information. FDA does not intend this change to have any substantive effect. It is being made solely to simplify the regulatory language and improve its readability.

III. Comments on the Proposed Rule

We received written comments from three pharmaceutical companies, two associations representing the drug and biologic industries, a law firm representing a manufacturer of nonprescription drug products marketed without approved applications, and an individual (seven commenters total). A summary of the comments contained in the submissions received, and our responses, follow.

A. Safety Reports Covered

(Comment 1) In the preamble to the proposed rule, we requested public comment on whether we should require the use of an electronic format for reports of serious adverse events required by then newly enacted section 760 of the FD&C Act for nonprescription human drug products marketed without an approved application. Two commenters supported requiring the use of an electronic format for the submission of reports required by section 760 of the FD&C Act. No comments were opposed to such a requirement.

(Response) As discussed in section I.B, we agree that the requirement that postmarketing safety reports be submitted electronically should extend to safety reports required to be submitted by section 760 of the FD&C Act. Electronic submission of safety reports required to be submitted by section 760 of the FD&C Act will allow FDA to process, review, and archive such reports more efficiently. Therefore, as described previously in this document, we have added 21 CFR part 329 to cover nonprescription human drug products subject to section 760 of the FD&C Act. Section 329.100 sets forth information to be included in safety reports that are required to be submitted by section 760 of the FD&C Act and requires that the reports be submitted in an electronic format that FDA can process, review, and archive. As with safety reports required by §§ 310.305, 314.80, and 600.80, § 329.100 also includes a provision allowing requests for a temporary waiver from the electronic submission requirement for good cause. As noted in the preamble to the proposed rule, nonprescription (OTC) drug products that are marketed under approved applications (NDAs or ANDAs) are not covered under section 760 of the FD&C Act. Those products are subject to the reporting requirements of §§ 314.80 and 314.98.

(Comment 2) One comment suggested that we develop an option to allow IND safety reports to be submitted electronically. The comment states that this option would reduce the burden for companies that must use two different systems.

(Response) The comment is beyond the scope of this rulemaking. This rule addresses only the electronic submission of postmarketing safety reports. Premarketing safety reports are transmitted directly to the review division of FDA that has responsibility for review of the IND and are not uploaded into the FAERS database.

(Comment 3) Although this rulemaking does not apply to biological product deviation reports (BPDRs), in the preamble to the proposed rule, we requested comment on requiring the electronic submission of BPDRs (required by §§ 600.14 and 606.171) in the future. One comment supported requiring the electronic submission of BPDRs and also suggested that the

[12] For products subject to § 310.305(c)(1)(i), a copy of the labeling is submitted to FDA in Structured Product Labeling (SPL) format as part of the electronic drug listing process. See the guidance for industry ''Providing Regulatory Submissions in Electronic Format—Drug Establishment Registration and Drug Listing'' (May 2009) available at *http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/default.htm* and FDA's Web site on Structured Product Labeling Resources at *http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm* for information on submitting labeling to FDA in electronic format.

current Web-based form available for the voluntary electronic submission of BPDRs be modified to allow more than 2,000 characters in the *event description field* to allow a complete description of the event.

(Response) We appreciate the comment. As addressed in section II.F, section 745A(a) of the FD&C Act provides that submissions under section 351(a) or (k) of the PHS Act, which include BPDRs, shall be submitted in such electronic format as specified by FDA in guidance. The Agency intends to address the implementation of section 745A(a) of the FD&C Act separately. In the meantime, parties wishing to submit BPDRs electronically are encouraged to do so through the existing Web-based system. We note that the current electronic system for BPDR reporting has been expanded to allow up to 3,999 characters for narrative entries.

(Comment 4) Two comments requested that we address the submission of postmarketing safety reports for combination drug and device products in the final rule. One comment noted specifically that reporting requirements for drugs and biologics differ from the reporting requirements of devices and therefore requested that we provide further information on how to submit safety reports for drug and device combination products.

(Response) These comments are beyond the scope of this rulemaking. This final rule requires electronic submission of required postmarketing safety reports for drugs and biological products (including vaccines). We note that on October 1, 2009, FDA published a proposed rule entitled ''Postmarketing Safety Reporting for Combination Products'' (74 FR 50744). When finalized, this new rule will clarify the safety reporting requirements for combination products such as drug and device combinations.

(Comment 5) One comment noted that the preamble to the proposed rule indicates that developments are underway for VAERS to receive ICSRs for vaccines through FDA's ESG. The comment stated, however, that no information is provided regarding how and when these submissions may be made to VAERS.

(Response) Modifications are still underway to permit VAERS to receive ICSRs through FDA's ESG, which will facilitate the submission of multiple reports without the need for manual data entry. FDA expects that VAERS will be able to receive ICSRs through the ESG by the time this final rule becomes effective.

B. FDA Web-Based Submission Portal

In the preamble to the proposed rule, we explained that a ''Web-based electronic submission portal'' was under development to allow the secure electronic submission of postmarketing ICSRs directly into FDA's AERS database once information is entered into a ''Web-based electronic form.'' We noted that the Web-based submission portal would allow electronic submission of ICSRs consistent with ICH standards and could be used as an alternative method for reporting adverse drug experiences to FDA electronically. We noted that this alternative electronic reporting method would be particularly useful for entities that submit a small number of safety reports because it would create a simpler and more efficient mechanism for reporting that would not require an internal database that is compatible with the ICH-based direct submission system.

(Comment 6) One comment requested clarification of the terms ''Web-based submission portal'' and ''Web-based form,'' noting that both terms are used in the preamble to the proposed rule.

(Response) In the proposed rule, we used the term ''Web-based submission portal'' (now referred to as the Safety Reporting Portal (SRP)) to describe a Web-based system that any person subject to FDA's postmarketing safety reporting requirements could use to submit ICSRs to FDA electronically. (See section II.A for further discussion of the SRP.) We used the term ''Web-based form'' to describe the on-screen interface into which users would enter the ICSR data elements. Users ''complete'' the ICSR by filling in the appropriate fields in the Web-based form and then submit the ICSR to the FAERS database through the Web-based submission portal.[13]

(Comment 7) One comment suggested that to eliminate any potential barriers for small companies, no charge should be associated with use of the Web-based system.

(Response) There will be no charge for electronic submission of safety reports to the FAERS database through the SRP. For submissions to VAERS using the eSubmitter tool, however, a digital security certificate will be necessary. These certificates allow users to sign and encrypt documents for transmission, ensuring that any electronic submissions are verifiable and secure. Digital certificates are available through many third-party vendors. A certificate generally lasts 1 to 3 years and typically costs $10 to $15. A digital certificate is also necessary to comply with FDA's electronic registration and listing requirements, so most companies already have digital certificates and will not need to obtain one to use the eSubmitter tool. Further information about digital security certificates is available on FDA's Electronic Drug Registration and Listing Instructions Web page at *http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway/ucm177328.htm.*

(Comment 8) One comment asked whether training or some type of qualification will be required to submit ICSRs through the Web-based system.

(Response) The SRP creates a simpler mechanism for electronic submission of safety reports. No special training or qualification will be required. The information for the ICSR is entered into the Web-based form and then submitted to FDA. However, prior to initial use of the SRP, companies will need to contact the FAERS Electronic Submissions Coordinator at *faersesub@fda.hhs.gov* to establish an account to submit safety reports through the SRP. Having an SRP account allows for faster data entry because certain fields will be pre-populated by information from the user account. Having an account also allows users to save a report and complete it later, allows users to see a list of reports that have been submitted, and allows for followup submissions as more information about the adverse drug experience becomes available. Further information on submitting ICSRs through the SRP is included in the postmarketing safety reports guidance.

For vaccine products, the eSubmitter tool can be used, instead of the SRP, as an alternative method for the electronic submission of ICSRs to VAERS. The eSubmitter tool provides a user-friendly method for submission of these reports, and no special training or qualification will be necessary. Firms will, however, need to contact FDA's ESG Help Desk to establish an ESG account and will need to obtain a digital security certificate (as described in the previous response), if these two steps have not already been completed to comply with FDA's electronic drug registration and establishment listing requirements. The first time firms submit a report to the VAERS database, they will also need to contact the CBER Electronic Submissions Program at *esgprep@fda.hhs.gov.*

(Comment 9) One comment suggested that companies should be able to use both the Web-based portal and the ESG

[13] As described in section II.A, the eSubmitter tool will be used instead of the SRP as an alternative method for the electronic submission of vaccine ICSRs into the VAERS database.

and should not have to choose one system.

(Response) FDA will not limit companies to one method for creating and transmitting ICSRs electronically to FDA. As described in this document, FDA offers both the direct database-to-database method and the SRP for submission of ICSRs into the FAERS database, and the direct database-to-database method and eSubmitter tool for submission of ICSRs into the VAERS database. FDA recommends that companies select the submission method that best suits their needs to submit a given report.

(Comment 10) One comment recommended that the Web-based portal provide a receipt or acknowledgement indicating whether the submission was successfully received or if the delivery failed. The comment noted that this will allow companies to take appropriate followup action.

(Response) When using the SRP to submit postmarketing safety reports, users will receive electronic acknowledgement indicating whether or not their submission was accepted into the FAERS database.[14] If notified that the submission was not accepted, users should resubmit the safety report to ensure that FDA receives the report. Further information about FAERS submission acknowledgement is provided in the postmarketing safety reports guidance.

(Comment 11) One comment stated that the Web-based portal should accept ICH-compliant XML files that may be generated and submitted to the Web-based portal and/or the ESG.

(Response) The SRP allows for the submission of ICH-compliant ICSRs. Once the data elements for the ICSR are entered into the Web-based form and submitted to FDA, the SRP generates an XML file which is then uploaded into the FAERS database (along with any ICSR attachments that may be included). The ESG will continue to accept ICH-compliant XML files. Similarly, for submission of vaccine reports, both the eSubmitter tool and the direct database-to-database transmission method generate ICH-compliant XML files that are submitted to FDA through the ESG.

(Comment 12) One comment asked whether followup links to the original report will be available when submitting the report through the Web-based system.

(Response) When the initial ICSR is submitted through the SRP, users will be able to return to the initial ICSR and submit followup reports as more information about the reported adverse experience becomes available. Users may log in to their SRP accounts, locate the ICSR record, and modify or add to the initial ICSR. Users may submit as many followup reports as necessary. More detailed information on how to modify or add to an initial ICSR is available on the SRP Web site.

Similarly, the eSubmitter tool, which can be used for the submission of vaccine reports through the ESG into VAERS, allows for the creation and submission of both initial reports and followup reports as more information regarding the adverse event becomes available. Use of the same unique case identification number for the initial ICSR and any followup reports will be essential to ensure that the reports are linked in the database.

C. Waivers

In the proposed rule, we proposed allowing for the submission of requests for temporary waivers from the electronic format requirement and stated that waivers would be granted on a time-limited basis for ''good cause'' shown. While noting that the details for submitting waiver requests would be announced in guidance, we requested comment on what circumstances would constitute ''good cause'' justifying a waiver from the electronic submission requirement.

(Comment 13) One comment requested a categorical exemption from the electronic reporting requirement for small business entities, which the comment defined as any business with fewer than 100 employees and less than $10,000,000 in annual sales. The comment noted difficulties that these entities had with FDA's system for electronic establishment registration and drug listing and expressed concern that these businesses would have similar difficulties with the electronic submission of safety reports.

(Response) FDA has concluded that it will not grant a categorical exemption from the electronic safety reporting requirement for small business entities. We anticipate that receiving all required postmarketing safety reports electronically will allow us to more rapidly review the reports, identify emerging safety problems, and disseminate safety information. We believe that any categorical exemption from the electronic submission requirement will significantly limit these important benefits. As we stated in the preamble to the proposed rule, we believe a waiver will only be needed in rare circumstances.

We appreciate the commenter's concern about potential difficulties with the electronic submission of safety reports through FDA's system. We believe that the SRP provides a simple, user-friendly system for submission of ICSRs into the FAERS database. The SRP is similar to systems used for online purchases and other Web-based transactions. FDA has been receiving safety reports through the SRP for the Center for Food Safety and Applied Nutrition, the Center for Veterinary Medicine, and the Center for Tobacco Products since 2010. In addition, FDA intends to provide technical assistance to help resolve any problems.

We believe that the eSubmitter tool, which may be used for the electronic submission of ICSRs for vaccines, provides a simple and straightforward method for submitting these reports. Furthermore, submission testing is available so that users will have the opportunity to try out the system before the rule becomes effective.

FDA has been working with both large and small companies and has been successfully receiving voluntary electronic submissions of ICSRs through the ESG since 2001. We believe our experience to date with the electronic submission of safety reports will help us to minimize problems with electronic submission that regulated entities may have, especially entities new to the system. We also believe that the effective date adopted in this rule will permit the Agency and industry sufficient time to ensure that the systems are fully functional and that any technical problems are worked out by the time the requirements of this rule become effective.

(Comment 14) One comment recommended allowing a good cause waiver in cases of natural or manmade disaster. The same comment also suggested allowing a time-limited waiver for companies bringing their first commercially available product to market.

(Response) We agree that natural or manmade disasters may present situations where a waiver from the electronic submission requirement would be appropriate. For example, in these situations, electricity may be unavailable for an extended period of time, and electronic submission of safety reports would not be feasible. We do not agree that a time-limited waiver for companies bringing their first commercially available product to market will be necessary or appropriate.

[14] Similarly, users submitting ICSRs for vaccines using the eSubmitter tool will receive an electronic confirmation. Further information about VAERS submission acknowledgement is provided in guidance available at *http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm*.

We believe the electronic submission systems are easy to use and will be fully functional by the time this rule becomes effective. Furthermore, as explained in the previous response, FDA is prepared to assist companies to ensure that any problems with electronic submission are resolved.

(Comment 15) One comment suggested that temporary waivers should be granted for unplanned, extended-duration ESG downtime; business continuity or disaster recovery situations where a company's pharmacovigilance system access may be down for a period of time and the volume of reports is too high to use the Web-based system requiring manual entry; or where human resources are greatly diminished, for example, as a result of pandemic or terror attack.

(Response) We agree that disaster recovery situations, pandemics, or terror attacks may present circumstances in which a waiver from the electronic submission requirement would be appropriate. We believe it is unlikely that the ESG would experience unplanned downtime of extended duration such that a waiver from the electronic submission requirement would be necessary. However, if such a situation were to occur, a waiver might be appropriate.

(Comment 16) One comment suggested that the components of a request for a waiver could include the nature of the inability to comply, the anticipated time to recover, and a crisis manager contact for the company who would be accountable to FDA for followup and resolution. The comment also requested that FDA include in its guidance the type of documentation that must be kept and the documentation FDA will provide as a record of the situation for future inspections or audits.

(Response) We agree with the suggestion that a waiver request should include the nature of the inability to comply, the anticipated time to recover, and a company contact. Though additional relevant information could also be included in a waiver request, the components suggested for inclusion would allow us to assess the reasonableness of a waiver request and would ensure that we are able to limit the waiver to the time necessary. Accordingly, in the postmarketing safety reports guidance issued today in conjunction with this rule, we have stated that a waiver request should include the reason for the request and a proposed end date for the waiver. To follow up with the company, FDA intends to contact the individual who submitted the request. Although not addressed in the postmarketing safety reports guidance, we believe that in the normal course of business, it would be usual and customary for companies to maintain adequate records of the situation leading to a waiver request and documentation related to the waiver request.

(Comment 17) Two comments stated that FDA should provide a telephone contact for requesting a temporary waiver, because during a crisis situation, it may be difficult to put together a comprehensive request. One of the comments also suggested fax as an alternative for submitting a waiver request.

(Response) Consistent with the procedures for requesting waivers of other FDA requirements, requests for waivers of the electronic safety reporting requirement should be submitted to FDA in writing by mail as described in the postmarketing safety reports guidance issued today. The Agency is exploring other methods that may facilitate submission of waiver requests, and we will update the postmarketing safety reports guidance, as appropriate, to reflect any changes in waiver request procedures.

D. ICSR Submissions

1. Content

(Comment 18) One comment requested clarification on the types of attachments that are required as part of an ICSR submission.

(Response) The final rule includes a definition of ''ICSR attachments'' for clarification, but the rule does not change the types of attachments that may be necessary as part of an ICSR submission. As noted previously in this document, in the proposed rule, and in final §§ 310.305(b), 314.80(a), and 600.80(a), examples of ICSR attachments that may be necessary include published articles that must accompany ICSRs based on scientific literature (§§ 314.80(d) and 600.80(d)) and other supporting information, such as hospital discharge summaries and autopsy reports.

(Comment 19) One comment asked whether the ICSR attachments will be made public and whether companies will be required to redact the patient information from the attachments. The comment noted that requiring the company to redact patient information, such as address and birth date would create a significant additional burden.

(Response) FDA will not publicly release names or any other identifying information about patients contained in ICSR attachments. FDA redacts patient names and other identifying information before publicly releasing information contained in postmarketing safety reports. Persons submitting reports should not redact information contained in ICSRs or ICSR attachments before submitting them to FDA. We understand that companies may receive documents from reporters that are already redacted. Those documents should be submitted to FDA as received from the reporter and should not be redacted any further.

(Comment 20) Proposed § 310.305(c)(1)(i) stated that each 15-day ''Alert report'' must be accompanied by the ''current content of the labeling'' in electronic format unless it is already on file at FDA. One comment requested clarification of what ''content of the labeling'' means, suggesting that it could refer to the entire label or only certain sections or certain types of information in the labeling.

(Response) As set forth in § 314.50(l)(1)(i), the ''content of labeling'' refers to the contents of the package insert or professional labeling. It is the information required by §§ 201.56, 201.57, and 201.80, in the format specified. For products subject to § 310.305(c)(1)(i), the content of labeling is submitted to FDA in Structured Product Labeling (SPL) format as part of the electronic drug listing process. Further information about electronic submission of content of labeling and SPL format is provided in the guidance for industry entitled ''Providing Regulatory Submissions in Electronic Format—Drug Establishment Registration and Drug Listing'' and the draft guidance ''SPL Standard for Content of Labeling—Technical Qs & As'' (available on FDA's Web site at *http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm)* which, when finalized, will represent the Agency's current thinking.

(Comment 21) Proposed §§ 310.305(d)(1)(i), 314.80(f)(1)(i), and 600.80(f)(1)(i) listed ''patient identification code'' as an element to be included in each ICSR. Proposed §§ 310.305(f), 314.80(i), and 600.80(i), entitled ''Patient privacy,'' stated: ''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.'' [15] One comment requested that we clarify

[15] Both proposed and final § 310.305(f) use the phrase ''manufacturers, packers, and distributors'' in place of the term ''applicant,'' because § 310.305 applies to prescription drugs for human use without approved NDAs. Proposed § 600.80(i) and final § 600.80(j) addressing patient privacy state: ''For nonvaccine biological products, an applicant should not include in reports . . .''

whether the term ''patient identification code'' (used in proposed §§ 310.305(d)(1)(i), 314.80(f)(1)(i), and 600.80(f)(1)(i)) and the term ''unique code for each report'' as used in the provisions addressing patient privacy (proposed §§ 310.305(f), 314.80(i), and 600.80(i)) are intended to be different codes.

(Response) The ''patient identification code'' listed as a reporting element to be included in ICSRs (in §§ 310.305(d)(1)(i), 314.80(f)(1)(i), and 600.80(f)(1)(i)) and the ''unique code for each report'' discussed in the provision on patient privacy (in proposed §§ 310.305(f), 314.80(i), and 600.80(i)) are referring to the same code. Entities that submit ICSRs for drug and nonvaccine biological products should not include names and contact information for patients in the ICSRs. Rather, a unique code should be used instead of the patient's name and contact information in the patient information section of the ICSR.[16] The intent of using such a code is to protect the privacy of patients who have experienced adverse events that are being reported to FDA, while allowing the submitter to know the patient's identity and contact information for reference purposes. We agree that as proposed, the requirement is unclear. Therefore, we are revising the sections entitled ''Patient privacy'' (§§ 310.305(f), 314.80(i), and 600.80(j)) to state: ''. . . should not include in reports under this section the names and addresses of individual patients; instead, the applicant should assign a unique code for identification of the patient.'' We believe this change to the final rule will make clearer that the ''patient identification code'' included in the list of ICSR reporting elements (for drug and nonvaccine biological products) and the code described in the sections on patient privacy are referring to the same code, which is intended to protect the identity of patients. Section 329.100(d) also uses the same language.

We note, however, that §§ 310.305(d), 314.80(f), 329.100(b), and 600.80(f) and (g) that set forth the ICSR reporting elements, as finalized, also require a ''unique case identification number'' for each ICSR. This unique case identification number is distinct from the patient identification code. The unique case identification number, which must be the same in the initial ICSR and any subsequent followup ICSR(s), was referred to as the Manufacturer Report Number on Form FDA 3500A and VAERS–1, and it allows FDA to track an individual case over its life cycle.

(Comment 22) One comment noted that, in the past, the ESG has accepted ICSRs for which the applicant does not have all categories of information. The comment sought to confirm that ICSRs would not be rejected by the ESG if there are any gaps in categories of information.

(Response) The ESG will continue to operate as it has and will accept ICSRs for which the applicant may not have all categories of information. Even though the ESG and SRP accept ICSRs for which there are gaps in certain categories of information, it is important for applicants to include all information about the reported event that is known to the applicant.

2. Timing of Report Submissions

(Comment 23) One comment requested confirmation that the ESG will be available 24 hours a day, 7 days a week, and that ICSRs submitted outside of business hours will be considered timely (if submitted within the required time frame). The comment also requested that we provide guidance on procedures for planned and unplanned downtime of the ESG and how the downtime affects submission deadlines.

(Response) FDA intends to make the ESG available 24 hours a day, 7 days a week to receive electronic submissions. Additional information explaining how submission dates are calculated if the ESG and/or the FAERS database is temporarily unavailable is provided in the postmarketing safety reports guidance issued today. We note that FDA also intends to make the SRP available 24 hours a day, 7 days a week to receive submissions.

E. International Harmonization

(Comment 24) One comment suggested that we reference the ICH Harmonized Tripartite Guideline instead of listing, in the rule, categories of information to be included in ICSRs.

(Response) We set forth the categories of information to be included in ICSRs because we believe that this is a clear and concise way to communicate the information to be included when reporting adverse events to FDA and to move away from reliance on paper forms. We considered the ICH guidelines when creating these categories and believe that the categories included are either consistent with international standards or can be accommodated as local requirements using international transmission standards.

(Comment 25) One comment asked what version of the ICH E2B standard (i.e., the ICH guideline on data elements for transmission of ICSRs) will be accepted.

(Response) It has been FDA's practice to accept both the latest version of the ICH E2B standard in addition to the previous version. This practice has allowed applicants reasonable time to transition to the updated ICH E2B standard. Any changes to submission standards will be provided in guidance, as appropriate.[17]

(Comment 26) One comment noted that the EU Drug Regulatory Authorities Pharmacovigilance system (EudraVigilance) has different validators than FDA's reporting system. As a result, some ICSRs would be accepted by FDA that would not be accepted by the European Medicines Agency. The comment requested that if new validators are placed on the ESG they be aligned with the EudraVigilance validators so that both systems accept the same reports.

(Response) It would not be functionally workable or practical to commit, in advance, to incorporating changes made by other regulatory bodies to ensure complete consistency among the reporting systems. FDA will continue to work with international standards organizations when developing new technical specifications so that differences in those specifications are kept to a minimum.

F. Technical Specifications

The proposed rule indicated that standards and technical specifications will be addressed in guidance documents rather than set forth in the final rule.

(Comment 27) One comment noted that changes to technical standards or specifications can increase costs to companies. The comment expressed concern that by adopting changes in guidance documents, the changes can occur more quickly and more frequently, resulting in a greater burden to companies. The comment stated that it is important that required technical standards or specifications not be changed frequently and that when they

[16] The patient's name and contact information should only be included in an ICSR when the patient is the reporter. Under those circumstances, the patient-reporter's name and contact information should be included in the initial reporter section of the ICSR but not in the patient information section of the ICSR. In the patient information section of the ICSR, a unique code should be used instead of the patient-reporter's name and contact information.

[17] Further information about E2B message standards accepted by FAERS is available on the FAERS Electronic Submissions Web page at *http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm115894.htm.*

are changed, adequate time be allowed for public comment.

(Response) We understand the concern that frequent changes in technical standards and specifications may increase the cost of compliance to companies. FDA does not anticipate frequent changes. However, it is important for FDA to retain flexibility so that we can be responsive to the rapidly changing technological environment. We believe that the use of guidance documents to communicate technical specifications will benefit both companies and the Agency. If FDA were to set forth technical specifications in regulations, the result could be that companies would be bound to standards and specifications that are outdated. Maintaining older systems can also be a resource burden to companies.

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, 745A, 760, and 801 of the FD&C Act (21 U.S.C. 321, 331, 351, 352, 353, 355, 355a, 356, 356a, 356b, 356c, 360, 371, 374, 375, 379k–1, 379aa, and 381); and the PHS 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 final rule under Executive Order 12866, Executive Order 13563, the Regulatory Flexibility Act (5 U.S.C. 601–612), and the Unfunded Mandates Reform Act of 1995 (Pub. L. 104–4). Executive Orders 12866 and 13563 direct 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). FDA believes that this final rule is not a significant regulatory action as defined by Executive Order 12866.

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 few safety reports and the Agency's Web-based system for submitting reports electronically will require little additional cost per report, the Agency believes that this final rule will not have a significant economic impact on a substantial number of small entities.

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 $141 million, using the most current (2013) Implicit Price Deflator for the Gross Domestic Product. FDA does not expect this final rule to result in any 1-year expenditure that would meet or exceed this amount.

The final rule requires the submission of all postmarketing safety reports, including periodic reports, to FDA in an electronic format. In addition, manufacturers of products distributed under a biologic license are required to submit lot distribution reports electronically. The public health benefits of this final rule, quicker access to postmarketing safety information, were not quantified. The final rule will generate an annual savings for the Agency of about $0.8 million, which is primarily a savings in the cost of processing paper. Total one-time costs to industry will be between $5.9 million to $7.5 million; the costs are for changing standard operating procedures (SOPs) and for training personnel. Annualized over 10 years at a 7 percent discount rate, the costs are from $0.8 million to $1.1 million. At a 3 percent discount rate over 10 years, the annualized costs are $0.7 million to $0.9 million.

The full assessment of economic impacts is available in Docket No. FDA–2008–N–0334 and at *http://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/EconomicAnalyses/default.htm* (Ref. 1).

VII. Paperwork Reduction Act of 1995

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

Title: Postmarketing Safety Reports for Human Drug and Biological Products: Electronic Submission Requirements.

Description: The final rule amends FDA's postmarketing safety reporting regulations for human drug and biological products under parts 310, 314, and 600, and adds part 329, 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 submit postmarketing safety reports to the Agency. Section 760 of the FD&C 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 serious adverse events associated with their products. Under § 600.81, applicants with approved BLAs must submit biological lot distribution reports to the Agency. In this rule, FDA is requiring that these postmarketing reports be submitted to the Agency in an electronic format that FDA can process, review, and archive. The final rule also states that FDA will 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 requires that they be submitted in an electronic format. Under §§ 310.305(e)(2), 314.80(g)(2), 329.100(c)(2), 600.80(h)(2), and 600.81(b)(2), we are also permitting those subject to mandatory reporting requirements 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 FDA 3500A) and 0910–0230. The information collection for part 600 is approved under OMB control numbers 0910–0291 (Form 3500A) and 0910–0308. The burdens currently estimated

under parts 310, 314, and 600, for submission of postmarketing safety reports to FDA for human drugs and biological products, do not change as a result of this final 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 final rule, including obtaining an electronic certificate, revising SOPs, and becoming familiar 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 § 600.81.

OMB has approved the burden associated with submissions required by section 760 of the FD&C Act under OMB control number 0910–0636.

In table 1 of this document, we have estimated the burdens associated with the submission of waivers, under §§ 310.305(e)(2), 314.80(g)(2), 329.100(c)(2), 600.80(h)(2), and 600.81(b)(2). We expect few waiver requests (see section II.C). We estimate that approximately one manufacturer will request a waiver annually under §§ 310.305(e)(2), 329.100(c)(2), and 600.81(b)(2), and five manufacturers will request a waiver annually under §§ 314.80(g)(2) and 600.80(h)(2). We estimate that each waiver request will take approximately 1 hour to prepare and submit to us.

Description of Respondents: Manufacturers, packers, and distributors of marketed prescription drug products that are not the subject of approved applications, applicants with approved NDAs, ANDAs, and BLAs, and those that market nonprescription drugs for human use without an approved application.

Burden Estimate: Table 1 of this document provides an estimate of the new annual reporting burden for submitting requests under the waiver requirement in this final rule.

TABLE 1—ESTIMATED ANNUAL REPORTING BURDEN

21 CFR Sections	Number of respondents	Number of responses per respondent	Total annual responses	Hours per response	Total hours
Waivers—Electronic Format for Submissions					
310.305(e)(2)	1	1	1	1	1
314.80(g)(2)	5	1	5	1	5
329.100(c)(2)	1	1	1	1	1
600.80(h)(2)	5	1	5	1	5
600.81(b)(2)	1	1	1	1	1
Total Reporting Burden					13

A. Reporting Costs

Based on the average hourly wage ($79) as calculated in section VI (Analysis of Impacts) of the final rule, the cost to respondents would be $1,027 (13 × $79).

Tables 2 through 5 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 2—OMB CONTROL NUMBER 0910–0291 "MEDWATCH: THE FDA MEDICAL PRODUCTS REPORTING PROGRAM"

21 CFR Sections	Number of respondents	Number of responses per respondent	Total annual responses	Hours per response	Total hours
Form FDA 3500A (MedWatch: The FDA Safety Information and Adverse Event Reporting Program—Mandatory) (§§ 310.305—Records and reports concerning adverse drug experiences on marketed prescription drugs for human use without approved new drug applications, 314.80—Postmarketing reporting of adverse drug experiences, 314.98—Postmarketing reports, and 600.80—Postmarketing reporting of adverse experiences)	600	683	409,608	1.1	450,568

Based on the average hourly wage ($79) as calculated in section VI (Analysis of Impacts) of the proposed rule, the cost to respondents would be $39,895,948 (505,012 × $79).

TABLE 3—OMB CONTROL NUMBER 0910–0230 ''ADVERSE DRUG EXPERIENCE REPORTING''

21 CFR Sections	Number of respondents	Number of responses per respondent	Total annual responses	Hours per response	Total hours
310.305(c)(5)—Reporting requirements	1	1	1	1	1
314.80(c)(2)—Periodic adverse drug experience reports	642	17.88	11,478	60	688,680
Total					688,681

Based on the average hourly wage ($79) as calculated in section VI of the proposed rule, the cost to respondents would be $54,405,799 (688,681 × $79).

TABLE 4—OMB CONTROL NUMBER 0910–0308 ''ADVERSE EXPERIENCE REPORTING FOR LICENSED BIOLOGICAL PRODUCT; AND GENERAL RECORDS''

21 CFR Sections	Number of respondents	Number of responses per respondent	Total annual responses	Hours per response	Total hours
600.80(c)(1)—Postmarketing 15-day ''Alert reports'' and 600.80(e)—Postmarketing studies	108	801.69	86,583	1	86,583
600.80(c)(2)—Periodic adverse experience reports	108	530.55	57,300	28	1,604,400
600.81—Distribution Reports	108	3.23	349	1	349
600.90—Waivers	21	1	21	1	21
Total					1,691,353

Based on the average hourly wage ($79) as calculated in section VI of the proposed rule, the cost to respondents would be $133,616,887 (1,691,353 × $79).

TABLE 5—OMB CONTROL NUMBER 0910–0636 ''GUIDE FOR INDUSTRY ON LABELING OF NONPRESCRIPTION HUMAN DRUG PRODUCTS MARKETED WITHOUT AN APPROVED APPLICATION AS REQUIRED BY THE DIETARY SUPPLEMENT AND NONPRESCRIPTION DRUG CONSUMER PROTECTION ACT''

	Number of respondents	Number of responses per respondent	Total annual responses	Hours per response	Total hours
Reports of serious adverse drug events under section 760 of the FD&C Act (21 U.S.C. 379aa((b) and (c))	50	250	12,500	2	25,000

Based on the average hourly wage ($79) as calculated in section VI of the proposed rule, the cost to respondents would be $1,975,000 (25,000 × $79).

B. Capital Costs

As explained in section VI (Analysis of Impacts), total one-time costs to industry would be between $5.9 million to $7.5 million; the costs are for changing standard SOPs and training personnel. Annualized over 10 years at a 7 percent discount rate, the costs will be from 0.8 million to $1.1 million. At a 3 percent discount rate over 10 years, the annualized costs are $0.7 million to $0.9 million.

The information collection provisions of this final rule have been submitted to OMB for review. Prior to the effective date of this final rule, FDA will publish a notice in the **Federal Register** announcing OMB's decision to approve, modify, or disapprove the information collection provisions in this final rule. An Agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

VIII. Federalism

FDA has analyzed this final 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. Reference

The following reference has been placed on display in the Division of Dockets Management (HFA–305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852 and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday, and is available electronically at *http://www.regulations.gov*.

1. Regulatory Impact Analysis, Regulatory Flexibility Analysis, and Unfunded Mandates Reform Act Analysis for Postmarketing Safety Reports for Human Drug and Biological Products; Electronic Submission Requirements; Final Rule, available at *http://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/EconomicAnalyses/default.htm*.

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 329

Administrative practice and procedure, Over-the-counter drugs, Reporting and recordkeeping requirements.

21 CFR Part 600

Biologics, Reporting and recordkeeping requirements.

Therefore, under the Federal Food, Drug, and Cosmetic Act, the Public Health Service Act, and under authority delegated to the Commissioner of Food and Drugs, 21 CFR parts 310, 314, and 600 are amended and a new part 329 is added as follows:

PART 310—NEW DRUGS

■ 1. The authority citation for 21 CFR part 310 is revised to read as follows:

Authority: 21 U.S.C. 321, 331, 351, 352, 353, 355, 360b–360f, 360j, 361(a), 371, 374, 375, 379e, 379k–1; 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 definitions of ''Individual case safety report (ICSR)'' and ''ICSR attachments'';
■ 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) removing ''(c)(4)'' and adding 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.

ICSR attachments. Documents related to the adverse drug experience described in an ICSR, such as medical records, hospital discharge summaries, or other documentation.

* * * * *

(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 ICSR 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 as an ICSR attachment unless it is already on file at FDA.

* * * * *

(3) *Submission of reports.* * * * 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 ICSR submission;

(iv) Description of adverse drug experience (including a concise medical narrative);

(v) Adverse drug experience term(s);

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

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

(3) *Suspect medical product(s).*

(i) Name;

(ii) Dose, frequency, and route of administration used;

(iii) Therapy dates;

(iv) Diagnosis for use (indication);

(v) Whether the product is a combination product as defined in § 3.2(e) of this chapter;

(vi) Whether the product is a prescription or nonprescription product;

(vii) Whether adverse drug experience abated after drug use stopped or dose reduced;

(viii) Whether adverse drug experience reappeared after reintroduction of drug;

(ix) Lot number;

(x) Expiration date;

(xi) National Drug Code (NDC) number; and

(xii) Concomitant medical products and therapy dates.

(4) *Initial reporter information.*

(i) Name, address, and telephone number;

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

(iii) Occupation, if a health care professional.

(5) *Manufacturer, packer, or distributor information.*

(i) Manufacturer, packer, or distributor name and contact office address;

(ii) Telephone number;

(iii) Report source, such as spontaneous, literature, or study;

(iv) Date the report was received by manufacturer, packer, or distributor;

(v) Whether the ICSR is a 15-day ''Alert report'';

(vi) Whether the ICSR is an initial report or followup report; and

(vii) Unique case identification number, which must be the same in the initial report and any subsequent followup report(s).

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

(2) 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. FDA will issue guidance on requesting a waiver of the requirements in paragraph (e)(1) of this section.

(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 for identification of the patient. The manufacturer, packer, and distributor should include the name of the reporter from whom the information was received as part of the initial reporter information, even when 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 is revised to read as follows:

Authority: 21 U.S.C. 321, 331, 351, 352, 353, 355, 356, 356a, 356b, 356c, 371, 374, 379e, 379k–1.

■ 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 definitions for ''Individual case safety report (ICSR)'' and ''ICSR attachments'';
■ 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 newly redesignated 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 by revising newly redesignated paragraph (i); and
■ 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.

ICSR attachments. Documents related to the adverse drug experience described in an ICSR, such as medical records, hospital discharge summaries, or other documentation.

* * * * *

(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 ICSR submission;

(iv) Description of adverse drug experience (including a concise medical narrative);

(v) Adverse drug experience term(s);

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

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

(3) *Suspect medical product(s).*

(i) Name;

(ii) Dose, frequency, and route of administration used;

(iii) Therapy dates;

(iv) Diagnosis for use (indication);

(v) Whether the product is a prescription or nonprescription product;

(vi) Whether the product is a combination product as defined in § 3.2(e) of this chapter;

(vii) Whether adverse drug experience abated after drug use stopped or dose reduced;

(viii) Whether adverse drug experience reappeared after reintroduction of drug;

(ix) Lot number;

(x) Expiration date;

(xi) National Drug Code (NDC) number; and

(xii) Concomitant medical products and therapy dates.

(4) *Initial reporter information.*

(i) Name, address, and telephone number;

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

(iii) Occupation, if a health care professional.

(5) *Applicant information.*

(i) Applicant name and contact office address;

(ii) Telephone number;

(iii) Report source, such as spontaneous, literature, or study;

(iv) Date the report was received by applicant;

(v) Application number and type;

(vi) Whether the ICSR is a 15-day ''Alert report'';

(vii) Whether the ICSR is an initial report or followup report; and

(viii) Unique case identification number, which must be the same in the initial report and any subsequent followup report(s).

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

(2) 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. FDA will issue guidance on requesting a waiver of the requirements in paragraph (g)(1) of this section.

* * * * *

(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 for identification of the patient. The applicant should include the name of the reporter from whom the information was received as part of the initial reporter information, even when 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 Federal Food, Drug, and Cosmetic Act for each of its approved abbreviated applications.

■ 6. Part 329 is added to read as follows:

PART 329—NONPRESCRIPTION HUMAN DRUG PRODUCTS SUBJECT TO SECTION 760 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT

Authority: 21 U.S.C. 321, 331, 351, 352, 353, 355, 371, 379aa.

§ 329.100 Postmarketing reporting of adverse drug events under section 760 of the Federal Food, Drug, and Cosmetic Act.

(a) *Reporting requirements.* Reports of serious adverse events required by section 760 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) must include the information specified in this section, as applicable. Except as provided in paragraph (c)(2) of this section, these reports must be submitted to the Agency in electronic format as described in paragraph (c)(1) of this section.

(b) *Contents of reports.* For purposes of reporting serious adverse events under section 760 of the FD&C Act, an individual case safety report (ICSR) constitutes the MedWatch form required to be submitted by section 760(d) of the FD&C Act. 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 event.*

(i) Outcome attributed to adverse drug event;

(ii) Date of adverse drug event;

(iii) Date of ICSR submission;

(iv) Description of adverse drug event (including a concise medical narrative);

(v) Adverse drug event term(s);

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

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

(3) *Suspect medical product(s).*

(i) Name;

(ii) Dose, frequency, and route of administration used;

(iii) Therapy dates;

(iv) Diagnosis for use (indication);

(v) Whether the product is a combination product as defined in § 3.2(e) of this chapter;

(vi) Whether the product is a prescription or nonprescription product;

(vii) Whether adverse drug event abated after drug use stopped or dose reduced;

(viii) Whether adverse drug event reappeared after reintroduction of drug;

(ix) Lot number;

(x) Expiration date;

(xi) National Drug Code (NDC) number; and

(xii) Concomitant medical products and therapy dates.

(4) *Initial reporter information.*

(i) Name, address, and telephone number;

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

(iii) Occupation, if a health care professional.

(5) *Responsible person (as defined in section 760(b) of the FD&C Act) information.*

(i) Name and contact office address;

(ii) Telephone number;

(iii) Report source, such as spontaneous;

(iv) Date the report was received by responsible person;

(v) Whether the ICSR is a 15-day report;

(vi) Whether the ICSR is an initial report or followup report; and

(vii) Unique case identification number, which must be the same in the initial report and any subsequent followup report(s).

(c) *Electronic format for submissions.* (1) Each report required to be submitted to FDA under section 760 of the FD&C Act, accompanied by a copy of the label on or within the retail package of the drug and any other documentation (as ICSR attachments), must be in an electronic format that FDA can process, review, and archive. FDA will issue guidance on how to provide the electronic submission (e.g., method of transmission, media, file formats, preparation, and organization of files).

(2) The responsible person may request, in writing, a temporary waiver of the requirements in paragraph (c)(1) of this section. These waivers will be granted on a limited basis for good cause shown. FDA will issue guidance on requesting a waiver of the requirements in paragraph (c)(1) of this section.

(d) *Patient privacy.* The responsible person should not include in reports under this section the names and addresses of individual patients; instead, the responsible person should assign a unique code for identification of the patient. The responsible person should include the name of the reporter from whom the information was received as part of the initial reporter

information, even when the reporter is the patient. The names of patients, health care professionals, hospitals, and geographical identifiers in adverse drug event reports are not releasable to the public under FDA's public information regulations in part 20 of this chapter.

PART 600—BIOLOGICAL PRODUCTS: GENERAL

■ 7. The authority citation for 21 CFR part 600 is revised to read as follows:

Authority: 21 U.S.C. 321, 351, 352, 353, 355, 360, 360i, 371, 374, 379k–1; 42 U.S.C. 216, 262, 263, 263a, 264, 300aa–25.

§ 600.2 [Amended]

■ 8. Section 600.2 is amended:
■ a. In paragraph (a) by removing the phrase ''paragraphs (c) or (d)'' and adding in its place ''paragraph (c)'', and by removing the phrase ''adverse experience reports'';
■ b. In paragraph (b) introductory text by removing the phrase ''paragraphs (b)(1), (b)(2), (b)(3), or (c)'' and adding in its place ''paragraphs (b)(1), (b)(2), or (c) ''
■ c. By removing paragraph (b)(2) and redesignating paragraph (b)(3) as paragraph (b)(2);
■ d. By removing paragraph (d) and redesignating paragraphs (e) and (f) as paragraphs (d) and (e).
■ e. In newly redesignated paragraph (e) by removing the Web address ''*http://www.fda.gov/cber/pubinquire.htm*'' and adding in its place ''*http://www.fda.gov/BiologicsBloodVaccines/default.htm*'' and by removing the Web address ''*http://www.fda.gov/cder/biologics/default.htm*'' and adding in its place ''*http://www.fda.gov/Drugs/default.htm*''.

■ 9. 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'' or ''licensed manufacturers'' each time it appears and by adding in its place the word ''applicant'' or ''applicants'' respectively;
■ c. By removing the phrase ''Licensed manufacturer'' or ''Licensed manufacturers'' each time it appears and by adding in its place the word ''Applicant'' or ''Applicants'' respectively;
■ d. In paragraph (a) by alphabetically adding the definitions for ''Individual case safety report (ICSR)'' and ''ICSR attachments'';
■ e. 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'';
■ f. In paragraph (c)(1)(ii) by removing the last sentence;
■ g. By removing paragraph (c)(1)(iv);
■ h. By revising paragraph (c) introductory text, the first and third sentences of paragraph (c)(1)(iii) introductory text, and paragraph (c)(2)(ii);
■ i. By removing paragraph (d)(2) and by redesignating paragraph (d)(1) as paragraph (d) and revising the first sentence of paragraph (d);
■ j. By removing paragraph (e)(2) and by redesignating paragraph (e)(1) as paragraph (e);
■ k. By revising paragraph (f);
■ l. By redesignating paragraph (g) through paragraph (*l*) as paragraph (i) through paragraph (n) and by revising newly redesignated paragraph (j); and
■ m. By adding new paragraphs (g) and (h) 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.

ICSR attachments. Documents related to the adverse experience described in an ICSR, such as medical records, hospital discharge summaries, or other documentation.

* * * * *

(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 (h)(1) of this section, except as provided in paragraph (h)(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 for nonvaccine biological product reports or by the unique case identification number for vaccine reports, 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 for nonvaccine biological product reports or by the unique case identification number for vaccine reports and adverse reaction term(s) for 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 reported on ICSRs for nonvaccine biological products.* ICSRs for nonvaccine biological products 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 (including a concise medical narrative);

(v) Adverse experience term(s);

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

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

(3) *Suspect medical product(s).*

(i) Name;

(ii) Dose, frequency, and route of administration used;

(iii) Therapy dates;

(iv) Diagnosis for use (indication);

(v) Whether the product is a combination product as defined in § 3.2(e) of this chapter;

(vi) Whether the product is a prescription or nonprescription product;

(vii) Whether adverse experience abated after product use stopped or dose reduced;

(viii) Whether adverse experience reappeared after reintroduction of the product;

(ix) Lot number;

(x) Expiration date;

(xi) National Drug Code (NDC) number, or other unique identifier; and

(xii) Concomitant medical products and therapy dates.

(4) *Initial reporter information.*

(i) Name, address, and telephone number;

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

(iii) Occupation, if a health care professional.

(5) *Applicant information.*

(i) Applicant name and contact office address;

(ii) Telephone number;

(iii) Report source, such as spontaneous, literature, or study;

(iv) Date the report was received by applicant;

(v) Application number and type;

(vi) Whether the ICSR is a 15-day ''Alert report'';

(vii) Whether the ICSR is an initial report or followup report; and

(viii) Unique case identification number, which must be the same in the initial report and any subsequent followup report(s).

(g) *Information reported on ICSRs for vaccine products.* ICSRs for vaccine products include the following information:

(1) *Patient information.*

(i) Patient name, address, telephone number;

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

(iii) Patient gender; and

(iv) Patient birth weight for children under age 5.

(2) *Adverse experience.*

(i) Outcome attributed to adverse experience;

(ii) Date and time of adverse experience;

(iii) Date of report;

(iv) Description of adverse experience (including a concise medical narrative);

(v) Adverse experience term(s);

(vi) Illness at the time of vaccination;

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

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

(3) *Suspect medical product(s), including vaccines administered on the same date.*

(i) Name;

(ii) Dose, frequency, and route or site of administration used;

(iii) Number of previous vaccine doses;

(iv) Vaccination date(s) and time(s);

(v) Diagnosis for use (indication);

(vi) Whether the product is a combination product (as defined in § 3.2(e) of this chapter);

(vii) Whether the adverse experience abated after product use stopped or dose reduced;

(viii) Whether the adverse experience reappeared after reintroduction of the product;

(ix) Lot number;

(x) Expiration date;

(xi) National Drug Code (NDC) number, or other unique identifier; and

(xii) Concomitant medical products and therapy dates.

(4) *Vaccine(s) administered in the 4 weeks prior to the vaccination date.*

(i) Name of vaccine;

(ii) Manufacturer;

(iii) Lot number;

(iv) Route or site of administration;

(v) Date given; and

(vi) Number of previous doses.

(5) *Initial reporter information.*

(i) Name, address, and telephone number;

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

(iii) Occupation, if a health care professional.

(6) *Facility and personnel where vaccine was administered.*

(i) Name of person who administered vaccine;

(ii) Name of responsible physician at facility where vaccine was administered; and

(iii) Name, address (including city, county, and state), and telephone number of facility where vaccine was administered.

(7) *Applicant information.*

(i) Applicant name and contact office address;

(ii) Telephone number;

(iii) Report source, such as spontaneous, literature, or study;

(iv) Date received by applicant;

(v) Application number and type;

(vi) Whether the ICSR is a 15-day ''Alert report'';

(vii) Whether the ICSR is an initial report or followup report; and

(viii) Unique case identification number, which must be the same in the initial report and any subsequent followup report(s).

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

(2) Persons subject to the requirements of paragraph (c) of this section may request, in writing, a temporary waiver of the requirements in paragraph (h)(1) of this section. These waivers will be granted on a limited basis for good cause shown. FDA will issue guidance on requesting a waiver of the requirements in paragraph (h)(1) of this section. Requests for waivers must be submitted in accordance with § 600.90.

* * * * *

(j) *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 for identification of the patient. The applicant should include the name of the reporter from whom the information was received as part of the initial reporter information, even when 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.

* * * * *

■ 10. 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 removing the word ''shall'' each time it appears and by adding in its place the word ''must'';

■ c. By designating the existing text as paragraph (a) and by adding a heading for newly designated paragraph (a);

■ d. In newly designated paragraph (a), by removing from the first sentence the phrase ''(see mailing addresses in § 600.2)''; and

■ e. 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 an electronic format that FDA can process, review, and archive. FDA will 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. FDA will issue guidance on requesting a waiver of the requirements in paragraph (b)(1) of this section. Requests for waivers must be submitted in accordance with § 600.90.

§ 600.90 [Amended]

■ 11. Section 600.90 is amended by removing the phrase ''licensed manufacturer'' or ''licensed manufacturer's'' each time it appears and by adding in its place the word ''applicant'' or ''applicant's'' respectively.

Dated: June 4, 2014.

Leslie Kux,

Assistant Commissioner for Policy.

[FR Doc. 2014–13480 Filed 6–9–14; 8:45 am]

BILLING CODE 4160–01–P

DEPARTMENT OF EDUCATION

34 CFR Chapter III

[Docket ID: ED–2014–OSERS–0013]

Final Priority. National Institute on Disability and Rehabilitation Research—Rehabilitation Research and Training Centers

[CFDA Number: 84.133B–4.]

AGENCY: Office of Special Education and Rehabilitative Services, Department of Education.

ACTION: Final priority.

SUMMARY: The Assistant Secretary for Special Education and Rehabilitative Services announces a priority for the Rehabilitation Research and Training Center (RRTC) Program administered by the National Institute on Disability and Rehabilitation Research (NIDRR). Specifically, we announce a priority for an RRTC on Health and Function of Individuals with Physical Disabilities. The Assistant Secretary may use this priority for competitions in fiscal year (FY) 2014 and later years. We take this action to focus research attention on an area of national need. We intend the priority to contribute to improved outcomes of health and function of individuals with physical disabilities.

DATES: This priority is effective July 10, 2014.

FOR FURTHER INFORMATION CONTACT: Patricia Barrett, U.S. Department of Education, 400 Maryland Avenue SW., Room 5142, Potomac Center Plaza (PCP), Washington, DC 20202–2700. Telephone: (202) 245–6211 or by email: *patricia.barrett@ed.gov.*

If you use a telecommunications device for the deaf (TDD) or a text telephone (TTY), call the Federal Relay Service (FRS), toll free, at 1–800–877–8339.

SUPPLEMENTARY INFORMATION: *Purpose of Program:* The purpose of the Disability and Rehabilitation Research Projects and Centers Program is to plan and conduct research, demonstration projects, training, and related activities, including international activities, to develop methods, procedures, and rehabilitation technology that maximize the full inclusion and integration into society, employment, independent living, family support, and economic and social self-sufficiency of individuals with disabilities, especially individuals with the most severe disabilities, and to improve the effectiveness of services authorized under the Rehabilitation Act of 1973, as amended (Rehabilitation Act).

Rehabilitation Research and Training Centers

The purpose of the RRTCs, which are funded through the Disability and Rehabilitation Research Projects and Centers Program, is to achieve the goals of, and improve the effectiveness of, services authorized under the Rehabilitation Act through well-designed research, training, technical assistance, and dissemination activities in important topical areas. These activities are designed to benefit rehabilitation service providers, individuals with disabilities, family members, policymakers, and other research stakeholders. Additional information on the RRTC program can be found at: *http://www2.ed.gov/programs/rrtc/index.html.*

Program Authority: 29 U.S.C. 762(g) and 764(b)(2).

Applicable Program Regulations: 34 CFR part 350.

We published a notice of proposed priority (NPP) for this program in the **Federal Register** on March 3, 2014 (79 FR 11738). That notice contained background information and our reasons for proposing the particular priority.

There are no differences between the proposed priority and this final priority.

Public Comment: In response to our invitation in the notice of proposed priority, six parties submitted comments on the proposed priority.

Generally, we do not address technical and other minor changes, or suggested changes the law does not authorize us to make under the applicable statutory authority. In addition, we do not address general comments that raised concerns not directly related to the proposed priority.

Analysis of Comments and Changes: An analysis of the comments and of any changes in the priority since publication of the NPP follows.

Comment: One commenter questioned the need for this priority.

Discussion: This priority, creating an RRTC on Health and Function of Individuals with Physical Disabilities, would help achieve the goals of, and improve the effectiveness of services authorized under, the Rehabilitation Act. By creating an RRTC on Health and Function for Individuals with Physical Disabilities, we are fulfilling the purposes established in NIDRR's Long-Range Plan for Fiscal Years 2013–2017 (Plan), which was published in the **Federal Register** on April 4, 2013 (78 FR 20299). More specifically, as we discuss in the NPP, there is a need to better understand how specific health problems are interrelated with optimal health and function; how they may affect community participation, work productivity, and quality of life; and how they may be prevented or mitigated. We believe this priority will focus research attention on this area of national need.

Changes: None.

Comment: One commenter recommended that the RRTC should focus on technology-based interventions to improve health and function outcomes of individuals with disabilities.

Discussion: NIDRR agrees that technology can be used to improve the health and function outcomes of individuals with physical disabilities. This is one of five broad areas described in the priority, under which applicants can propose research and related activities. NIDRR does not wish to limit applicants' ability to address the other areas in the priority by requiring a focus