Postmarketing Safety Reports for Human Drug and Biological Products: Electronic Submission Requirements – Final Rule

RIN # 9010-AF96

SUPPORTING STATEMENT

A. Justification

1. Circumstances Making the Collection of Information Necessary

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

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

The final rule requires the use of an electronic format for the submission of postmarketing safety reports, which is an important step toward improving the Agency's systems for collecting and analyzing these reports. The rule: (1) Eliminates the time and costs associated with submitting paper reports (for industry) and converting data from paper reports into electronic format for review and analysis (for the Agency); (2) Expedites the Agency's access to safety information and provide data to the agency in a format that would support more efficient and comprehensive reviews; and (3) Enhances our ability to rapidly communicate information about suspected problems to health care providers, consumers, applicants, and sponsors within the United States and internationally in support of FDA's public health mission.

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

Section 11.2(b)(2) currently provides that regulatory submissions may be voluntarily provided to the Agency in electronic form if the submissions are identified by FDA in its electronic submissions public docket as submissions the agency will accept in electronic form.[1] Postmarketing safety reports for drug and nonvaccine biological products have been identified in the docket as submissions the agency can accept in electronic format. If the reporter elects to file the safety report in electronic format rather than on paper, current §§ 310.305(d), 314.80(f), and 600.80(f) require that the ICSRs in the electronic report include the same information as the paper FDA Form 3500A or CIOMS I form. Accordingly, under current regulations, an ICSR submission can take the form of a paper FDA Form 3500A, a paper CIOMS I form, or comparable information submitted in electronic format. Each of these is a different method of transmitting to FDA the same basic elements of the ICSR, whether on paper or in electronic format. ICSR attachments and the descriptive information portions of periodic safety reports may also be submitted electronically.

Adverse experience reporting for vaccine products may be submitted to the Vaccine Adverse Event Reporting System (VAERS). VAERS is a computerized information database designed to support the Centers for Disease Control and Prevention's (CDC's) and FDA's postmarketing surveillance program for vaccine products. Postmarketing ICSRs for vaccines can be submitted on a VAERS paper form[2] or reported on-line using the VAERS secure web-based system[3]. Each of these is a different method of transmitting to CDC/FDA the same basic elements of the ICSR. Currently, VAERS does not have the capability to receive electronic ICSRs submitted through the FDA's electronic submissions gateway. However, developments are underway to implement this submission capability.

2. Purpose and Use of the Information Collection

FDA is requiring that all postmarketing safety reports for human drugs and biological products be submitted in electronic format. Requiring submission of these 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 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 an all electronic system that would increase the accuracy of information and reduce the need for manual data entry. The final rule will expedite the identification of emerging safety problems, improve the speed and efficiency of industry and agency operations, and further the international harmonization of

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

2 The VAERS form can be accessed on the Internet at http://secure.vaers.org/vaersdataentryintro.htm.

3 Report on-line at https://secure.vaers.org

safety reporting.

3. Use of Improved Information Technology and Burden Reduction

The final rule uses improved information technology by requiring that all postmarketing safety reports for human drugs and biological products be submitted in electronic format instead of current paper-based submissions.

4. Efforts to Identify Duplication and Use of Similar Information

This rulemaking would not result in duplicate reporting. Electronic format submissions would replace current paper-based submissions, unless a waiver request is granted.

5. Impact on Small Businesses or Other Small Entities

The final rule discusses the impact of the rulemaking on small entities, and concludes that because the average small entity submits very few safety reports and the Agency's Web-based method to submit reports electronically would require little additional cost per report, the final rule would not have a significant economic impact on a substantial number of small entities.

6. Consequences of Collecting the Information Less Frequently

The following benefits could not be achieved without the final rule: (1) Eliminate the time and costs associated with submitting paper reports (for industry) and converting data from paper reports into electronic format for review and analysis (for the Agency); (2) Expedite the agency's access to safety information and provide data to the Agency in a format that would support more efficient and comprehensive reviews; and (3) Enhance our ability to rapidly communicate information about suspected problems to health care providers, consumers, applicants, and sponsors within the United States and internationally in support of FDA's public health mission.

7. Special Circumstances Relating to the Guidelines in 5 CFR 1320.5

There are no special circumstances for the collection of information.

8. Comments in Response to the Federal Register Notice and Efforts to Consult Outside the Agency

FDA published a proposed rule for public comment in the FEDERAL REGISTER of 08/21/2009 (74 FR 42184). There were seven comments received, but none of the comments pertained to the information collection.

9. Explanation of Any Payment or Gift to Respondents

FDA has not provided and does not intend to provide any payment or gift to respondents under this provision.

10. Assurance of Confidentiality Provided to Respondents

Confidentiality of the information submitted is safeguarded by 21 CFR 314.430 and 21 CFR part 20.

11. Justification for Sensitive Questions

This information collection does not contain questions pertaining to sex, behavior, attitude, religious beliefs, or any other matters that are commonly considered private or sensitive in nature.

12. Estimates of Annualized Burden Hour and Costs

12a. Annualized Hour Burden Estimate

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.

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	No. of Respondents	No. of Responses Per Respondent	Total Annual Responses	Average Burden Per Response	Total Hours
	Waivers--Electronic Format for Submissions					
31	310.305(e)(2)	1	1	1	1	1
31	314.80(g)(2)	5	1	5	1	5
32	329.100(c)(2)	1	1	1	1	1
60	600.80(h)(2)	5	1	5	1	5
60	600.81(b)(2)	1	1	1	1	1
	Total Reporting Burden					13

12b. Annualized Cost Burden Estimate -- 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	No. of Respondents	No. of Responses per Respondent	Total Annual Responses	Average Burden 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	409,800	1.1	450,780

Annualized Cost Burden Estimate -- 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	No. of Respondents	No. of Responses per Respondent	Total Annual Responses	Average Burden 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

Annualized Cost Burden Estimate -- 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	No. of Respondents	No. of Responses per Respondent	Total Annual Responses	Average Burden 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

Annualized Cost Burden Estimate -- 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 "Guidance 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"

	No. of Respondents	No. of Responses per Respondent	Total Annual Responses	Average Burden 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

Annualized Cost Burden Estimate -- 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).

13. Estimates of Other Total Annual Costs to Respondents and/or Recordkeepers/Capital Costs

As explained in section VI of the final rule (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.

14. Annualized Cost to the Federal Government

The final rule describes the reductions that will result from this rulemaking in FDA's current costs associated with processing postmarketing safety reports that are received via paper format. By receiving these reports electronically, FDA will be able to access the safety information more quickly and also reduce data entry errors that could occur during entry of the information from the paper reports into the electronic system, and will result in quicker access to postmarketing safety information and faster identification of safety problems. The final rule will also reduce the Agency's costs for converting paper records in a variety of formats into electronic form. Resources that are now used to manually enter the reports into FDA's electronic database could be redirected to monitoring drug safety or other agency initiatives.

15. Explanation for Program Changes or Adjustments

The information collection request revises the currently approved collection under OMB Control No. 0910-0770. The "Stage of Rulemaking" was mistakenly entered in ROCIS as a Proposed Rule, and should have been entered as a Final Rule. There are no other changes to this information collection request.

16. Plans for Tabulation and Publication and Project Time Schedule

No comprehensive tabulation of the data is planned or anticipated.

17. Reason(s) Display of OMB Expiration Date is Inappropriate

The FDA forms involved in this collection will continue to display the OMB expiration date.

18. Exceptions to Certification for Paperwork Reduction Act Submissions

There are no exceptions to the certification.