SUPPORTING STATEMENT

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

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 proposed rule would require the use of an electronic format for the submission of postmarketing safety reports, which would be an important step toward improving the agency's systems for collecting and analyzing these reports. The proposal would: (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.

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),

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

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

3. Use of Improved Information Technology and Burden Reduction

The proposed 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

---

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

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

Section VI (Analysis of Impacts) of the proposed rule discussed the impact of the rulemaking on small entities, and concludes: "Because the average small entity submits very few safety reports and the agency's proposed Web-based method to submit reports electronically would require little additional cost per report, the agency does not believe that this proposed rule would have a significant economic impact on a substantial number of small entities."

6. Consequences of Collecting the Information Less Frequently

The following benefits could not be achieved without the proposed 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

None of the collection requirements are inconsistent with 5 CFR 1320.5(d)(2).

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

The public will have the opportunity to comment on the proposed rule. All comments will be summarized and responded to in the final rule.

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 Hour Burden and Costs

Annualized Hour Burden --

The proposed rule would amend FDA's postmarketing safety reporting regulations for human drug and biological products, under parts 310, 314 and 600, to require that persons subject to mandatory reporting requirements submit safety reports in an electronic format that FDA can process, review, and archive. Under §§ 310.305, 314.80, 314.98 and 600.80, manufacturers, packers, and distributors, and applicants with approved NDAs, ANDAs and BLAs and those that market prescription drugs for human use without an approved application must currently submit postmarketing safety reports to the agency. Under § 600.81, applicants with approved BLAs must currently submit biological lot distribution reports to the agency. In this rule, FDA is proposing to require that these postmarketing reports be submitted to the agency in an electronic format that FDA can process, review and archive. We also propose to add language to these sections which states that FDA will periodically issue guidance on how to provide the electronic submissions (e.g., method of transmission, media, file formats, preparation and organization of files). This rule does not change the content of these postmarketing reports. It only proposes to require that they be submitted in an electronic form. Under §§ 310.305(e)(2), 314.80(g)(2), 600.80(g)(2), and 600.81(b)(2), we are also proposing to permit manufacturers, packers, and distributors, and applicants with approved NDAs, ANDAs and BLAs and those that market prescription drugs for human use without an approved application to request a waiver from the electronic format requirement.

We currently have OMB approval for submission of postmarketing safety reports to FDA under parts 310, 314, and 600. The information collection for part 310 and part 314 is approved under OMB Control Numbers 0910-0291 (Form 3500A) and 0910-0230. The information collection for part 600 is approved under OMB Control Numbers 0910-0291 (Form 3500A) and 0910-0308. We do not expect that the burdens currently estimated, under parts 310, 314 and 600, for submission of postmarketing safety reports to FDA for human drugs and biological products would change as a result of this proposed rule. This is because: (1) Current burden estimates associated with these regulatory requirements have taken into account voluntary submission of these reports in an electronic format and those applicants, manufacturers, packers, and distributors that already submit these reports in an electronic format would have no new reporting burdens, and (2) new burdens for establishing the means for submitting postmarketing safety reports in electronic form to comply with this proposed rule, including obtaining an electronic certificate, revising SOPs, and familiarity with the system, would be negated by the savings in burden from not having to print out the report and mail it to FDA. These assumptions also apply to applicants submitting biological lot distribution reports under proposed § 600.81. We invite comment on the number of respondents not currently submitting safety reports in electronic format who would need to convert from paper submission. We also invite comment on the reduction in burden associated with not printing out reports and mailing them to FDA and

whether this burden reduction is offset by the cost associated with obtaining an electronic certificate, revising SOPs, and familiarizing firms with the system.

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

In Table 1, we have estimated the burdens associated with submission of waivers, under proposed § 310.305(e)(2), 314.80(g)(2), 600.80(g)(2), 600.81(b)(2), and 21 U.S.C. 379aa((b) and (c)). We expect very few waiver requests (for reasons explained in section III.C of the proposed rule). We estimate that approximately one manufacturer would request a waiver annually under §§ 310.305(e)(2), 600.81(b)(2), and 21 U.S.C. 379aa((b) and (c)), and five manufacturers would request a waiver annually under §§ 314.80(g)(2) and 600.80(g)(2). We estimate that each waiver request would take approximately 1 hour to prepare and submit to us.

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

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

Table 1.--Estimated Annual Reporting Burden For This Proposed Rule

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

Reporting Cost –

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

Tables 2-5 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 above, 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

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

Reporting Cost –

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

Table 3.-- OMB Control Number 0910-0230

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

Reporting Cost –

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

Table 4.-- OMB Control Number 0910-0308

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

Table 4.-- OMB Control Number 0910-0308

21 CFR Sections	Number of Respondents	Number of Responses Per Respondent	Total Annual Responses	Hours Per Response	Total Hours
Total					636,430

Reporting Cost –

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

Table 5.-- OMB Control Number 0910-0636

21 CFR Sections	Number of Respondents	Number of Responses Per Respondent	Total Annual Responses	Hours Per Response	Total Hours
Reports of serious adverse drug events (21 U.S.C. 379aa((b) and (c))	50	250	12.500	2	25,000
Total					25,000

Reporting Cost –

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

13. Estimates of Other Total Annual Cost Burden to Respondents and Recordkeepers

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

14. Annualized Cost to the Federal Government

Section VI (Analysis of Impacts) of the proposed rule describes the reductions that would 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 would be able to access the safety information more quickly and also reduce data entry errors that could occur during entry of the information from the paper reports into the electronic system, and would result to quicker access to postmarketing safety information and faster identification of safety problems. The proposed rule would also reduce the agency's costs for

converting paper records in a variety of formats into electronic form. Resources that are now used to manually enter the reports into FDA's electronic database could be redirected to monitoring drug safety or other agency initiatives. More specifically, the analysis states that FDA currently receives more than 445,000 postmarketing ICSRs per year. In fiscal year 2006, 65 percent of ICSRs (15-day Alert and periodic) were submitted in paper form. It takes from 3 to 14 days before a submitted paper record of a 15-day Alert report is available for analysis in the AERS database. Periodic ICSRs submitted on paper may not be entered into AERS for up to 60 days. With a standardized electronic format, records would become available for analysis in AERS as soon as they were processed by FDA (within 2 days of receipt by the agency). In addition, FDA currently spends about $5.4 million annually on conversion of paper ICSRs to an electronic format, which includes data entry and quality control. The proposal would result in reduced costs associated with controlling and ensuring the quality of the data. Assuming that the number of reports remains fairly constant over time, the proposal would save about $2.4 million annually in contracting costs by not having to convert paper copies to an electronic format.

15. Explanation for Program Changes or Adjustments

This request for OMB approval is for a proposed rule and has not been submitted previously.

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 statement identified in Item 19, A Certification for Paperwork Reduction Act Submission, of OMB Form 83-I.