DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

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

Docket No. FDA- 2008-N-0334

Final Regulatory Impact Analysis
Final Regulatory Flexibility Analysis
Unfunded Mandates Reform Act Analysis

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I. Introduction

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 (Public Law 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 certifies 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 (2012) 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.

II. Regulatory Impact Analysis

A. Summary

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 final rule affects all persons required to submit postmarketing safety reports under §§ 310.305, 314.80, 314.98, 600.80, 600.81, and section 760 of the FD&C Act. This rule will not change the content of the postmarketing safety reports or the frequency of required reporting. The final rule is part of the Agency's initiative to adopt electronic technologies to improve the quality of our operations and increase our efficiency.

The major benefit of this final rule would be to public health. FDA will have quicker access to postmarketing safety information, which will allow for more efficient reviews of safety data and will enhance our ability to rapidly disseminate information to health care providers, consumers, applicants, sponsors, and other regulatory authorities in support of FDA's public health mission. In addition, 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.

Requiring electronic submission of postmarketing safety reports is necessary because the majority of the benefits from increased effectiveness of FDA use of adverse drug experience reports will accrue to the Agency and to public health, while the costs are borne by industry.

Many firms lack sufficient private incentive to divert resources to develop electronic submission capabilities on their own, at least in the short run. In other words, for many firms, the expected present value of the cost savings from eliminating paper reports is less than the cost of switching to electronic reports. Without required electronic submissions, the Agency would need to maintain adequate resources to convert paper reports to electronic records until all companies adopt an electronic submission format, possibly years in the future. Although this rule, in part, could merely shift costs of adopting the electronic format from FDA to industry, the additional social benefit arises from the increased speed and effectiveness of FDA analyses and action based on adverse drug experience reports. The need for requiring electronic submission of postmarketing safety reports stems from the benefits to the public health from more rapid identification and action on adverse drug experiences.

FDA currently accepts postmarketing safety reports submitted electronically using ICH standards. Both the EU and Japan have mandated electronic submissions for postmarketing safety reports using these standards. The final rule requiring electronic submission of postmarketing safety reports will allow FDA to review the safety reports more quickly and will facilitate the exchange of appropriate information among these regulatory bodies. In this way, the final rule may increase the use of international data and international comparisons, which could contribute to more rapid identification and action on serious and unexpected adverse drug experiences.

B. Benefits

Once implemented, the rule will reduce FDA's 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 manual entry of the information from the paper reports into our electronic system. The major benefits of this rule are to the Agency and public health in terms of quicker access to postmarketing safety information, which in turn should lead to faster identification of safety problems. The rule will also reduce the Agency's costs for converting paper records in a variety of formats into electronic form. Resources that are used to manually enter the reports into FDA's electronic database can be redirected to monitoring drug safety and to other Agency initiatives.

In 2010, more than 644,000 postmarketing 15-day Alert and periodic ICSRs were entered into the AERS database. Approximately 88 percent of the ICSRs that were entered into AERS were submitted electronically. That is more than double the 2006 rate we reported in the proposed rule. At this time, it takes an average of 10 days before a submitted paper record of a 15-day Alert report is available for analysis in the FAERS database. Periodic ICSRs submitted on paper may not be entered into FAERS for up to 60 days. With a standardized electronic format, records will become available for analysis in the FAERS database as soon as they are processed by FDA (generally within 2 days of receipt by the Agency). We also receive about 14,000 reports to VAERS and 172 lot distribution reports annually. A rule to require electronic submissions is still necessary even with the dramatic increase over time in the electronic submission of ICSRs because only about 100 firms are using the ESG, while there are over 2,000 firms subject to this rule.

The Agency currently spends about $14.21 to process a paper postmarketing safety report, while the cost of processing an electronic report is $3.36, less than 25 percent of the cost to process a paper report.[1] The final rule will also result in reduced costs associated with controlling and ensuring the quality of the data. Assuming that the number of reports remains

[1] Cost to convert paper reports to electronic format from FDA FAERS data entry contract.

fairly constant over time and the same cost structure and percent of electronically submitted reports submitted to FAERS are electronically submitted to VAERS and the lot distribution database, we estimate that we would save about $800,000 annually in processing costs by not having to convert paper copies to an electronic format. [((644,000 + 14,000 + 172) × 0.12 × $14.21) – ((644,000 + 14,000 + 172) x 0.12 × $3.36)]

Obtaining postmarketing safety reports in an electronic format is an important and necessary step toward attaining the public health benefits associated with more timely identification of drug safety problems. Furthermore, using internationally harmonized data standards enables more efficient use of industry resources and facilitates sharing of important safety information between FDA and regulators in other countries.

C. Costs

FDA estimates that there are approximately 2,200 firms affected by this rule. Table 1 lists the number of firms affected by type of product marketed. To comply with the rule, firms will incur one-time costs to modify SOPs and train appropriate personnel on the new procedures. There will not be any change in the actual time required to research and prepare the report, nor are there any additional reporting requirements as a result of this final rule.

As explained previously in this document, firms marketing nonprescription drug products without an approved application are subject to safety reporting requirements as a result of section 760 of the FD&C Act. This final rule requires that these reports be submitted in an electronic format that FDA can process, review, and archive. Because the final rule does not change the substantive reporting requirements of section 760 of the FD&C Act, in this analysis, we are only accounting for the cost to submit the report in electronic format, not the cost to set up a reporting system and research and prepare the reports.

1. One-time Cost: Rewriting SOPs

Almost all companies will have to make some changes to their SOPs to reflect the different requirements for electronic submission as opposed to mailing the reports to the Agency. Most companies that submit postmarketing safety reports to FDA on paper are small and submit few safety reports to the Agency. In the proposed rule, we estimated that for small companies submitting reports using the Web-based system described in the proposed rule, it would require about 10 hours to change SOPs and to train the appropriate employees; we estimated that companies with proprietary computer systems used to generate and store safety reports would require about 50 hours for this task. We received some comments on the proposed rule suggesting that we underestimated the time needed for both Web-based and ICH-compatible database systems; however, no alternative estimates were suggested. Based on the comments, we have reconsidered our estimates and increased the time required for these requirements for some types of firms. We estimate 10 hours to change SOPs and train appropriate personnel for medical gas firms. For drug and biologic firms submitting small numbers of reports using the SRP or the eSubmitter tool (for vaccine reports), we estimate the time required to be 20 hours, and for firms submitting large numbers of reports using the ICH-compatible database-to-database system, 100 hours.

About 1,200 medical gas firms would require 10 hours each, about 500 drug and biologic firms would require 20 hours each, and about 150 drug or biologic firms would require 100 hours each to modify SOPs and train the appropriate personnel. (These figures exclude firms primarily marketing nonprescription drug products without an approved application, which are discussed separately, in the next paragraph of this document.) At an average wage rate including benefits of $79 per hour, the total one-time incremental cost for this requirement is about $2.9

million [(1,200 × 10 hours x $79) + (500 × 20 hours x $79) + (150 × 100 hours × $79)] (see table 1 of this document).[2] A small subset of biological product firms (about 40) that are required to submit lot distribution reports will also have to change SOPs to reflect the requirement that these reports be submitted electronically. We estimate these firms will require about 20 hours to modify their SOPs and train the appropriate personnel for a total one-time cost of $63,200 (20 hours × 40 firms × $79).

Firms producing primarily nonprescription drug products without an approved application will have to establish SOPs for submitting ICSRs in electronic format. We estimate that it will take between 24 and 40 hours to write the new SOPs and another 5 to 10 hours to train the appropriate personnel, depending on the size of the firm (Ref. 1). At an average wage cost of $79 per hour, and at the mid-point of the range of hours, the cost would be about $1.1 million (40 hours x $79 × 345 firms).

2. One-time Cost: Training Costs to Prepare Reports for Submission

ICSRs will be submitted electronically to FDA using one of three methods: Using the SRP (designed for firms with small numbers of reports for FAERS), the eSubmitter tool (designed for firms with small numbers of reports for VAERS), or by transmitting reports directly from the firm's database electronically through the ESG in accordance with ICH E2B standards. To submit ICSRs and ICSR attachments using the eSubmitter tool or the direct database transmission method, a firm will need to: (1) Establish an ESG account and obtain a digital security certificate and (2) contact the FAERS or VAERS Electronic Submission Coordinator, who will provide advice on how to begin submitting ICSRs electronically.

[2] Wage derived from 2010 Bureau of Labor Statistics Occupation Employment Statistics Survey, standard occupation code 11-3131, training and development manager for pharmaceutical medicine and manufacturing--mean wage rate $56.71 + 40 percent for nonwage benefits and rounded to $79, at http://www.bls.gov.

In the proposed rule, we estimated one-time costs for firms to set up an ESG account and to acquire an electronic certificate for an electronic signature. Recurring costs to maintain the certificate plus, for some firms, the recurring cost to upgrade to high speed Internet access were also estimated as part of the cost of these requirements. We included these costs in the proposed rule because at the time, it was the first proposed rule published by the Agency that required an electronic signature from these firms. At that time, use of electronic signatures and use of the ESG were voluntary. In the interim, since publication of the proposed rule, FDA began requiring all drug and biological product establishments to register and list electronically using FDA's ESG. To do this, firms needed to acquire an ESG account and an electronic certificate to serve as an electronic signature. In the proposed rule, we also estimated the cost for companies that maintained their records in a paper format to convert their periodic reports and any attachments to ICSRs in Portable Document Format (PDF) files. Those costs included purchasing an optical scanner and the appropriate optical character recognition software or paying a service provider, such as a copy center, to transform the documents into an electronic PDF file. These costs are no longer applicable to the final rule because each firm is required to submit registration and listing information electronically via the ESG and, as a part of electronic listing, submit its labeling in SPL format and submit a copy of the product's label in a PDF file. Therefore, for this final rule, we are estimating only the cost to train the appropriate personnel how to properly prepare and submit to FDA electronically the ICSRs, any attachments, and periodic reports.

Large firms that intend to use the direct database-to-database system and are not currently submitting reports electronically will need to train the appropriate personnel on how to prepare and submit the ICSRs and periodic reports using this system. We estimate that 50 hours will be required for this task. Smaller firms will require fewer hours because they have fewer employees

that will need training and will most likely use the SRP or the eSubmitter (for vaccine reports); we estimate that 10 to 20 hours would be required. The total cost for this task would range from $1.8 million to $3.4 million ([(50 hours × 50 firms × $79 per hour) + (10 hours × 2,045 firms × $79)] or [(50 hours × 50 firms × $79 per hour) + (20 hours × 2,045 firms × $79)]).

Table 1.--One-Time Costs by Firm Type

Type of Firm	Total No. of Firms	Modifying SOPs	Training Employees on New Procedures (Low)	Training Employees on New Procedures (High)	Total Low	Total High
Drug and Biologic Products Subject to Parts 310, 314, and 600	650	$1,975,000	$592,500	$987,500	$2,567,500	$2,962,500
Nonprescription Drug Products Marketed Without an Approved Application	345	1,090,200	272,550	545,100	1,362,750	1,635,300
Medical Gas	1,200	948,000	948,000	1,896,000	1,896,000	2,844,000
Submit Lot Distribution Reports	N/A	63,200	N/A	N/A	63,200	63,200
Total	2,195	$4,076,400	$1,813,050	$3,428,600	$5,889,450	$7,505,000
Annualized at 7% Over 10 Years					$838,525	$1,068,543
Annualized at 3% Over 10 Years					$690,423	$879,815

D. Summary of Benefits and Costs

The principal benefit of this final rule will be the public health benefit associated with more rapid processing and analysis of the almost 79,000 ICSRs currently submitted on paper.[3] In addition, requiring electronic submission would reduce FDA's annual operating costs by about $800,000.

The total one-time cost for modifying SOPs and preparing PDF files for electronic submission capabilities is estimated to range from $5.9 million to $7.5 million. The annualized

[3] Data reflecting calendar year 2010.

cost of the final rule, at a 7-percent discount rate over 10 years, would be from $0.8 million to $1.1 million and $0.7 million to $0.9 million at a 3-percent discount rate.

E. Alternatives Considered

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

Another alternative was to allow small entities a longer period of time to comply with the electronic submission requirements. This alternative would have allowed small entities to delay the expense of compliance. This alternative would delay our receiving the full benefits of quicker access to adverse drug event reports. Compliance costs for small entities are estimated to be low, from $2,370 to $3,160 in one-time costs (sum of cost of training and changing SOPs), which should not impose an economic hardship on the small entities.

We also considered requiring electronic submissions but not specifying that the electronic format must be one we can process, review, and archive. This alternative would still eliminate the costs to firms associated with paper submissions. However, because receiving reports in many different electronic formats would continue to require the Agency to convert some of the reports into a standard electronic format that we can process, review, and archive for analysis, this alternative would delay the full public health benefits of quicker FDA access to these reports.

III. Regulatory Flexibility Analysis

FDA has examined the economic implications of the final rule as required by the Regulatory Flexibility Act. If a rule will have a significant economic impact on a substantial number of small entities, the Regulatory Flexibility Act requires agencies to analyze regulatory options that would lessen the economic effect of the rule on small entities. The Small Business Administration defines an entity in the pharmaceutical industry as small if it has fewer than 750 employees and a biologic entity as small if it has fewer than 500 employees. Based on this definition, about 90 percent of the drug and biologic entities are small. The impact on each entity will vary depending on its electronic submission capabilities when the rule is implemented. The incremental costs of this final rule are for the writing of SOPs and employee training and range from $2,370 to $3,160 per small entity. Based on 2007 Economic Census data, the average small drug establishment had value of shipments of $61.0 million and the average small biological products establishment had value of shipments of $38.2 million.

Because the estimated incremental one-time costs per entity are low, even in comparison with annual revenues, and because we received no comments to the contrary, we certify that this final rule will not have an economic impact on a substantial number of small entities.

IV. References

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