DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

Postmarketing Safety Reports for Approved New Animal Drugs; Electronic Submission Requirements

Docket No. FDA-2017-N-6381

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

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I. Introduction

We have examined the impacts of the proposed rule under Executive Order 12866, Executive Order 13563, Executive Order 13771, 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 us 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). Executive Order 13771 requires that the costs associated with significant new regulations "shall, to the extent permitted by law, be offset by the elimination of existing costs associated with at least two prior regulations." We believe that this proposed rule is not a significant regulatory action as defined by Executive Order 12866.

The Regulatory Flexibility Act requires us to analyze regulatory options that would minimize any significant impact of a rule on small entities. Because the costs of the rule are minimal in both absolute value and in comparison to average yearly sales of small firms in this industry, we propose to certify that the proposed rule will not have a significant economic impact on a substantial number of small entities.

The Unfunded Mandates Reform Act of 1995 (section 202(a)) requires us to 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 $148 million, using the most current (2016) Implicit Price Deflator for the Gross Domestic Product. This proposed rule would not result in an expenditure in any year that meets or exceeds this amount.

The purpose of this proposed rule is to require electronic submission of certain postmarketing safety reports for approved new animal drugs. The rule, if finalized, would also provide a procedure for requesting a temporary waiver of the electronic reporting requirement for "good cause" shown, such as a natural disaster. As currently proposed, this rule would not change the content of the postmarketing safety reports or the frequency of the reporting requirements.

Currently, most submitters have chosen, voluntarily, to use electronic submission for the reports that would be affected by this proposed rule. As of 2016, approximately 99.7 percent of postmarketing safety reports eligible for electronic submission were electronically submitted. Thus, this proposed rule would affect a small proportion of these reports.

The major benefits of this proposed rule, if finalized, would be to animal health and the Agency in the form of quicker access to postmarketing safety information; the annual cost savings to the Agency is estimated at $7,535. The present value of these benefits over ten years is $64,272 at a 3 percent discount rate, and $52,920 at a 7 percent discount rate.

Total one-time costs to industry would be $61,311 for changing standard operating procedures (SOPs) and training employees to electronically submit postmarketing safety reports in accordance

with the new SOPs. Recurring costs to the Agency would be $153 per year, for processing the waivers to the electronic reporting requirement. Annualizing these costs over a ten year period, we estimate total annualized costs to be $7,131 at a 3 percent discount rate, and $8,310 at a 7 percent discount rate. The present value of these costs over ten years is $60,823 at a 3 percent discount rate, and $58,368 at a 7 percent discount rate.

Table 1. Summary of Benefits, Costs and Distributional Effects of the Proposed Rule

Category		Primary Estimate	Low Estimate	High Estimate	Units			Notes
					Year Dollars	Discount Rate	Period Covered	
Benefits	Annualized Monetized $/year	$7,535			2016	7%	10 years	
		$7,535			2016	3%	10 years	
	Annualized Quantified					7%		
						3%		
	Qualitative							
Costs	Annualized Monetized $/year	$7,131			2016	7%	10 years	
		$8,310			2016	3%	10 years	
	Annualized Quantified					7%		
						3%		
	Qualitative							
Transfers	Federal Annualized Monetized $millions/year					7%		
						3%		
	From/ To	From:			To:			
	Other Annualized Monetized $millions/year					7%		
						3%		
	From/To	From:			To:			
Effects	State, Local or Tribal Government: Small Business: Will not have a significant impact on a substantial number of small entities. Wages: Growth:							

We have developed a comprehensive Economic Analysis of Impacts that assesses the impacts of the proposed rule. The full analysis of economic impacts is available in the docket for this proposed rule (Ref. FDA-) and at http://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/EconomicAnalyses/default.htm.

II. Regulatory Impact Analysis

A. Background

The purpose of this proposed rule is to require the electronic submission of certain postmarketing safety reports for approved new animal drugs. The proposed rule would also establish a new

procedure for requesting a temporary waiver of the electronic reporting requirement, which would allow paper submissions for "good cause" shown. The proposed rule affects all groups (i.e., both applicants and nonapplicants) required to submit postmarketing safety reports under §§ 514.80(b)(1), 514.80(b)(2)(i), 514.80(b)(2)(ii), 514.80(b)(3), 514.80(b)(4)(iv)(A), and 514.80(b)(4)(iv)(C) of the Federal Food, Drug, and Cosmetic Act. This rule, if finalized, would not change the contents of these postmarketing safety reports or the frequency of the required reporting. These reports are submitted to the Center for Veterinary Medicine (CVM) at the Food and Drug Administration (FDA), FDA District Offices, or local FDA resident posts.

Postmarketing safety reports are an important resource for FDA. These reports are the primary means by which we obtain information regarding problems with the safety or effectiveness of marketed approved new animal drugs, as well as product or manufacturing problems. (Ref. 1) The reports include information regarding the suspected adverse event, such as: the date, the drug, the type of animal affected (including specific animal characteristics), the reporter, whether the drug was used on label or an extralabel manner, and a detailed description of the adverse event. These adverse events and product or manufacturing problems are typically reported to the applicant or nonapplicant by the animal's owner or the treating veterinarian. The reports are then forwarded by the applicant or nonapplicant to CVM or the appropriate FDA District Office or local FDA resident post for review and assessment.

There are several postmarketing safety reports that would be affected by this proposed rule. First is the 3-day alert report (Form FDA 1932) that must be submitted by applicants. This report currently must be submitted on paper to the FDA District Office or local FDA resident post, but an additional copy may also be submitted on paper or electronically directly to CVM. The proposed rule would require that any optional additional copies submitted directly to CVM be submitted electronically.

Second, is the 15-day alert report that applicants must submit to us. If finalized, the proposed rule would require all 15-day alert reports from applicants to be submitted electronically. Product/manufacturing defect and adverse drug experience reports must be submitted by nonapplicants to the applicant, but an additional copy may also be submitted on paper or electronically directly to CVM. The proposed rule would also require that any optional additional copies submitted directly to CVM from nonapplicants be submitted electronically.

Product/manufacturing defect and adverse drug experience reports (including reports of previously not reported adverse drug experiences that occur in postapproval studies) are currently required to be submitted on Form FDA 1932 as an attachment to the periodic drug experience report (Form FDA 2301). The proposed rule, if finalized, would require that these reports be submitted electronically rather than on paper Forms FDA 1932 as an attachment to the periodic drug experience report (Form FDA 2301).

The proposed rule would also create a procedure for requesting from CVM a temporary waiver of the electronic reporting requirement for "good cause" shown (e.g., a natural disaster that makes electronic submission impossible).

B. Market Failure Requiring Federal Regulatory Action

Ensuring that new animal drugs are safe and effective is a key Agency mission. Post-approval marketing surveillance is important to ensure the continued safety and effectiveness of new animal drugs. Drug effects can change over time and other effects may not manifest until years after the approval. Electronic reporting of these postmarketing safety events allows CVM to review, assess, and make a determination on the potential for new issues earlier and faster than when paper reporting is used. Utilizing electronic reporting may therefore increase the health of animals with earlier identification of problems. Additionally, it will save valuable Agency resources, which can be used on other important objectives.

While the vast majority of reports are voluntarily submitted electronically, there are still a small number submitted on paper. The reluctance of these firms to move to electronic reporting may be due to one-off paper reporting by contractors or apprehension of potential costs incurred for business process changes associated with moving to electronic reporting. At the same time, the use of paper-based reporting generates social costs, including government processing costs, which are not internalized by firms when making decisions about the format used for safety reporting. Without regulation, this sub-optimal utilization of electronic reporting is unlikely to resolve itself as long as, for some firms, the private costs exceed the private benefits of electronic reporting when compared with paper-based reporting. Regulation is therefore necessary to generate socially optimal levels of electronic reporting.

C. Baseline Conditions

Currently, the majority of submitters have voluntarily chosen to use electronic submission for the postmarketing safety reports that would be affected by this proposed rule. In calendar year 2016, 99.7% of all postmarketing safety reports eligible for electronic submission were voluntarily submitted electronically. (Table 2) The proposed rule would therefore only affect 0.3% (270) of the reports currently submitted on paper. (This does not include the voluntarily submitted additional copies of the 3-day field reports.) Additionally, from 2011—2015, only 15 companies submitted paper reports. This proposed rule, therefore, would affect only a small number of entities and a small proportion of total reports.

From 2015 through 2016, the number of reports that were submitted on paper dropped significantly. This was due primarily to two factors: (1) some large companies, which submit a large number of reports, switched to completely electronic reporting; and (2) some industry consolidation, whereby larger firms (that submit electronically) bought smaller firms (that may have historically submitted on paper), and all subsequent reports by the new company were submitted electronically. Because we believe that these market changes are permanent, we use the number of 2016 paper reports for this analysis, rather than an average, as the baseline number of reports affected by the rule.

Table 2. Summary of the Baseline Conditions

21 CFR Section or Section of the Act	FDA Form Number	Affected by the Rule	CY2014	CY2015	CY2016
514.80(b)(1)	3-day Field Alert Report1932 (Paper)	No	225	302	337
514.80(b)(1)	3-day Field Alert Report1932 (Additional Copy)	Yes	18	114	95
514.80(b)(2)(i) and (ii) And 514.80(b)(3), together	1932 (Electronic)	No	38,300	41,673	47,978
514.80(b)(4)	1932 (Electronic)	No	49,419	45,389	50,850
514.80(b)(2)(i) and (ii) And 514.80(b)(3) together	1932 (Paper)	Yes	125	242	93
514.80(b)(4)	1932 (Paper) Accompanying 2301	Yes	1570	1059	177

For this analysis, we estimate the costs and benefits of the proposed rule associated with moving from paper reports to electronic reports. However, we do not include the optional additional 3-day field reports in the analysis. We exclude these reports because they are optional copies, and the rule does not change their reporting status (it only mandates that they can only be submitted electronically). We assume that firms using paper reporting will simply stop sending additional copies, rather than incurring the costs of switching to electronic reporting. Because of the optional nature of these reports, we assume this change will incur no additional costs or benefits to firms or FDA.

D. Benefits of this Proposed Rule

The purpose of this proposed rule is to require the electronic submission of certain postmarketing safety reports for approved new animal drugs. By requiring electronic submission, FDA expects that a number of benefits should accrue. First, electronic submission should increase the speed at which CVM is able to review, identify, and analyze new postmarketing events, which could reduce the time it takes to identify any new safety, efficacy, or manufacturing problems. This should increase the potential health and safety of animals. Second, electronic submissions remove the costs to CVM of inputting data from paper submissions into the electronic system. These cost-savings include: reducing the cost of physically handling the paper reports; reducing the cost of manually entering the data from them into the electronic database; and reducing the possibility of errors that can occur during data entry. Resources that are now used to handle paper reports and

manually enter the data could be redirected to other public health initiatives.

The proposed change would assist CVM in more rapidly reviewing postmarketing safety reports, identifying emerging safety problems, and disseminating safety information in support of the public health mission. In addition, the proposed amendments would facilitate international harmonization and exchange of safety information. While these are important benefits of the proposed rule, they are difficult to quantify and monetize. Therefore, the benefits section of this proposed rule will focus on the cost savings to the Agency resulting from eliminating the need to physically handle paper reports and to manually enter the data from them into the electronic database.

The main quantified benefit of this proposed rule, if finalized, would be the cost savings to CVM resulting from eliminating the need to physically handle paper postmarketing safety reports and to enter the data from them into the electronic database. CVM received 270 of the affected postmarketing safety reports in 2016. The primary costs for handling paper reports and entering the data from them into the electronic database are the costs of the Document Control Unit employee time and the data entry contractor time. We estimate that to register, copy, triage, and route a paper report takes a Document Control Unit employee 10 more minutes per report than would be required for an electronically submitted report. We also estimate that it takes a data entry contractor, on average, 15 minutes to enter the data from a paper report into our electronic database, which is unnecessary for electronically submitted reports.

To estimate the cost savings of the time no longer spent processing paper reports, we first estimate the costs of each type of employee. We estimate the cost of the Document Control Unit employee at the standard cost of an FDA FTE, with benefits, which is currently assessed at $120.19 per hour. We estimate the cost of a data entry contractor according to the Bureau of Labor Statistics (BLS) estimate of the average hourly wage for data entry personnel in the medical field, and double the wage to account for benefits and other overhead. (Ref. 2) The BLS hourly wage estimate is $15.19; doubling the wage, we estimate that the average hourly cost of a data entry contractor to process the paper reports is $30.38.

Using the 2016 estimate of 270 paper reports, we calculate the expected annual cost savings of the proposed rule due to decreased costs of processing paper reports to be $7,459 ((270*($120.19/6))+(270*($30.38/4)). Adjusting to 2016 dollar, this becomes $7,535. Accrued over 10 years, the present discounted value of the benefits of this proposed rule is $64,272 (at a 3% discount rate) or $52, 920 (at a 7% discount rate).

E. Costs of this Proposed Rule

There are two main monetized costs associated with this proposed rule. First, there is the one-time cost to firms to comply with the rule. This cost includes both the cost of creating new SOPs to submit the reports electronically and the cost of training employees to electronically submit postmarketing safety reports in accordance with the new SOPs. We estimate that there would be no annually recurring costs to firms because this proposed rule, if finalized, would not change the contents of these postmarketing safety reports or the frequency of the required reporting. The

second cost of the rule is the annual cost to FDA to administer a temporary waiver of the electronic submission requirement.

FDA estimates that approximately 15 firms would be affected by this proposed rule. This estimate is based on the number of firms that, from 2011—2015, submitted a paper postmarketing safety report to CVM. We use this estimate of 15 affected firms when calculating the cost of complying with this rule.

To estimate the one-time cost to firms of complying with this proposed rule, we must calculate two separate costs. First, we calculate the cost of creating new SOPs, and we then calculate the cost of training employees to electronically submit postmarketing safety reports to CVM in accordance with the new SOPs. We assume that there are no capital costs associated with firms implementing this proposed rule (i.e., firms in the pharmaceutical industry already have the computer and internet capacity necessary to electronically submit postmarketing safety reports). We request comment and data on this assumption.

We expect it will take approximately 20 hours per firm to create new SOPs for electronic submission of postmarketing safety reports. (Ref. 3) The SOPs would be created by training and development managers; we use the respective BLS occupation code, 11-3131, for "management, scientific and technical consulting services." (Ref. 4) The mean hourly wage for this group is $50.58, which we double to account for benefits and overhead, for a final hourly wage of $101.16. Therefore, we calculate the per firm cost of creating SOPs to be $2,023.20; adjusting to 2016 dollar, this becomes $2,043.70. With an estimated 15 firms being affected by the rule, we estimate a total one-time cost of creating new SOPs to be $30,655.

The second cost to firms for complying with this proposed rule is associated with training employees to electronically submit postmarketing safety reports in accordance with the new SOPs. We estimate the time per firm to complete this training to also be 20 hours, with the main cost being the time employees spend in this training. (Ref. 3) We use the hourly wage (plus benefits and overhead) of the trainer, who we assume to be the same person who would create the SOP, to proxy for the value of all employee time. Therefore, we estimate the per firm cost of employee training to be $2,043.70, and the total one-time cost of training for all 15 affected firms to be $30,655.

Based on these two cost estimates, we estimate that the total one-time costs to firms to implement this proposed rule would be $61,311, with an average one-time cost per firm of $4,087.39.

There are also costs to FDA associated with this proposed rule. CVM will need to create and administer a waiver process for accepting paper reports on a limited basis. CVM estimates that there would be no more than one waiver request per year, which would take 1.25 hours for staff to review. Assuming an FTE FDA employee cost (salary, plus benefits and overhead) of $120.19 per hour, the annual cost of administering the waiver program would be approximately $150.61. There would also be some diminishment of benefits (in terms of the incremental reduction due to processing paper reports) because of this waiver process. However, the total reduction in benefits would depend on the number of paper reports submitted during the timeframe covered by a waiver. Because we estimate that requests for a waiver would be rare, and because of the uncertainty of

how many paper reports would be submitted during any waiver period, the potential reduction in benefits due to waivers is not estimated here.

Table 3. Costs of the Proposed Rule (in 2016 dollars)

Cost Type	Total Cost in Year 1	Total Costs in Year 2 and each subsequent year
For Firms		
SOP Creation (one-time)	$30,655	
Training (one-time)	$30,655	
For FDA		
Waiver Process (annual)	$150.61	$150.61
Total	$61,153.61	$150.61

F. Summary of Benefits and Costs

The principal unquantified benefit of this proposed rule would be the animal health benefits associated with more rapid processing and analysis of postmarketing safety reports submitted on paper. The principal quantified benefit of this proposed rule is the expected annual cost savings to FDA of $7,535 due to decreased costs of physically handling paper reports and manually entering the data from them into the electronic database.

The total one-time costs to affected industry are creating new SOPs and training employees to electronically submit postmarketing safety reports to CVM in accordance with the new SOPs, and are estimated at $61,311. The annual cost to the FDA of administering the waiver process is estimated at $151. Additional costs to FDA of processing the paper reports during a waiver period are not quantified, due to uncertainty surrounding the number of reports that may be submitted.

Table 4. Summary of the Costs and Benefits of the Proposed Rule (in 2016 dollars)

	Year 1 Effects	Year 2 and Each Subsequent Year Effects	Annualized Over a 10-Year Period	
Costs			3% discount rate	7% discount rate
For Firms				
SOP Creation	$30,655	-	$3,701	$3,846
Training	$30,655	-	$3,701	$3,846
For FDA				
Waiver Process	$151	$151	$151	$151
Total	$61,311	$151	$7,131	$8,310

Benefits				
FDA Costs Savings from More Efficient Report Processing	$7,535	$7,535	$7,535	$7,535

G. Alternatives Considered

The rule proposes a 12-month compliance period. In this analysis, we consider two alternative regulatory approaches: requiring compliance with the rule within 6 months, and requiring compliance within 18 months. It is expected that shortening the timeframe for compliance with the rule would allow the unquantified benefits of the rule to accrue earlier. However, cost to firms would increase, although this increase is not substantial. (Table 5)

Table 5. Changes to the Costs & Benefits of the Proposed Rule Under a 6-month Regulatory Compliance Period (in 2016 dollars)

	Present Value		Annualized Costs Over a 10-Year Period	
	3% discount rate	7% discount rate	3% discount rate	7% discount rate
Costs				
6-month compliance period	$61,728	$60,376	$7,237	$8,596
Difference from 12-month compliance period	$906	$2,008	$106	$286
Benefits				
6-month compliance period	$65,228	$54,740	$7,647	$7,794
Difference from 12-month compliance period	$957	$1,821	$112	$260

Lengthening the timeline for compliance would decrease costs to firms by allowing more time to implement new SOPs associated with the rule. However, this decrease is also not substantial. (Table 6) Lengthening the compliance period would also decrease the quantified benefits of the proposed rule.

Table 6. Changes to the Costs & Benefits of the Proposed Rule Under an 18-month Regulatory Compliance Period (in 2016 dollars)

	Present Value		Annualized Costs Over a 10-Year Period	
	3% discount rate	7% discount rate	3% discount rate	7% discount rate
Costs				
18-month compliance period	$59,931	$56,247	$7,025	$8,034

Difference from 12-month compliance period	$(892)	$(1,941)	$ (105)	$(277)
Benefits				
18-month compliance period	$63,328	$51,159	$7,424	$7,284
Difference from 12-month compliance period	$(942)	$(1,761)	$(110)	$ (251)

Note: Numbers in parentheses denote a reduction relative to the proposed rule impacts.

III. Small Entities Analysis

We have examined the economic implications of this proposed 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 1,250 employees.

We estimate that up to 15 firms would be affected by this proposed rule. (From 2011—2015, 15 firms submitted at least one postmarketing safety report in paper format.) To determine whether these firms are small businesses, we analyzed the number of employees that each firm had using Dun & Bradstreet. We found that 11 of these firms would be considered small businesses under the Small Business Administration definition.

The one-time costs of implementing this proposed rule per firm was estimated at $4,087.39. Of the 11 small business firms that may be affected by this rule, for which Dun & Bradstreet had sales data, the mean yearly sales per firm is $42 million (minimum of $104,000 and maximum of $222 million).

Because the estimated one-time costs per firm are low, even in comparison with annual revenues, we propose to certify that this rule, if finalized, will not have a significant economic impact on a substantial number of small entities.

IV. References

(1) Food and Drug Administration. "Veterinary Adverse Event Reporting for Manufacturers". 2016. http://www.fda.gov/AnimalVeterinary/SafetyHealth/ReportaProblem/ucm212682.htm.

(2) Bureau of Labor Statistics. "Occupational Employment and Wages, May 2015: 43-9021

Data Entry Keyers". 2016. http://www.bls.gov/oes/current/oes439021.htm.

(3) 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.

(4) Bureau of Labor Statistics. "Occupational Employment and Wages, May 2015: 11-3131 Training and Development Managers". 2016. http://www.bls.gov/oes/current/oes113131.htm.