IDEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Postmarketing Safety Reporting for Combination Products

Docket No. FDA-2008-N-0424

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

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Table of Contents

I. Introduction and Summary 3

A. Introduction 3

B. Summary of Costs and Benefits 4

C. Comments on the Preliminary Regulatory Impact Analysis and Our Responses 6

II. Final Regulatory Impact Analysis 6

A. Background 6

B. Need for the Rule 8

C. Purpose of the Rule 8

D. Baseline Conditions 9

E. Benefits of the Rule 10

F. Costs of the Rule 11

1. Affected Entities 11

2. Administrative Costs 11

3. Reporting Costs 13

4. Total Costs of the Rule 18

G. International Effects 19

H. Uncertainty Analysis 19

III. Final Small Entity Analysis 19

A. Description and Number of Affected Small Entities 19

B. Description of the Potential Impacts of the Rule on Small Entities 20

I. Introduction and Summary

A. Introduction

We have 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 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). We have developed a comprehensive Economic Analysis of Impacts that assesses the impacts of the final rule. We believe that this final 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 final rule essentially describes the application of existing postmarketing safety reporting regulations to certain combination products, we certify that the final 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 issuing "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 $146 million, using the most current (2015) Implicit Price Deflator for the Gross

Domestic Product. This final rule would not result in an expenditure in any year that meets or exceeds this amount.

B. Summary of Costs and Benefits

The final rule will generate one-time administrative costs from reading and understanding the rule, assessing current compliance, modifying existing standards of practice, changing storage and reporting software, and training personnel on the requirements under this rule. Firms that do not currently comply with the reporting requirements specified by the final rule will also incur annual reporting costs from the submission of field alert reports, 5-day reports, malfunction reports, correction or removal reports, and biological product deviation reports, as applicable. The annualized total costs of the rule are between $1.36 and $2.68 million at a 7 percent discount rate and between $1.35 and $2.65 million at a 3 percent discount rate.

The final rule will benefit firms through reduced uncertainty about the reporting requirements for their specific combination product and through decreased potentially duplicative reporting. The final rule will also benefit public health by helping to ensure that important safety information is submitted and directed to the appropriate components within the Agency, so that we may receive and review this important information in a timely manner for the protection of public health.

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

Category		Primary Estimate	Low Estimate	High Estimate	Units			Notes
					Year Dollars	Discount Rate	Period Covered	
Benefits	Annualized Monetized $millions/year				2016	7%	10 years	
					2016	3%	10 years	
	Annualized Quantified				2016	7%	10 years	
					2016	3%	10 years	
	Qualitative	Firms will benefit from reduced uncertainty about reporting requirements. The rule will benefit public health by helping to ensure Agency components' timely receipt of postmarketing safety reports.						
Costs	Annualized Monetized $millions/year		$1.36	$2.68	2016	7%	10 years	
			$1.35	$2.65	2016	3%	10 years	
	Annualized Quantified				2016	7%	10 years	
					2016	3%	10 years	
	Qualitative							
Transfers	Federal Annualized Monetized $millions/year				2016	7%	10 years	
					2016	3%	10 years	
		From:			To:			
	Other Annualized Monetized $millions/year				2016	7%	10 years	
					2016	3%	10 years	
		From:			To:			
Effects	State, Local or Tribal Government: Small Business: Wages: Growth:							

C. Comments on the Preliminary Regulatory Impact Analysis and Our Responses

Comment 1. Some comments suggested that the economic analysis for the proposed rule underestimated the incremental administrative cost to comply with the rule. In particular, two comments noted that we did not estimate the cost of change to computerized reporting systems, which could represent a large one-time cost to manufacturers. Another comment suggested that we include the cost to train personnel on the reporting requirements.

Response 1. We agree that the analysis for the proposed rule underestimated the one-time administrative costs of the rule. In the final economic analysis, we have included estimates of the costs to change electronic reporting and storage systems, and to train personnel on the requirements under this rule. We also estimated the cost to read and understand the rule and assess current compliance.

Comment 2. A comment suggested that we underestimated the time needed to prepare postmarketing safety reports.

Response 2. We agree that we underestimated the incremental time needed to prepare some of the reports required by the rule, and increased our cost estimates in response. However, we note that our estimates reflect the incremental increase in the time to prepare and submit postmarketing safety reports from this rule, not the time it takes to research, prepare, and submit a complete report.

II. Final Regulatory Impact Analysis

A. Background

A combination product may be a drug-device, biologic-device, drug-biologic, or drug-device-biologic. There are three categories of combination products. When a single product

physically, chemically, or otherwise combines or mixes two or more regulated components, it forms a "single-entity" combination product. A "co-packaged" combination product consists of two or more separate products combined in the same package or packaged together as a unit. Finally, a "cross-labeled" combination product consists of a separately packaged drug and device, biologic and device, drug and biologic or drug, device and biologic that are intended for use with one another (investigational or approved) where each is required to achieve the intended use, indication, or effect of the combination product, among other criteria.

We refer to the regulated components (drug, device, or biological product) of a combination product as the "constituent parts." For example, a pre-filled syringe consists of a device constituent part (the syringe) and a drug constituent part (the drug within the syringe). From a regulatory perspective, the combination product retains the regulatory identities of its constituent parts. In regards to postmarketing safety reporting, in general the safety reporting requirements for each constituent part of a combination product apply to the combination product itself. For example, for a drug-device combination product, in general the postmarketing safety reporting requirements for both drugs and devices apply to that product.

The postmarketing safety reporting requirements for drugs, devices, and biological products share many similarities and have a common purpose – to protect the public health by monitoring a product's continued safety and effectiveness. Although similar, each set of regulations has certain reporting standards and timeframes with unique requirements based in part on the characteristics of the type of product.

In this final rule, we included definitions for "applicant," "combination product applicant," and "constituent part applicant," to help clarify which entities are subject to which duties under this rule. Moreover, we explain which postmarketing safety reporting requirements

apply depending on the application type under which the combination product or constituent part received marketing authorization. For example, combination product applicants and constituent part applicants must comply with the postmarketing safety reporting requirements for medical devices under 21 CFR parts 803 and 806 if their product received marketing authorization under a PMA, PDP, HDE, de novo classification request, or premarket notification submission. Combination product applicants and constituent part applicants must comply with the postmarketing safety reporting requirements for drugs under 21 CFR part 314 if their product received marketing authorization under an NDA or ANDA. Combination product applicants and constituent part applicants must comply with the postmarketing reporting requirements for biological products under 21 CFR parts 600 and 606 if their product received marketing authorization under a BLA. For combination product applicants, the final rule also requires the submission of additional specified reports based on the constituent parts included in the combination product. For constituent part applicants, the final rule also requires that they share with one another certain postmarketing safety information they receive.

B. Need for the Rule

In the past, we did not clearly communicate our expectations for postmarketing safety reporting of combination products. Our lack of clarity about our expectations resulted in confusion in the industry and created inefficiencies in postmarketing safety reporting for combination products. This final rule will remove this institutional failure and help to ensure appropriate and consistent postmarketing safety reporting for certain combination products.

C. Purpose of the Rule

The final rule describes how combination product applicants and constituent part applicants must comply with the postmarketing safety reporting regulations for their products. A rule specifically addressing combination products can clarify for industry how to apply these largely similar provisions to combination products, and avoid applying potentially duplicative or unnecessary requirements.

D. Baseline Conditions

Using FDA registration and listing data, we find that there are approximately 1,076 combination products on the market, produced by approximately 466 firms. The majority of combination products (74 percent) have 510(k)'s or PMAs, while 19 percent have ANDAs or NDAs and 7 percent have BLAs (Table 2). We estimate that between 25 percent and 50 percent of the firms already comply with this final rule, and submit postmarketing safety reports for all the constituent parts of their products to their respective centers. However, the remaining 50 percent to 75 percent noncompliant firms may only report to their center of initial application, rather than the centers for all of their products' constituent parts.

Table 2. Number of Combination Products by Center of Application and Combination Type

Combination Type	CBER Application	CDER Application	CDRH Application	Total
Convenience Kit or Co-Package	8	65	32	105
Prefilled Drug Delivery Device/System	11	102	1	114
Prefilled Biologic Delivery Device/System	40	2	0	42
Device Coated/Impregnated/Otherwise Combined with Drug	0	5	584	589
Device Coated or Otherwise Combined with Biologic	0	0	58	58
Drug/Biologic Combination	4	11	0	15
Separate Products Requiring Cross	0	12	34	46

Combination Type	CBER Application	CDER Application	CDRH Application	Total
Labeling				
Possible Combination Product Based on Cross Labeling of Separate Products	0	0	29	29
Other Type of Combination Product	13	11	54	78
Total	76	208	792	1,076

E. Benefits of the Rule

Firms will benefit from reduced uncertainty regarding how to apply the separate postmarketing safety reporting regulations to combination products. The reduced uncertainty should decrease the time required to comply with existing reporting requirements. Additionally, the postmarketing safety reporting requirements for drugs, devices, and biological products are similar in many respects. Full reporting for all the constituent parts of a combination product may result in duplicative reporting. The final rule identifies the specific reports required for each type of combination product, and avoids the submission of duplicate information. Firms may therefore benefit from the decreased time spent submitting duplicate reports to the Agency. We do not know the extent to which firms spend time understanding the reporting requirements for their individual product or the amount of duplicative reporting that occurs, and therefore lack data to quantify these benefits.

Postmarketing safety reporting helps us identify any safety issues that arise after a product is marketed and used in real world settings. This final rule helps to ensure that firms submit necessary reports, direct their reports to the appropriate Agency component, and maintain records for the appropriate length of time. As a result, the final rule will potentially benefit public health by contributing to the development of a faster response to adverse events and safety concerns.

F. Costs of the Rule

1. Affected Entities

The final rule will affect all of the approximately 466 manufacturers of combination products, producing about 1,076 combination products. Of these firms, approximately 63 percent produce only one combination product, while only about 12 percent produce five or more combination products. We determine the number of products subject to this final rule using the combination product types and centers of application listed in Table 2. We assume that firms already follow postmarketing safety reporting requirements for the center of their initial application. For example, we assume that the 584 products with CDRH applications that are devices coated, impregnated, or otherwise combined with drug constituent parts already submit medical device postmarketing safety reports. The rule will clarify that the applicants for these products must also submit drug postmarketing safety reports.

2. Administrative Costs

Firms will incur one-time costs to read and understand the rule, assess their current compliance with the requirements, change or add standard operating procedures (SOPs), including those SOPs related to recordkeeping practices, modify their recordkeeping and reporting software, and train their personnel on the requirements under this rule.

The 25 percent to 50 percent of firms that already comply with this final rule will incur negligible incremental costs. The incremental costs to the 50 percent to 75 percent of firms that are not already compliant will be higher.

All firms that produce combination products and that are subject to this final rule will incur a one-time cost to read and understand the rule. Using the word count of the preamble and assuming an average reading speed of between 200 and 250 words per minute, we estimate that it will take each firm between 1.5 and 2 hours to read and understand the rule. Additionally, we assume that it will take between 1 and 2 hours for firms to assess their compliance with the rule. We use $78.64 as the hourly full labor cost[1]. The total cost to read and understand the rule, and assess compliance ranges from $91,616 (2.5 hours x 466 firms x $78.64 hourly wage) to $146,585 (4 hours x 466 firms x $78.64 hourly wage).

Firms that do not already comply with the requirements of this final rule will have to change their SOPs to reflect the reporting requirements in this rule. We assume that changing SOPs will take between 10 to 15 hours. The total cost to change an SOP ranges from $183,231 (10 hours x 50% non-compliance x 466 firms x $78.64 hourly wage) to $412,270 (15 hours x 75% non-compliance x 466 firms x $78.64 hourly wage).

Large firms often have more complex computerized storage and reporting systems. These firms may also incur incremental costs to make changes to their software and validate those changes. We assume that it will take large firms between 50 and 75 hours to modify their software. The total cost to change computerized storage and reporting systems ranges from $106,164 (50 hours x 50% non-compliance x 12% large firms x 466 firms x $78.64 hourly wage) to $238,869 (75 hours x 75% non-compliance x 12% large firms x 466 firms x $78.64 hourly wage).

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1 The base wage is the mean wage for a compliance officer in pharmaceutical and medicine manufacturing (standard occupational code 13-1041 and NAICS industry code 325400) from the 2014 Bureau of Labor Statistics' National Industry Specific Occupational Employment and Wage Estimate survey. We increase the base wage of $39.32 by 100% to account for benefits, for a full labor cost of $78.64.

Finally, non-compliant firms will also have to train the appropriate personnel on the new procedures. We estimate each firm would require about 10 to 15 hours for the incremental training on the provisions applicable to the products they produce. The total one-time industry cost for training ranges from $183,231 (10 hours x 50% non-compliance x 466 firms x $78.64 hourly wage) to $412,270 (15 hours x 75% non-compliance x 475 firms x $78.64 hourly wage). Table 3 summarizes the total one-time administrative costs of the final rule.

Table 3. One-Time Administrative Costs

Administrative Cost Type	Low Estimate ($ millions)	High Estimate ($ millions)
Read and understand the rule and assess compliance	$0.09	$0.15
Modify SOPs	$0.18	$0.41
Change storage and reporting software	$0.11	$0.24
Training	$0.18	$0.41
Total	$0.56	$1.21

3. Reporting Costs

The reporting requirements in the final rule will generate annually recurring costs for some firms. Table 4 describes the reporting requirements in the final rule, other than those associated with the application type, for each type of product by its application type and constituent part type.

Table 4. Reporting Requirements in the Final Rule

Application Type	New Reporting Requirements for Drug Constituent Part Type	New Reporting Requirements for Device Constituent Part Type	New Reporting Requirements for Biological Product Constituent Part Type
Drug	-	5-day report, malfunction report, correction or removal report	Biological product deviation report
Device	Field alert report, 15-day report	-	Biological product deviation report, 15-day report
Biological Product	Field alert report	5-day report, malfunction report, correction or removal report	-

The final rule will require combination products with drug constituent parts and biologics applications to submit field alert reports. It will require combination products with drug constituent parts and device applications to submit field alert reports and 15-day reports. It will require combination products with device constituent parts and drug or biologics applications to submit 5-day reports, malfunction reports, and correction or removal reports. It will require products with biological product constituent parts and device applications to submit biological product deviation reports and 15-day reports. Finally, it will require products with biological product constituent parts and drug applications to submit biological product deviation reports. Table 5 estimates the annual number of reports not associated with the application type (for ease of reference, these are referred to as new reports), by report type specified in the final rule, based on the average number of reports currently submitted per product.

Table 5. Estimated Number of New Reports

Report Type	Number of Products Subject to the Requirements for Report Type	Average Number of Reports Submitted per Product	Total Average Annual Number of New Reports – Low (50% compliance)	Total Average Annual Number of New Reports – High (25% compliance)
Field Alert Report	600	0.78	233.96	350.95
5-Day Report	160	0.001	0.07	0.11
Malfunction Report	160	95.95	7,675.80	11,513.69
Correction or Removal Report	160	0.06	4.48	6.72
Biological Product Deviation Report	71	50.58	1,795.52	2,693.27

The majority of combination products (approximately 55 percent) are devices coated, impregnated, or otherwise combined with a drug. The final rule will require firms producing combination products with drug constituent parts and device or biologics applications to submit field alert reports. We estimate that each field alert report will require 5 to 10 hours to complete. The average incremental annual cost for submitting field alert reports will range from $91,995 (233.96 new reports x 5 hours x $78.64 hourly wage) to $275,985 (350.95 new reports x 10 hours x $78.64 hourly wage).

With regard to 5-day reports and malfunction reports[2] for combination products with drug and device constituent parts, we expect that relevant information for these types of reports is generally collected under the postmarketing safety reporting associated with the application type. The final rule will require firms to collect little additional information, if any. Therefore,

[2] If an adverse event requires that firms submit both a malfunction report and a 15-day report, firms may either submit malfunction reports as separate reports or as part of 15-day reports. We conservatively assume that all firms submit all malfunction reports separately from 15-day reports.

the sole cost of the reporting requirement for 5-day reports and malfunction reports only includes the cost to write and submit the report. For any reports with information that firms already collect under current regulatory practice, we estimate that the incremental time to comply with these requirements is between 1.5 and 2 hours per requirement. The average incremental annual cost of new 5-day reports ranges from $9 (0.07 new reports x 1.5 hours x $78.64 hourly wage) and $18 (0.11 new reports x 2 hours x $78.64 hourly wage). The average incremental annual cost of new malfunction reports ranges from $905,437 (7,675.80 new reports x 1.5 hours x $78.64 hourly wage) to $1,810,874 (11,513.69 new reports x 2 hours x $78.64 hourly wage).

Because there is no analog to correction and removal reports in current drug and biologics reporting requirements, new correction and removal reports for combination products with device constituent parts and biologic or drug applications will require more time to complete. We estimate that each new correction or removal report will take 8 hours to complete. The average incremental annual cost of the new correction and removal reports is between $2,818 (4.48 new reports x 8 hours x $78.64 hourly wage) and $4,226 (6.72 new reports x 8 hours x $78.64 hourly wage).

There are relatively few products subject to the requirement for biological product deviation reporting. Based on our experience with current reporting practices we estimate the reports will take about 2 hours to complete for a average incremental annual cost for such reports between $282,399 (1,795.52 new reports x 2 hours x $78.64 hourly wage) and $423,598 (2,693.27 new reports x 2 hours x $78.64 hourly wage).

Finally, drugs, devices, and biological products have slightly different reporting requirements in response to certain adverse events. Drug products and biological products submit 15-day reports for serious, unexpected adverse events, while devices submit 30-day

reports for device-related deaths and serious injuries. There is significant overlap between the types of events that trigger a 15-day report for drugs and biological products and the events that trigger a 30-day report for devices. However, in a few cases, some adverse events may trigger a 15-day report, but not a 30-day report. In these situations, under the final rule, combination products with drug or biological product constituent parts and device applications will submit a 15-day report within 30 days. Therefore, the final rule may generate a few new 30-day reports from products with a device application and a drug constituent part or products with a device application and a biological product constituent part. However, we believe that these instances will be rare, and the incremental reporting cost will be insignificant.

A small subset of the firms that produce cross-labeled combination products that received marketing authorization under separate applications held by different applicants will have a new requirement to share with the other applicant information received regarding certain postmarketing adverse events involving the combination product. These products make up less than 7 percent of marketed combination products. The incremental time required to perform this requirement would be minimal because the firm is only required to share the information they receive with the other applicant, not prepare or create an additional report for the other applicant. Many firms may already share such information because of contractual obligations, or for liability purposes. Because the time cost of this reporting requirement is so low, we expect the cost of complying with this requirement to be negligible. We summarize the annual reporting costs of the rule in Table 6.

Table 6. Annual Reporting Costs

Report Type	Number of Reports – Low	Number of Reports - High	Time Cost, Hours - Low	Time Cost, Hours – High	Average Annual Cost - Low ($ millions)	Average Annual Cost - High ($ millions)
Field Alert Report	234	351	5	10	$0.09	$0.28
5-Day Report	1	1	1.5	2	$0.00	$0.00
Malfunction Report	7676	11514	1.5	2	$0.91	$1.81
Correction or Removal Report	5	7	8	8	$0.00	$0.00
Biological Product Deviation Report	1796	2694	2	2	$0.28	$0.42
Total	9712	14567	18	24	$1.28	$2.51

4. Total Costs of the Rule

The final rule will result in one-time administrative costs that range from $0.56 million to $1.21 million and annual reporting costs that range from $1.28 million to $2.51 million. Table 7 reports the present value of the total costs over 10 years and the annualized total costs. The present value of total costs range from $11.83 million to $23.30 million with a 3 percent discount rate and range from $10.20 million to $20.11 million with a 7 percent discount rate. Annualized costs range from $1.35 million to $2.65 million with a 3 percent discount rate, and range from $1.36 million to $2.68 million with a 7 percent discount rate.

Table 7. Summary of Total Costs

Cost Type	Low Estimate ($ millions)	High Estimate ($ millions)
Present Discounted Value (3%)	$11.83	$23.30
Present Discounted Value (7%)	$10.20	$20.11
Annualized Costs (3%)	$1.35	$2.65
Annualized Costs (7%)	$1.36	$2.68

G. International Effects

While some of the affected entities are international firms, the final rule does not differentiate between domestic and international firms. We therefore believe the international effects of the final rule to be minimal.

H. Uncertainty Analysis

We are uncertain of current compliance with the postmarketing safety reporting requirements associated with the report types specified in this final rule. We are also uncertain of the precise time firms will spend complying with this final rule. However, we built uncertainty into our estimates, offering an estimated range of current compliance and time estimates. The uncertainty in these values results in uncertainty of about $200,000 for our estimated annualized costs.

III. Final Small Entity Analysis

A. Description and Number of Affected Small Entities

We estimate that about 86 percent of the firms affected by this final rule are small businesses, based on the Small Business Administration's (SBA) definition of a small entity. Table 8contains the SBA's small entity definitions and the percent of establishments that meet these definitions for each of the industries covered by this final rule.

Table 8. Affected Small Entities

NAICS Code	Industry Description	SBA Threshold	% Small Establishments
325413	In-Vitro Diagnostic Substances Manufacturing	1,250 employees	97.9%
334510	Electro-medical and Electrotherapeutic Apparatus Manufacturing	1,250 employees	98.6%
334517	Irradiation Apparatus Manufacturing	1,000 employees	98.2%
339112	Surgical and Medical Instrument Manufacturing	1,000 employees	98.7%
339113	Surgical Appliances and Supplies Manufacturing	750 employees	99.7%
339114	Dental Equipment and Supplies Manufacturing	750 employees	99.7%
339115	Ophthalmic Goods Manufacturing	1,000 employees	99.7%
325412	Pharmaceutical Preparation Manufacturing	1,250 employees	98.4%
325414	Biological Product (Except Diagnostic) Manufacturing	1,250 employees	97.8%
621991	Blood and Organ Banks[3]	$3.25 million revenue	11.1%

B. Description of the Potential Impacts of the Rule on Small Entities

The impact on individual firms will depend on the nature of the changes to SOPs, the number and type of combination products produced, and the number of reports filed annually. Most firms with combination products have fewer than 10 products. One potential cost will be one-time administrative costs to implement the requirements under this rule. The cost to make such modifications is generally lower for small firms than for large firms, primarily because small firms are less likely to have complex computerized reporting systems. If a small firm is currently non-compliant with the provisions in the final rule, the administrative cost of the rule

[3] While the SBA uses the NAICS code for "Blood and Organ Banks" for the small business threshold of blood establishments, no organ banks are subject to the final rule.

would be between $1,769.40 (22.5 hours x $78.64 hourly wage) and $2,673.76 (34 hours x $78.64 hourly wage).

Small firms will also face new annual reporting costs that depend on the type of combination product that they produce. In Table 9, we estimate the total reporting cost to a small firm with a single combination product, using the average number of reports submitted by product. The annual cost for a product with a device application ranges from $306.65 to $7,954.89. The annual cost for a product with a drug application ranges from $7,954.89 to $15,125.98. The annual cost for a product with a biologics application ranges from $306.65 to $15,125.98.

Table 9. Reporting Costs for Small Firms by Application Type and Constituent Part Type

Application Type	Constituent Part Type	Reporting Cost - Low	Reporting Cost - High
Device	Drug	$307	$613
	Biologic	$7,955	$7,955
Drug	Device	$11,353	$15,126
	Biologic	$7,955	$7,955
Biologic	Device	$11,353	$15,126
	Drug	$307	$613

Using the one-time administrative costs and the information in Table 9, we estimate the average annualized cost to a small firm with a single combination product by industry (Table 10). For the purposes of our analysis, we assume that firms in a device industry submit device applications, firms in a drug industry submit drug applications, and firms in a biologic industry submit biologics application. In Table 10, we also estimate the average annual revenue by small businesses for each industry using the 2012 Economic Census and determine the share of average total revenue represented by the annualized cost to a small business.

Table 10. Annualized Costs to Small Business as a Fraction of Average Total Revenue, by Industry

NAICS Code[4]	Avg. Annual Revenue	Avg. Annualized Total Costs[5]	Share of Revenue
325413	$38,191,832	$4,460	0.012%
334510	$25,371,444	$4,460	0.018%
334517	$32,049,878	$4,460	0.014%
339112	$21,411,437	$4,460	0.021%
339113	$9,481,662	$4,460	0.047%
339114	$4,266,076	$4,460	0.105%
339115	$8,082,071	$4,460	0.055%
325412	$97,830,708	$10,850	0.011%
325414	$59,196,922	$7,103	0.012%
621991	$1,451,510	$7,103	0.489%

The annualized total costs of the final rule represent between 0.011 percent (for drug manufacturers) and 0.489 percent (for blood banks) of average annual revenues. We therefore conclude that this cost is not significant and therefore certify that the final rule will not have a significant economic impact on a substantial number of small entities.

4 See Table 8 for the industry descriptions that correspond to these NAICS codes.

5 In this table, we annualize the total costs to a small business over a 10 year period with a 3% discount rate. Using a 7% discount rate yields similar results.