DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Permanent Discontinuance or Interruption in Manufacturing of Certain Drug or Biological Products; Final Rule

Docket No. FDA- 2011-N-0898

Regulatory Impact Analysis
Regulatory Flexibility Analysis
Unfunded Mandates Reform Act Analysis

Economics Staff
Office of Planning
Office of Policy, Planning, Legislation, and Analysis
Office of the Commissioner

Table of Contents

I. Final Regulatory Impact Analysis

A. Introduction and Summary

1. Introduction

The Food and Drug Administration (FDA or the Agency) 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). The Agency believes that this final rule is a significant regulatory action under 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. The estimated per notification cost for small business entities, $227, represents a small percentage of average annual sales (up to 0.10 percent) for all entities covered by the final rule. Although the final rule does not require specific mitigation strategies, for firms that choose to implement mitigation or prevention strategies, there could be additional costs of $113,000 associated with labor resources. For pharmaceutical companies with fewer than 20 workers, these could be 2 to 7.8 percent of average annual sales. In FDA's experience 4-5 small business entities per year have been affected by a shortage. For these companies the average annual sales was $17.54 million, and the estimated costs of implementing mitigation or prevention strategies would represent 0.64 percent of their average annual sales. The Agency certifies that the 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 (2013) 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.

2. Public Comments Concerning the Preliminary Regulatory Impact Analysis

FDA received one comment on the Preliminary Regulatory Impact Analysis for the proposed rule. The commenter requested more details on the annual costs of interventions, noted that the costs and benefits of alternative policy options were not quantified, and questioned whether compliance costs are included in the analysis. Costs of interventions are described in E.1 and E.2 of this Final Regulatory Impact Analysis. FDA does not have the data to monetize or quantify the costs and benefits of the identified alternatives and therefore only provides a

qualitative description. This approach is supported by OMB Circular A-4. We assume 100% compliance with the rule, and in Section I. Uncertainties, provides an estimate of what the compliance costs would be when the assumption of 100% compliance is relaxed.

The comment also states that the analysis is inadequate, as it is "based on a series of assumptions extrapolating crudely estimated costs and benefits." Assumptions in the economic analysis are evidence-based. Throughout the preliminary regulatory impact analysis, FDA is transparent in acknowledging limitations of the estimates and requested data to support other estimates. We do not revise the estimates in this final regulatory impact analysis because new or improved data are not available as of this writing.

The comment expressed concern that the rule could create an incentive for companies to threaten shortages in anticipation of FDA relaxing safety standards. A requirement for companies to notify FDA should not change their incentives, as they could already have been notifying FDA of shortages if they believed it was in their interest to do so. In addition, manufacturers would not want to unnecessarily publicize any safety issues associated with their drugs, as this could have a negative effect on public perception of the company.

The comment suggests that the rule may allow violations of antitrust policy, as FDA could act as a conduit of production information. It is unclear how the flow of production information would have an adverse impact on consumers in this case, or how companies would be able to manipulate the process to transmit information to their benefit.

3. Summary

The rule amends FDA's regulations to implement sections 506C and 506E of the Federal Food, Drug and Cosmetic Act (FD&C Act), as amended by the Food and Drug Administration Safety and Innovation Act (FDASIA) of July 9, 2012, Public Law No. 112-144. The rule requires all applicants[1] of covered, approved prescription drug or biological products other than blood or blood components for transfusion (referred to as blood or blood components), all applicants of blood or blood components that manufacture a significant percentage of the U.S. blood supply, and all manufacturers of covered prescription drugs marketed without an approved application, to notify FDA electronically of a permanent discontinuance or an interruption in manufacturing of the product that is likely to lead to a meaningful disruption in supply (or a significant disruption in supply for blood or blood components) of the product in the United States 6 months in advance of the permanent discontinuance or interruption in manufacturing, or, if that is not possible, as soon as practicable. The final rule also describes how to submit such a notification, the information required to be included in such a notification, the consequences for failure to submit a required notification, the disclosure of shortage-related information, and the meaning of certain terms.

[1] Throughout this analysis we collectively refer to applicants holding an abbreviated new drug application (ANDA), new drug application (NDA), or biologics license application (BLA) and unapproved drug manufacturers subject to this rule as the "applicant." However, we recognize that an unapproved drug manufacturer is not an applicant. As needed, we may also individually refer to the ANDA, NDA, and BLA applicant or unapproved drug manufacturer as needed, if the context requires distinguishing between these entities. Moreover, we may refer to applicants and manufacturers interchangeably.

The final rule would impose annual costs of up to $40.54 million on those applicants or entities affected by the rule, and up to $6.38 million on FDA in preventive costs. Estimated total annual costs of the interactions between industry and FDA range between $14.54 million and $46.92 million. Discounting over 20 years, annualized quantified benefits from avoiding the purchase of more expensive alternative products, managing product shortages, and life-years gained, would range from $30.45 million to $98.65 million using a 3 percent discount rate, and from $30.39 million to $98.42 million using a 7 percent discount rate. Annualized over 20 years, net benefits range between $15.90 million and $51.72 million using a 3 percent discount rate; they range between $15.85 million and $51.50 million using a 7 percent discount rate. The public health benefits, mostly non-quantified, include the value of information that would assist FDA, manufacturers, healthcare providers, and patients in evaluating, mitigating, and preventing shortages of drug and biological products that could otherwise result in non-fatal adverse events, errors, delayed patient treatment or interruption in clinical trial development. The costs and benefits are summarized in Table 1 below.

Under the current environment all notifications provide meaningful information to identify a shortage or to prevent one, but there is uncertainty whether the scope of the rule could result in notifications that do not provide information about any shortage and lead to additional costs.

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

Category	Primary Estimate	Low Estimate	High Estimate	Year Dollars	Discount Rate	Period Covered	Notes
Benefits							
Annualized Monetized (millions $/year)	$64.545	$30.445	$98.645	2013	3%	2015-34	There is uncertainty surrounding these estimates because some underlying estimates came from non-representative studies.
	$64.408	$30.390	$98.425	2013	7%	2015-34	
Annualized Quantified					3%	2015-34	17-55 preventable shortages per year.
					7%	2015-34	
Qualitative	Reduction in errors and non-fatal adverse events associated with shortages; uninterrupted patient access to drugs and biological products necessary for treatment; continued access to drugs used in clinical trial development.						
Costs							
Annualized Monetized (millions $/year)	$30.731	$14.540	$46.921	2013	3%	2015-34	There is uncertainty about potential noise from notifications that might not provide meaningful information, but which could result in additional review costs. In addition, these estimates assume that applicants will participate in mitigation or preventive strategies.
	$30.731	$14.540	$46.921	2013	7%	2015-34	

Annualized Quantified	None estimated
Qualitative	None estimated.
Federal Annualized Monetized (millions $/year)	None estimated
Other Annualized Monetized (millions $/year)	None estimated.
State, Local or Tribal Gov't	None
Small Business	Based on the analysis small business entities covered by the final rule could incur small costs, $227 per notification or up to 0.10 percent of their average annual sales. Although the final rule would not require it, some firms may choose to incur additional costs associated with mitigation or prevention strategies.
Wages	No estimated effect.
Growth	No estimated effect.

B. Need for Regulation

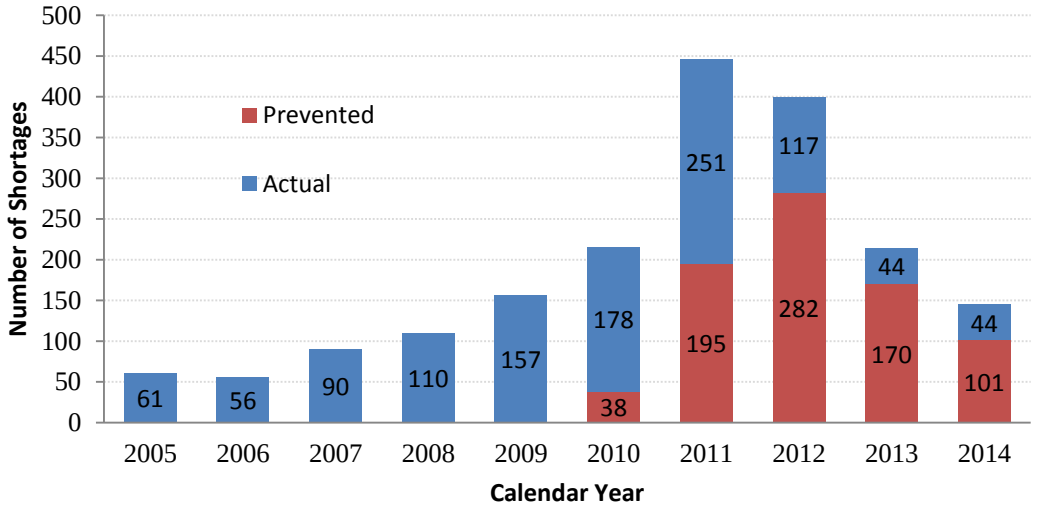
FDA Drug Shortages Staff (DSS) receives notifications which assist FDA in identifying shortages. It is through the Drug Shortages Staff review of the notifications and associated actions between FDA and industry that it is determined whether a shortage is either prevented or unavoidable. Before discussing our analysis further we define the following terms:

- Prevented shortage: Complete aversion of a shortage that was identified in a notification submitted to FDA and which was accomplished in collaboration between FDA and industry.
- Actual shortage: A shortage that was identified in a notification submitted to FDA and which was not avoidable (prevented) despite efforts between FDA and industry.
- Potential shortage: The sum of actual and prevented shortages.

Shortages of various medical products in the United States have occurred for many years. Figure 1 below presents data from FDA's Drug Shortages Staff in the Center for Drug Evaluation and Research on actual shortages for the period 2005-2014. Data limitations allow us to only present data on both the number of prevented and actual shortages between 2010 and 2014, but the number of actual shortages is comparable for the period 2005-2014. Furthermore, we note that every notification submitted to FDA provides meaningful information in identifying a potential shortage. Early notification of potential drug shortages enables FDA to work with manufacturers to mitigate or prevent such events. Figure 1 shows that early notifications about potential shortages submitted to FDA by manufacturers led to the prevention of 282 drug shortages in 2012, 170 in 2013, and

101 in 2014..

Figure 1. Estimated Number of Actual and Prevented Shortages



Note: * Potential shortages is the sum of actual shortages (shortages that could not be prevented) and prevented shortages. FDA began collecting data on prevented shortages in 2010. Source: FDA, Drug Shortage Staff

Drug and biological product shortages may result in delays or interruptions in patient treatment and suboptimal patient care. A recent survey of 245 oncologists reported that 92 percent indicated that their patients' treatment was affected and that 83 percent of survey respondents said they were unable to prescribe standard chemotherapy to their patients because of a shortage in an oncology drug (Ref. 1). The survey found that respondents switched regimens (79%), substituted drug partway through therapy (77%), delayed treatment (43%), chose among patients (37%), reduced doses (20%), and referred patients to other practices (17%) in response to a drug shortage. A separate survey of anesthesiologists representing 50 states showed that respondents said patients experienced: longer recovery times (52.8%), and a less optimal outcome (66.7%) (Ref. 2). Shortages also increase the risk of medication errors and adverse events, because providers might be unaware that the alternative product may vary in strength, dosage, time to onset of action, and duration of action (Refs. 3-5). For example, a national survey of acute care hospitals reported that they experienced serious medication error or adverse reaction (14%) (Ref. 5). (See also Section B.3.b "Non-fatal Adverse Events" for further discussion on adverse events.)

In addition to compromising patient care, and increasing the level of frustration of health care providers (Ref. 6) shortages may also increase health care costs: Some report an average markup price of 650 percent for drugs in short supply and in some cases the drugs were sold up to 4,533 percent over their typical contract price when bought in the gray market (Ref. 7). Shortages also impose an economic burden on health care professionals and providers who must devote considerable resources to tracking available inventories, complying with recommendations, purchasing products outside their usual supply channels, and informing patients when the product becomes available**.** Moreover, shortages delay clinical research critical to the development of innovative drugs. For example, Goozner (2012, Ref. 8) discusses several cases where enrollment of patients for clinical trials involving cancer treatment cannot begin because a drug that is part of the study is in shortage. McBride et al 2013 (Ref. 4) report that 44 percent of responding hospitals

experienced delays in enrolling patients in cancer clinical trials. By contrast, Emmanuel (2013, Ref. 1) reports that findings from a survey of oncologists show that in nearly 13 percent of the time, shortages prevented enrollment, delayed administration of a study drug, or suspended involvement of patients on clinical trials.

On October 31, 2011, President Obama issued Executive Order (E.O.) 13588 directing FDA to take steps necessary to prevent or mitigate disruptions in the supply of lifesaving medicines (Ref. 9). On the same day, FDA issued a letter to industry encouraging them to voluntarily report any manufacturing issues that could potentially lead to disruptions in supply or drug shortages (Ref. 10). In response to E.O. 13588, on December 19, 2011, FDA published an interim final rule (IFR) (effective January 18, 2012) modifying § 314.81 related to drug shortages (Ref. 11). The IFR requires that sole manufacturers of a drug product approved under a new drug application (NDA) or abbreviated new drug application (ANDA) that is life supporting, life sustaining, or intended for use in the prevention of a debilitating disease or condition, and that was not originally derived from human tissue and replaced by a recombinant product, notify FDA of a discontinuance of the drug product, whether the discontinuance is temporary or permanent. Taken together, E.O. 13588, FDA's letter to industry, and promulgation of the IFR resulted in a significant increase in the number of early notifications of potential drug shortages received by the Agency.

On July 9, 2012 President Obama signed FDASIA into law. Among other things, FDASIA significantly amended section 506C of the FD&C Act to expand the scope and extent of drug shortage early notification requirements. Specifically, under the IFR, only sole manufacturers of NDA and ANDA products are required to notify FDA about a discontinuation in manufacture. By contrast, under the final rule, all manufacturers of covered prescription NDA, ANDA, BLA products, and covered prescription unapproved products are required to notify FDA of a discontinuation or interruption. FDASIA requires FDA to issue a final regulation by January 9, 2014 implementing these amended drug shortage early notification requirements. FDASIA also authorizes the Agency to consider applying these requirements, via regulation, to biological products if it would benefit public health. This final rule responds to the statutory requirement in FDASIA to implement the drug shortages provision through notice and comment rulemaking.

The final rule requires all applicants of covered prescription drug products with an approved NDA or ANDA (§ 314.81), all manufacturers of covered prescription drug products without an approved application (§ 310.306), all applicants of covered prescription biological products with an approved biologics license application (BLA) other than blood or blood components (§ 600.82), and all applicants of blood or blood components that manufacture a significant percentage of the U.S. blood supply (§ 600.82) to notify FDA of a permanent discontinuance of the product, or an interruption in manufacturing of the product that is likely to lead to a meaningful disruption in the supply (or a significant disruption in supply for blood or blood components) of the product in the United States and the reason for the permanent discontinuance or interruption in manufacturing. Prescription drug and biological products that are life supporting, life sustaining, or intended for use in the prevention or treatment of a debilitating disease or condition, including any such drug used in emergency medical care or during surgery, and excluding radiopharmaceutical products, are subject to the notification requirements. Notification must be provided at least 6 months in advance of the permanent discontinuance or

interruption in manufacturing, or, if that is not possible, as soon as practicable thereafter. The requirements expand the scope of products subject to early notification and the pool of applicants or manufacturers required to report a permanent discontinuance or interruption in manufacturing to FDA. These notifications would further enable FDA to distribute information on potential supply disruptions to appropriate physician and patient organizations, and to work with manufacturers and other stakeholders to prevent or mitigate shortages of these products. The final rule also describes how to submit such a notification, the information required to be included in such a notification, the consequences for failure to submit a required notification, the disclosure of shortage-related information, and the meaning of certain terms.

C. Background

Early notification of a discontinuance or interruption in supply is a critical tool for FDA in addressing drug shortages. These notifications allow FDA to identify products in potential shortage, and to work with manufacturers and other stakeholders to prevent the shortage or mitigate the impact of an unavoidable shortage.[2]

One notification of a discontinuance or interruption in supply may cover multiple products--for example, if a manufacturer notifies FDA of a single interruption in supply (e.g., shut down of a manufacturing line) that may affect multiple different products—or, one shortage may cover multiple products (current shortages covered at least 800 different products as indicated by their national drug code (NDC)). In 2011 FDA received 220 notifications covering 446 potential shortages (251 actual shortages and 195 prevented shortages); on average, each notification referred to two potential shortages. Data for 2012 indicate that, on average, one notification covered one potential shortage (see table 2A). For 2013 and 2014, the average number of shortages per notification was less than one.

Data from 2011 to 2012 show an increase in the number of shortages that were prevented as well as an increase in the number of early notifications. In 2011, 44 percent (=195/446) of the potential shortages identified was prevented, but in 2012, the percentage of prevented shortages increased to 71 percent and the number of notifications increased from 220 to 392. Part of this increase in prevented shortages and notifications could be attributed to the various policies regarding early notification, such as Executive Order 13588, FDA's letter to industry, the IFR, and FDASIA. The number of actual shortages decreased to 44 in 2013 and 44 in 2014, and the number of prevented shortages also decreased to 170 in 2013 and 101 in 2014. The number of notifications also decreased from 2012.

Table 2A.—Notifications, Potential Shortages and their Outcomes, 2011-2014

Description	2011	2012	2013	2014	Average

[2] We note that when we talk about a prevented shortage we refer to a shortage that was averted entirely, and that when we talk about an actual (or new) shortage we describe a shortage that was not averted but for which mitigation efforts were allocated.

Panel A. Shortages										
Actual Shortages	251	56%	117	29%	44	21%	44	30%	114	38%
Prevented Shortages	195	44%	282	71%	170	79%	101	70%	187	62%
Potential Shortages	446	100%	399	100%	214	100%	145	100%	301	100%
Panel B. Notifications										
Notifications	220		392		240		240		306	
Potential Shortages per Notification	2.0		1.0		0.9		0.6		1.1	

Source: FDA DSS.

FDA estimates that the final rule would lead to an increase of 23 to 74 notifications a year. Estimates for approved drugs are based on estimates from the IFR (9 to 24 notifications, Ref. 11)[3]. Because the IFR estimates included sole manufacturers, which account for approximately 30 percent of approved drug manufacturers covered by the final rule, the estimates for the final rule are adjusted up. Thus, we estimate the final rule would result in 21 (=9*7/3) to 56 (=24*7/3) additional notifications from approved drug manufacturers. Estimates for biologics and unapproved drugs are based on FDA Drug Shortages Staff predictions. Table 2B below presents the breakdown of notifications by drug and biologics; however, the rest of the analysis assumes there is no difference between these products, and aggregates them into one range of notifications (low (23) and high (74)).

Table 2B. Estimated Number of Notifications Due to the Final Rule

Product	Low	High
Approved Drugs	21	56
Unapproved Drugs	1	12
Biologics	1	6
Total	23	74

Expanding the notification requirements would result in an increase in notifications that would enhance FDA's ability to identify potential shortages and thereby improve its ability to prevent more shortages (and reduce the number of actual shortages). Using the average ratio of potential shortages per notification (1.1) shown in table 2A, the estimated increase in potential shortages is between 26 (=23*1.1) and 84 (=74*1.1). As mentioned above, potential shortages can either be averted or become actual shortages. In figures 2A (2B) we show how, holding the range

[3] Recent data indicate that between 2011 and 2012 sole-manufacturers submitted 69 additional notifications, which would suggest that the IFR estimates were underestimated. However, the additional number of notifications that came after the IFR may have included a backlog of notifications that may not be representative of the overall long-term trend.

of notifications constant at a range of 23 and 74, increasing (decreasing) the assumed prevention percentage increases (decreases) the estimated number of prevented (actual) shortages.

Using a range of average prevention rates, we estimate a range of shortages that can be prevented and a range of shortages that may be unavoidable. The ratio of shortages to notifications was smaller in 2013 and 2014. If 2013 and 2014 are indicative of future trends for drug shortages and notifications, estimates of prevented shortages at the lower end of the range may be more accurate.

Figure 2A.--Range of Estimated Prevented Shortages

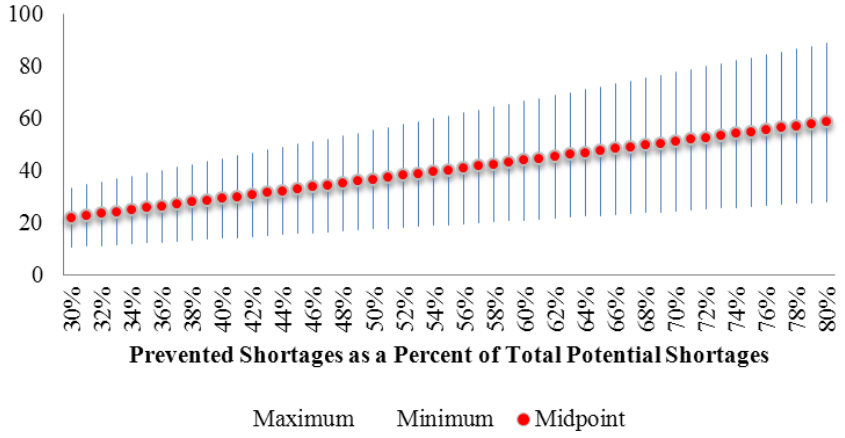
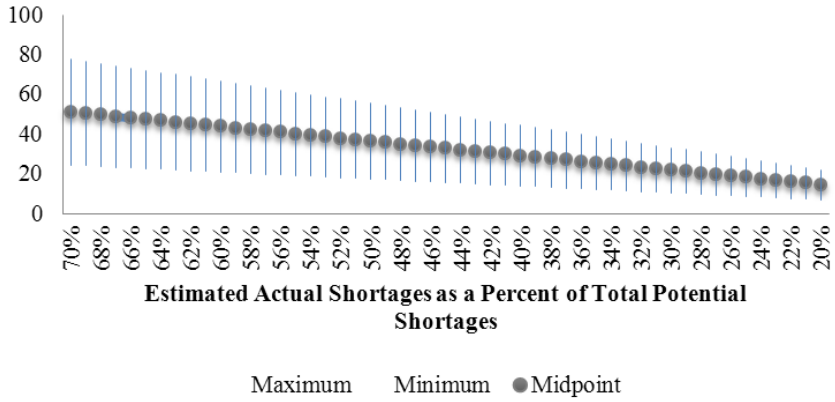


Figure 2B.--Range of Estimated Actual Shortages



Various activities can result from FDA's efforts to prevent or mitigate shortages. These activities include notifying and encouraging manufacturers of the same or similar products to increase their production, finding another manufacturer to begin production of the product, using regulatory discretion with regard to selective release of product when accompanied by appropriate warnings or remedies (e.g., filters for products contaminated with particulates), expedited review of an ANDA, expedited review of new manufacturing lines or raw material sources to help firms increase production. Table 2C below presents FDA's findings of the overall response to potential notifications for the most recently available data covering 2011 (Ref. 12). In 2011, most of the potential shortages involved regulatory discretion (33 percent), expedited review (26 percent), and working with manufacturers to increase production (34 percent). For purposes of this analysis, we

combine regulatory discretion and expedited review as one category (FDA Review) and examine the other categories separately (see table 2C). We note that the distribution of the outcomes presented in table 2C can vary if we separate the analysis into actual and prevented shortages, and can vary over time as well. However, given the unavailability of the data at the time of this analysis, we use the distribution implied by table 2C to estimate the distribution of anticipated actions for actual and prevented shortages due to the rule (see table 2D). For instance, to determine the range of actual shortages that may require FDA review we multiply the estimated range of prevented shortages (17 to 55) by 59%, which results in an estimated range between 10 and 33; the rest of cells in table 2D are calculated in a similar fashion.

Table 2C.—Outcome of Managing Potential Shortages by FDA DSS, 2011

Type of Action	Overall
FDA Review	59%
Increase Production	34%
Other/No Action Taken	7%

Source: FDA Report, Figure 5. (Ref. 1)

Table 2D.—Estimated Outcome for Shortages due to the Final Rule

Type of Action	Actual Shortages	Prevented Shortages	Potential Shortages
FDA Review	5-18	10-33	16-50
Increase Production	3-10	6-19	9-29
Other/No Action Taken	1-2	1-3	2-5
Estimated Shortages	9-29	17-55	26-84

Note: Numbers may not add up due to rounding. Estimates assume 66 percent of potential shortages are prevented. Total potential shortages are estimated to be between 26 and 84. Estimates assume that 59 percent of shortages may be prevented or mitigated by FDA Review, and 34 percent may be mitigated by an increase in production.

In the sections that follow, we discuss the benefits and costs arising from the estimated number of notifications, as well as the activities associated with managing or preventing shortages.

D. Benefits

One of the benefits of the final rule would be to further reduce and mitigate drug and biological product shortages. Averting shortages could result in savings related to avoiding costs associated with managing such events for both industry and FDA, and from buying more expensive alternative treatments for healthcare providers. In addition, there would be a decrease in the number of patients affected by shortages. These benefits are in turn explained below.

1. Managing Shortages

The American Society of Health-System Pharmacists (ASHP) reported that annual labor costs to manage drug shortages are approximately $216 million ($227.48 million in 2013 dollars) in the United States (Ref. 13). This estimate included the time spent by pharmacists, pharmacy technicians, physicians and nurses managing drug shortages during 2010. More specifically, the activities included gathering details, identifying alternatives, managing inventory, communicating information, and managing information systems. The survey found an association between the costs and the number of shortages; that is, the more shortages a health provider experiences, the

higher the costs of managing shortages. Averaging over the average number of prevented shortages between 2011 and 2014 (187 shortages), we estimate that preventing one shortage could save $1.216 million (2013 dollars) in labor costs. Thus, if 17 to 55 shortages could be prevented (see table 2D above), annual savings associated with managing shortages could range between $20.68(=17*$1.216) million and $66.91(=55*$1.216) million.

We note that the estimated labor costs were based on results from a non-representative sample of 353 members of ASHP who identified themselves as directors of a pharmacy and who responded to the survey. In particular, the sample was overrepresented by directors of larger hospitals. The non-representative nature of the survey indicates that there is uncertainty associated with our estimates. In this study, the cost to hospitals with more than 400 beds was almost twice as much as the cost to hospitals with fewer than 100 beds. If, in general, smaller hospitals incur higher costs than larger hospitals (because, for example, it might be more difficult to reallocate resources effectively compared with larger hospitals), the estimated benefits might be underestimated. If, on the other hand, hospitals not represented in this survey incur lower costs, then the estimated benefits would be overestimated.

2. Purchasing More Expensive Alternatives

There may also be additional costs because the product in short supply is bought outside of the usual, e.g., certified, contracted, or authorized, supply channel (gray market), or because of rush processing costs (Ref. 14). In the presence of a shortage, manufacturers may be asked to increase production to levels higher than anticipated and thereby see an increase in their production costs. In table 2C above we see that in 34 percent of the potential shortages identified, FDA worked with manufacturers to increase the supply of a product potentially in shortage. This would increase the unit production costs (i.e. marginal costs) of these manufacturers, which would be reflected in a higher market price. Moreover, in the presence of a shortage, gray market distributors may buy up available supplies and sell them to end purchasers at significantly higher prices. Thus, healthcare providers may pay more for shortage products—whether bought through the gray market or through traditional sources. Some of the additional price represents a distributional effect from buyers to secondary-market distributors, but we lack data with which to quantify the portion that consists of transfers as opposed to social costs.

Total savings from avoiding purchases of more expensive alternatives would depend on the number of providers experiencing shortages, the frequency of shortages, and the additional cost associated with paying for alternative treatment. The American Hospital Association reported that 5,754 hospitals were in business in 2011. [4] Using the average number of preventable drug shortages between 2011 and 2014, we assume that on average 31 (=5754/187) different hospitals are affected by one drug shortage. Thus, 17 to 55 prevented shortages could affect between 523

[4] American Hospital Association. "Facts on US Hospitals," http://www.aha.org/research/rc/stat-studies/fast-facts.shtml, accessed November 2, 2012, and August 1, 2013.

(=(5754/187)*17) and 1,692 (=(5754/187)*55) hospitals. [5] Using estimates of the average annual increase in off-contract purchases of $36,606,[6] we estimate the rule-induced savings from avoiding purchasing alternative products could be between $19.15million (=$36,606*17*(5754/187)) and $61.95million (=$36,606*55*(5754/187)). Part of this estimate includes mitigation costs that must be excluded from the benefits because they could not be avoided as a result of the rule—and may actually be encouraged by FDA's intervention (e.g., the cost of producing filters to accompany a drug contaminated by particulates). We are unable to disentangle these two estimates and as a conservative measure we adjust the benefits down by 50 percent, and include the remaining 50 percent in the cost Section E.3. Thus, the estimated annual savings from purchasing more expensive alternatives ranges between $9.57 million and $30.97 million. We note, however, that the estimated benefits could be higher if the annual cost is higher than the $210 million we assume in this analysis. On the other hand, the benefits could be smaller if all else remains the same, but the number of shortages prevented is lower.

3. Preventing Deaths and Reducing Non-fatal Adverse Events

In addition to the costs associated with purchasing alternative therapies in the event of a shortage, delaying treatment or using alternative therapies as a result of a drug shortage can increase the risk of medication errors and adverse events or lead to premature patient death. According to the Institute for Safe Medication Practices, 64 percent of 1,800 healthcare practitioners (68% pharmacists) who participated in a survey on drug shortages conducted during July-September 2010 indicated that drug shortages increase errors and the risk of adverse patient outcomes (Ref. 6). Lack of a suitable alternative product, medication errors (such as overdose) and adverse events that arise when using unfamiliar alternative products can lead to patient injuries or death.

a. Prevented Deaths

A report suggested that one death a month occurs around the country because of drug shortages (Refs. 16). This estimate translates into approximately 12 deaths a year. We use this number to estimate the value of deaths averted because of the rule, but note that it was obtained from interviews and a non-representative survey of a very small sample of experts. If 17 to 55 shortages were averted, one (17*[12 deaths/187 drug shortages]) to four (55*[12 deaths/187 drug shortages]) deaths could be prevented.

The appropriate means of valuing life extensions is to measure the affected group's willingness-to-pay to avoid fatal risks. Three life-year values (also known as values of a statistical life-year, or VSLY) used frequently in the literature and in previous analyses are $100,000,

[5] In one survey of hospitals, 99.5 percent reported experiencing at least one serious drug shortage from January to June 2011. American Hospital Association, AHA Survey on Drug Shortages (July 12, 2011), http://www.aha.org/content/11/drugshortagesurvey.pdf, accessed November 2, 2012.

[6] Premier Healthcare Alliance estimated that having to purchase substitutes because of a drug shortage costs hospitals at least $200 million annually ($210.63 in 2013 dollars) (Ref. 15). This would translate into an average annual cost of $36,606 per hospital.

$200,000 and $300,000 (Cutler, 2008 (Ref. 17); Murphy and Topel, 2006 (Ref. 18); 74 FR 33030, July 9, 2009), which we update to $112,415, $224,831 and $337,246 in 2013 prices. These values constitute our estimates of willingness-to-pay for a year of life preserved in the present. However, because some of the patients affected by shortages may have conditions and co-morbidities that alter their willingness to accept risk, and hence their VSLY, it is possible that these measures could represent an upper bound. In this analysis, as a conservative measure we use the lower bound VSLY, and do not adjust for the effects of rising income on VSLY. The value of this gain is equal to the expected number of life-years saved multiplied by the VSLY. We do not have the age profile of the prevented deaths; however, the majority of drug shortages involve sterile injectables used in cancer treatment. Lakdawalla et al (2010) (Ref.19) estimate that treatments for colorectal and non-Hodgkin's lymphoma increased the overall life expectancy by 1.7 and 3.5 years, respectively. The Centers for Disease Control and Prevention reported that in 2009, colon and rectum cancer was the third highest type of cancer diagnosed in the United States; non-Hodgkin lymphoma was sixth.[7] Furthermore, the American Cancer Association lists 6 different drugs that are most commonly used to treat non-Hodgkin's lymphoma and 18 different drugs to treat non-Hodgkin's lymphoma.[8] Using the National Institutes of Health's DailyMed's query system we found that 83 percent and 78 percent of the drugs most commonly used to treat colorectal and non-Hodgkin's Lymphoma, respectively, are sterile injectables.[9] As a conservative measure we use Lakdawalla et al's estimate on colorectal cancer as the life-years gained per averted death.[10] We use 3 percent and 7 percent discount rates to calculate the present value of the life-years gained from the prevented drug shortages induced by the final rule (see table 3A). The annualized estimated benefits from life-years gained over twenty years range between $0.191 million and $0.764 million using a 3 percent discount rate, and between $0.136 million and $0.544 million using a 7 percent discount rate.

---

[7] U.S. Cancer Statistics Working Group. *United States Cancer Statistics: 1999–2009 Incidence and Mortality Web-based Report*. Atlanta: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention and National Cancer Institute; 2013. Available at: www.cdc.gov/uscs, accessed September 16, 2013.

[8] American Cancer Association, "Drugs Used to Treat Non-Hodgkin Lymphoma," http://www.cancer.org/cancer/non-hodgkinlymphoma/detailedguide/non-hodgkin-lymphoma-treating-chemotherapy; American Cancer Association, "Drugs Used to Treat Colorectal Cancer," http://www.cancer.org/cancer/colonandrectumcancer/detailedguide/colorectal-cancer-treating-chemotherapy, accessed September 16, 2013.

[9] National Institutes of Health, DailyMed Search Query on Drug Dosage & Administration, http://dailymed.nlm.nih.gov/, accessed September 16, 2013.

[10] A national survey conducted by McBride et al (Ref. 4) shows that 78 percent of respondents indicated changing their patients' regimen because of a shortage in fluorouracil, a sterile injectable used to treat colorectal cancer.

Table 3A.-- Rule-induced Avoidance of Product Shortage-Related Deaths

Description	Low	High
Annual Deaths Averted	1	4
Annual Life-Years Gained	1.700 (3%) 1.211 (7%)	6.800 (3%) 4.842 (7%)
VSLY	$112,415	$112, 415
Annual Life-Year Gained, Monetized ($millions)	$0.191 (3%) $0.136 (7%)	$0.764 (3%) $0.544 (7%)
Monetized Life-Years Gained Over 20 Years Present Value ($millions)	$2.843 (3%) $1.442 (7%)	$11.373(3%) $5.767 (7%)

Note: Discount rate in parentheses. Life-years gained are discounted in Lakdawalla et al, as more than one year is gained per event.

b. Non-fatal Adverse Events

The estimated benefits presented so far in this section only include benefits associated with averting a lower bound of the number of deaths averted by the final rule. These estimates do not include the benefits associated with reducing non-fatal adverse events. Although some survey results point to the potential significant impact on patient safety and non-fatal adverse events, the results from some of these surveys are not representative and vary significantly (as discussed below). Thus, we are unable to quantify these additional benefits.

A survey conducted by the Institute for Safe Medication Practices (ISMP) covering March 2011 to March 2012 (Ref. 3) reported that 35 percent of the respondents indicated that using alternative medication led to inadequate patient treatment, and that 33 percent of the respondents said there was an error related to the form, strength or compounding of a drug in shortage. Most of the frequent adverse events occurred with chemotherapy (27 percent) and opioids analgesics (17 percent). Respondents to the survey provided the following as examples of patient harm during drug shortages: prolonged progression of a disease, behavioral status changes, medication overdoses, respiratory depression and excessive sedation, debilitating and life-threatening side effects from alternative drug, infections and cross-contamination, temporary to permanent neurological harm, permanent vascular harm, untreated pain, repeated surgical procedures, prolonged hospitalization, and inability to work. A national survey of healthcare professionals (97% pharmacists) involved in the care of patients with cancers reported various types of errors, e.g., wrong dosage conversion (47%), wrong drug concentration (20%), delayed or omitted drug (7%)), and adverse events such as increased toxicity (50%) and cardiac event (5%), associated with drug shortages in oncology—one of the areas most affected by drug shortages (Ref. 4). Data from the National Cancer Institute indicate that for every 100,000 individuals, 465 suffer from cancer.[11] Thus, the potential benefit of the final rule could affect a significant portion of the population.

A review of other non-representative surveys highlights the reported variation on the incidence of errors or adverse events. For instance, the incidence of errors associated with drug

[11] National Cancer Institute, "Table 1.4. Age-Adjusted SEER Incidence and U.S. Death Rates and 5-Year Relative Survival (Percent). By Primary Cancer Site, Sex and Time Period," http://seer.cancer.gov/csr/1975_2009_pops09/results_single/sect_01_table.04_2pgs.pdf, accessed April 16, 2013.

shortages has been reported to be as low as 10%, or as high as 33% (Refs. 3, 5). Similar variation can be observed in other reported outcomes: inadequate patient treatment (35% or 67%), prolonged recovery time (31% or 53%), and adverse patient outcomes (20% or 64%) (Refs. 2, 3, 5, 6). As mentioned above, given the limitations of the data, we are unable to quantify the potential savings from non-fatal adverse events.

4. Efforts to Mitigate or Prevent Shortages

Some of FDA's actions in response to a potential shortage include, among others, expediting review. These activities incur costs irrespective of whether the potential shortage is prevented or not and are thus discussed in the cost section.

5. Summary of Benefits

Taken together, the costs associated with shortages are substantial. Therefore, the potential benefits of the final rule as a result of prevention or mitigation of drug and biological product shortages could be substantial from both an economic and public health viewpoint. Table 3D below presents a summary of the benefits. Discounted over 20 years and using a 3 percent discount rate, estimated annualized benefits range between $30.45 million and $98.65 million. These estimates include the cost savings from buying more expensive treatment, managing shortages, and deaths averted. Similarly, using a 7 percent discount rate, the estimated annualized benefits range from $30.39 to $98.42 million.

We reiterate that there are uncertainties associated with the quantified estimates. These estimates do not include the cost-savings associated with non-fatal adverse events and reduction in error due to shortages. In addition, anecdotal evidence suggests that drug shortages delay clinical investigations. For instance, enrollment in oncology clinical trials may be delayed because the medication needed to conduct the investigational study is in shortage (Refs. 1, 4, 8). The benefits of reducing the likelihood of this occurrence are not included in our estimates. Furthermore, since some underlying estimates are not representative of the shortages experienced by all stakeholders, our estimates should be interpreted with caution.

Table 3D.--Summary of Benefits of the Final Rule

Description of Benefits	Estimated Annual Savings/Benefits	
	Low	High
Monetized (millions $)		
Buying more expensive treatment	$9.57	$30.97
Managing shortages	$20.68	$66.91
Life-years gained	$0.19 (3%) $0.14 (7%)	$0.76 (3%) $0.54(7%)
Total Monetized	$30.45 (3%) $30.39 (7%)	$98.65 (3%) $98.42 (7%)
Quantified		
Product shortages averted	17	55
Qualitative	Reducing medication errors and non-fatal adverse events associated with shortages. Uninterrupted clinical trial development of products.	

Note: Discount rates in parentheses. Totals may not add up due to rounding.

E. Costs

1. Notifications to FDA

We estimate that notifications, usually prepared by a regulatory affairs manager, will require 2 labor hours to prepare and submit (72 FR at 58999, October 18, 2007 and 76 FR at 78535, December 19, 2011). Labor hours are valued using the median hourly wage for Management Occupations (occupation code 11-0000) in Pharmaceutical and Medicine Manufacturing (North American Industry Notification, NAICS, code 32400) as reported by the Bureau of Labor Statistics 2012 Employment Occupational Statistics (Ref. 20). The median hourly wage, after adjusting for 100 percent overhead, is $112 ($113.69 in 2013 dollars). The estimated cost is $227 ($113.69*2) per notification, and the estimated total annual costs range between $5,230 and $16,827 (see table 4A below).

Table 4A.--Estimated Cost of Additional Notifications

Type of Product	Annual Cost	
	Low	High
Approved Drugs	$4,775	$12,734
Unapproved Drugs	$227	$2,729
Biologics	$227	$1,364
Total	$5,230	$16,827

There are currently 13 full-time equivalent employees (FTEs) handling drug shortage related-issues in CDER's Drug Shortages Staff. The number of FTEs has increased from 3 in 2010. CDER Drug Shortage Staff does not anticipate additional FTEs to review the additional notifications (additional labor hours are estimated for potential shortages that need expedited review, which is discussed in the following subsection). The implied assumption is that FDA Drug Shortages Staff employees, as they review more notifications, gain knowledge and experience that can result in a reduction of labor hours required per notification. On the other hand, since the final rule would expand the scope of notifications to biological products, the Center for Biologics Evaluation and Research (CBER) anticipates that between 0.5 and 1.5 additional FTEs would be

required to manage additional notifications reviewed by CBER. Using the average cost per FTE of $294,000, the additional annual cost for the increase in the number of FTEs would be between $147,000 (=0.5*294,000) and $441,000 (=1.5*294,000).

2. FDA Efforts to Mitigate or Prevent Shortages

Activities to avert or mitigate shortages include, among others, expedited review and exercising regulatory discretion. These activities incur costs beyond the costs of reviewing notifications. For instance, there may be reallocation of staff activities or resources in order to determine and implement the action plan under an expedited review. Thus, costs may be incurred by both industry and FDA.

In estimating the costs of these actions, we make the following assumptions. First, we assume that review of a prevented or an actual shortage incurs the same resources. Second, we use the median duration of resolved shortages as reported in FDA's 2011 report (Final Economics Ref. 12) as the additional labor spent in reviewing potential shortages under expedited review. The reported duration is 62.5 days, which would translate into 0.24 ((62.5/5)/52) FDA FTEs, or approximately 500 ((62.5/5)*40) hours. Hourly wages for industry is $113 (Final Economics Ref. 21), which includes benefits and overhead, the cost of one FDA FTE is $294,000. Third, we assume that industry incurs twice the labor hours incurred by FDA.

In the background section and table 2D above, we estimated that there could be between 16 and 50 potential shortages that could involve FDA action, 9-29 where there manufacturers are encouraged to increase production and 2-5 where there is another action. Because FDA and manufacturers would work together whether or not the shortage is prevented, we use the range of potential shortages as the basis to calculate labor costs associated with industry and FDA coordinated efforts to prevent or mitigate shortages. Table 4B presents the estimated costs. Annual costs to FDA range between $1.85 million (=26*0.24*$294,000) and $5.94 million (=84*0.24*$294,000). Similarly, costs to industry range between $2.97 million (=26*1000*$113) and $9.55 million (=84*1000*$113). Total costs range from $4.81 and $15.49 million.

Table 4B.--Estimated Annual Costs of Managing Shortages

Description	Low	High
Potential Shortages	26	84
Costs to FDA ($million)	$1.85	$5.94
Costs to Industry ($million)	$2.97	$9.55
Total	$4.81	$15.49

Notes: Costs assume 0.24 FDA FTEs valued at $294,000 for one FTE, and 1000 industry labor hours valued at $113 per hour, including benefits and overhead. Totals may not add due to rounding.

3. Cost of Ramping up Production

FDA does not have the authority to require that manufacturers increase production of a product in shortage. However, FDA does work with manufacturers to identify products in potential shortage and from which an increase in production could be beneficial to patients. Table 2C above showed that in more than a third of the potential shortages reviewed by FDA, FDA encouraged manufacturers to ramp up production. Increasing production—whether it be by

switching production to another product line or merely increasing current production in an existing line—is a decision that is voluntarily made by the manufacturers. For some products, e.g., sterile injectables, manufacturing costs involve high fixed costs and low variable costs, which can make switching production to another product line costly. It is for this reason that some portion of price mark-ups that occur during an actual shortage may represent additional social costs, rather than consisting entirely of transfers from buyers to secondary-market distributors. We estimate additional costs to be between $9.57 million and $30.97 million. This was determined by adjusting the initial range of estimates ($19.15-$61.95 million) from purchasing more expensive alternatives discussed in section D.2.

4. Summary of Costs

Rule-induced costs associated with notifications appear in table 4C. Total monetized costs to industry are between $12.55million and $40.54 million. On the other hand, estimated total annual costs to FDA range from $1.99 million to $6.38 million. Total combined costs of the interactive efforts of FDA and industry range from $14.54 million to $46.92 million per year. Additional uncertainties are associated with these cost estimates, but are not reflected in the ranges reported above. We have identified two reasons to believe the cost results in this section could be overestimates and one reason to believe they could be underestimates.

Historical data for drug products indicate that in the period October-December 2011 CDER's Drug Shortage Staff received on average 60 notifications per month, an increase from 10 notifications per month before October 2011. However, this spike occurred after publication of E.O. 13558, the FDA letter to industry, and the IFR. In the year 2012, the average number of notifications fluctuated. While the final rule broadens the scope of the products and entities affected by the final regulation, many of the affected parties should already be providing the required information under FDASIA and notifying FDA of permanent discontinuances or interruptions in manufacturing covered by the final rule. Consequently, it is possible that the estimated number of additional notifications, and the related costs and benefits, could be an overestimate. Estimated notifications per month were 20 in 2013 and 2014, providing further evidence that the costs and benefits associated with notifications may be an overestimate.

There is uncertainty surrounding a possible change in behavior from industry that would result in notifications that are not meaningful and yet would still result in additional FDA review costs. In this case, costs would be underestimated, and FDA's ability to mitigate or prevent shortages would not be as effective.

Furthermore, we note that in estimating costs we assumed there would be 100 percent compliance from industry, and that industry will work with FDA to prevent or mitigate shortages. Under regulation, FDA would issue letters to entities subject to the final rule who fail to timely notify FDA about a product shortage (referred to as noncompliance letters). Because noncompliance letters would be made public, entities covered by this final rule will have an incentive to comply with the regulation to avoid potential damages to the firm's and product's reputation. If the 100 percent assumption of compliance is relaxed, estimated cost could be higher (see section titled, "Other Uncertainties" for further discussion). In addition, if firms do not

coordinate with FDA to prevent or mitigate shortages, there could be higher social costs associated with product unavailability.

Table 4C.--Summary of Estimated Annual Costs of the Final Rule

Description of Estimated Costs	Estimated Annual Costs	
	Low ($million)	High ($million)
Industry:		
FDA Review	$2.97	$9.55
Notifications	$0.01	$0.02
Ramping up Production	$9.57	$30.97
Subtotal	$12.55	$40.54
FDA:		
FDA Review	$1.85	$5.94
Notifications	$0.15	$0.44
Subtotal	$1.99	$6.38
Total	$14.54	$46.92

Note: Totals may not add up due to rounding.

F. Summary of Benefits and Costs

Table 5 below presents the quantified net benefits (benefits minus costs) of the final rule. As discussed above, we estimate cost-savings from managing shortages ($20.68to $66.91 million per year) and the ability to avoid purchasing more expensive alternatives ($9.57 to $30.97million per year). We also estimate savings from deaths averted due to prevented shortages. Because the final rule broadens the scope of who is required to notify, associated costs of reporting and implementing preventive measures, (e.g., expedited review, ramping up production), for industry and FDA. Discounting over 20 years at a 7 percent discount range, the range of estimated net benefits is between $15.85 million and $51.50 million.

Table 5.--Summary of Annual Net Benefits of the Final Rule

Description of Estimated Benefits (Costs)	Estimated Annual Net Benefits	
	Low ($millions)	High ($millions)
Monetized		
Hospitals and Manufacturing Industry:		
Managing Shortages	$20.68	$66.91
Buying More Expensive Alternatives	$9.57	$30.97
Ramping up Production	($9.57)	($30.97)
Regulatory Discretion & Expedited Review	($2.97)	($9.55)
Notifications	($0.01)	($0.02)
FDA		
Regulatory Discretion & Expedited Review	($1.85)	($5.94)
Notifications	($0.15)	($0.44)
Consumers		
Life-Years Gained		
3% Discount Rate	$0.19	$0.76
7% Discount Rate	$0.14	$0.54
Total Monetized		
3% Discount Rate	$15.90	$51.72
7% Discount Rate	$15.85	$51.50

Note: Numbers in parentheses denote costs. Totals may not add up due to rounding.

G. Analysis of Regulatory Alternatives to the Final Rule

FDA identified the following alternatives to the final rule: (1) no change in regulation, (2) publish guidance, and (3) require that manufacturers of all medical products regulated by FDA—not just those listed in this final rule—notify FDA of a shortage.

1. No Change in Regulation

A simple alternative would be to leave the current regulation unchanged; that is, leave the IFR in effect. While this alternative would not impose additional costs, the additional benefits from expanding the scope of the reporting requirements discussed above would not be realized. Furthermore, a review of public comments and results of a survey indicate that there is support for expanding the scope of early notification requirements so that all applicants of approved and unapproved drugs as well as biological products are required to notify FDA of potential product shortages. Finally, as we discussed above, FDASIA significantly amended the drug shortage provisions of the FD&C Act to expand the early notification requirements (among other things) and to require FDA to issue a final rule implementing the new notification provisions. Accordingly, we are bound by law to publish a new rule superseding the IFR.

2. Publish Guidance

Another alternative would be for FDA to draft additional guidance to encourage voluntary notification of upcoming permanent discontinuances. While guidance and letters to industry can lead to voluntary reporting, such documents are not legally binding and cannot impose regulatory requirements. Without regulation that requires manufacturers to notify FDA about potential

product shortages, FDA may not have adequate information to distribute to physician and patient organizations and to work effectively with manufacturers and other stakeholders to better prevent and/or mitigate shortages.

3. Require Notifications from All Manufacturers

A stricter alternative would be for FDA to require all manufacturers—not only those manufacturing products covered in this final rule—to notify FDA of a permanent discontinuance or interruption in manufacturing. This alternative would increase costs associated with notifications, but may also increase benefits. This alternative may also require additional legislation granting FDA such authority.

H. International Effects

Foreign applicants marketing products covered by the final rule in the United States would incur the same costs associated with the preparation and submission of notifications, and responses to noncompliance letters (see next section) as incurred by firms operating in the United States. The final rule would be unlikely to alter the current mix of foreign and domestic manufacturing for the affected products.

I. Other Uncertainties

Under the final regulation, FDA would issue noncompliance letters to entities subject to the final rule who fail to timely notify FDA about a product shortage. Because noncompliance letters would be made public, an entity covered by this final rule would have an incentive to comply with the final regulation to avoid potential damages to the firm's and product's reputation; thus, with this additional deterrent in place it was assumed there would be 100 percent compliance. In this section we relax this assumption and assume there could be between 2 and 7 noncompliance letters each year: 1 to 6 letters would be associated with approved and unapproved covered drug products, and at most 1 noncompliance letter would be associated with covered biological products.

FDA management and legal counsel would allocate between 1 and 4 hours to prepare and issue a noncompliance letter. In valuing the cost of preparing the noncompliance letter, FDA distributes the time evenly among management and legal counsel time. Once the noncompliance letter is issued, the recipient must respond within 30 days; therefore, there would be costs to industry to prepare and submit a response. In addition to establishing the basis for noncompliance, the respondent would be required to provide the required notification. Data indicate that industry's median time to respond to Form 483 is 13 working days. Because a response to Form 483 is more complex, we estimate it would take at most 5 business days or 40 hours (=5*8) to prepare a response to a noncompliance letter.

Table 6A below summarizes the estimated labor hours by cost factor and sector.

Table 6A.—Other Uncertainties: Estimated Labor Hours to Prepare and Respond to a Noncompliance Letter

	FDA		Industry	
Labor Hours	Low	High	Low	High
Management	0.5	2	4	20
Legal	0.5	2	4	20
Total	1	4	8	40

Note: We assume that it takes 1 to 5 work days to prepare a response by industry. Each day is assumed to include 8 work hours.

The median hourly wage, after adjusting for benefits and overhead, is $113 for management occupations, and $151 for legal occupations.[12] The estimated cost to FDA of preparing a noncompliance letter ranges between $132 (=0.50*$113 + 0.5*$151) and $530 (=2*$113 + 2*$151). On the other hand, the cost to industry per response is between $1,060 (=4*$113 + 4*$151) and $5,299 (=20*$113 + 20*$151) (see table 6B below). The total cost to FDA for issuing between 2 and 7 noncompliance letters ranges between $265 ($132*2) and $3,710 (=$530*7), and total cost to industry to respond could be between $2,120 (=$1060*2) and $37,095 (=$5,299*7) (see table 6C).

Table 6B.—Other Uncertainties: Estimated Cost per Noncompliance Letter

	FDA		Industry		Total	
Cost Factor	Low	High	Low	High	Low	High
Management (rounded)	$56.8	$227	$455	$2,274	$512	$2,501
Legal (rounded)	$76	$303	$605	$3,025	$681	$3,328
Total (rounded)	$132	$530	$1,060	$5,299	$1,192	$5,829

Note: Total may not add up due to rounding.

Table 6C.—Other Uncertainties: Estimated Total Annual Cost from Noncompliance Letters

	Annual Cost to FDA		Annual Cost to Industry		Total	
Type of Product	Low	High	Low	High	Low	High
Approved and unapproved drugs	$132	$3,179.61	$1,059.87	$31,796.10	$1,192	$34,976
Biologics	$132	$529.94	$1,059.87	$5,299.35	$1,192	$5,829
Total	$265	$3,710	$2,120	$37,095	$2,385	$40,805

Note: Totals may not add up due to rounding.

We note that negative news about a company may adversely affect the revenue of the firm. Recent research by Conti et al. (2011) (Ref. 21), which investigates the impact of FDA advisories on branded pharmaceutical firms' valuation and promotion, showed that firms targeted by an advisory, on average, experienced a decline in their stock following the release of the advisory of 3 percent for three days, and 11 percent for five days. Moreover, Conti et al.'s study also concluded that physician-directed promotion, journal ads, and detailing visits also decreased significantly six months after the release. These results suggest that negative news could have a negative impact on

[12] Management and counsel hours are valued using the median hourly wage for Management Occupations (occupation code 11-0000) and Lawyers (occupation code 23-1011), respectively, in Pharmaceutical and Medicine Manufacturing (North American Industry Notification, NAICS, code 32400) as reported by the Bureau of Labor Statistics 2012 Employment Occupational Statistics (Ref. 20). Both numbers are in 2013 dollars.

the value of a firm, and therefore shareholders' wealth. We do not have the information to determine the effect of noncompliance letters on shareholders' value. However, any loss in revenue due to a potential negative impact from a noncompliance letter would be a distributive cost.

II. Regulatory Flexibility Analysis

The Regulatory Flexibility Act requires agencies to prepare a regulatory flexibility analysis if a final rule would have a significant effect on a substantial number of small businesses, non-profit organizations, local jurisdictions or other entities. The final rule would directly impact a significant percentage of small business entities. The analysis that follows shows that the estimated cost per required notification, $227, represents a small percentage of their average annual sales (up to 0.10 percent). However, for firms that choose to work with FDA in mitigation or prevention strategies, the costs could be $113,227 (=$227 + $113,000), which could be 2 percent of average sales for establishments hiring fewer than 20 employees. Because the costs of these mitigation or prevention strategies are not a regulatory burden but a cost of production for a product that will be sold by the manufacturer, FDA certifies that this rule will not have a significant economic impact on a substantial number of small entities.

A. Who is Affected

The Small Business Administration (SBA) uses different definitions of small entity for different industries. Table 7 below summarizes the size standards to determine a small business entity based on the SBA standards and the North American Industrial Classification System (NAICS) (Ref. 22).

Table 7.--Small Business Size Standards

NAICS Code	Description	Size Standards (million $)	Size standards (Number of Employees)
325412	Pharmaceutical Preparation Manufacturing		750
325414	Biological Product (except Diagnostic) Manufacturing		500
621991	Blood and Organ Banks	$10.0	

The currently available data from the 2007 Economic Census (Ref. 23) show that at least 92 percent of these establishments in pharmaceutical preparation—our measure for manufacturers of drug and unapproved drugs covered by the final role—would be considered small by SBA standards.[13] Furthermore, linking data that include biological product establishments, other than establishments of blood or blood components, registered with FDA to proprietary sales data provided by Dun & Bradstreet, Inc., we estimate that approximately 23 percent of the 89 establishments subject to the final rule would be considered small. Similarly, we identified 411

[13] Although the SBA standard indicates that a firm in NAICS 325412 would be considered small if it employs fewer than 750 employees, due to data limitations our estimate is based on the number of establishments with 500 or more employees.

establishments of blood or blood components that operate under four different licensed firms that would be affected by the final rule. All of the licensed firms are non-profit organizations, but none of them would be considered small by SBA standards.

B. Economic Impact on Small Entities

Under the final rule, affected parties who notify FDA of a shortage would incur costs associated with preparing the notification ($227 per notification), and additional costs of $113,000 (=1,000 hours *$113) associated with actions associated with coordinating efforts with FDA to prevent or mitigate a shortage. Tables 8A-8C below present the cost of the final rule as a percent of average sales for a typical firm among the three industry categories affected by the final rule.

Table 8A presents the estimated costs for affected parties marketing approved and unapproved drugs covered by this rule. The estimated notification cost as a percent of average sales for a typical establishment is negligible—0.0002 percent. Similarly, when we calculate the cost as a percent of average sales of all entities employing fewer than 500 employees, the cost of the final rule is small, between 0.0004 (including just notification costs) and 0.1841 percent (including both notification and mitigation costs). However, as part of SBA guidelines[14] we also examine whether there is a disproportionate effect among small business entities by calculating the impact for establishments with 0-9, 10-19, 20-99 and 100-499 employees. We find that for small business entities employing fewer than 10 workers, the economic impact, when mitigation or prevention strategies are involved, could be up to 7.8 percent of their average annual sales. Our estimates indicate that establishments with fewer than 10 workers represent 41 percent of the total number of establishments in this industry.

[14] Small Business Administration, "A Guide for Government Agencies: How to Comply with the Regulatory Flexibility Act," June 2010. http://www.sba.gov/sites/default/files/rfaguide.pdf, accessed August 1, 2013.

Table 8A.--Estimated Cost of the Final Rule: Pharmaceutical Preparation Manufacturing

Number of Employees	Number of Establishments	Percent of Establishments	Average Value of Shipments ($1000)	Approved and Unapproved Drugs ($227 per Notification as a Percent of Average Sales)
0-9	408	41%	$1,433	0.0156%
10-19	77	8%	$5,574	0.0040%
20-99	249	25%	$39,756	0.0006%
100-499	182	18%	$246,856	0.0001%
0-499	916	92%	$60,962	0.0004%
500+	75	8%	$1,160,470	0.0000%
All	991	100%	$144,174	0.0002%

Note: Per notification cost is $227. Cost per expedited review or regulatory discretion is $113,000. The SBA defines a small business in the pharmaceutical industry as one that employs more than 750 employees. However, data limitations do not allow us to disaggregate the information for those entities.
Source: 2007 Economic Census for Pharmaceutical Preparation Manufacturing (NAICS 325412).

In the biological drugs manufacturing industry (excluding blood or blood component manufacturing), the estimated notification cost would be small for both small and large-size establishments, less than 0.01 percent of their average annual sales.

Table 8B.—Estimated Cost of the Final Rule: Biological Drugs Manufacturers (Excluding Blood and Blood Component Manufacturers)

Number of Employees	Number of Establishments	Percent of Establishments	Average Annual Sales ($1000)	Biological Drugs ($227 per Notification as a Percent of Average Sales)
0-4	1	1.3%	$244	0.0932%
20-49	7	8.0%	$1,337,064	0.0000%
50-499	12	13.3%	$65,751	0.0003%
0-499	20	22.7%	$505,992	0.0000%
500+	69	77.3%	$25,290,694	0.0000%
All	89	100.0%	$25,796,686	0.0000%

Note: The database did not include any establishments employing 5-19 employees. Estimated cost per notification is $227. Cost per expedited review or regulatory discretion is $113,000. Average annual sales is determined based on 75 establishments for which the data were available at the time of the analysis.
Source: FDA Registration and Listing, and Dun & Bradstreet, Inc.

For applicants of licensed blood or blood components that manufacture a significant percentage of the U.S. blood supply, the overall estimated cost as a percent of average sales is 0.0001 percent. None of these applicants would be considered small under SBA standards (see table 8C).

Table 8C.--Estimated Cost of the Final Rule: Licensed Blood or Blood Components Manufacturers

Small by SBA Standards? (less than $10 million in annual sales)	Number of Establishments	Percent of All Establishments	Average Annual Sales ($1000)	Blood or Blood Components Manufacturers ($227 per Notification as a Percent of Average Sales)
No	411	100%	$416,636	0.0001%
Yes	0	0%	N/A	N/A
Total	411	100%	$416,636	0.0001%

Note: The data include four applicants of licensed blood or blood components that manufacture a significant percentage of the U.S. blood supply. Estimated cost per notification is $227. Cost per expedited review or regulatory discretion is $113,000.
Source: FDA Registration and Listing, and Dun & Bradstreet, Inc.

FDA estimates that when this final rule becomes final, FDA might receive two additional notifications from small manufacturers of approved and unapproved drugs, and one additional notification from small applicants of biological drugs, including blood or blood components. We note that, historically, drug and biologic product shortages have been predominantly experienced and reported by large-sized firms. For instance, on average, each year FDA has received two notifications from a small entity that manufactures approved drugs and one notification from a small entity that manufacturers unapproved drugs. Furthermore, data from 2010 to mid-2013 indicate that between 4 and 5 manufacturers affected by a shortage would be considered small. Revenue data for these manufacturers indicate that annual sales for these small entities averages $17.54 million. The estimated costs would then represent 0.64 percent of average annual sales. Based on past FDA experience on the size and revenues of firms affected by shortages. Moreover, the costs of these mitigation or prevention strategies are not a regulatory burden but a cost of production for a product that will be sold by the manufacturer. Thus, FDA certifies that the final rule will have no significant impact on a substantial number of small entities.

C. Additional Flexibility

In this section, we identify alternatives that would present reductions in costs to small entities.

1. Alternative 1: Exempt All Small-sized Entities

The estimated cost of notifying FDA of a drug or biological product shortage is $227dollars. This cost would represent up to 0.093 percent of average annual sales of biological drug applicants, and even less for all others covered under the final rule. Although firms are not required to work with FDA to help mitigate or prevent shortages, our estimates indicate that the associated costs of doing so could be significant for some small entities. Exempting small-sized businesses from the final requirements would reduce the economic impact to small businesses by almost 8 percent of average annual sales for more than 400 establishments in the pharmaceutical industry and by 47 percent for one establishment in biological drug manufacturing. However, these reporting requirements enable FDA to distribute information to physician and patient

organizations, to assess potential drug shortages, and to evaluate mitigation and prevention strategies. Thus, exempting small business entities from the final requirements may, in the long-term, lead to high social costs associated with outcomes such as worsening of conditions for patients for whom these products are necessary. Moreover, as described above, FDA is required by law to issue a regulation implementing the new drug shortages provisions of FDASIA.

2. Alternative 2: Extend the Compliance Period for Small Businesses

Another alternative to reduce costs would be to extend the compliance period for small-sized entities. While a longer compliance period may enable small businesses to reduce labor costs, it would delay FDA's receipt of notices of permanent discontinuances and limit the Agency's ability to distribute information to physician and patient organizations, to assess potential drug and biological product shortages, and to work with manufacturers and other stakeholders to prevent or mitigate shortages. Moreover, as described above, FDA is required by law to issue a regulation implementing the new drug shortages provisions of FDASIA.

III. References

1. Ezekiel J. Emanuel, Katie Shuman, Derek Chinn, Keerthi Gogineni; Impact of Oncology Drug Shortages, *Journal of Clinical Oncology* 31, 2013 (suppl; abstract CRA6510) http://meetinglibrary.asco.org/content/117789-132, accessed August 3, 2013.

2. American Society of Anesthesiologists, ASA Drug Shortages Survey Results, April 17, 2012, http://www.asahq.org/For-Members/Advocacy/Washington-Alerts/2012-ASA-Drug-Shortage-Survey-Results.aspx, accessed April 16, 2013.

3. Institute for Safe Medication Practices, "A Shortage of Everything except Errors: Harm Associated with Drug Shortages," from the April 19, 2012 issue of *ISMP Medication Safety Alert!* http://www.ismp.org/newsletters/acutecare/showarticle.asp?id=20, accessed April 16, 2013.

4. McBride, A., L. M. Holle, C. Westendoref, M. Sidebottom, et al. 2013. National Survey on the Effect of Oncology Drug Shortages on Cancer Care, *American Journal of Health-System Pharmacists, Vol. 70,* 609-61.

5. Baumer, A.M., A.M. Clark, D.R. Witmer, et al. 2004. National Survey of the Impact of Drug Shortages in Acute Hospital Settings, *American Journal of Health-System Pharmacists,* Vol. 1: 2015-2022.

6. Institute for Safe Medication Practices, "Drug Shortages: National Survey Reveals High Level of Frustration, Low Level of Safety", Special Issue from the September 23, 2010 Issue of the *ISMP Medication Safety Alert!* http://www.ismp.org/Newsletters/acutecare/articles/20100923.asp, accessed November 2, 2012.

7. Premiere Healthcare Alliance, *Buyer Beware: Drug Shortages and the Gray Market* (August, 2011), https://www.premierinc.com/about/news/11-aug/Gray-Market/Gray-Market-Analysis-08152011.pdf, accessed August 2, 2013.

8. Goozner, M. 2012. "Drug Shortages Delay Cancer Clinical Trials," *Journal of the National Cancer Institute,* 891-892. http://jnci.oxfordjournals.org/content/early/2012/06/14/jnci.DJS293.full.pdf+html, accessed April 16, 2013.

9. The White House. "Executive Order 13588 -- Reducing Prescription Drug Shortages," Office of the Press Secretary, October 31, 2011, http://www.whitehouse.gov/the-press-office/2011/10/31/executive-order-reducing-prescription-drug-shortages, accessed November 2, 2012

10. U.S. Food and Drug Administration. Letter to Industry, October 31, 2012. http://www.fda.gov/Drugs/DrugSafety/DrugShortages/ucm277675.htm, accessed November 2, 2012.

11. 76 Federal Register 78530-78540, December 19, 2011. http://www.gpo.gov/fdsys/pkg/FR-2011-12-19/html/2011-32434.htm, accessed November 2, 2012.

12. U.S. Food and Drug Administration. "A Review of FDA's Approach to Medical Product Shortage," October 31, 2011, http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/UCM277755.pdf, accessed August 3, 2013.

13. Kaakeh, R., B.V. Sweet, C. Reilly, C. Bush, et al. 2011. "Impact of Drug Shortages on U.S. Health Systems," American Journal of Health-System Pharmacists, 68: 1811-1819, http://www.ajhp.org/content/68/19/1811.full.pdf, accessed November 2, 2012.

14. Institute for Safe Medication Practices, "Gray Market, Black Heart: Pharmaceutical Gray Market Finds a Disturbing Niche During the Drug Shortage Crisis", August 11, 2011, http://www.ismp.org/Newsletters/acutecare/showarticle.asp?ID=3, accessed August 2, 2013.

15. Cherici, C., J. Frazier, M. Feldman, B. Gordon, C.A. Petrykiw, et al. "Navigating Drug Shortages in American Healthcare: A Premier HealthCare Alliance Analysis," March 2011, https://www.premierinc.com/about/news/11-mar/drug-shortage-white-paper-3-28-11.pdf, accessed November 2, 2012.

16. Johnson, LA. "Drug Shortage Stirs Fears," Associated Press. Philly.com, September 24, 2011, http://www.ismp.org/sc?k=dssf, accessed April 16, 2013.

17. Cutler, D. 2008, "Are We Finally Winning the War on Cancer?" Journal of Economic Perspectives 22:3-26.

18. Murphy, K.M., and R.H. Topel, 2006. "The Value of Health and Longevity," Journal of Political Economy 114 (5): 871–904.

19. Lakdawalla, D.N., E.C. Sun, A. B. Jena, C.M. Reyes, D. P. Goldman, and T. J. Philipson. 2010. "An Economic Evaluation of the War on Cancer," Journal of Health Economics, 29: 333-346.

20. U.S. Bureau of Labor Statistics. "May 2012 National Occupational Employment and Wage Estimates," May 2012 Occupational Employment Statistics, http://data.bls.gov/oes/, accessed August 1, 2013.

21. Conti, R.M., A., H.A., Huskamp, and E.R. Berndt. "The Effects of FDA Advisories on Branded Pharmaceutical Firms' Valuation and Promotion Efforts," NBER Working Paper No. 17528, October 2011, http://www.nber.org/papers/w17528, accessed November 2, 2012.

22. U.S. Small Business Administration. "Table of Small Business Size Standards Matched to North American Industry Classification System Codes," March 26, 2012. http://www.sba.gov/sites/default/files/files/Size_Standards_Table.pdf, accessed December 7, 2012, and April 18, 2013.

23. U.S. Census Bureau, "Industry Statistics for Subsectors and Industries by Employment Size: 2007 Economic Census", American FactFinder, data downloaded December 11, 2012, http://factfinder2.census.gov/, accessed December 11, 2012.