DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

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

Docket No. FDA- 2011-N-0898

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

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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). OMB has determined that this proposed rule may be an economically significant regulatory action as defined by Executive Order 12866.

The Regulatory Flexibility Act requires agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. The estimated per notification cost for small business entities, $224, represents a small percentage of average annual sales (up to 0.10 percent) for all entities covered by the proposed 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 $112,000 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 anticipates that the proposed rule will not have a significant economic impact on a substantial number of small entities, and seeks comments on its Initial Regulatory Flexibility Analysis.

Section 202(a) of the Unfunded Mandates Reform Act of 1995 requires that agencies prepare a written statement, which includes an assessment of anticipated costs and benefits, before proposing "any rule that includes any Federal mandate that may result in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of $100,000,000 or more (adjusted annually for inflation) in any one year." The current threshold after adjustment for inflation is $141 million, using the most current (2012) Implicit Price Deflator for the Gross Domestic Product. FDA does not expect this final rule to result in any 1-year expenditure that would meet or exceed this amount.

2. Summary

The proposed rule would amend 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 proposed rule would require 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 proposed 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.

The proposed rule would impose annual costs of up to $39.34 million on those applicants or entities affected by the rule, and up to $8.29 million on FDA in preventive costs. Estimated total annual costs of the interactions between industry and FDA range between $14.99 million and $47.62 million. Discounting over 20 years, annual quantified benefits from avoiding the purchase of more expensive alternative products, managing product shortages, and life-years gained, would range from $27.56 million to $86.77 million using a 3 percent discount rate, and from $27.50 million to $86.61 million using a 7 percent discount rate. Annualized over 20 years, net benefits range between $12.57 million and $39.15 million using a 3 percent discount rate; they range between $12.51 million and $38.99 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 proposed rule could result in notifications that do not provide information about any shortage and lead to additional costs. FDA seeks comments on this issue.

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

Category	Primary Estimate	Low Estimate	High Estimate	Year Dollars	Discount Rate	Period Covered	Notes
Benefits							
Annualized Monetized (millions	$57.165	$27.556	$86.773	2012	3%	2014-33	There is uncertainty surrounding these estimates because
	$57.055	$27.501	$86.609	2012	7%	2014-33	

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[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 proposed 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.

|							
$/year)							some underlying estimates came from non-representative studies.
Annualized Quantified					3%	2014-33	20-63 preventable shortages per year.
					7%	2014-33	
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)	$31.306	$14.990	$47.621	2012	3%	2014-33	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.
	$31.306	$14.990	$47.621	2012	7%	2014-33	
Annualized Quantified	None estimated						
Qualitative	None estimated.						
Transfers							
Federal Annualized Monetized (millions $/year)	None estimated						
Other Annualized Monetized (millions $/year)	None estimated.						
Effects							
State, Local or Tribal Gov't	None						
Small Business	Based on the analysis small business entities covered by the proposed rule could incur small costs, $224 per notification or up to 0.10 percent of their average annual sales. Although the proposed 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 2005-2012. Data limitations allow us to only present data on both the number of prevented and actual shortages between 2010 and 2012, but the number of actual shortages is comparable for the period 2005-2012. Furthermore, we note that every notification submitted to FDA provides meaningful information in identifying a potential shortage. Figure 1 indicates that the number of actual drug shortages more than doubled, from 61 to 251, between 2005 and 2011. 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 alone.

Figure 1. Estimated Number of Actual and Prevented Shortages
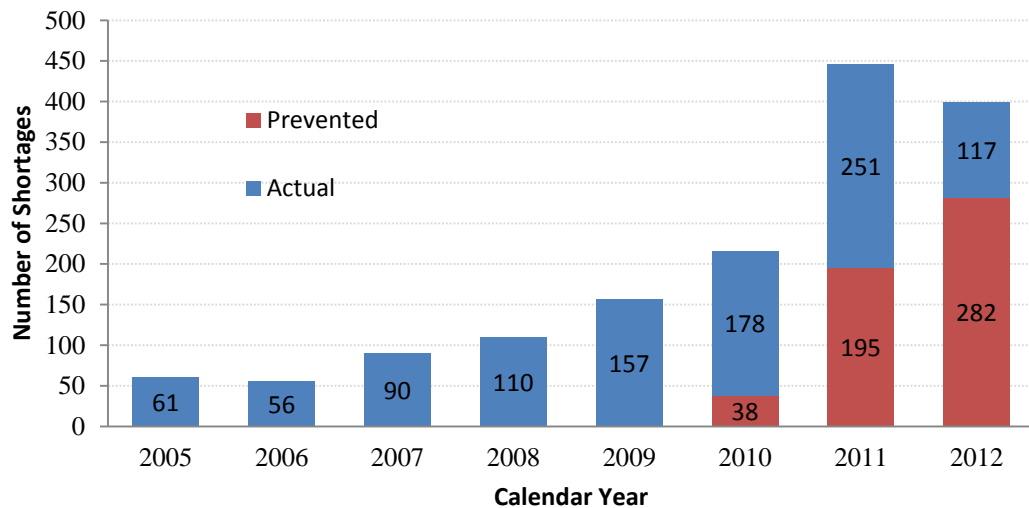
Note: * Potential shortages is the sum of actual shortages (shortages that could not be prevented) and prevented shortages. FDA began collecting data on prevented shortages in 2010.

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 (Proposed Rule Economics 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%) (Proposed Rule Economics 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 (Proposed Rule Economics Refs. 3-5). For example, a national survey of acute care hospitals reported that they experienced serious medication error or adverse reaction (14%) (Proposed Rule Economics 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 on health care providers (Proposed Rule Economics 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 (Proposed Rule Economics 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 is available. Moreover, shortages delay clinical research critical to the development of innovative drugs. For example, Goozner (2012, Proposed Rule Economics 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 (Proposed Rule Economics Ref. 4) report that 44 percent of responding hospitals experienced delays in enrolling patients in cancer clinical trials. By contrast, Emmanuel (2013, Proposed Rule Economics 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 (Proposed Rule Economics 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 (Proposed Rule Economics 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 (Proposed Rule Economics 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 proposed 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 proposed rule responds to the statutory requirement in FDASIA to implement the drug shortages provision through notice and comment rulemaking.

The proposed rule would require 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 proposed requirement would 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 proposed 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] When FDA receives a notification of a discontinuance or interruption in supply, the notification is meaningful and the eventual outcome is either a prevented shortage or an actual shortage.[3]

One notification of a discontinuance or interruption in supply may cover one or 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. By contrast, data for 2012 indicate that, on average, one notification covered one potential shortage (see table 2A).

Data from the last two years 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 and the number of notifications increased to 71 percent, and 392. Part of this increase in prevented shortages and notifications could be attributed to the various policies encouraging early notification, such as Executive Order 13588, FDA's letter to industry, the IFR, and FDASIA.

Table 2A.—Notifications, Potential Shortages and their Outcomes, 2011-2012

Description	2011	2012	Average
Panel A. Shortages			
Actual Shortages	251 (56%)	117 (29%)	184 (43%)
Prevented Shortages	195 (44%)	282 (71%)	239 (57%)
Potential Shortages	446 (100%)	399 (100%)	423 (100%)
Panel B. Notifications			
Notifications	220	392	306
Potential Shortages per Notification	2.0	1.0	1.5

Source: FDA DSS.

FDA estimates that the proposed rule would lead to an increase between 23 and 74 notifications a year. Estimates for approved drugs are based on estimates from the IFR (9 to 24 notifications, Proposed Rule Economics, Ref. 11)[4]. Because the IFR estimates included sole manufacturers, which account for approximately 30 percent of approved drug manufacturers

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[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.

[3] Data from the last two years indicate that one shortage occurred which was not preceded by a notification.

[4] Recent data indicate that between 2012 and 2011 sole-manufacturers submitted 69 additional notifications, which would suggest that the IFR estimates were underestimated. However, the additional number of notifications may include a pent-up effect that may not be representative of the overall long-term trend.

covered by the proposed rule, the estimates for the proposed rule are adjusted up. Thus, we estimate the proposed 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)). FDA seeks comments or data to support other estimates or assumptions made in this analysis.

Table 2B. Estimated Number of Notifications Due to the Proposed 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 (1.5) shown in table 2A, the estimated increase in potential shortages is between 35 (=23*1.5) and 111 (=74*1.5). As mentioned above, potential shortages can either be averted or become actual shortages. In figures 2A (2B) we show how, holding the range 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 the average prevention rate in 2011 and 2012, we estimate a range between 20 (=35*0.57) and 63 (=111*0.57) shortages that can be prevented, and between 15 (=35*0.43) and 48 (=111*0.43) shortages that may be unavoidable.

Figure 2A.--Range of Estimated Prevented Shortages

Prevented Shortages as a Percent of Total Potential Shortages

Maximum   Minimum   ● Midpoint
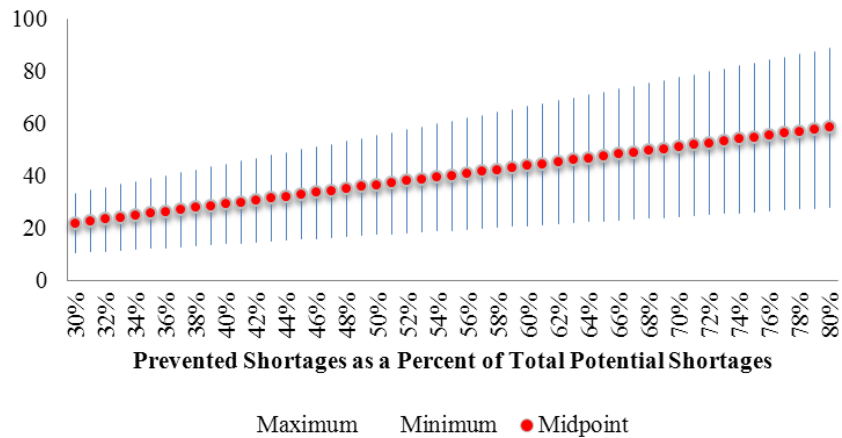
Figure 2B.--Range of Estimated Actual Shortages
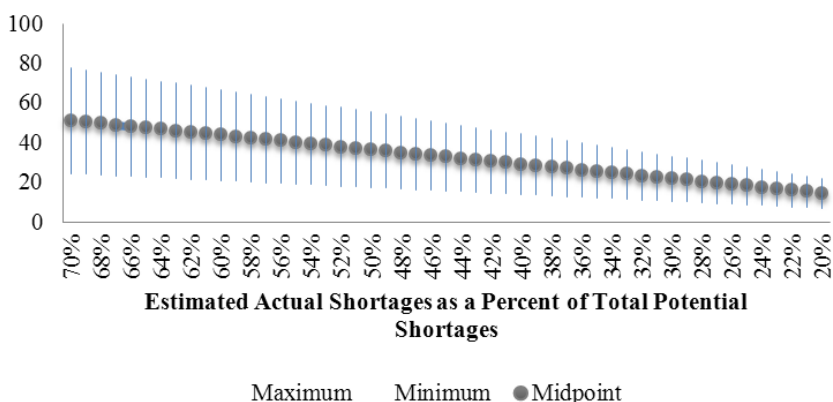
Various activities can result from FDA's efforts to prevent or mitigate shortages. These activities—some of which would violate antitrust rules if pursued by manufacturers in the absence of FDA's intervention—include notifying and encouraging manufacturers of the same or similar products to increase 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 (Proposed Rule Economics 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 proposed rule (see table 2D). For instance, to determine the range of actual shortages that may require FDA action we multiply the estimated range of prevented shortages (20 to 63) by 59%, which results in an estimated range between 9 and 28; 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 Proposed Rule

Type of Action	Actual Shortages	Prevented Shortages	Potential Shortages
FDA Review	9-28	12-37	21-65

Increase Production	5-16	7-22	12-38
Other/No Action Taken	1-3	1-4	2-8
Estimated Shortages	15-48	20-63	35-111

Note: Numbers may not add up due to rounding. Estimates assume 57 percent of potential shortages are prevented. Total potential shortages are estimated to be between 35 and 111. Estimates assume that 59 (34) percent of shortages may be prevented or mitigated by FDA Review (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 proposed 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 ($224.55 million in 2012 dollars) in the United States (Proposed Rule Economics 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 shortages in 2011 and 2012 (239 shortages), we estimate that preventing one shortage could save $0.942 million (2012 dollars) in labor costs. Thus, if 20 to 63 shortages could be prevented (see table 2D above), annual savings associated with managing shortages could range between $18.83 (=20*$0.942) million and $59.32 (=63*$0.942) 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 (Proposed Rule Economics 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. [5] Using the average number of drug shortages in 2011 and 2012, we assume that on average 24 (=5754/239) different hospitals are affected by one drug shortage. Thus, 20 to 63 prevented shortages could affect between 483 (=(5754/239)*20) and 1,520 (=(5754/239)*63) hospitals. [6] Using estimates of the average annual increase in off-contract purchases of \$35,380,[7] we estimate the rule-induced savings from avoiding purchasing alternative products could be between \$17.07 million (=\$35,380*20*(5754/239)) and \$53.77 million (=\$35,380*63*(5754/239)). 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. We seek comments on this approach. Thus, the estimated annual savings from purchasing more expensive alternatives ranges between \$8.54 million and \$26.89 million. We note, however, that the estimated benefits could be higher if the annual cost is higher than the \$200 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.

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[5] 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.

[6] 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.

[7] Premier Healthcare Alliance estimated that having to purchase substitutes because of a drug shortage costs hospitals at least \$200 million annually (\$203.57 in 2012 dollars) (Proposed Rule Economics Ref. 15). This would translate into an average annual cost of \$35,380 per hospital.

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 (Proposed Rule Economics 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 (Proposed Rule Economics 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 20 to 63 shortages were averted, one (20*[12 deaths/239 drug shortages]) to three (63*[12 deaths/239 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, $200,000 and $300,000 (Cutler, 2008 (Proposed Rule Economics Ref. 17); Murphy and Topel, 2006 (Proposed Rule Economics Ref. 18); 74 FR 33030, July 9, 2009), which we update to $111,776, $223,551 and $335,327 in 2012 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) (Proposed Rule Economics 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.[8] 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

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[8] 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.

treat non-Hodgkin's lymphoma.[9] 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.[10] As a conservative measure we use Lakdawalla et al's estimate on colorectal cancer as the life-years gained per averted death.[11] 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 proposed rule (see table 3A). The annualized estimated benefits from life-years gained over twenty years range between $0.190 million and $0.570 million using a 3 percent discount rate, and between $0.135 million and $0.406 million using a 7 percent discount rate.

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

Description	Low	High
Annual Deaths Averted	1	3
Annual Life-Years Gained	1.700 (3%)	5.100 (3%)
	1.211 (7%)	3.632 (7%)
VSLY	$111,776	$111,776
Annual Life-Year Gained, Monetized ($millions)	$0.190 (3%)	$0.570 (3%)
	$0.135 (7%)	$0.406 (7%)
Monetized Life-Years Gained Over 20 Years Present Value ($millions)	$2.827 (3%)	$8.481 (3%)
	$1.433 (7%)	$4.300 (7%)

Note: Discount rate in parentheses.

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 proposed 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 (Proposed Rule Economics 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

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[9] 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.

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

[11] A national survey conducted by McBride et al (Proposed Rule Economics 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.

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 (Proposed Rule Economics Ref. 4). Data from the National Cancer Institute indicate that for every 100,000 individuals, 465 suffer from cancer.[12] Thus, the potential benefit of the proposed 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 shortages has been reported to be as low as 10%, or as high as 33% (Proposed Rule Economics 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%) (Proposed Rule Economics 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 proposed 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 $27.56 million and $86.77 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 $27.50 and $86.61 million.

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[12] 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.

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 (Proposed Rule Economics 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. FDA requests comments on these results and all aspects of our benefits estimation.

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

Description of Benefits	Estimated Annual Savings/Benefits	
	Low	High
Monetized (millions $)		
Buying more expensive treatment	$8.54	$26.89
Managing shortages	$18.83	$59.32
Life-years gained	$0.19 (3%) $0.14 (7%)	$0.57 (3%) $0.41(7%)
Total Monetized	$27.56 (3%) $27.50 (7%)	$86.77 (3%) $86.61 (7%)
Quantified		
Product shortages averted	20	63
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 (Proposed Rule Economics Ref. 20). The median hourly wage, after adjusting for benefits and overhead, is $112. The estimated cost is $224 ($112*2) per notification, and the estimated total annual costs range between $5,152 and $16,576 (see table 4A below).

Table 4A.--Estimated Cost of Additional Notifications

Type of Product	Annual Cost	
	Low	High
Approved Drugs	$4,704	$12,544
Unapproved Drugs	$224	$2,688
Biologics	$224	$1,344
Total	$5,152	$16,576

There are currently 11 full-time equivalent employees (FTEs) handling drug shortage related-issues in CDER's Drug Shortages Staff (DSS). 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 proposed 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 (Proposed 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 $112 (Proposed 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 21 and 65 potential shortages that could involve FDA action, 12-38 where there manufacturers are encouraged to increase production and 2-8 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 $2.44 million (=35*0.24*$294,000) and $7.84 million

(=111*0.24*$294,000). Similarly, costs to industry range between $2.31 million (=35*1000*$112) and $12.43 million (=111*1000*$112). Total costs range from $6.30 and $20.28 million.

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

Description	Low	High
Potential Shortages	35	111
Costs to FDA ($million)	$2.44	$7.84
Costs to Industry ($million)	$3.86	$12.43
Total	$6.30	$20.28

Notes: Costs assume 0.24 FDA FTEs valued at $294,000 for one FTE, and 1000 industry labor hours valued at $112 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 $8.54 million and $26.89 million. This was determined by adjusting the initial range of estimates ($17.07-$53.77 million) from purchasing more expensive alternatives discussed in section D.2. FDA seeks data to support other estimates on this issue.

4. Summary of Costs

Rule-induced costs associated with notifications appear in table 4C. Total monetized costs to industry are between $12.40 million and $39.34 million. On the other hand, estimated total annual costs to FDA range from $2.59 million to $8.29 million. Total combined costs of the interactive efforts of FDA and industry range from $14.99 million to $47.62 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 has fluctuated. While the proposed rule broadens the scope of the products and entities affected by the proposed 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 proposed rule. Consequently, it

is possible that the estimated number of additional notifications, and the related costs and benefits, could be an overestimate.

Under the current environment, every notification that FDA receives provides meaningful information and results in either an actual shortage or a prevented shortage. However, 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. We seek comments or data on this issue.

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 the proposed regulation, FDA would issue letters to entities subject to the proposed 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 proposed rule will have an incentive to comply with the proposed 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 Proposed Rule

Description of Estimated Costs	Estimated Annual Costs	
	Low ($million)	High ($million)
Industry:		
FDA Review	$3.86	$12.43
Notifications	$0.01	$0.02
Ramping up Production	$8.54	$26.84
Subtotal	$12.40	$39.34
FDA:		
FDA Review	$2.44	$7.84
Notifications	$0.15	$0.44
Subtotal	$2.59	$8.29
Total	$14.99	$47.62

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 proposed rule. As discussed above, we estimate cost-savings from managing shortages ($18.83 to $59.32 million per year) and the ability to avoid purchasing more expensive alternatives ($8.54 to $26.89 million per year). We also estimate savings from deaths averted due to prevented shortages. Because the proposed 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 $12.51 million and $38.99 million.

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

Description of Estimated Benefits (Costs)	Estimated Annual Net Benefits	
	Low ($millions)	High ($millions)
Monetized		
Hospitals and Manufacturing Industry:		
Managing Shortages	$18.83	$59.32
Buying More Expensive Alternatives	$8.54	$26.89
Ramping up Production	($8.54)	($26.89)
Regulatory Discretion & Expedited Review	($3.86)	($12.43)
Notifications	($0.01)	($0.02)
FDA		
Regulatory Discretion & Expedited Review	($2.44)	($7.84)
Notifications	($0.15)	($0.44)
Consumers		
Life-Years Gained		
3% Discount Rate	$0.19	$0.57
7% Discount Rate	$0.14	$0.41
Total Monetized		
3% Discount Rate	$12.57	$39.15
7% Discount Rate	$12.51	$38.99

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

G. Analysis of Regulatory Alternatives to the Proposed Rule

FDA identified the following alternatives to the proposed 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 proposed 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. Moreover, as described above, FDA is required by law to issue a regulation implementing the new drug shortages provisions of FDASIA. We may not do this by guidance.

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 proposed 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 proposed 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 proposed rule would be unlikely to alter the current mix of foreign and domestic manufacturing for the affected products.

I. Other Uncertainties

Under the proposed regulation, FDA would issue noncompliance letters to entities subject to the proposed rule who fail to timely notify FDA about a product shortage. Because noncompliance letters would be made public, an entity covered by this proposed rule would have an incentive to comply with the proposed 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 (response to warning letters) 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, but we seek comments on this assumption. 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

Labor Hours	FDA		Industry	
	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 $112 for management occupations, and $149.02 for legal occupations.[13] The estimated cost to FDA of preparing a noncompliance letter ranges between $131 (=0.50*$112 + 0.5*$149.02) and $522 (=2*$112 + 2*$149.02). On the other hand, the cost to industry per response is between $1,044 (=4*$112 + 4*$149.02) and $5,220 (=20*$112 + 20*$149.02) (see table 6B below). The total cost to FDA for issuing between 2 and 7 noncompliance letters ranges between $262 ($131*2) and $3,654 (=$522*7), and total cost to industry to respond could be between $2,088 (=$1,044*2) and $36,542 (=$5,220*7) (see table 6C).

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

Cost Factor	FDA		Industry		Total	
	Low	High	Low	High	Low	High
Management (rounded)	$56	$224	$448	$2,240	$504	$2,464
Legal (rounded)	$75	$298	$596	$2,980	$671	$3,278
Total (rounded)	$131	$522	$1,044	$5,220	$1,175	$5,742

Note: Total may not add up due to rounding.

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

Type of Product	Annual Cost to FDA		Annual Cost to Industry		Total	
	Low	High	Low	High	Low	High
Approved and unapproved drugs	$131	$3,132	$1,044	$31,322	$1,175	$34,455
Biologics	$131	$522	$1,044	$5,220	$1,175	$5,742
Total	$262	$3,654	$2,088	$36,542	$2,350	$40,197

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) (Proposed Rule Economics 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

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[13] 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 (Proposed Rule Economics Ref. 20).

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 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.   Initial Regulatory Flexibility Analysis

The Regulatory Flexibility Act requires agencies to prepare an initial regulatory flexibility analysis if a proposed rule would have a significant effect on a substantial number of small businesses, non-profit organizations, local jurisdictions or other entities. The proposed rule would directly impact a significant percentage of small business entities. The analysis that follows shows that the estimated cost per required notification, $224, 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 $112,224 (=$224 + $112,000), 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 anticipates that this rule will not have a significant economic impact on a substantial number of small entities. FDA invites comments from stakeholders on this conclusion.

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) (Proposed Rule Economics 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 (Proposed Rule Economics 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 proposed role—would be considered small by SBA standards.[14] Furthermore, linking data that include biological product

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[14] 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, 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 proposed rule would be considered small. Similarly, we identified 411 establishments of blood or blood components that operate under four different licensed firms that would be affected by the proposed 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 proposed rule, affected parties who notify FDA of a shortage would incur costs associated with preparing the notification ($224 per notification), and additional costs of $112,000 (=1,000 hours *$112) associated with actions associated with coordinating efforts with FDA to prevent or mitigate a shortage.   Tables 8A-8C below present the cost of the proposed rule as a percent of average sales for a typical firm among the three industry categories affected by the proposed 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 proposed 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[15] 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.

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[15] 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 Proposed Rule: Pharmaceutical Preparation Manufacturing

Number of Employees	Number of Establishments	Percent of Establishments	Average Value of Shipments ($1000)	Approved and Unapproved Drugs ($224 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 $224. Cost per expedited review or regulatory discretion is $112,000. 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 Proposed 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 ($224 per Notification as a Percent of Average Sales)
0-4	1	1.3%	$240	0.0934%
20-49	7	8.0%	$1,317,144	0.0000%
50-499	12	13.3%	$64,771	0.0003%
0-499	20	22.7%	$498,454	0.0000%
500+	69	77.3%	$24,913,908	0.0000%
All	89	100.0%	$15,404,344	0.0000%

Note: The database did not include any establishments employing 5-19 employees. Estimated cost per notification is $224. Cost per FDA review is $112,000. 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 Proposed 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 ($224 per Notification as a Percent of Average Sales)
No	411	100%	$410,429	0.0001%
Yes	0	0%	N/A	N/A
Total	411	100%	$410,429	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 $224. Cost per expedited review or regulatory discretion is $112,000.
Source: FDA Registration and Listing, and Dun & Bradstreet, Inc.

FDA estimates that when this proposed 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 proposes to certify that the proposed rule will have no significant impact on a substantial number of small entities. FDA invites comments on the assumptions and conclusion of this analysis.

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 $224 dollars. 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 proposed 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 proposed 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 proposed 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.

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