DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Medication Guides: Patient Medication Information

Docket No. FDA-_____

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

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I. Introduction and Summary

A. Introduction

We have examined the impacts of the proposed rule under Executive Order 12866, Executive Order 13563, the Regulatory Flexibility Act (5 U.S.C. 601-612), and the Unfunded Mandates Reform Act of 1995 (Pub. L. 104-4). Executive Orders 12866 and 13563 direct us to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). We believe that this proposed rule is a significant regulatory action as defined by Executive Order 12866.

The Regulatory Flexibility Act requires us to analyze regulatory options that would minimize any significant impact of a rule on small entities. Because we find the cost of the proposed rule to be a substantial percentage of sales for small businesses, we find that the proposed rule will have a significant economic impact on a substantial number of small entities.

The Unfunded Mandates Reform Act of 1995 (section 202(a)) requires us to prepare a written statement, which includes an assessment of anticipated costs and benefits, before proposing "any rule that includes any Federal mandate that may result in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of $100,000,000 or more (adjusted annually for inflation) in any one year." The current threshold after adjustment for inflation is $165 million, using the most current (2021) Implicit Price Deflator for the Gross Domestic Product. This proposed rule would not result in an expenditure in any year that meets or exceeds this amount.

B. Summary of Costs and Benefits

This proposed rule would require that human prescription drug products used, dispensed, or administered on an outpatient basis, including blood and blood components transfused in an outpatient setting, be accompanied by a one-page product information document, or Medication Guide, known as Patient Medication Information (PMI). Manufacturers of these products would be required to create PMI according to standardized content and format requirements. PMI would be reviewed and approved by FDA and stored in an online, central repository accessible to the public. Firms would incur costs to develop PMI. FDA would incur costs to review PMI as well as to establish and maintain the online database. For a small subset of drug products, FDA would also incur costs to develop a template for PMI. Dispensers may face additional costs to print and distribute PMI. Firms that currently produce Consumer Medication Information (CMI) may also incur costs associated with switching to a new business model. PMI would provide the public with FDA-approved labeling that is created specifically for patients. The public would benefit from this labeling with decreased search costs for information. The public may also benefit from a reduction in risk associated with their drug products, including blood and blood component products transfused in outpatient settings, due to the availability of PMI if the new labeling helps patients make better healthcare decisions.

In our primary analysis, we assume that all products subject to the rule would stay on the market. However, we observe that the costs of creating, updating, or submitting PMI could exceed the profits for certain low-revenue drug products. Some of these products would be eligible for a waiver or extension of the requirements of PMI if complying with the requirements could contribute to a drug shortage or otherwise impede patient access. For those products not eligible for a waiver or extension, firms may choose to discontinue marketing the drugs, which would lead to additional social costs under the proposed rule. We perform additional analyses to

better understand how the costs and benefits of the rule would be affected by waivers and extensions or discontinuations of drug products.

The costs and benefits of the proposed rule are summarized in Table 1. Summary of Benefits, Costs, and Distributional Effects of the Proposed Rule. This table shows the estimated average annualized net costs of this rule, using both 7 and 3 percent annual discount rates over a ten-year evaluation period. We estimate that the present value of net costs over ten years would range from $105.0 to $312.5 million, with a primary estimate of $192.8 million, at a 3 percent discount rate and from $89.0 to $263.6 million, with a primary estimate of $162.6 million, at a 7 percent discount rate. Annualizing these costs over ten years, we estimate the cost would range from $12.3 to $36.6 million per year at a 3 percent discount rate, with a primary estimate of $22.6 million per year, and from $12.7 to $37.5 million per year using a discount rate of 7 percent, with a primary estimate of $23.2 million.

Table 1 also shows the estimated annualized benefits and other qualitative benefits that cannot be quantified. The monetized benefit of this rule would result from decreased search costs for information pertaining to drug, blood, and blood component products received in outpatient settings. We estimate that the present discounted value of these potential benefits from PMI over ten years would range between $127.5 million and $1.6 billion using a 3 percent discount rate, with a primary estimate of $874.9 million; using a 7 percent discount rate, the present-value benefits from PMI would range between $101.0 million and $1.3 billion, with a primary estimate of $691.7 million. Annualized over ten years, we estimate that the benefit from PMI would range between $14.9 and $190.5 million per year, with a primary estimate of $102.6 million, using a 3 percent discount rate; with a 7 percent discount rate, we estimate the annualized benefit to range between $14.4 and $182.5 million, with a primary estimate of $98.5

million per year. In addition to these monetized benefits, patients may experience a reduction in risk associated with drug, blood, and blood component products if PMI leads them to make better, more informed healthcare decisions.

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

Category		Primary Estimate	Low Estimate	High Estimate	Units			Notes
					Year Dollars	Discount Rate	Period Covered	
Benefits	Annualized Monetized $m/year	$98.5	$14.4	$182.5	2020	7%	10 years	
		$102.6	$14.9	$190.5	2020	3%	10 years	
	Annualized Quantified					7%		
						3%		
	Qualitative	Risk reduction from improved access to information						
Costs	Annualized Monetized $m/year	$23.2	$12.7	$37.5	2020	7%	10 years	
		$22.6	$12.3	$36.6	2020	3%	10 years	
	Annualized Quantified					7%		
						3%		
	Qualitative							
Transfers	Federal Annualized Monetized $m/year					7%		
						3%		
	From/ To	From:			To:			
	Other Annualized Monetized $m/year					7%		
						3%		
	From/To	From:			To:			
Effects	State, Local or Tribal Government: No effect Small Business: Potential for significant impact on the smallest firms Wages: No effect Growth: No effect							

In calculating the costs discussed above, we have netted out the cost savings that would stem from this proposed rule. PMI would replace the current Medication Guides and Patient Package Inserts; therefore, manufacturers would not need to create or submit updates to their

Medication Guides and Patient Package Inserts, which would result in cost savings to those manufacturers.

II. Preliminary Regulatory Impact Analysis

A. Background

According to a meta-analysis of 328 studies, the average percent adherence across studies of medication treatment regimens was 79.4%. (DiMatteo, 2004). This prescription medication non-adherence can lead to drug-related adverse events, worsening of medical conditions, and increased healthcare costs. Some experts believe that this non-adherence may be due, at least in part, to a lack of accessible, easy-to-understand information about the prescription drugs that patients receive (Osterberg and Blaschke, 2005; Bosworth et al., 2011).

B. Need for Federal Regulatory Action

Currently, FDA requires that patients receive information about select prescription drugs in the form of Medication Guides for Prescription Drug Products (hereafter referred to simply as Medication Guides) or Patient Package Inserts (PPI); however, this information is not required to be provided with all prescription drugs, which can lead to gaps in information. In some instances, private industry has attempted to fill this information gap. Many pharmacies purchase prescription drug information in the form of Consumer Medication Information (CMI) to be provided to patients along with their medications. According to a 2008 study by Kimberlin et al., 94 percent of prescriptions were dispensed with CMI; however, only 75 percent of those

reviewed met certain criteria for usefulness to patients (Kimberlin et al., 2008). CMI is often lengthy, written in technical language that exceeds the reading comprehension level of the average American, and presented in a font and format that makes reading difficult (Aker et al., 2013). These characteristics of CMI increase the likelihood that it will go unread by patients, thereby failing to fill the information gap that may contribute to non-adherence and the corresponding social losses associated with suboptimal consumption of medication (Osterberg & Blaschke, 2005).

Markets have also responded to the demand for prescription drug information by posting that information on healthcare-related websites. Many of these websites are financially supported by advertisers and provide their content to the public for free; however, the information on these websites may suffer from many of the same criticisms as CMI. In addition, healthcare-related websites are only available to those with an internet connection; therefore, they fail to fill the information gap for individuals without access to the internet.

Patients may be willing to pay for improvements in or easier access to information about their prescription drugs; however, the market structure for prescription drugs may prevent that. Like many aspects of healthcare in the U.S., the market for prescription drugs is dominated by a principal-agent structure with a third-party payer. In the case of prescription drugs, the principal is the pharmacy or pharmacist, the agent is the patient, and the third-party payer is the insurer (either private or public). The retail price for prescription drugs is negotiated between the principal and the third-party payer, both of which are operating under the goal of profit maximization or cost minimization. If an individual agent were willing to pay a higher retail price for their drugs in order to receive improvements in the information that accompanies them, the current market structure would prevent that transaction from occurring.

C. Purpose of the Proposed Rule

Through this rulemaking, FDA proposes to require that Patient Medication Information (PMI) be provided to patients with all human prescription drug products used, dispensed, or administered on an outpatient basis, including blood and blood components transfused in an outpatient setting. Throughout the PRIA, we refer to these products simply as "drug products" and "blood and blood component products." PMI must meet standardized format and content requirements and be reviewed and approved by FDA. PMI would be submitted to FDA under a five-year, staggered implementation timeline. The timeline would require that manufacturers of drugs that currently have a Medication Guide or Patient Package Insert (PPI), or that have a Medication Guide or PPI currently under review at FDA, submit PMI in the first year the final rule takes effect. Manufacturers of all other drugs would submit PMI in one of the following four years depending on the approval date of the most recent efficacy supplement or the original approval date for drugs without approved efficacy supplements.

PMI would be housed in a publicly accessible online repository. This online database of PMI is a public good (although it is potentially excludable), with zero marginal cost of providing access to the database. Once established, the socially optimal price for access to the database is zero. Private firms do provide prescription drug information in the form of CMI and they could, in principle, establish an online database of CMI and devise a pricing or fee mechanism; however, as described above, the CMI currently available has failed to fully promote prescription drug knowledge, adherence, and safe use. Further, Aker et al. (2013) show that patients prefer to receive information in a style and format that is more similar to what FDA intends with PMI than what is currently available in CMI. Therefore, FDA proposes to improve the quality of

prescription drug information that patients receive by establishing a public database of PMI that would meet format, content, readability, and comprehension guidelines to make it easier for patients to use their medications correctly.

D. Baseline Conditions

This rule would require PMI to be provided to patients with human prescription drug products used, dispensed, or administered on an outpatient basis, including blood and blood component products transfused in an outpatient setting. Human prescription drug products include small molecule drugs regulated by the Center for Drug Evaluation and Research (CDER), therapeutic biologics (including interchangeable biosimilars and non-interchangeable biosimilars) regulated by CDER, and some biologics regulated by the Center for Biologics Evaluation and Research (CBER). For drug products, the firm that submits or owns the approved New Drug Application (NDA), Biologic License Application (BLA), or Abbreviated New Drug Application (ANDA) subject to the rule would be responsible for PMI; throughout this analysis, we refer to that firm as the manufacturer of the product.

PMI would be developed for most NDA and BLA products; we refer to PMI for these products as "reference PMI." Manufacturers of ANDA products would submit PMI based on the reference PMI submitted for the NDA referenced by the ANDA. PMI for NDA and BLA products would be submitted to FDA in a prior approval supplement (PAS). PMI for ANDA products would be submitted either in a prior approval supplement (PAS) or in a changes being effected (CBE-0) supplement. In general, manufacturers of ANDA products would be expected to submit PMI as a CBE-0 supplement when the proposed PMI is the same as the reference PMI.

In instances where the PMI for the ANDA product is significantly different than the reference PMI, the manufacturer of the ANDA product would be expected to submit PMI as a PAS.

In conducting this analysis, we make three assumptions about how manufacturers would comply with this proposed rule. First, for actively marketed products, we assume that manufacturers would create PMI. Second, for products whose approval has been withdrawn, we assume that manufacturers would not create PMI. Third, for products that have discontinued marketing but whose approval has not been withdrawn, we assume that manufacturers would apply for and be granted waivers or extensions of the requirements of this proposed rule. We request comment on these assumptions, particularly our third assumption, as we recognize that manufacturers of discontinued products, in complying with this proposed rule, may opt to develop and submit PMI or request withdrawal of their applications rather than seek waivers or extensions of the PMI requirements. ANDA products that reference NDA products that are no longer active would, therefore, not have a reference PMI on which to base their submission. In the case of NDA products for which approval of the applications have been withdrawn, FDA would create a PMI template for the manufacturers of the corresponding ANDA products to use. FDA would not create such a template for NDA products that have been granted waivers or extensions; therefore, we expect ANDA products that reference discontinued NDA products with waivers or extensions of the PMI requirements to not submit PMI.

A single PMI document may be used for multiple strengths of the same drug. So, if a pharmaceutical company has multiple products with the same active ingredient, dosage form, and route of administration but with varying strengths, all strengths of the drug can utilize the same PMI; however, if a pharmaceutical company has multiple products with the same active ingredient but with different dosage forms and routes of administration, each of those products

would potentially require its own PMI. Thus, for purposes of this analysis, we define a unique drug product corresponding to a unique PMI to be one that has a unique combination of active ingredient, dosage form, and route of administration regardless of strength.

1. Reference Listed Products

Using the Orange Book and our definition of a unique drug product stated in the previous paragraph, we identify 2,640 unique prescription NDA products on the market as of May 2018 (FDA, 2018). This is our upper bound of the number of PMI documents that would need to be created for prescription NDA products. This may overstate the number of PMI submissions for NDA products because PMI would only be required for drugs distributed on an outpatient basis. We lack a list of drugs that are used only in outpatient settings but identify the count of injectable drugs as a reasonable proxy for the upper bound of the number of drugs available only in inpatient settings. We consider this proxy an upper bound because we acknowledge that many injectable drugs are available in outpatient settings and thus would be subject to this rule. Based on a count of injectable drugs available in 2016, we estimate that up to 30 percent of active NDA products are injectable. Adjusting by this percentage, we estimate that there are 1,848 unique, non-injectable, prescription NDA products on the market as of May 2018. This serves as our lower bound of the number of prescription NDA products that would require PMI. For our primary estimate, we use the midpoint of the lower and upper bounds, which is 2,244 unique prescription NDA products. Thus, we estimate that the number of NDA products for which PMI would need to be developed is between 1,848 and 2,640, with a primary estimate of 2,244.

Using the Purple Book, we identify 185 unique therapeutic biologics regulated by CDER on the market as of January 2020 (FDA, 2020a). We assume that all of these would be subject to this rule. In addition, in March 2020, CBER identified 215 biologics that would require PMI.

There are five blood and blood component products intended for transfusion on an outpatient basis that would need PMI: whole blood, red blood cells, platelets, plasma, and Cryoprecipitate AHF. Based on past experience with the development of information dispensed with human blood and blood components [see Ref. Circular of Information; http://www.aabb.org/tm/coi/Pages/default.aspx], FDA assumes that industry would collaborate to create a single PMI document for each blood or blood component product that would be used by all manufacturers of that product; thus, FDA assumes that five PMI documents would be created initially for blood and blood component products. We invite comment on this assumption.

Table 2 shows our estimate of the number of reference listed products for which PMI would need to be developed. In addition, NDAs and BLAs submitted in the future would need to include PMI. Using data from the annual PDUFA Performance Reports, we estimate that between fiscal years 1993 and 2014, there were 119 NDAs and BLAs submitted to FDA each year on average. We adopt this historical average as a forecast of the number of NDAs and BLAs submitted with PMI to FDA each year.

Table 2. Number of Existing Reference Products

	Low Estimate	Primary Estimate	High Estimate
NDA Products	1,848	2,244	2,640
BLA Products	400	400	400
Blood Products	5	5	5
Total	**2,253**	**2,649**	**3,045**

This proposed rule would include a staggered implementation plan to distribute the initial burden of developing PMI over five years. Under this implementation plan, all drug products that have Medication Guides or PPI would submit PMI to FDA in the first year. All other drug products would submit PMI according to a schedule based on the date of the latest efficacy supplement approval or the date of the initial approval for products without efficacy supplements.

Drug products whose latest approval was in 2013 or later would submit PMI in year two. Drug products whose latest approval was in 2008 through 2012 would submit PMI in year three. Drug products whose latest approval was in 2003 through 2007 would submit PMI in year four. Drug products whose latest approval was prior to 2003 would submit PMI in year five.

There are five blood and blood component products intended for transfusion on an outpatient basis that would need PMI: whole blood, red blood cells, platelets, plasma, and Cryoprecipitate AHF. For this analysis, we assume that PMI for these blood and blood component products would be submitted in the middle of the implementation plan in year three. Based on FDA's experience with other forms of labeling dispensed with blood and blood component products, we assume that industry would collaborate to create a single PMI document for each blood or blood component product that would be used by all manufacturers of that product. Therefore, we assume that five PMI documents would be initially created for blood and blood component products and submitted to FDA in year three. We invite comment on these assumptions.

Table 3 shows the number of PMI documents we expect to be submitted in each year for existing reference listed products, including blood and blood component products, based on the implementation schedule discussed above.

Table 3. PMI Implementation Timeline for Existing Reference Products

	Low Estimate	Primary Estimate	High Estimate
Year 1	555	569	582
Year 2	421	492	564
Year 3	207	257	307
Year 4	191	240	290
Year 5	879	1090	1301

2. ANDA Products

Each ANDA product would be required to submit PMI that is the same as that of the NDA it references, except for minor permissible differences. We use data from the Orange Book from May 2018 to count the number of ANDA products that we expect will submit PMI. We estimate that there are 5,792 ANDA products that reference active NDA products; these ANDA products would submit PMI based on that of the NDA products they reference. We also estimate that there are 147 ANDA products that reference NDA products that have been withdrawn and 262 ANDA products that have no identifiable reference listed products, for a combined total of 409 ANDA products with no approved reference listed products. For these 409 ANDA products, FDA would create PMI templates that manufacturers would use to submit PMI for their products. Amongst these 409 ANDA products, there are 148 unique drug products (unique combination of active ingredient, dosage form, and route of administration); therefore, we estimate that FDA would create 148 PMI templates. Combining the 5,792 ANDA products that would submit PMI based on the reference PMI submitted by the NDA products with the 409 ANDA products that would submit PMI based on the FDA-created PMI template, we estimate that 6,201 ANDA products would submit PMI.

Manufacturers of existing ANDA products would submit PMI after the approval of PMI for the NDA products they reference. We assume that the proportion of PMI for ANDA products submitted in each of the first five years is the same as that of the reference listed products.[1] In Table 4, we present the number of ANDA products that we expect would submit PMI in each of the first five years.

Table 4. PMI Implementation Timeline for All Existing Non-Reference Products

	Low Estimate	Primary Estimate	High Estimate
Year 1	1531	1333	1187
Year 2	1161	1155	1151
Year 3	558	591	616
Year 4	526	564	592
Year 5	2426	2557	2655

Among the PMI submissions for existing ANDA products, we estimate that at least 2,117 and as many as 3,225 of them would be submitted in a PAS due to differences between the PMI submitted for the ANDA product and either the reference PMI or the FDA-created PMI template representing a major change.[2] Those with either no differences or only minor differences would

[1] We are unable to determine exactly when during the implementation timeline PMI for each particular ANDA product would be submitted because we have difficulty linking ANDA products to the specific NDAs they reference.

[2] CDER has identified 2,117 ANDA products that reference an active NDA that has at least one method of use patent or exclusivity. When the manufacturers of these ANDA products submit PMI, they would be required to carve out any protected information. These carve-outs would cause the PMI for the ANDA product to be significantly different from the PMI for the NDA product. We expect there may be some other circumstances that would also cause the PMI for an ANDA product to be significantly different from its reference PMI (e.g. allowable

be submitted in a CBE-0 supplement. In Table 5, we present our estimate of the percent of PMI submissions for ANDA products that would be submitted to FDA each year with significant differences from the reference PMI.

Table 5. PMI Implementation Timeline for Existing ANDA Products: Percent of PMI with Significant Differences from the Reference PMI

	Low Estimate	Primary Estimate	High Estimate
Year 1	34%	47%	52%
Year 2	34%	47%	52%
Year 3	34%	47%	52%
Year 4	34%	47%	52%
Year 5	34%	47%	52%

In addition to the existing ANDA products, ANDAs submitted to FDA in the future would need to include PMI. We estimate that there are, on average, 1,328 ANDAs submitted to FDA each year. We use this as our estimate of the number of future ANDA submissions that would include PMI each year. We assume that the same percentage of PMI for future ANDA products would have significant differences from its reference PMI as PMI for existing products. We apply those percentages to our estimate of the number of future PMI submissions for ANDA products to estimate how many would have significant differences from their reference PMI and how many would have only minor differences. We estimate that between 485 and 690 PMI documents for future ANDA products would be submitted to FDA each year with significant

differences under 314.94(a)(8)(iv)); therefore, we consider these 2,117 ANDA products with carve-outs to represent a lower bound on the number of ANDA products that would have PMI that is significantly different from the reference PMI.

differences while between 637 and 874 would be submitted to FDA each year with only minor differences.

E. Benefits of the Proposed Rule

Under this proposed rule, PMI would be provided to patients each time they receive a drug, blood, or blood component product in an outpatient setting. For patients who seek out written information about their medical products, this could reduce their search costs in two ways. First, it could reduce the amount of time they spend trying to find the information because there would be more complete coverage of written information distributed with prescription products. Second, it could reduce the amount of time they spend reading the information because PMI would be standardized and designed to be easier to read than much of the information that is currently available.

The Experimental Study of Patient Information Prototypes conducted by authors at RTI International found that it took individuals between 2.5 and three fewer minutes to read a PMI prototype than it did to read a current Medication Guide (Kelly et al., 2013). In addition, we conducted our own informal comparison of the time required to read a PMI prototype and the time required to look up prescription drug information on some popular websites and found that reading a PMI prototype was approximately two minutes faster than looking up the information online. Therefore, we estimate that PMI would save an individual between two and three minutes each time he reads the entire document, with a primary estimate of 2.5 minutes saved.

To estimate the value of this search time saved, we use the mean, after-tax, hourly wage as a proxy for the value of time (HHS, 2017). The mean hourly wage in 2020 was $27.07 (BLS, 2020b). Adjusting for the mean income tax rate of 25 percent, we calculate the value of time in

2020 as $20.30 per hour (HHS, 2017). Multiplying this value by the search time saved, we estimate that PMI would save an individual between $0.68 and $1.02, with a primary estimate of $0.85, each time they search for information about their drug, blood, and blood component products.

Data from IQVIA National Prescription Audit New to Brand (NPA NTB™) extracted in March 2019 show that in 2018, there were approximately 721.9 million instances in which a prescription was dispensed to a patient who had not taken a drug in the same therapeutic class in the past 12 months. We refer to this measure as "new therapy starts;" it captures each time a patient starts taking a prescription drug in a therapeutic class that he has not been exposed to in the past 12 months. We believe that patients with new therapy starts would be the most likely to benefit from PMI because they are not only taking drugs that are new to them, but they are starting a class of therapy that is new to them as well; however, we recognize that this may be a lower bound for two reasons. First, the new therapy starts represent only a fraction of the 3.8 billion prescriptions that were dispensed in 2018 (IQVIA, 2019). Second, the measure does not include individuals receiving blood or blood component products, who would also receive PMI under this proposed rule.

While we believe that the new therapy starts measure captures individuals most likely to benefit from PMI, we recognize that not all of them will read PMI. In a review of the literature, we have identified three studies that estimate the percentage of patients who read all of the information they receive with their drugs. In a survey by Harris Interactive (2002), 5 percent of individuals reported reading all of the labeling information when they purchase over-the-counter drugs. In studies conducted by Raynor and Knapp (2000) and Enger et al. (2013), 35 percent and 43 percent of patients, respectively, reported reading all of the information leaflet or Medication

Guide they received with their prescription drug. We seek comment on any additional studies that have been published estimating the percent of patients who read all of the information that accompanies their medications.

One must read the PMI in order to benefit from it; therefore, we multiply the number of new therapy starts by the percent of people who read all of the information that accompanies their drugs in order to estimate the number of people who would benefit from this proposed rule. For our lower bound in this calculation, we use the estimate of 5 percent found by Harris Interactive (2002). For our upper bound, we use the estimate of 43 percent found by Enger et al. (2013). For our primary estimate, we take an average of the three estimates from the literature, which comes to 28 percent. Multiplying these percentages by the number of new therapy starts, we estimate that PMI would be read in its entirety between 36.1 and 310.4 million times each year.

Multiplying the number of times PMI would be read each year by the value of the search time saved due to PMI, we obtain the monetized benefit of PMI in terms of reduced search costs if all products were to have PMI. However, not all products would have PMI. As discussed above, PMI would be implemented over a five-year period; and even after the first five years, we expect some ANDA products with discontinued reference listed products would not submit PMI. We account for this by multiplying the full value of the search time saved by the percentage of products we expect to have PMI in each year. Our estimate of the monetized annual benefit is presented in Table 6. We estimate that the reduced search costs would amount to between $4.9 and $49.4 million in the first year and would increase annually over the first five years as the proposed rule is implemented. Beginning in the fifth year and for each year thereafter, we

estimate that the reduced search costs would amount to between $19.7 and $258.0 million annually.

Table 6. Annual Monetized Benefit (millions) of PMI: Reduced Search Costs

	Low Estimate	Primary Estimate	High Estimate
Year 1	$4.9	$29.5	$49.4
Year 2	$8.5	$55.1	$97.3
Year 3	$10.3	$68.1	$122.9
Year 4	$12.0	$80.6	$147.5
Years 5+	$19.7	$137.2	$258.0

We calculate the present discounted value and annualized value of these benefits over ten years using both 3 and 7 percent discount rates. These are presented in Table 7. We estimate that PMI would result in reduced search costs over ten years ranging between $127.5 million and $1.6 billion using a 3 percent discount rate, with a primary estimate of $874.9 million. Using a 7 percent discount rate, we estimate the reduced search costs over ten years would range between $101.0 million and $1.3 billion, with a primary estimate of $691.7 million. Annualized over ten years using a 3 percent discount rate, we estimate these benefits would range between $14.9 and $190.5 million, with a primary estimate of $102.6 million per year; using a 7 percent discount rate, we estimate the annualized benefits would range between $14.4 and $182.5 million, with a primary estimate of $98.5 million per year.

Table 7: Present Discounted Value and Annualized Benefit of PMI: Reduced Search Costs

	Low Estimate	Primary Estimate	High Estimate
Present Discounted Value over 10 Years (millions, 2020 dollars, 3% discount rate)	$127.5	$874.9	$1,624.8

Present Discounted Value over 10 Years (millions, 2020 dollars, 7% discount rate)	$101.0	$691.7	$1,282.0
Annualized over 10 Years (millions, 2020 dollars, 3% discount rate)	$14.9	$102.6	$190.5
Annualized over 10 Years (millions, 2020 dollars, 7% discount rate)	$14.4	$98.5	$182.5

The benefits estimated here should be taken as lower bounds on the true benefits for a variety of reasons. First, we estimate the reduced search cost only for those who would read the entire PMI document; however, there would likely be some time savings for those who would read only a portion of the document. In our review of the literature, we found a very wide range in the percent of people who read some, but not all, of the information that accompanies their medications. Raynor and Knapp (2000) found that 19 percent of patients who received an information leaflet with their prescription drug read some but not all of it. Enger et al. (2013) found that 43 percent of patients read some but not all of the Medication Guide they received with their prescription drug. The Harris Interactive survey (2002) found that 90 percent of people read some but not all of the information on the labels of over-the-counter drugs when they purchase them. In addition, we found some studies that report the percent of individuals who read the information that accompanies their prescription drugs without differentiating between reading some or all of it. Wolf et al. (2006) found that 23 percent of patients report having

previously attended to the information included with their prescription drugs. Nathan et al. (2007) found that 49 percent of patients always read the leaflet when they receive a new prescription drug and 22 percent of patients always read the leaflet when they receive a refilled prescription drug.

If the standardized format of PMI would make the information that patients are looking for easier to find, there would be a reduction in search costs for these individuals who read some, but not all, of the information. We are currently unable to estimate the value of this reduction in search costs for individuals who read some, but not all, of the information and request comment on methods for valuing this benefit.

Second, there would likely be other, health-related benefits associated with PMI that we are unable to quantify at this time. Research has shown that patients who receive PMI have greater knowledge about their prescription drugs and comprehend the information better than patients who receive the current CMI or current Medication Guides (Aker et al., 2013; Boudewyns et al., 2015). This improved knowledge may help patients better understand how to follow their indicated course of treatment in terms of taking their prescription drugs more consistently, in the right dosage, and at the correct time with better information on safe and effective use. It may also improve patients' ability to recognize adverse drug outcomes or serious side effects and provide them with instructions on what to do when they experience these events. In addition to these potential health benefits, patients have expressed a preference for PMI over the information leaflets they currently receive with their prescription drugs (Kish-Doto et al., 2014).

Although we are currently unable to quantify these additional benefits of PMI, we do recognize their potential. The additional reduction in search costs not quantified in our analysis,

the improvements in health that may result from improved knowledge about prescription drugs, and any utility gained from the consumption of information as a commodity could all cause the full benefits of this proposed rule to be understated in this analysis. Ideally, we would measure the full benefit of this proposed rule by estimating patients' willingness to pay (WTP) for PMI. As a measure of benefits, WTP would encompass any conceivable benefit patients would gain from PMI, including the expected health benefits and time savings from, and preferences for, improved access to information. Dealy et al. (2021) find that the WTP for standardized informational leaflets similar to PMI was approximately $1.37 per household per month among a convenience sample of federal government employees. Although this sample was not representative of the U.S. population, when the authors extrapolate the result to all U.S. households, they find that the aggregate WTP for leaflets similar to PMI could exceed $1.9 billion per year. Given that the results from Dealy et al. (2021) are not meant to be representative of the U.S. population, we are unable to use them to estimate benefits of this proposed rule. If, however, similar estimates were available from a representative sample of the U.S. population, such estimates would provide a more complete measure of the benefits to be gained from this proposed rule. FDA invites comment on the use of contingent valuation methods to estimate benefits in this context. To our knowledge, such estimates are not available at this time.

F. Costs of the Proposed Rule

We have identified several sources of costs that would be associated with this proposed rule. For existing and future products, there would be costs associated with the development, submission, and review of PMI. There would also be costs associated with making changes to

PMI after it has been approved. In addition, there would be costs associated with reading the rule, making modifications to Risk Evaluation and Mitigation Strategies (REMS), and establishing and maintaining the online repository. There would also be cost savings to manufacturers of drugs with REMS. We describe each of these costs below.

1. Reading the Rule

We assume that all firms that manufacture drug products would read this proposed rule. The current version of the proposed rule contains approximately 30,000 words. Assuming that the average adult reads approximately 200 words per minute, we estimate that it would take approximately 2.5 hours (30,000 words / 200 words per minute / 60 minutes per hour = 2.5 hours) to read the rule. Using data from the Orange Book, we count that there are 1,416 firms that manufacture drug products. We use this number as an estimate for the number of firms that would need to read this proposed rule and seek comment on the precision of this estimate.

We assume that the person reading the rule at each firm is a lawyer or other managerial equivalent, and we request comment on this assumption. According to the Bureau of Labor Statistics, the mean hourly wage of lawyers in the Pharmaceutical and Medicine Manufacturing (NAICS Code 325400) industry was $79.36 in 2020 (BLS, 2020a). Doubling this wage to account for benefits and other indirect costs, we assume that the individuals reading the rule earn a mean fully loaded hourly wage of $158.72. Multiplying the number of firms by the time to read the rule, and then multiplying that product by the mean fully loaded hourly wage, we estimate that the total cost to read the rule would be $561,869. This would be a one-time cost that accrues in the first year.

2. Developing, Submitting, and Reviewing PMI

Manufacturers of both reference listed and ANDA products would incur costs associated with developing PMI and submitting it to FDA. FDA would incur costs associated with reviewing the PMI submissions. We discuss these costs in detail below, separately for reference listed and ANDA products.

a. Reference Listed Products

Existing and future reference listed products would be required to develop PMI and submit it to FDA for review and approval. To estimate the costs associated with this, we use our Labeling Cost Model developed by RTI International and estimate the cost to industry of creating an extensive change to over-the-counter (OTC) drug labeling as a proxy for the cost of developing and submitting PMI for a single reference listed product (Muth et al., 2015). We assume that this change would occur over a five-year compliance period and would include recordkeeping costs but not testing costs. Inflating the cost estimates from the model to 2020 dollars using the GDP deflator, we estimate the cost to industry of creating an extensive change in OTC drug labeling would range between $11,606 and $41,098, with a primary estimate of $23,645. We use these estimates as proxies for the cost of creating PMI for reference listed products and request comment on these estimates. We estimate that FDA's review of PMI for a single reference listed product would require between 24 and 33 FTE hours. Using an hourly FTE cost of $142.20, we estimate that the cost to FDA to review PMI for a single product would range between $3,413 and $4,693. We use the midpoint of these values, $4,053, as our primary estimate of the cost to FDA to review a single PMI. Combining the cost to industry to develop and submit PMI with the cost to FDA to review PMI, we estimate the total cost of development,

submission, and review of a single PMI document for a reference listed product to range between $15,019 and $45,791, with a primary estimate of $27,697.

Multiplying these cost estimates by the number of reference listed products that we expect to submit PMI in each year (described in Section II.D), we obtain the annual cost of development, submission, and review of PMI for reference listed products. These estimates are presented in Table 8.

Table 8. Cost of Development, Submission, and Review of PMI for Reference Products (millions)

	Low Estimate	Primary Estimate	High Estimate
Year 1	$9.7	$18.6	$31.5
Year 2	$7.7	$16.5	$30.7
Year 3	$4.5	$9.9	$19.0
Year 4	$4.2	$9.5	$18.2
Year 5	$14.6	$33.0	$64.5
Years 6+	$1.4	$2.8	$4.9

b. ANDA Products

ANDA products would also be required to submit PMI to FDA for review; however, the cost of doing so would be significantly less than the cost associated with PMI for reference listed products because ANDA products will use either the PMI of the reference listed product or the FDA-created PMI template as the basis for their submissions. As described in Section II.D., PMI for ANDA products would be submitted to FDA in either a CBE-0 supplement or a PAS. The RIA for the Supplemental Applications Proposing Labeling Changes for Approved Drugs and Biological Products (FDA, 2013a) assumes that it would take an applicant between four and twelve hours to submit an original CBE-0 supplement to FDA. We use this range as the estimate of the amount of time required to prepare and submit PMI through a CBE-0 supplement, with a

primary estimate of eight hours. To estimate the amount of time required to prepare and submit PMI through a PAS, we double the estimates for the CBE-0 supplement; thus, we assume it would take between eight and twenty-four hours to prepare and submit PMI through a PAS, with a primary estimate of sixteen hours.

Once again following the RIA for the Supplemental Applications Proposing Labeling Changes for Approved Drugs and Biological Products, we assume that preparation of the PMI for ANDA products would require clerical, medical, and legal input and review (FDA, 2013a). We use data from the Bureau of Labor Statistics on the Pharmaceutical and Medicine Manufacturing (NAICS Code 325400) industry-specific mean hourly wages for Office and Administrative Support Occupations ($23.94), Lawyers ($79.36), and Management Occupations ($73.41) and, assuming weights of 25 percent, 25 percent, and 50 percent respectively, calculate a weighted average wage of $62.53 (BLS, 2020a). We then double this amount to account for benefits and other indirect costs, resulting in a fully loaded composite wage of $125.06.

Multiplying the hours estimate by the composite wage, we estimate that it would cost the pharmaceutical industry between $1,000 and $3,001 to prepare and submit, via a PAS, PMI for a single ANDA product, with a primary estimate of $2,001. For PMI submitted in a CBE-0 supplement, we estimate the cost to industry would be between $500 and $1,501 per ANDA product, with a primary estimate of $1,000.

FDA estimates it would take between four and seven FTE hours to review PMI for a single ANDA product, regardless of whether it is submitted as a CBE-0 supplement or a PAS. Multiplying by the hourly FTE cost of $142.20, we estimate the cost to FDA to review PMI for a single ANDA product to be between $569 and $995. We use the midpoint of this range, $782, as our primary estimate of the cost of FDA review of PMI for a ANDA product.

Combining the cost to industry to create and submit PMI for an ANDA product with the cost to FDA to review PMI for an ANDA product, we obtain the total cost associated with submission and review of PMI for a single ANDA product. For PMI with only minor differences from the reference PMI, that cost would range between $1,069 and $2,496, with a primary estimate of $1,783. For PMI with significant differences from the reference PMI, the cost would range between $1,569 and $3,997, with a primary estimate of $2,783. Multiplying by the number of ANDA products that we expect would submit PMI in each year (presented in Section II.D.), we obtain our estimates of the total annual cost of PMI associated with ANDA products. These annual costs are presented in Table 9.

Table 9. Cost of Creation, Submission, and Review of PMI for Non-Reference Products (millions)

	Low Estimate	Primary Estimate	High Estimate
Year 1	$3.5	$6.0	$8.2
Year 2	$3.1	$5.6	$8.1
Year 3	$2.3	$4.3	$6.4
Year 4	$2.3	$4.3	$6.3
Year 5	$4.7	$8.8	$13.0
Years 6+	$1.6	$3.0	$4.3

3. Changes to PMI

Each year, there are changes made to approximately 30 percent of current Medication Guides and PPI due to changes in product labeling. We assume that the same percentage of PMI for existing products would need to be changed each year, and there would be costs associated with making those changes. We assume that only new PMI would be submitted in the first year following the effective date of the final rule and that changes to PMI would be submitted

beginning in the second year. In this section, we consider separately the costs of making changes to PMI for both reference listed and ANDA products.

a. Reference Listed Products

We assume that the cost to industry of making a change to PMI for a reference listed product would range between 10 and 25 percent of the original cost of developing PMI. Using our cost estimate described above, this amounts to between $1,161 and $10,275. We use the midpoint of this range, $5,718, as our primary estimate of the cost to industry to make a change to PMI for a reference listed product. We estimate that FDA's review of the change in PMI for a single reference listed product would require between 24 and 33 FTE hours. Using an hourly FTE cost of $142.20, we estimate that the cost to FDA to review the change in PMI for a single reference listed product would range between $3,413 and $4,693. Combining the cost to industry to make the change with the cost to FDA to review the change, we estimate the total cost of making a change to PMI for a reference listed product to range between $4,573 and $14,967. We use the midpoint of these values, $9,770, as our primary estimate.

To estimate the number of changes to reference PMI that would be submitted each year, we multiply the initial number of existing reference listed products that would have submitted PMI in any previous year by thirty percent. We then multiply the number of changes to reference PMI in each year by the total cost of changing a reference PMI. These estimates of the annual cost associated with changes to reference PMI are presented in Table 10.

Table 10. Cost (millions) Associated with Changes to PMI for Reference Products

	Low Estimate	Primary Estimate	High Estimate
Year 1	$0.0	$0.0	$0.0
Year 2	$0.8	$1.7	$2.6
Year 3	$1.3	$3.1	$5.1
Year 4	$1.6	$3.9	$6.5

Year 5	$1.9	$4.6	$7.8
Years 6+	$3.1	$7.8	$13.7

b. ANDA Products

If changes were made to PMI for a reference listed product, the manufacturer of any ANDA product that references that product in its application would be required to submit corresponding changes to PMI. As with reference PMI, we assume that the cost of making a change to PMI for an ANDA product would range between 10 and 25 percent of the cost of creating the initial PMI. Multiplying the cost of creating PMI for an ANDA product by these percentages, we obtain estimates of the cost of making a change to PMI for an ANDA product that range from $100 to $750 for changes submitted through a PAS and from $50 to $375 for changes submitted through a CBE-0 supplement. We use the midpoints of these ranges, $445 for PAS submission and $213 for CBE-0 supplement submission, as our primary estimates of the cost to industry to make changes to PMI for an ANDA product. We assume that the cost to FDA to review changes to PMI for an ANDA product is the same as the cost to FDA to review the initial PMI for an ANDA product, between $569 and $995 with a primary estimate of $782.

Combining the cost to industry to make changes to PMI for an ANDA product with the cost to FDA to review changes to PMI for an ANDA product, we obtain the total cost associated with changes to PMI for a single ANDA product. For PMI submitted through a CBE-0, that cost ranges between $619 and $1,371, with a primary estimate of $995. For PMI submitted through a PAS, the cost ranges between $669 and $1,746, with a primary estimate of $1,207.

We assume that of those ANDA products whose PMI was initially significantly different from the reference PMI, between 5 and 25 percent of the changes to PMI would also come in as prior approval supplements, with our primary estimate being that 15 percent would be submitted

as prior approval supplements; the remainder would be submitted as CBE-0 supplements. For ANDA products whose PMI initially had only minor differences from the reference PMI, we assume that changes to the PMI would be submitted as CBE-0 supplements. Multiplying the estimated costs associated with changes to PMI for an ANDA product by the expected number of changes to PMI by supplement type, we obtain estimates of the total cost associated with making changes to PMI for ANDA products each year. These estimates are presented in Table 11.

Table 11. Cost (millions) Associated with Changes to PMI for Non-Reference Products

	Low Estimate	Primary Estimate	High Estimate
Year 1	$0.0	$0.0	$0.0
Year 2	$0.3	$0.4	$0.5
Year 3	$0.5	$0.8	$1.0
Year 4	$0.6	$1.0	$1.3
Year 5	$0.7	$1.2	$1.5
Years 6+	$1.2	$2.0	$2.6

4. FDA-Created Templates

As discussed in Section II, FDA would create PMI templates for ANDA products to use in cases where either no reference listed product exists or the reference listed product has voluntarily withdrawn approval of its application for reasons other than safety or efficacy. We estimate that FDA would create 148 of these PMI templates and that each template would take between 80 and 240 FTE hours to create. Multiplying the hours required to create a template by the hourly FTE cost of $142.20, we estimate that each template would cost FDA between $11,376 and $34,129 to create. We use the midpoint of this range, $22,753, as our primary estimate for the cost to FDA to create a PMI template.

The templates would be created over the five-year implementation period, with the cost spread evenly over those five years. To calculate the annual cost to FDA to create the PMI templates over the five-year implementation period, we multiply the per-template cost estimate by the 148 total PMI templates FDA would create and divide by 5 years. Doing so, we obtain estimates of the annual cost to FDA of creating the PMI templates that range between $336,740 and $1,010,220, with a primary estimate of $673,480 per year, over the first five years only. After the end of the fifth year, FDA would not incur any additional costs associated with creating PMI templates.

5. REMS Modifications

REMS that currently include Medication Guides would need to be modified to replace the current version of Medication Guides with PMI. Prescription drug manufacturers and FDA would incur costs associated with this switch. These costs would be incurred in the first year following the effective date of the rule because the rule would require manufacturers to submit PMI for drugs with Medication Guides in the first year.

For each drug with a REMS that includes a Medication Guide, the manufacturer would need to submit to FDA a modification to the REMS to make the switch from the current Medication Guide to PMI. FDA would then need to review and approve the modification. We estimate that the cost to industry of developing and submitting the modification would be similar in magnitude to the cost to develop PMI, described above; we estimate this cost to range from $11,606 to $41,098, with a primary estimate of $23,645 per modification submitted. We invite comment on this estimate. We estimate that each REMS modification would require between sixty and 200 FDA FTE hours to review, with a primary estimate of 130 FDA FTE hours. Multiplying by the cost per FTE hour of $142.20, this equates to an FDA cost ranging between

$8,532 and $28,441 to review and approve each REMS modification, with a primary estimate of $18,487.

There are currently 110 products with REMS that include Medication Guides for which this switch would be made. Multiplying those 110 products by the cost of developing and submitting the REMS modification, we estimate the total cost to industry of making the REMS modifications to range between $1.3 and $4.5 million, with a primary estimate of $2.6 million. Multiplying the 110 products by the cost to FDA to review and approve the REMS modifications, we estimate a total cost to FDA to review and approve REMS modification that ranges between $0.9 and $3.1 million. Summing the total cost to industry with the total cost to FDA, we obtain estimates of the total cost associated with REMS modifications ranging from $2.2 to $7.6 million, with a primary estimate of $4.6 million by the end of the first year only.

6. Establishing and Maintaining the Online Repository

Under this proposed rule, FDA would be required to establish and maintain an online repository to house PMI. The costs to FDA to establish and maintain this online repository for PMI would likely be similar to the costs for other FDA databases. Using the cost estimates of the Global Unique Device Identification Database as a proxy and inflating to 2020 dollars, we estimate it would cost FDA $6.6 million to establish the database in the first year and $2.2 million annually after that to maintain it (FDA, 2013b).

7. Total Costs Associated with PMI

Combining all of the costs described above, we estimate the total cost of this proposed rule in each year. We also calculate the present discounted value and annualized value of total

costs over ten years, using discount rates of 3 and 7 percent. These estimates are presented in Table 12.

Table 12. Total Cost (millions) of the Proposed Rule

	Low Estimate	Primary Estimate	High Estimate
Year 1	$23.0	$37.0	$55.6
Year 2	$14.3	$27.0	$45.1
Year 3	$11.2	$21.0	$34.6
Year 4	$11.3	$21.4	$35.4
Year 5	$24.3	$50.3	$90.0
Years 6+	$9.4	$17.7	$27.7
Present Discounted Value over 10 Years (2020 dollars, 3% discount rate)	$114.3	$213.0	$346.8
Present Discounted Value over 10 Years (2020 dollars, 7% discount rate)	$96.6	$179.3	$291.9
Annualized over 10 Years (2020 dollars, 3% discount rate)	$13.4	$25.0	$40.7
Annualized over 10 Years (2020 dollars, 7% discount rate)	$13.8	$25.5	$41.6

8. Cost Savings Associated with Medication Guides and PPI

Under this proposed rule, FDA would remove the current requirements for Medication Guides and PPI. This would likely result in some cost savings for the pharmaceutical industry and for FDA. Some drugs that will be approved in the future would have the currently-required Medication Guides or PPI in the absence of this proposed rule. Under this proposed rule, the applications for those drugs would include PMI, so there would be cost savings from the manufacturers of those drugs not having to create currently-required Medication Guides and PPI and from FDA not having to review and approve those Medication Guides and PPI. For drugs currently on the market with a Medication Guide or PPI, there is some cost associated with

continuing to comply with the current Medication Guide and PPI requirements because approximately 30 percent of these documents must be updated each year. Assuming that manufacturers of all drugs that have Medication Guides or PPI would comply with this proposed rule, there would be cost savings from those manufacturers not having to update the Medication Guides and PPI and from FDA not having to review and approve these updates.

a. Cost Savings Associated with Future Drug Products

To calculate the cost savings from future drugs not having the currently-required Medication Guides and PPI, we must first estimate the number of future drugs that would have the currently-required Medication Guides and PPI without this proposed rule. To estimate the cost savings, we then multiply that estimate by the sum of the cost to industry to create a currently-required Medication Guide or PPI, which we assume to be the same as the cost to create PMI, and the cost to FDA to review and approve a currently-required Medication Guide or PPI.

As discussed previously, we estimate that there are between 2,173 and 2,965 currently-approved NDA and BLA products that would be required to have PMI; of those, we estimate that between 555 and 582 currently have Medication Guides or PPI. Dividing 555 by 2,965, we obtain our lower bound estimate that 18.3 percent of reference listed products currently have Medication Guides or PPI. Dividing 582 by 2,173, we obtain our upper bound estimate that 25.9 percent of reference listed products currently have Medication Guides or PPI. For our primary estimate, we divide the midpoint of 555 and 582 (568.5) by the midpoint of 2,173 and 2,965 (2,569) to obtain our primary estimate that 21.5 percent of reference listed products currently have Medication Guides or PPI. We then multiply these percentages by the 119 new submissions for reference listed products we expect each year. From these calculations, we

estimate that between 22 and 31 new Medication Guides and PPI would be created each year in the absence of this rule, with a primary estimate of 26.

Assuming that the cost to industry to develop a currently-required Medication Guide or PPI is the same as the cost to develop PMI (between $11,606 and $41,098, with a primary estimate of $23,645), we can multiply by the number of currently-required Medication Guides and PPI avoided in the future to estimate the cost savings to industry associated with future reference listed products. Doing so, we find that between $252,137 and $1.3 million in industry costs can be saved each year, with a primary estimate of $604,987. Assuming that the cost to FDA to review a new Medication Guide or PPI is the same as the cost to review a new reference PMI (between $3,413 and $4,693 with a primary estimate of $4,053), we can multiply by the number of currently-required Medication Guides and PPI avoided in the future to estimate the cost savings to FDA associated with future reference listed products. Doing so, we find that between $74,146 and $144,577 in FDA costs can be saved each year, with a primary estimate of $103,699.

b. Cost Savings Associated with Existing Drug Products

We estimate that there are currently between 555 and 582 drug products with Medication Guides or PPI that would be required to have PMI under this proposed rule. Of those, approximately 30 percent have updates to their Medication Guides or PPI each year. Multiplying the number of existing drug products with Medication Guides or PPI by the percent updated each year, we estimate that between 167 and 175 updates to Medication Guides or PPI would be avoided each year under this proposed rule, with a primary estimate of 171. To calculate the cost savings associated with drugs currently on the market with Medication Guides

and PPI, we multiply these estimates by the cost to industry to update an existing Medication Guide or PPI and by the cost to FDA to review and approve an update.

We assume that the cost to industry to update an existing Medication Guide or PPI would be the same as the cost to update PMI, ranging between $1,161 and $10,275, with a primary estimate of $5,718. Multiplying this cost estimate by the number of updates avoided, we estimate the annual cost savings to industry to range between $193,235 and $1.8 million, with a primary estimate of $975,127.

Similarly, we assume that the cost to FDA to review an update to an existing Medication Guide or PPI would be the same as the cost to review reference PMI, ranging from $3,413 to $4,693, with a primary estimate of $4,053. Multiplying the estimated review cost by the number of updates avoided, we estimate the annual cost savings to FDA to range between $568,248 and $819,353, with a primary estimate of $691,209.

c. Total Cost Savings

Summing our cost savings estimates described above, we estimate the total annual cost savings to range between $1.1 and $4.0 million, with a primary estimate of $2.4 million. We also calculate the present discounted value total cost savings over ten years, using discount rates of 3 and 7 percent. These estimates are presented in Table 13.

Table 13. Total Cost Savings (millions) of the Proposed Rule

	Low Estimate	Primary Estimate	High Estimate
Annual Cost Savings	$1.1	$2.4	$4.0
Present Discounted Value over 10 Years (2020 dollars, 3% discount rate)	$9.3	$1.9	$3.3
Present Discounted Value over 10 Years (2020 dollars, 7% discount rate)	$7.6	$1.5	$2.5

9. Net Costs Associated with PMI

Taking our total cost estimates for each year as described above and subtracting the estimated annual cost savings, we estimate the yearly net cost associated with this proposed rule. We also calculate the present discounted value and annualized value of net costs over ten years, using discount rates of 3 and 7 percent. These estimates are presented in Table 14.

Table 14. Net Cost (millions) of the Proposed Rule

	Low Estimate	Primary Estimate	High Estimate
Year 1	$21.9	$34.6	$51.6
Year 2	$13.2	$24.6	$41.1
Year 3	$10.1	$18.6	$30.6
Year 4	$10.2	$19.0	$31.4
Year 5	$23.2	$48.0	$86.0
Years 6+	$8.3	$15.3	$23.7
Present Discounted Value over 10 Years (2020 dollars, 3% discount rate)	$105.0	$192.8	$312.5
Present Discounted Value over 10 Years (2020 dollars, 7% discount rate)	$89.0	$162.6	$263.6
Annualized over 10 Years (2020 dollars, 3% discount rate)	$12.3	$22.6	$36.6
Annualized over 10 Years (2020 dollars, 7% discount rate)	$12.7	$23.2	$37.5

10. Other, Unquantified Costs

In addition to the costs that we are able to monetize, we speculate that there may be other costs associated with PMI. First, there may be costs to the dispensers of drugs, blood, and blood component products from printing and distributing PMI that are not completely offset by the cost savings associated with the elimination of current Medication Guides, PPI, and CMI. We are currently unable to estimate just how large these costs may be. There may also be costs to the producers of CMI if drug dispensers choose to stop purchasing CMI and provide patients only

PMI instead. We request comment on the size of these costs as well as any other sources of costs or cost savings we have not identified here.

G. Break-Even Analysis

As discussed above, we are unable to monetize the full benefit that would stem from this proposed rule because we lack quantitative estimates of the health effects of PMI. Instead, we use a break-even analysis to show that PMI need only provide a small, monetary benefit to those taking prescriptions drugs in order for the benefits of the proposed rule to outweigh the estimated net costs.

Data from IQVIA National Prescription Audit New to Brand (NPA NTB™) extracted in March 2019 show that in 2018, there were approximately 721.9 new therapy starts (IQVIA, 2019). If we divide the annualized net costs of the proposed rule over ten years by the number of new therapy starts in a given year, we obtain the cost of the rule per person who would be most likely to benefit from PMI. Performing this calculation, we estimate that the annual cost per person who would benefit ranges between $0.02 and $0.05 using a 3 percent discount rate, with a primary estimate of $0.03. The estimates are the same using a 7 percent discount rate due to rounding. Thus, the annual per-person monetary benefit of PMI needed in order to equate the benefits of the proposed rule with the costs ranges from $0.02 on the low end up to $0.05 on the high end, with a primary estimate of $0.03. If the per-person monetary benefit of the proposed rule is larger than these estimates, the benefits would outweigh our estimated costs.

H. Uncertainty Analysis

Until now, we have considered the costs of this proposed rule assuming that no products would exit the market in response to the rule. In this section, we relax the assumption of no product exit and consider the possibility that the cost of creating and submitting PMI could lead manufacturers of some low-revenue products to withdraw them from the market if they are not exempted from the PMI requirements. As part of this analysis, we provide alternative cost estimates that account for product exit.

Drugs may have low revenues for a variety of reasons. A drug may have low demand due to serving a small patient population or because other drugs are preferred as the primary course of treatment for a disease. A drug may be off-patent and facing substantial generic competition, thereby reducing the revenue and bringing the economic profit of all manufacturers of the drug, including the branded product, down to zero.[3]

Manufacturers may be able to obtain a waiver or extension of the PMI requirements of this proposed rule, if finalized, if complying with the requirements would lead a manufacturer to

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[3] Economic profit is defined as revenue minus costs, where costs include both monetary and other opportunity costs. Monetary costs are the direct costs of doing business and include things like wages and capital costs. The opportunity cost of producing a drug is the amount of profit that the firm could have made in its next most profitable endeavor; therefore, opportunity cost captures the fact that a drug manufacturer, in choosing to devote resources to manufacturing a given product, has necessarily chosen not to use those resources to produce something else. It is important to keep in mind that economic profit differs from the traditional concept of accounting profit in that accounting profit does not take opportunity cost into account. When a firm is making zero economic profit in producing a good, it means that the firm's accounting profit from producing and selling that good is just as large as its next most profitable endeavor, so the firm is indifferent between producing the current product and its next most profitable product.

cease marketing a drug resulting in a drug shortage or otherwise preventing patient access to the drug. If a waiver or extension of the PMI requirements is granted, the drug would remain on the market but would not be accompanied by PMI; the manufacturer would not incur the costs associated with PMI for that drug and patients would not benefit from PMI for that drug. Low-revenue products that do not qualify for a waiver or extension may find it in their best economic interest to discontinue marketing the drug rather than face the costs associated with PMI. This exit could result in greater market power among drug manufacturers and slightly higher prices for those drugs.

We focus this analysis on drug products, in particular, because those are the only products for which we have sales data from IQVIA. We begin by assessing whether manufacturers have sufficient revenues from those products to cover the initial costs of PMI on top of their baseline costs of production. For those products that we find to have insufficient revenue to cover the costs, we then consider whether they might qualify for a waiver or extension that would allow them to stay on the market without incurring the costs associated with PMI or whether they would instead exit the market. Finally, we present the impact that this proposed rule could have on these low-revenue products, including a discussion of how our baseline costs would be affected by products exiting the market or being granted waivers from the requirements of the proposed rule, if finalized. We perform the analysis separately for three groups of drug products: branded drugs without generic competition, branded drugs with generic competition, and generic products. We use the "brand" and "generic" distinctions here instead of referring to products based on their application type because that is how IQVIA classifies products; however, branded products will generally correspond with NDA and BLA products whereas generic products will be mostly ANDA products.

We collect annual sales estimates from IQVIA (USA) National Sales Perspective for the years 2016, 2017, and 2018 for each prescription drug product approved prior to 2016 (IQVIA, 2018).[4,5] We collect data from the 10-k Annual Reports for 2014 filed with the U.S. Securities and Exchange Commission (SEC) on the revenue and costs of U.S. pharmaceutical companies. On average, the costs of producing and selling pharmaceutical products make up approximately 63 percent of a firm's revenue; therefore, the remaining 37 percent of revenue can be thought of as a proxy for accounting profit. We deflate the cost of creating PMI to 2018 dollars and divide that amount by that 37 percent to estimate the amount of sales necessary in 2018 to cover the cost of PMI without resulting in negative accounting profit. We perform this calculation using the cost estimates for both reference PMI and PMI for ANDA products. This estimate of the minimum sales necessary to cover the cost of PMI becomes our threshold by which we compare product sales. For reference PMI, the threshold ranges between $30,090 and $106,555, with a primary estimate of $61,303. For PMI for an ANDA product submitted through a PAS, we estimate the threshold to be between $2,703 and $8,109, with a primary estimate of $5,406; for PMI for an ANDA product submitted through a CBE-0 supplement, the threshold ranges from $1,352 to $4,055, with a primary estimate of $2,703. For any product with positive annual sales less than its corresponding threshold in each of 2016, 2017, and 2018, we determine that product

[4] We exclude drugs approved in 2016 and later so as to ensure that we have a full year of sales data for each drug in 2016.

[5] This document contains proprietary drug use data obtained by FDA under contract. The drug use data/information cannot be released to the public/non-FDA personnel without contractor approval obtained through the FDA/CDER Office of Surveillance and Epidemiology.

to be at risk of exiting the market if it is not granted a waiver or extension of the requirements of PMI.[6] We refer to these products throughout the remainder of this section as "at-risk" products.[7]

Our calculations described in the previous paragraph rely on estimates of accounting profit rather than economic profit because we are unable to estimate economic profit for drug products. Accounting profit is generally greater than or equal to economic profit; therefore, using accounting profit in the calculations results in threshold values that are smaller than if we were to use economic profit. Because of this, our estimates of at-risk products may represent lower bounds.

In our analysis, we separately consider the impact of the rule on branded products with and without generic competition, as well as on generic products. We do not have a reliable way of knowing which drugs currently face generic competition; however, Grabowski and Vernon (2000) estimate that drugs average approximately twelve years of effective patent life once they enter the market. Hemphill et al. (2012) confirm that this twelve-year average length of marketing exclusivity has remained stable through at least 2010. Based on these estimates, we assume any branded product that entered the market prior to 2004 was facing pressure from

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[6] A product must have sales greater than zero but less than the threshold in all three years to be considered at risk of exiting the market. Products with zero sales have already discontinued marketing; we would not expect them to create PMI and do not consider them at risk of exit. For products with positive sales, looking at sales in all three years allows us to identify products that consistently have low revenue year after year; these are the products we consider to be at risk of exit.

[7] Note that the term "at-risk" does not imply that the drug would exit the market. As we discuss, some products would be granted exemptions or deferrals from the PMI requirements that would enable them to stay on the market without producing PMI.

generic competition in 2016. We request comment on this assumption and any more recent studies on the timing of generic entry.

1. Count of At-Risk Products

Comparing the IQVIA sales data with the minimum sales thresholds needed to cover the initial cost of PMI, we estimate that there are two or three branded products without generic competition that would be at risk of exiting the market due to PMI; however, because these products likely do not have generic alternatives, their exit from the market would result in drug shortages for these products, so they may qualify for exemptions or deferrals from the requirements of this proposed rule. Therefore, we expect two or three branded products to apply for waivers or extensions of the requirements of this proposed rule, if finalized.

Among branded products that likely do have generic competition, we estimate that between 12 and 33 would be at risk of exiting the market due to sales that are below our estimated thresholds. These products would likely not qualify for a waiver or extension if there are generic versions of the products available. In that case, we expect that these products would exit the market and possibly withdraw their applications from FDA rather than absorb the costs associated with PMI. If the applications are withdrawn, FDA would create the PMI template for these products so that the generic versions of the product would still be accompanied by PMI.

Among generic products, we estimate that between 112 and 258 do not have sales large enough to absorb the initial cost of creating and submitting PMI through a CBE-0 supplement and between 200 and 383 do not have sales large enough to absorb the initial cost of creating and submitting PMI through a PAS. We assume that these products would not qualify for a waiver or extension if there are other generic or branded versions available; under that assumption,

between 112 and 383 generic products would be at-risk of exiting the market. If, on the other hand, there are limited other generic or branded versions of the products available such that drug shortages could arise if these generic products were to exit the market, we expect that these generic products would qualify for waivers or extensions of the PMI requirements under this proposed rule.

2. Alternative Cost Estimates

If the at-risk products choose to exit the market or request waivers or extensions rather than produce PMI, the costs of the proposed rule would be slightly smaller than we estimated above. In Table 15, we present alternative cost estimates, which take into account the products that we expect would not produce PMI and the additional PMI templates that we expect FDA would create as a result of reference listed product exit. These alternative cost estimates do not include costs associated with waivers and extensions, and we request comment the size of these potential costs. Annualized over ten years, these alternative costs are between $0.05 and $1.0 million per year less than our primary cost estimates.

Table 15. Alternative Total Cost (millions) of the Proposed Rule with Low-Revenue Products Exiting

	Low Estimate	Primary Estimate	High Estimate
Year 1	$23.0	$36.7	$55.1
Year 2	$14.3	$26.6	$44.5
Year 3	$11.1	$20.5	$33.8
Year 4	$11.2	$21.0	$34.7
Year 5	$24.1	$48.9	$86.9
Years 6+	$9.4	$17.2	$26.8
Present Discounted Value over 10 Years (2020 dollars, 3% discount rate)	$113.8	$208.4	$337.9
Present Discounted Value over 10 Years (2020 dollars, 7% discount rate)	$96.3	$175.6	$284.7

Annualized over 10 Years (2020 dollars, 3% discount rate)	$13.3	$24.4	$39.6
Annualized over 10 Years (2020 dollars, 7% discount rate)	$13.7	$25.0	$40.5
Difference in Annualized Cost from the Primary Analysis (2020 dollars, 3% discount rate)	-$0.05	-$0.5	-$1.0
Difference in Annualized Cost from the Primary Analysis (2020 dollars, 7% discount rate)	-$0.05	-$0.5	-$1.0

I. Distributional Effects

The benefits of this proposed rule, if finalized, would confer to all patients using prescription medications on an outpatient basis in the U.S.; however, it is possible that some groups may benefit more than others. This proposed rule would provide patients with written information about their prescription drugs that is easier to read and understand than much of what is currently available. Patients with lower health literacy, for whom the currently-available information is difficult to read and understand, may stand to benefit the most from this proposed rule. Patients with higher health literacy, or those who are satisfied with the information that is currently available, may stand to benefit the least.

J. International Effects

The requirements of this proposed rule, if finalized, would apply to both foreign and domestic manufacturers of prescription drug, blood, and blood component products marketed in the U.S. in an outpatient setting. The benefits of improved prescription drug information that would stem from this proposed rule would accrue largely to patients in the U.S.; however,

because PMI would be accessible in an online database, individuals outside the U.S. could also access and benefit from it as long as they have internet access. The costs of this proposed rule would be borne by any manufacturer of the covered products; this includes both foreign and domestic firms. The total and net costs estimated in this Preliminary Regulatory Impact Analysis would be shared by all affected entities, both foreign and domestic, operating in the U.S. market.

K. Analysis of Regulatory Alternatives to the Proposed Rule

The principal regulatory alternatives considered are as follows: (1) requiring consumer testing of PMI; and (2) requiring PMI only for high-risk products that currently have Medication Guides or PPI. The following sections discuss the costs and benefits associated with these alternatives.

1. Regulatory Alternative 1: Consumer Testing of PMI

Under this alternative, PMI would be developed, submitted, and reviewed as described in our primary analysis; however, PMI for reference listed products would undergo consumer testing for readability and comprehension prior to being submitted to FDA. This consumer testing would consist of both qualitative and quantitative testing by focus groups.

The purpose of the consumer testing would be to ensure that some minimum level of readability and comprehension is met. If consumer testing were successful at improving the quality of PMI along these dimensions, it could result in benefits that are larger than those estimated in our primary analysis. Although we lack data on the additional benefit that consumer testing would bring about, it may be reasonable to assume that a document that is easier to read and comprehend due to undergoing consumer testing would require less time to read than a

similar document that was not subject to consumer testing. If this were the case, the benefits in terms of search time saved would be larger than we estimate in our primary analysis.

We estimate the additional cost that would be incurred as a result of requiring consumer testing of PMI. Using GSA-approved rates for focus groups along with labor costs estimated from prior FDA focus group research, we estimate that the testing cost for a single reference PMI would be $107,580. This additional cost would be incurred by manufacturers for each reference listed product, both existing and future, at the time PMI is developed.

Assuming that all other costs of the rule are as described in our primary analysis, we can estimate the total cost of this regulatory alternative. Those estimates are presented in Table 16. Under this regulatory alternative, the annualized costs over ten years, using a 3 percent discount rate, would be between $38.7 and $47.6 million larger than in our primary analysis; using a 7 percent discount rate, the annualized costs over ten years would be between $40.8 and $50.1 million larger.

Table 16. Total Cost (millions) Associated with Alternative 1: Consumer Testing of PMI

	Low Estimate	Primary Estimate	High Estimate
Year 1	$95.5	$111.0	$131.0
Year 2	$72.4	$92.8	$118.6
Year 3	$46.3	$61.5	$80.5
Year 4	$44.6	$60.1	$79.5
Year 5	$131.7	$180.4	$242.8
Years 6+	$22.2	$30.5	$40.5
Present Discounted Value over 10 Years (2020 dollars, 3% discount rate)	$444.3	$581.0	$752.8
Present Discounted Value over 10 Years (2020 dollars, 7% discount rate)	$383.1	$498.6	$643.9
Annualized over 10 Years (2020 dollars, 3% discount rate)	$52.1	$68.1	$88.3
Annualized over 10 Years (2020 dollars, 7% discount rate)	$54.6	$71.0	$91.7

Difference in Annualized Cost from the Primary Analysis (2020 dollars, 3% discount rate)	$38.7	$43.1	$47.6
Difference in Annualized Cost from the Primary Analysis (2020 dollars, 7% discount rate)	$40.8	$45.5	$50.1

2. Regulatory Alternative 2: PMI only for Products with Currently-Required Medication Guides or PPI

Under this alternative, PMI would only be developed for those products that currently or in the future would otherwise have currently-required Medication Guides or PPI. As described previously, there are between 555 and 582 existing reference listed products with Medication Guides and PPI that would be subject to this rule. In addition, we estimate that between 22 and 31 new reference listed products with currently-required Medication Guides or PPI are approved each year. These existing and future reference listed products, along with any ANDA products that reference them, would have PMI under this regulatory alternative; all other products would not have PMI.

To estimate the benefit associated with this regulatory alternative, we first calculate that between 16 and 20 percent of all existing products would have PMI under this alternative. We multiply the full annual benefit estimate from our primary analysis by these percentages to obtain the annual benefit under this alternative. We estimate that the annual benefit would range between $4.9 and $49.4 million, with a primary estimate of $29.5 million, if PMI were only required for products with currently-required Medication Guides or PPI. These estimates are between $10.1 and $141.1 million less than the annualized benefits from our primary analysis using a 3 percent discount rate; with a 7 percent discount rate, the annual benefits under this

alternative are between $9.5 and $133.1 million less than the annualized benefits from our primary analysis. These estimates are presented in Table 17.

Table 17. Total Benefit (millions) Associated with Alternative 2: PMI for High-Risk Products Only

	Low Estimate	Primary Estimate	High Estimate
Annual Benefit	$4.9	$29.5	$49.4
Present Discounted Value over 10 Years (2020 dollars, 3% discount rate)	$41.4	$251.6	$421.3
Present Discounted Value over 10 Years (2020 dollars, 7% discount rate)	$34.1	$207.2	$346.9
Difference in Annualized Benefit from the Primary Analysis (2020 dollars, 3% discount rate)	-$10.1	-$73.1	-$141.1
Difference in Annualized Benefit from the Primary Analysis (2020 dollars, 7% discount rate)	-$9.5	-$69.0	-$133.1

To estimate the costs of this regulatory alternative, we multiply the costs of development, submission, and review of PMI described in our primary analysis by the number of products we expect to have PMI. Under this alternative, we expect that the 555 to 582 existing reference listed products with Medication Guides and PPI would submit PMI in the first year. We also expect that the ANDA products that would submit PMI in the first year under the primary analysis would also submit PMI in the first year under this regulatory alternative. In each year after that, we expect between 22 and 31 new reference listed products with currently-required Medication Guides or PPI would submit PMI with their applications. In addition to the costs associated with development, submission, and review of PMI, the costs described in the primary analysis associated with reading the rule and establishing and maintaining the online repository would be the same under this regulatory alternative. Furthermore, because some of these products with currently-required Medication Guides also have REMS, the costs described in the

primary analysis associated with REMS modifications would also hold under this regulatory alternative. Summing all the costs under this regulatory alternative, we obtain the total costs associated with implementing a rule that would require PMI only for products with currently-required Medication Guides or PPI. These costs are presented in Table 18. We estimate that the annualized total costs under this alternative would be between $9.0 and $32.3 million less per year than in our primary analysis at a 3 percent discount rate; at a 7 percent discount rate, the annualized cost estimates under this alternative would be between $9.0 and $32.4 million less per year than in our primary analysis.

Table 18. Total Cost (millions) Associated with Alternative 2: PMI for High-Risk Products Only

	Low Estimate	Primary Estimate	High Estimate
Year 1	$19.6	$30.5	$45.3
Year 2	$2.5	$2.9	$3.6
Year 3	$2.5	$2.9	$3.6
Year 4	$2.5	$2.9	$3.6
Year 5	$2.5	$2.9	$3.6
Years 6+	$2.5	$2.9	$3.6
Present Discounted Value over 10 Years (2020 dollars, 3% discount rate)	$37.8	$51.3	$71.0
Present Discounted Value over 10 Years (2020 dollars, 7% discount rate)	$33.5	$46.0	$64.1
Annualized over 10 Years (2020 dollars, 3% discount rate)	$4.4	$6.0	$8.3
Annualized over 10 Years (2020 dollars, 7% discount rate)	$4.8	$6.5	$9.1
Difference in Annualized Cost from the Primary Analysis (2020 dollars, 3% discount rate)	-$9.0	-$19.0	-$32.3
Difference in Annualized Cost from the Primary Analysis (2020 dollars, 7% discount rate)	-$9.0	-$19.0	-$32.4

III. Initial Small Entity Analysis

The Regulatory Flexibility Act requires Agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. Because the cost of producing PMI represents a substantial share of revenue for several small businesses, in particular those with fewer than 6 employees, we find that the proposed rule will have a significant economic impact on a substantial number of small entities. This analysis, as well as other sections in this document, serves as the Initial Regulatory Flexibility Analysis, as required under the Regulatory Flexibility Act.

A. Description and Number of Affected Small Entities

The affected entities can be divided into two industries: pharmaceutical preparation manufacturing (NAICS code 325412) and biological product (except diagnostic) manufacturing (NAICS code 325414). The affected entities in the pharmaceutical preparation manufacturing industry are those that manufacture at least one drug product. The affected entities in the biological product (except diagnostic) manufacturing industry are those that manufacture blood or blood component products available on an outpatient basis. The Small Business Administration (SBA) determines the size standards of small businesses matched to the industries described in the North American Industry Classification System (NAICS). Firms are considered small in both of these industries if they employ 1,250 or fewer employees (SBA, 2017).

For firms that manufacture at least one NDA or BLA product, we use data on total employment in the U.S. from Dun and Bradstreet to determine whether or not the firm is classified as a small business. Of the 408 firms with NDA and BLA products, we are able to

obtain employment data on 252 firms. Of those 252 firms, 195 have 1,250 or fewer employees in the U.S. Therefore, we further disaggregate the affected firms based on the number of employees to ascertain the impact of this proposed rule on very small firms as well as larger small firms. For firms that manufacture ANDA drug products, we assume that the distribution of costs to industry of PMI for ANDA products is similar to the distribution of costs to industry of PMI for NDA and BLA. Applying this assumption, we extrapolate the share of costs borne by firms with NDA and BLA products to firms of similar size for ANDA products. For firms that manufacture blood and blood component products, we are unable to obtain employment data to identify which firms are small businesses; therefore, we conduct the analysis for all firms that manufacture blood and blood component products assuming they would be classified as small entities.

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

1. Impact to Small Entities that Manufacture NDA and BLA Products

To determine the impact of the proposed rule on small entities that manufacture NDA and BLA products, we compare the cost of the rule to the total U.S. sales, as reported by Dun and Bradstreet, of the small entities. Just as before, small entities would incur initial costs associated with reading the rule and developing PMI for existing products. These businesses would also incur recurring costs from making changes to PMI. Small entities would incur additional costs for any new reference listed products that are approved in the future; however, as we cannot forecast how many new reference listed products each small entity would produce in the future, we exclude those costs from this analysis.

Using the cost estimates described previously for developing PMI and changes to PMI, we estimate that the annualized cost of PMI over ten years for a single NDA or BLA product would range between $1,629 and $7,409 using a 3 percent discount rate, with a primary estimate of $4,211. With a 7 percent discount rate, the annualized cost of PMI for a single NDA or BLA product over ten years would range from $1,846 to $8,141, with a primary estimate of $4,633. Additionally, each firm would incur $397 as an initial cost of reading the rule. When annualized over a 10-year period, this is $45 per firm using a 3% discount rate or $53 per firm using a 7% discount rate.

For each manufacturer of an NDA or BLA product, we multiply the annualized cost of PMI for one reference listed product by the number of NDA and BLA products manufactured by the firm, and then add the annualized cost of reading the rule. This calculation provides an estimate of the annualized cost of PMI for each firm. Ideally, we would like to compare the costs of the rule to an estimate of a firm's profit. Lacking data to estimate the firm's cost function, we instead compare the annualized cost for each firm to the firm's total U.S. sales obtained from Dun and Bradstreet. Dividing the annualized cost by the total U.S. sales, we obtain the firm's cost as a percent of sales.

Across all manufacturers of NDA and BLA products, we estimate the average cost of PMI as a percent of sales to range between 0.2 to 0.7 percent of sales. For the smallest group of firms, with one to five employees, we estimate that the cost of PMI would range between 1.4 and 7.1 percent of sales. For firms with six to twenty employees, we estimate the cost of PMI to range between 0.4 and 1.8 percent of sales. For firms with twenty-one to 100 employees, we estimate the cost of PMI to range between 0.0 to 0.2 percent of sales. For larger firm sizes, we estimate the cost of PMI to be below 0.1 percent of sales. These estimates are presented in Table

19. Given that we find the cost of the proposed rule to be a substantial percentage of sales for small businesses, the agency concludes that this rule, if finalized, would have a significant economic impact on a substantial number of small entities.

Table 19. Average Annualized Cost of PMI for Manufacturers of NDA and BLA Products as a Percent of Sales by Firm Size

	3 Percent Discount Rate			7 Percent Discount Rate		
Firm Size (Number of Employees)	Low Estimate	Primary Estimate	High Estimate	Low Estimate	Primary Estimate	High Estimate
1-5	1.4%	3.7%	6.5%	1.6%	4.1%	7.1%
6-20	0.4%	1.0%	1.7%	0.4%	1.0%	1.8%
21-100	0.0%	0.1%	0.2%	0.0%	0.1%	0.2%
101-500	0.0%	0.0%	0.1%	0.0%	0.0%	0.1%
501-1,000	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
More than 1,000	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
All Small Businesses (1,000 or fewer employees)	0.2%	0.5%	0.9%	0.2%	0.6%	1.0%
All Firms	0.2%	0.4%	0.7%	0.2%	0.4%	0.8%

2. Impact to Small Entities that Manufacture ANDA Products

We also considered the impact of the proposed rule on small entities that manufacture ANDA products. We begin this analysis by recalling the costs to industry of PMI for existing ANDA products, as well as the costs associated with future changes to PMI documents. These costs are reported yearly in Tables 9 and 11. We combine these costs and report the annualized total costs to industry using a 3 percent and a 7 percent discount rate. The next step in our analysis is to estimate the share of these costs borne by small entities.

Due to analytical limitations, we are unable to reliably match these costs to particular firms. For purposes of this analysis, we assume that the distribution of costs to industry of PMI for ANDA products is similar to the distribution of costs to industry of PMI for reference listed products. Applying this assumption, we extrapolate the share of costs borne by firms with reference listed products to firms of similar size for ANDA products. As one example calculation, we identified 37 firms with fewer than 20 employees that combine to produce 77 reference listed products. These 37 firms represent 14.7% of the firms in our matched sample

(37/252=0.147), but only 3.8% of the matched reference listed products (77/2003=0.038). This means the average firm with fewer than 20 employees would incur about 0.10% (3.8%/37) of the cost to industry of PMI for reference listed products. These shares are reported in Table 20. We also report estimated receipts per firm for each size category for later comparison (U.S. Census, 2015).

Table 20. Estimated Cost Shares for Manufacturers by Firm Size

Firm Size (Number of Employees)	Number of Firms	Reference Listed Products	Cost Share per Firm	Estimated Receipts Per Firm
1-19	37	77	0.10%	$8,374,909
20-99	55	112	0.10%	$18,480,449
100-499	57	210	0.18%	$108,779,470
1-499	149	399	0.13%	$23,388,875
More than 500	103	1604	0.78%	$1,346,467,777
All Firms	252	2003	0.40%	$75,478,302

Using the firm cost shares reported in Table 20, we calculate the average annualized cost of PMI for manufacturers of ANDA products by firm size in Table 21. As an example, firms with fewer than twenty employees would, on average, incur between $3,346 to $8,495 in annualized costs for ANDA products using a 3 percent discount rate, with a primary estimate of $5,978. These costs represent about or below 0.1% of the estimated receipts per firm reported in Table 20.

Table 21. Average Annualized Cost of PMI for Manufacturers of ANDA Products by Firm Size

	3 Percent Discount Rate			7 Percent Discount Rate		
Firm Size (Number of Employees)	Low Estimate	Primary Estimate	High Estimate	Low Estimate	Primary Estimate	High Estimate
1-19	$3,346	$5,978	$8,495	$3,371	$6,018	$8,553
20-99	$3,274	$5,849	$8,313	$3,298	$5,888	$8,369
100-499	$5,923	$10,583	$15,039	$5,967	$10,653	$15,141
1-499	$4,305	$7,692	$10,931	$4,337	$7,743	$11,006
More than 500	$25,035	$44,733	$63,570	$25,222	$45,030	$64,002
All Firms (Average)	$12,778	$22,832	$32,446	$12,874	$22,984	$32,667
All Firms (Total)	$3,220,083	$5,753,575	$8,176,508	$3,244,140	$5,791,880	$8,232,001

3. Impact to Small Entities that Manufacture Blood and Blood Component Products

We also considered the impact of the proposed rule on small entities that manufacture blood and blood component products. To do so, we first estimate the average cost of the proposed rule to each firm that manufactures blood and blood component products by calculating the total cost to the biologics industry and dividing by the number of registered manufacturers of blood and blood component products. As described previously, FDA expects that the blood products industry would collaborate to produce PMI so that one PMI document would be produced for each of the five blood and blood component products available on an outpatient basis.

As described above, the annualized cost of PMI over ten years for one product is estimated to range between $1,629 and $7,409 using a 3 percent discount rate. With a 7 percent discount rate, the annualized cost of PMI for a single product over ten years would range from $1,846 to $8,141. Multiplying by the five blood and blood component products that would require PMI, we estimate that the annualized cost of PMI for blood and blood component products over ten years would range between $8,147 and $37,046 using a 3 percent discount rate.

Using a 7 percent discount rate, we estimate the annualized cost of PMI for blood and blood component products over ten years to range between $9,231 and $40,704.

All owners or operators of establishments that manufacture blood products are required to register with the FDA, pursuant to section 510 of the Federal Food, Drug, and Cosmetic Act, unless they are exempt under 21 CFR 607.65. According to the Blood Establishment Registration and Product Listing, there are 105 licensed manufacturers and 940 registered facilities manufacturing blood and blood component products, for a total 1,045 manufacturers (FDA, 2020a). Dividing the annualized cost of PMI over ten years for blood and blood component products by the total number of manufacturers yields the average cost of PMI per manufacturer. We estimate this average annualized cost per manufacturer to range between $8 and $35 using a 3 percent discount rate and between $9 and $39 using a 7 percent discount rate. These estimates are presented in Table 22.

Table 22. Average Annualized Cost of PMI for Blood and Blood Component Products

	3 Percent Discount Rate			7 Percent Discount Rate		
	Low Estimate	Primary Estimate	High Estimate	Low Estimate	Primary Estimate	High Estimate
Total Cost of PMI for Blood and Blood Component Products	$8,147	$21,056	$37,046	$9,231	$23,166	$40,704
Average Cost per Manufacturer	$8	$20	$35	$9	$22	$39

We also obtained sales data for U.S. firms that manufacture blood and blood component products from Dun and Bradstreet. Of the blood and blood component product manufacturers, the firm with the lowest revenue had annual sales of $77,955. This means that the annualized

cost of PMI using a 7 percent discount rate would represent less than one tenth of a percent of annual sales under any cost or discounting scenario.

C. Alternatives to Minimize the Burden on Small Entities

The Regulatory Flexibility Act requires Agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. Here, we extend our earlier discussion of the policy option of requiring PMI only for high-risk products to consider its effect on small entities.

Under this approach, firms would be required to develop PMI only for those high-risk products that currently or in the future would otherwise have currently-required Medication Guides or PPI. Recalling the earlier discussion, we estimate that between 562 and 589 existing products, or about 17% of existing reference listed products, would be subject to this proposal. Since PMI for these products would be developed in the first year of the five-year implementation schedule, costs corresponding to these products under this proposal represent about 20% of the costs compared to the costs of the rule.

Although we do not match these high-risk products to firms, this proposal would significantly reduce the number of products subject to the rule and would therefore reduce the number of firms affected by the requirement to produce PMI. As in the previous section, these figures allow us to compare the cost of PMI to the average sales of reference listed product manufacturers by firm size. This information can be found in Table 23. Although the average cost of PMI as a share of firm revenue decreases under this policy option, these reductions would only apply to firms that do not produce high-risk reference listed products.

Table 23. Average Annualized Cost of PMI for Manufacturers as a Percent of Sales by Firm Size Under Regulatory Option 1: Reduced Testing Requirement for PMI

	3 Percent Discount Rate			7 Percent Discount Rate		
Firm Size (Number of Employees)	Low Estimate	Primary Estimate	High Estimate	Low Estimate	Primary Estimate	High Estimate
1-5	0.5%	0.9%	1.3%	0.6%	1.9%	4.6%
6-20	0.1%	0.2%	0.3%	0.1%	0.5%	1.2%
21-100	0.0%	0.0%	0.0%	0.0%	0.1%	0.1%
101-500	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
501-1,000	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
More than 1,000	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
All Small Businesses (1,000 or fewer employees)	0.1%	0.1%	0.2%	0.1%	0.3%	0.7%
All Firms	0.1%	0.1%	0.1%	0.1%	0.2%	0.5%

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