DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

Premarket Tobacco Product Applications and Recordkeeping Requirements

Docket No. FDA-2019-N-2854

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

Economics Staff
Office of Economics and Analysis
Office of Policy, Legislation, and International Affairs
Office of the Commissioner

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I. Introduction and Summary

A. Introduction

We have examined the impacts of the final rule under Executive Order 12866, Executive Order 13563, the Regulatory Flexibility Act (5 U.S.C. 601-612), and the Unfunded Mandates Reform Act of 1995 (Pub. L. 104-4). Executive Orders 12866 and 13563 direct us to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). This final 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. We expect that the final rule will generate net benefits or negligible net costs for most affected small entities. Therefore, we certify that the final rule will not have a significant economic impact on a substantial number of small entities.

The Unfunded Mandates Reform Act of 1995 (section 202(a)) requires us to prepare a written statement, which includes an assessment of anticipated costs and benefits, before 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 $158 million, using the most current (2020) Implicit Price Deflator for the Gross Domestic Product. This final rule will not result in an expenditure in any year that meets or exceeds this amount.

B. Summary of Costs and Benefits

The final rule will require manufacturers of Pre-Existing Tobacco Products[1] and manufacturers of products that are exempt from the requirements of demonstrating substantial equivalence to maintain records to demonstrate that they can legally market their products. For products that receive a Premarket Tobacco Product Application (PMTA) marketing granted order, the final rule will require certain postmarket reporting, including periodic reporting and adverse experience reporting. The final rule will also implement and set forth requirements for the content and format of PMTAs and the general procedures we intend to follow in reviewing and communicating with applicants.

The final rule will make the review of PMTAs more efficient. As a result, the final rule will create cost savings for FDA related to the review of some PMTAs. The final rule will also create cost savings for FDA and for PMTA applicants by reducing the number of PMTAs submitted. In Table 1, we present the annualized benefits of the final rule. We estimate that annualized benefits over 20 years will equal $2.04 million at a 7 percent discount rate, with a low estimate of $1.36 million and a high estimate of $2.85 million. We estimate that annualized

[1] We referred to these products as “Grandfathered Tobacco Products” in the Preliminary Regulatory Impact Analysis and the proposed rule. We changed the term to “Pre-Existing Tobacco Products” in this document and the final rule because it more appropriately describes these products.

benefits over 20 years will equal $2.08 million at a 3 percent discount rate, with a low estimate of $1.43 million and a high estimate of $2.84 million.

This is the first regulation to address the costs of PMTA requirements for new, originally regulated tobacco products. While we already included the costs to submit and review PMTAs for deemed tobacco products in the final regulatory impact analysis for the Deeming Rule, no regulatory impact analysis includes the costs to submit and review PMTAs for originally regulated tobacco products. Therefore, we include the costs to prepare and review PMTAs for these tobacco products in this analysis.

The final rule will increase the cost for applicants to prepare a PMTA. As a result, the final rule will generate incremental costs related to the preparation of PMTAs for ENDS products. Firms will incur costs to maintain and submit postmarket reports and we will incur costs to review these reports. Finally, firms will incur costs to read and understand the rule and costs to maintain records for some Pre-Existing Tobacco Products. In Table 1, we present the annualized costs of the final rule. We estimate that annualized costs over 20 years will equal $4.73 million at a 7 percent discount rate, with a low estimate of $2.63 million and a high estimate of $7.45 million. We estimate that annualized costs over 20 years will equal $4.86 million at a 3 percent discount rate, with a low estimate of $2.50 million and a high estimate of $7.95 million.

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

Category		Primary Estimate	Low Estimate	High Estimate	Units			Notes
					Year Dollars	Discount Rate	Period Covered	
Benefits	Annualized Monetized ($m/year)	$2.04	$1.36	$2.85	2019	7%	20 years	All quantified benefits are cost savings.
		$2.08	$1.43	$2.84	2019	3%	20 years	
	Annualized Quantified							
	Qualitative	Benefits from postmarket surveillance.						
Costs	Annualized Monetized ($m/year)	$4.73	$2.63	$7.45	2019	7%	20 years	
		$4.86	$2.50	$7.95	2019	3%	20 years	
	Annualized Quantified							
	Qualitative							
Transfers	Federal Annualized Monetized ($m/year)							
		From:			To:			
	Other Annualized Monetized ($m/year)							
		From: Currently marketed tobacco products			To: New tobacco products with PMTA marketing orders			
Effects	State, Local, or Tribal Government: None Small Business: None							

	Wages: None Growth: None	

C. Terminology

In Table 2, we provide definitions for several terms we use in this document. We note that these definitions only apply to this document.

Table 2. Terms used in the Regulatory Impact Analysis

Term	Description
We, our, us	We use these terms to refer to the United States Food and Drug Administration.
Originally Regulated Tobacco Products	The Tobacco Control Act (TCA) gave us immediate authority to regulate cigarettes, cigarette tobacco, smokeless tobacco, and roll-your-own tobacco under Chapter IX of the Federal Food, Drug and Cosmetics Act (FD&C Act). We refer to these types of products as originally regulated tobacco products.
New Tobacco Product	As defined in section 910(a)(1)(A) of the FD&C Act, a new tobacco product is any tobacco product (including those products in test markets) that was not commercially marketed in the United States on February 15, 2007, or any modification of a tobacco product where the modified tobacco product was commercially marketed after February 15, 2007. New tobacco products are subject to the premarket requirements of the FD&C Act.
Pre-Existing Tobacco Product	A tobacco product (including those products in test markets) that was commercially marketed in the United States on February 15, 2007, is known as a Pre-Existing Tobacco Product. Such products are not subject to the premarket requirements of the FD&C Act.
Premarket Tobacco Product Application (PMTA)	A PMTA is a type of application for new tobacco products described in section 910(b) of the FD&C Act. Applicants may submit a PMTA for any new tobacco product to obtain a marketing order. To receive a marketing granted order, we must determine in our review of the PMTA, among other things, that permitting the marketing of the product is appropriate for the protection of public health. This term includes the initial premarket tobacco product application and all subsequent amendments.
Substantial Equivalence (SE) Report	An SE Report is another type of application for new tobacco products submitted under section 905(j)(1)(A)(i) of the FD&C Act. Applicants may submit an SE Report for any new tobacco product to obtain an SE order. To receive an SE order, we must find in our review of the SE Report that the product has the same characteristics as a predicate product or has different characteristics than the predicate product but any differences in characteristics do not cause the new tobacco product to raise different questions of public health. Eligible predicate products are Pre-Existing Tobacco Products and tobacco products previously found to be substantially equivalent by FDA and in compliance with the requirements of the FD&C Act.
Exemption Request	An Exemption Request is another type of application for new tobacco products submitted under section 905(j)(3) of the FD&C Act. Applicants may submit an Exemption Request for any new tobacco product. To find a new tobacco product exempt, we must determine that: the new tobacco product is modified by adding or deleting a tobacco additive or increasing or decreasing the quantity of an existing tobacco additive; the proposed modification is minor

Term	Description
	and to a legally marketed tobacco product; an SE Report is not necessary to ensure that permitting the tobacco product to be marketed would be appropriate for the protection of the public health; and an exemption is otherwise appropriate.
Standalone Pre-Existing Tobacco Product Submission	A Standalone Pre-Existing Tobacco Product Submission is a voluntarily-submitted request for a Pre-Existing Tobacco Product status determination of a tobacco product. These submissions include: a description of the product, including the name it was commercially marketed under on February 15, 2007, and characteristics that uniquely identify it; a statement that the product was commercially marketed in the United States as of February 15, 2007; and dated evidence that shows the product was commercially marketed in the United States as of February 15, 2007.
Deeming Rule	We use this term to refer to the 2016 final rule entitled "Deeming Tobacco Products to be Subject to the Federal Food, Drug, and Cosmetic Act, as Amended by the Family Smoking Prevention and Tobacco Control Act; Restrictions on the Sale and Distribution of Tobacco Products and Required Warning Statements for Tobacco Products." The Deeming Rule deemed products meeting the statutory definition of "tobacco product," except accessories of the newly deemed tobacco products, to be subject to the tobacco product provisions of Chapter IX of the FD&C Act. Examples of deemed products include cigars, pipe tobacco, waterpipe tobacco, and ENDS.
Deeming Analysis	We use this term to refer to the Regulatory Impact Analysis for the Deeming Rule.
Deemed Tobacco Product	We use this term to refer to cigars, pipe tobacco, waterpipe tobacco, ENDS, and other tobacco products deemed to be subject to Chapter IX of the FD&C Act by the Deeming Rule.
Deeming Compliance Date	Some deemed tobacco products are currently on the market under FDA's compliance policy. The current compliance policy for certain deemed tobacco products lasts until September 9, 2020. Products currently being marketed under FDA's compliance policy, and for which no premarket applications are submitted by September 9, 2020, will no longer be subject to the compliance policy after that date. In this analysis, we refer to the date September 9, 2020 as the Deeming Compliance Date.
Expected Period for Existing Product Submissions	Many deemed tobacco products meet the statutory definition of a new tobacco product. Some deemed tobacco products are currently on the market under FDA's compliance policy, which ends on the Deeming Compliance Date for those products for which no premarket applications are submitted. In this analysis, we refer to the time that it takes for new tobacco products currently on the market to comply with the premarket requirements as the Expected Period for Existing Product Submissions. Commenters suggested that some applicants will be unable to prepare initial PMTAs in time for the Deeming Compliance Date. Therefore, for the purposes of this final regulatory impact analysis only, we assume that the Expected Period for Existing Product Submissions will last until the end of 2022. That is, we assume that applicants will submit PMTAs for existing products before the end of 2022. In our model, applicants that submit PMTAs for currently marketed products after the Deeming Compliance Date will cease marketing until they receive a marketing granted order.

Term	Description
Expected Period for Future Product Submissions	In this analysis, we refer to the years following the Expected Period for Existing Product Submissions as the Expected Period for Future Product Submissions. During this period, we assume that all PMTAs submitted for deemed products are for products that are not currently marketed. This period begins in 2023.
ENDS	"ENDS" refers to electronic nicotine delivery systems that deliver aerosolized e-liquid when inhaled. Generally, ENDS include e-cigarettes and e-liquids.
E-Cigarette	An e-cigarette refers to an electronic device that delivers e-liquid in aerosol form into the mouth and lungs when inhaled. It is also referred to as an aerosolizing apparatus. See the final rule for a more detailed definition of an e-cigarette. The term e-cigarette in this analysis corresponds to the term "delivery system" used in the regulatory impact analysis for the Deeming Final Rule.
E-Liquid	E-liquids generally refer to liquid nicotine and nicotine-containing e-liquids. Generally, e-liquids include liquid nicotine, nicotine-containing liquids (i.e., liquid nicotine combined with colorings, flavorings, and/or other ingredients), and liquids that do not contain nicotine or other material made or derived from tobacco, but that are intended or reasonably expected to be used with or for the human consumption of a tobacco product.
PMTA Bundle	We use the term PMTA bundle to refer to a set of individual PMTAs submitted at the same time for which the costs of submission and review overlap substantially. Though each separate tobacco product requires a separate PMTA, applicants can rely on many of the same studies for these PMTAs and we can review these PMTAs as a group. The term "PMTA bundle" in this analysis corresponds to the term "PMTA application process" used in the regulatory impact analysis for the Deeming Final Rule.
Original PMTA	We use this term to refer to a PMTA that is not a supplemental PMTA or a resubmission.
Supplemental PMTA	A supplemental PMTA is a streamlined PMTA format for a new tobacco product that is a modification to a product with an existing marketing granted order. Subject to the conditions described in this final rule, applicants submitting a supplemental PMTA may satisfy PMTA content requirements by cross-referencing previously reviewed PMTAs.
Resubmission	A resubmission is a streamlined PMTA format that applicants who are seeking a marketing granted order for a tobacco product will use to respond to deficiencies outlined in a marketing denial order. An applicant may submit a resubmission for the same tobacco product that received a marketing denial order or for a different new tobacco product that results from changes necessary to address the deficiencies outlined in the marketing denial order. Subject to the conditions described in this final rule, applicants making a resubmission may satisfy PMTA content requirements by cross-referencing previously reviewed PMTAs. Applicants may not use the abbreviated resubmission format for PMTA bundles that we refused to accept or refused to file, or for PMTA bundles that were withdrawn during review.
Initial Submission or Review	We use the term "initial" in this analysis to refer to the first submission or review of a given PMTA bundle. This term includes first submissions and reviews of both original bundles and supplemental bundles.

Term	Description
Follow-On Submission or Review	We use the term "follow-on" in this analysis to refer to the second submission or review of a given PMTA bundle. In our analysis, follow-on submissions or review may include the second submissions or reviews for products that we refused to accept or refused to file, or a resubmission of a PMTA as defined in this table of terms.
Deficiency Letter	A deficiency letter is a request from us to a firm for an amendment to a PMTA. These letters pause the 180-day review period.
Complete Bundle	We call a PMTA bundle "complete" if we complete our initial review of that bundle after the substantive review.
Partially Complete Bundle	We call a PMTA bundle "partially complete" if the initial review of that bundle stops with the filing review. Partially complete bundles include bundles that we refuse to file in our review and bundles that firms withdraw during filing review.
Incomplete Bundle	We call a PMTA bundle "incomplete" if the initial review of that bundle stops with the acceptance review. Incomplete bundles include bundles that we refuse to accept in our review and bundles that firms withdraw during acceptance review.

D. Comments on the Preliminary RIA and Our Responses

In 2019, we published the proposed rule "Premarket Tobacco Product Applications and Recordkeeping Requirements" and prepared a preliminary regulatory impact analysis. In the following paragraphs, we describe and respond to comments we received on our analysis of the impacts of the proposed rule. We have numbered each comment to help distinguish between the different comment themes. The number assigned to each comment is purely for organizational purposes and does not signify the comment's value, or the order in which it was discussed by the commenter(s).

(Comment 1). Many comments stated that we failed to account for many of the costs that would result from the requirement to prepare and submit PMTAs for deemed tobacco products. Comments discussed impacts for deemed tobacco products including: reduced variety in the market; the development of a black market for deemed tobacco products; prohibitively high PMTA submission costs; exit of small businesses, including vape shops manufacturing e-liquids; and fewer incentives to develop innovative, harm-reducing tobacco products.

(Response 1). The Deeming Final Rule (May 2016) extended FDA's regulatory authority to all tobacco products (excluding accessories of such products), and thus all premarket requirements apply to deemed new tobacco products. We attribute any costs that result from the requirement to prepare and submit PMTAs for deemed new tobacco products to the Deeming Final Rule and not this rule. We therefore consider most aspects of these comments out-of-scope.

For this final regulatory impact analysis, we assume that applicants will prepare and submit these applications even without this final rule. In this analysis, we estimate the incremental impact of this final rule, relative to the compliance costs attributable to the Deeming Final Rule.

However, the market authorization system established for originally-regulated products by the Tobacco Control Act and extended to more products by subsequent regulation has been

characterized by trial-and-error inefficiencies that are consistent with the public feedback and that form the government failure that this final rule is intended to address, with the term "government failure" used in the sense of economic conceptual analysis, indicating a gap between the status quo and the theoretical ideal. We incorporate these inefficiencies into our baseline estimates by considering the "completeness" of PMTAs.

(Comment 2). Some comments expressed concern that we did not consider whether it is possible to complete PMTAs by the May 12, 2020 deeming compliance date. A comment suggested that much of the data required for filing, including clinical studies, non-clinical studies, long-term studies, and long-term epidemiological data, is not available for all products.

(Response 2). First, due to the COVID-19 pandemic, we have requested and received from the U.S. District Court from the District of Maryland an extension of the Deeming Compliance Date to September 9, 2020. Second, this final rule will not impact the Deeming Compliance Date or the ability of applicants to meet the requirements for filing PMTAs. Therefore, we consider this comment out-of-scope. However, we recognize that even with this extension some applicants may be unable to submit applications before the Deeming Compliance Date. To account for delays in submission of PMTAs, we have changed our assumptions about submissions so that applicants submit the initial round of PMTAs in the Expected Period for Existing Product Submissions, which, for the purposes of this analysis only, lasts until December 31, 2022.

(Comment 3). Some comments believe that we underestimated the cost per PMTA bundle by using the estimates from the Deeming Analysis. Furthermore, some commenters believe that the requirements in this final rule are more burdensome than those contemplated in the Deeming Analysis.

(Response 3). We believe that the estimates of the costs of studies in the Deeming Analysis continue to reflect the best available estimates of the cost of studies for a complete PMTA and that the final rule will not impact these costs. However, in response to this comment, we increased the incremental impact of the final rule on the administrative cost to submit each PMTA bundle. We also conduct a sensitivity analysis in the Regulatory Flexibility Analysis in which we assume that we underestimated the baseline cost to prepare a PMTA by 50 percent. In general, this sensitivity analysis supports our conclusion that the final rule will not have a significant impact on a substantial number of small entities.

(Comment 4). Multiple comments suggested that we improperly proposed to certify that the proposed rule would not have significant impact on a substantial number of small entities because we used cost estimates from the Deeming Analysis.

(Response 4). We disagree with this comment. We believe that this comment conflates the impacts of the Deeming Rule with the impacts of this final rule. In the final regulatory flexibility analysis for the Deeming Rule, we concluded that the Deeming Rule will have a significant economic impact on a substantial number of small entities. Specifically, applying premarket review to ENDS manufacturers, including vape shops, will result in significant compliance costs and market exit. Because the analysis for the Deeming Rule already accounted for these impacts, we only consider the incremental change in the costs of premarket review for ENDS products created by this rule in this analysis.

E. Summary of Changes

In response to comments and newly available data, we made the following changes for the final regulatory impact analysis:

- We updated wages and other estimates to 2019 dollars.
- We updated estimates of the number of expected bundles using 2019 sales data.
- We used two different data definitions for a PMTA bundle, as described in the appendix, representing uncertainty in the degree of market consolidation that will occur come the Deeming Compliance Date.
- We assumed that applicants will submit PMTAs for currently marketed deemed products until the end of 2022.
- We reorganized the analysis to clarify the difference between the impacts of this final rule and the impacts of the Deeming Rule.

II. Final Regulatory Impact Analysis

A. Background

1. Marketing Tobacco Products

The Tobacco Control Act[2] (TCA) established requirements for premarket authorization of new tobacco products. Products that firms commercially marketed in the United States as of February 15, 2007, called "Pre-Existing Tobacco Products," do not require premarket authorization (see Table 2). If a firm would like the agency to determine whether their tobacco product is a Pre-Existing Tobacco Product, they may voluntarily submit a Pre-Existing Tobacco Product Submission and we will determine if the tobacco product is a Pre-Existing Tobacco Product.

In general, a new tobacco product is any tobacco product that firms did not commercially market in the U.S. on February 15, 2007 (Table 2). Generally, to market a new tobacco product, manufacturers must obtain marketing authorization through one of three premarket review pathways:

1. Premarket tobacco product applications (PMTA pathway);
2. Applications intending to demonstrate that the new tobacco product is substantially equivalent to a predicate tobacco product (SE pathway);
3. Requests for an exemption from the requirement of demonstrating substantial equivalence (Exemption Request pathway).

2. The PMTA Pathway

Manufacturers may use the PMTA pathway to obtain marketing authorization for any new tobacco product. We review each submission through the PMTA pathway to determine whether to issue a marketing granted order for the new tobacco product. To issue a marketing

[2] The Family Smoking Prevention and Tobacco Control Act of 2009, also called the Tobacco Control Act, amended the Federal Food, Drug, and Cosmetic Act (FD&C Act), giving us the authority to regulate tobacco products under Chapter IX of the FD&C Act.

granted order for a new tobacco product through the PMTA pathway, we need sufficient information to find that:

1. Permitting the marketing of the new tobacco product would be appropriate for the protection of public health;
2. Firms manufacture, process, or pack the new tobacco product in accordance with tobacco product manufacturing regulations promulgated under section 906(e) of the FD&C Act;
3. The new tobacco product's proposed labeling is not false or misleading;
4. The new tobacco product complies with any applicable product standards or there is adequate information to justify deviation from the standards.

3. The Deeming Rule

The TCA gave us immediate authority to regulate cigarettes, cigarette tobacco, smokeless tobacco, and roll-your-own tobacco. We call these "originally regulated" tobacco products. In 2016, the Deeming Rule expanded the scope of products subject to our regulatory authority to include tobacco products such as cigars, pipe tobacco, waterpipe tobacco, ENDS, and other novel tobacco products. We call these "deemed" tobacco products.

The TCA required firms to obtain marketing authorization for new originally regulated tobacco products starting in March 2011. Because the Deeming Rule extended FDA's regulatory authority to all tobacco products (excluding accessories of such products), all premarket requirements apply to both deemed and originally regulated tobacco products.

Our compliance policy regarding premarket authorization of deemed products has shifted over time. As of the publication of this rulemaking, in order to fall under the compliance policy, firms must submit applications to obtain marketing authorization for new deemed tobacco products by September 9, 2020. For companies that submit timely applications, we may continue to exercise enforcement discretion, meaning that we expect that applicants will generally continue marketing products until September 9, 2021, unless we take a negative action on their application prior to that date.

In the Deeming Analysis, we estimated the use of each premarket review pathway by different types of deemed tobacco products and assumed that all of the deemed tobacco products utilizing the PMTA pathway are ENDS. We provide these estimates in Table 3 below.

Table 3. Use of Marketing Pathways by Deemed Products Seeking Marketing Authorization

Product Type	Existing Product Submissions			Future Product Submissions		
	PMTA	SE	SE Exempt	PMTA	SE	SE Exempt
Cigars	0%	71%	29%	0%	75%	25%
Pipe and Waterpipe Tobacco	0%	67%	33%	0%	75%	25%
Pipes and Waterpipes	0%	80%	20%	0%	80%	20%
E-Liquids	100%	0%	0%	40%	0%	60%
E-Cigarettes	78%	22%	0%	35%	10%	55%

B. Market or Government Failure Requiring Federal Regulatory Action

In the absence of regulatory action, tobacco firms seeking marketing authorization through the PMTA pathway will rely on the FD&C Act, published guidance, and trial-and-error to understand the information a PMTA must contain for FDA to determine whether a product should receive a marketing granted order. Trial-and-error creates inefficiencies that unnecessarily increase the costs of premarket review and delay marketing of products that meet the conditions for a marketing granted order. These inefficiencies, created by the general language in the FD&C Act and extended to more products by subsequent regulatory actions, represent a failure that we can alleviate by providing additional requirements for the format and content of PMTAs.

Premarket review allows us to evaluate important information about tobacco products before firms start marketing them. However, new tobacco products require continuous close monitoring to identify characteristics that contribute to adverse health outcomes and consumers may have inadequate information about characteristics that contribute to adverse health outcomes. For example, consumers may not learn of serious and unexpected adverse experiences associated with the consumption of specific tobacco products. Without this information, consumers often fail to internalize all adverse health outcomes when choosing tobacco products. Postmarket surveillance, addressed in this rulemaking through periodic and adverse experience reporting requirements, could help reduce the market failure created by consumers' failure to internalize adverse health outcomes associated with the consumption of tobacco products.

C. Structure of the Final Rule

1. Recordkeeping Requirements

The final rule will require that tobacco manufacturers of Pre-Existing Tobacco Products and products that are exempt from the requirements of demonstrating substantial equivalence maintain records to demonstrate that they can legally market their products. We will require firms manufacturing Pre-Existing Tobacco Products to maintain records demonstrating their Pre-Existing Tobacco Product status. The final rule describes the types of records that these firms can use to demonstrate their Pre-Existing Tobacco Product status, the required format for these records, and how long firms will need to retain these records. We will also require firms marketing new tobacco products under the Exemption Request pathway to maintain all records necessary to support the exemption. The final rule describes the types of records that these firms must maintain and how long firms will need to retain these records.

2. Format and Content Requirements for PMTAs

The final rule will codify the format and content requirements for PMTAs based on our best understanding of what information we need to conduct a substantive review of the application. Primarily, the rule explains how to present and organize information already required by statute. However, the rule does include a few new requirements for PMTAs, including a requirement to submit an application summary.

The final rule will also allow for two streamlined types of PMTA formats: resubmissions and supplemental PMTAs. An applicant may submit a resubmission for a tobacco product that received a marketing denial order. A resubmission is a streamlined PMTA that addresses the

deficiencies described in the marketing denial order and cross-references the original PMTA to form a complete PMTA. An applicant may submit a supplemental PMTA for a new tobacco product that results from modification of a tobacco product that received a PMTA marketing granted order. A supplemental PMTA is a streamlined PMTA that cross-references the original PMTA to form a complete PMTA.

3. PMTA Review

The final rule will codify and make our procedures for PMTA review more efficient. When an applicant submits a PMTA, we will conduct three levels of review, each more in depth than the previous level:

1. Acceptance Review
2. Filing Review
3. Substantive Review

During acceptance review, we perform a quick, high-level check to see if a submission generally includes required information before FDA accepts a PMTA and proceeds to filing review. Filing review is a more in-depth review to ensure the application contains sufficient information for initiating substantive review. Though these procedures already exist in current practice, the final rule will clarify requirements for acceptance and filing reviews so that we can avoid accepting and filing PMTAs that lack information needed for substantive review.

In general, we expect our review will take 180 days from the receipt of a complete PMTA. The final rule describes the types of events that could pause or restart the 180-day review period. For example, we may identify deficiencies in a PMTA during our substantive review and request that applicants submit additional information. In this case, we will pause the 180-day review period while applicants submit amendments to their PMTAs containing the required information.

4. Postmarket Requirements

The final rule will require applicants that receive a marketing granted order through the PMTA marketing pathway to establish and maintain records and to submit certain postmarket reports. We will require that applicants submit two types of reports after receiving a marketing granted order: periodic reports and serious and unexpected adverse event reports.

The final rule describes in detail the content requirements for periodic reports. We will review these reports to ensure that continued marketing of products with marketing granted orders remains appropriate for the protection of public health. We initially expect to require periodic reports annually. However, we may require in specific marketing granted orders that applicants submit reports more frequently or less frequently.

The final rule will also require applicants with marketing granted orders to submit reports for any serious and unexpected adverse experiences associated with the marketed tobacco product within 15 days of receiving or becoming aware of the adverse experience. Currently, firms can submit voluntary adverse experience reports for tobacco products. The final rule will make reporting mandatory for serious and unexpected adverse experiences associated with products subject to a marketing granted order.

D. Baseline Conditions

1. Description of the Baseline

a. Post-Deeming Baseline for ENDS Products

The Deeming Rule implemented premarket review for ENDS products. In the Deeming Analysis, we accounted for the benefits and costs of implementing premarket review for ENDS products, including the costs for applicants to prepare and submit PMTAs, costs for us to review PMTAs, and costs associated with the exit of businesses that are unable to afford the PMTA process.

We use a post-Deeming baseline for ENDS products in this analysis. This baseline reflects the state of the world in which applicants submit PMTAs to comply with the Deeming Final Rule in the absence of this rulemaking. By using a post-Deeming baseline, this analysis captures only the incremental change in the benefits and costs of premarket review of ENDS associated with this rulemaking.

b. Pre-Statutory Baseline for Originally Regulated Products

We expect that some manufacturers of new originally regulated tobacco products will seek marketing granted orders through the PMTA pathway. For such products, this final rule implements the statutory requirements for PMTAs in the TCA. Therefore, we use a pre-statutory baseline for originally regulated tobacco products, in which this final rule implements the statutory requirements attributable to the TCA. In this baseline, both FDA and industry incur zero costs related to PMTA submission and review of originally regulated tobacco products. In our uncertainty analysis, we use an alternative, post-statutory baseline for these products.

2. Key Inputs

a. The Cost of Labor

Following guidelines from the Department of Health and Human Services,[3] we estimate the cost of labor as the fully loaded wage. The fully loaded wage is the hourly wage including benefits and overhead. We assume that benefits and overhead equal 100 percent of the mean wage. For industry wages, we use 2019 mean wage estimates from the Bureau of Labor Statistics' National Industry-Specific Occupational Employment and Wage Estimates[4] for the tobacco manufacturing industry. For staff from our Center for Tobacco Products (CTP), we use current data on FDA fully loaded full-time equivalent costs to estimate the fully loaded wage. In Table 4, we present the mean wages and fully loaded wages used in this analysis.

Table 4. Wages Used to Evaluate the Cost of Labor

Occupation	Mean Wage	Fully Loaded Wage
Management	$65.52	$131.04
Lawyers	$75.53	$151.06
Administrative Staff	$21.38	$42.76

[3] Available at https://aspe.hhs.gov/system/files/pdf/242926/HHS_RIAGuidance.pdf.
[4] Available at https://www.bls.gov/oes/current/oessrci.htm.

Scientists	$33.51	$67.02
Engineers	$48.24	$96.48
Composite Wage for Preparing PMTAs and Related Reports[5]	$41.96	$83.92
CTP Staff	$62.88	$125.75

Note: All wages are in 2019 dollars.

b. Inflation Adjustments

All estimates in this analysis are in 2019 dollars. We use GDP price indices from the Bureau of Economic Analysis to adjust for inflation. In Table 5, we present GDP price indices and inflation factors for the different inputs that we adjust for inflation in this analysis.

Table 5. Inflation Factors for Inputs in the Analysis

Type of Input	Year of Estimate	GDP Price Index	Inflation Factor[a]
Cost inputs from the Deeming Analysis	2014	103.65	1.08
Private sector wages	2019	112.36	1.00
Sales of ENDS products	2019	112.36	1.00
Wage for CTP staff	2020[b]	113.40	0.99

[a] The inflation factor equals the GDP Price Index for 2019 divided by the GDP Price Index for the year of the estimate. To adjust a value for inflation, we multiply that value by the inflation factor.
[b] We use the GDP price index from the first quarter of 2020 for the 2020 GDP price index.

3. Number of Affected Entities

Because the final rule will impact manufacturers of both originally regulated and deemed tobacco products, we expect the final rule will impact all tobacco product manufacturers. To estimate the number of affected entities, we combine 2019 tobacco establishment registration data from FDA's internal Tobacco Registration and Listing Module (TRLM) with information from Dun and Bradstreet (D&B). We estimate that there are approximately 2,567 firms with registered tobacco establishments. Firms that only own vape shop establishments represent approximately 846 of the 2,567 firms. According to the D&B data, about 88 percent of the firms registered with FDA have fewer than 1,500 employees.[6]

4. PMTA Bundles

Applicants must submit PMTAs for individual products. However, applicants may rely on the same studies and research for similar products to complete their PMTAs. As a result, many of the costs to prepare and submit PMTAs for similar products significantly overlap. We permit and have created a mechanism[7] to assist applicants to complete a "bundled" submission for PMTAs that contain overlapping information. Therefore, throughout this analysis, we refer to PMTA bundles rather than individual PMTAs.

[5] Following the Deeming Analysis, the composite wage is a weighted average of the wages for lawyers, administrative staff, scientists, and engineers.
[6] We use D&B's small business indicator to determine whether a firm is a small business.
[7] See Form FDA 4057b

We have received 18 PMTA bundles as of December 2019.[8] The number of individual PMTAs within a bundle varies. While we have received bundles containing a single PMTA, we have also received a PMTA bundle that included 287 different products. Using data from Nielsen Retail Measurement Services (RMS)[9] data, we estimate that e-liquid PMTA bundles include an average of 9.0 individual PMTAs and that e-cigarette PMTA bundles include an average of 3.2 individual PMTAs.[10]

Few of the bundles we have received have contained enough information for us to begin substantive review. As of December 2019, we had accepted 9 bundles and filed 8 of these bundles. Moreover, we refused to accept 7 bundles (about 365 PMTAs) for deemed tobacco products as of December 2019 because these applications lacked the basic information that we need to conduct filing review.[11] At the time of publication, we have completed review of just 4 bundles.[12] Our experience indicates that applicants are uncertain about the format and content requirements of PMTAs.

To address this uncertainty, we introduce the concept of PMTA bundle "completeness" in this analysis. We designate three different levels of completeness:

1. We call PMTA bundles that stop their review at the acceptance review stage "incomplete" bundles.
2. We call PMTA bundles that stop their review at the filing review stage "partially complete" bundles.
3. We call PMTA bundles that enter substantive review "complete" bundles.

Based on these definitions and the bundles we have received to date, we estimate that, in the baseline, 50 percent of bundles are incomplete, 6 percent of bundles are partially complete, and 44 percent of bundles are complete.

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[8] We have received PMTAs both leading up to and following the Deeming Compliance Date in September 2020. However, we have not yet reviewed all these applications as of the publication of this final rule. We therefore rely on data from before the Deeming Compliance Date to characterize the baseline completeness of PMTA bundles.

[9] FDA's own analyses and calculations are informed, in part, by data reported by The Nielsen Company through its RMS service for the electronic vapor and smokeless product categories for the 52-week period beginning December 30, 2018 and ending December 28, 2019 for the total United States market and Convenience Stores and Expanded All Outlets Combined (xAOC) channels. The conclusions informed by the Nielsen data are those of FDA and do not reflect the views of Nielsen. Nielsen is not responsible for and had no role in and was not involved in analyzing and preparing the results reported herein, or in developing, reviewing, or confirming the research approaches or methodologies used in connection with this report, including without limitation, the bundle compositions. All references to Nielsen in this document refer to the data described above and are subject to the above disclaimer.

[10] We base these estimates on data definitions of a "bundle" as a set of products with similar characteristics. These definitions inherently assume that the ability of applicants to bundle submissions for different products correlates with the similarity of products across observable characteristics.

[11] On August 8, 2016, we published a direct final rule (and a companion proposed rule) entitled "Refuse to Accept Procedures for Premarket Tobacco Product Submissions (RTA)". This direct final rule specified the basic information we require to conduct our acceptance review. We received comments on the direct final rule and subsequently published the final rule on December 29, 2016. We have accepted few of the PMTAs we have received since the RTA final rule. We therefore expect that the RTA rule did not completely eliminate uncertainty about our expectations for the information needed for acceptance of a PMTA.

[12] See https://www.fda.gov/tobacco-products/premarket-tobacco-product-applications/premarket-tobacco-product-marketing-orders.

Incomplete and partially complete bundles create inefficiencies in the PMTA review process. If an applicant still wishes to obtain a marketing granted order for incomplete or partially complete bundles, they need to begin the review process again with an application that meets the PMTA format and content requirements. This second, or "follow-on" review[13] creates additional costs for FDA and delays the marketing of the products in the PMTA bundles.

5. Overview of the PMTA Pathway Model

In the remainder of the Baseline section, we lay out the baseline inputs that make up the total cost of the PMTA pathway to industry and to FDA. We use Figure 1 and Figure 2 to illustrate how these inputs fit together to output the total baseline costs to industry and FDA. Note that though we refer to these estimates as costs in this section, the costs to prepare and review PMTAs *exist in the baseline* for ENDS products and therefore do not represent the costs of this final rule. The Deeming Rule subjected ENDS to premarket review and the Deeming Analysis accounted for the costs of premarket review for ENDS. The impacts of this final rule are the incremental changes in these costs created by this rule.

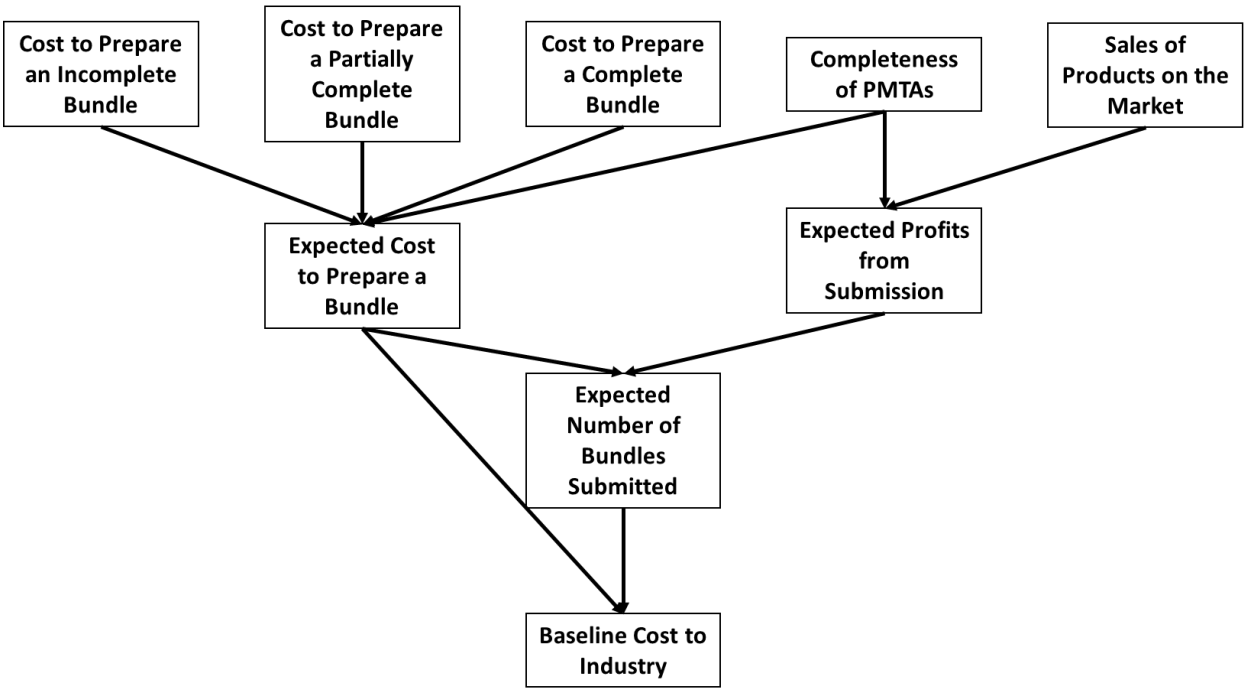

Figure 1. Model for the Baseline Cost of the PMTA Pathway to Industry

As shown in Figure 1, the expected cost to prepare a PMTA bundle depends on the costs to prepare incomplete, partially complete, and complete bundles and the "completeness" of PMTAs. The expected profits from submitting a PMTA for a bundle depend on the bundle's existing sales and the completeness of PMTAs. The expected number of bundles submitted depends on the expected profits from submission and the expected cost to prepare a bundle.

[13] We use the term "follow-on" to refer to these second submissions and reviews. A follow-on bundle may be a bundle that we refused to accept or refused to file in initial review. A follow-on bundle may also be a resubmission, as defined by the final rule.

Finally, the total baseline cost to industry equals the expected cost to prepare a bundle times the expected number of bundles submitted.

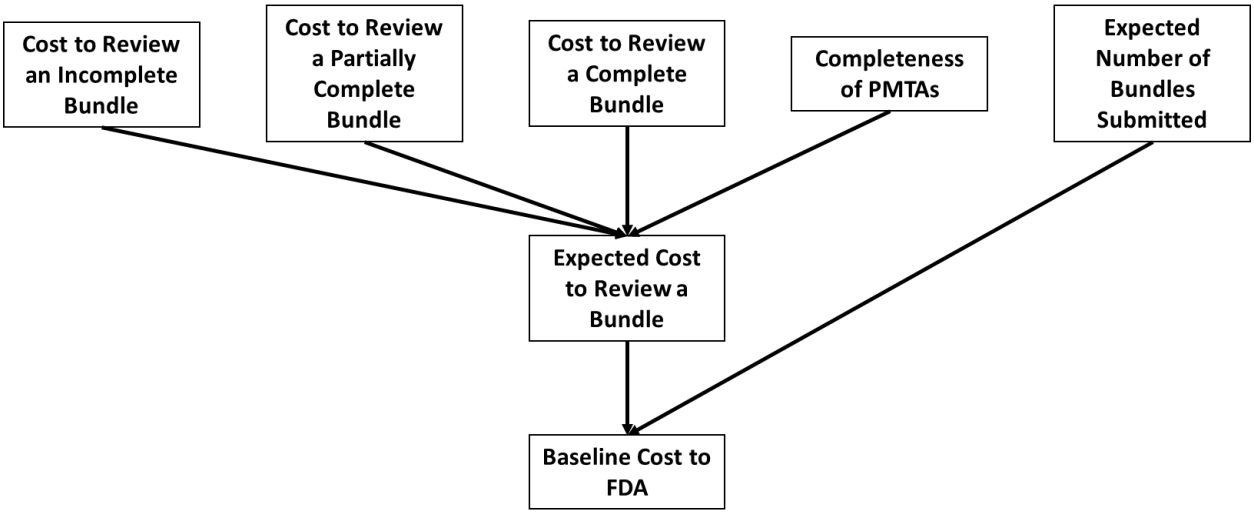

Figure 2. Model for the Baseline Cost of the PMTA Pathway to FDA

As shown in Figure 2, the expected cost to review a PMTA bundle depends on the costs to review incomplete, partially complete, and complete bundles and the "completeness" of PMTAs. Then, the total baseline cost to FDA equals the expected cost to review a bundle times the expected number of bundles submitted.

6. Baseline Cost to Prepare a PMTA Bundle

In the Deeming Analysis, we estimated the cost to prepare PMTAs for e-liquid and e-cigarette tobacco products. In Table 6, we present those estimates, updated to 2019 dollars.

Table 6. Deeming Estimates of the Cost to Prepare a PMTA Bundle

Product Type	Type of PMTA	Cost per Bundle[a]
E-Liquid	Original	$1,208,666
	Supplemental	$1,149,347
E-Cigarette	Original	$836,022
	Supplemental	$447,937

[a] All estimates are in 2019 dollars.

The Deeming Analysis accounted for differences in costs by product type (that is, costs for e-liquids as opposed to costs for e-cigarettes) and by type of PMTA.[14] However, the Deeming Analysis assumed that all PMTAs will be complete upon initial submission and therefore did not account for differences in costs by PMTA completeness.

[14] The Deeming Analysis did not refer to original and supplemental PMTAs specifically. However, the Deeming Analysis assumed that the cost to prepare a PMTA will fall over time as applicants are able to meet PMTA content requirements by cross-referencing the PMTAs of products with marketing granted orders. To be consistent with this final rule, we assumed that these reduced-cost PMTAs are supplemental PMTAs as defined in this final rule.

Incomplete bundles and partially complete bundles are initially less costly than complete bundles. An incomplete bundle does not meet the requirements for filing review, while a partially complete bundle does not meet the requirements for substantive review. Meeting these requirements has a cost; therefore, incomplete and partially complete bundles cost less than complete bundles.

However, applicants expecting substantial profits from obtaining marketing granted orders have incentives to submit follow-on bundles, even if we refused to accept or refused to file their initial submissions. Applicants will then incur costs to complete their PMTAs so that they meet the requirements for filing and substantive review.

In Table 7, we estimate the total cost to bring a bundle to substantive review, discounted relative to the time of initial submission. We derive these cost estimates in more detail in the technical appendix. For simplicity, our estimates rely on a few key assumptions:

- All PMTAs eventually receive marketing granted orders.
- Applicants always submit follow-on PMTAs if they do not initially receive a marketing granted order.
- All follow-on submissions are complete.
- It takes an average of 2 years for applicants to prepare complete follow-on submissions.
- In addition to the cost to complete an incomplete or partially complete PMTA, applicants incur an additional administrative cost for all follow-on submissions.

Table 7. Discounted Cost to Prepare a PMTA Bundle in the Baseline by Completeness ($m)

Product Type	Type of PMTA		Cost per Complete Bundle		Cost per Partially Complete Bundle	Cost per Incomplete Bundle	
		7%	3%	7%	3%	7%	3%
E-Liquid	Original	$1.21	$1.21	$1.15	$1.18	$1.10	$1.15
	Supplemental	$1.15	$1.15	$1.09	$1.12	$1.04	$1.10
E-Cigarette	Original	$0.84	$0.84	$0.80	$0.82	$0.77	$0.80
	Supplemental	$0.45	$0.45	$0.43	$0.44	$0.41	$0.43

7. Baseline Cost to Review a PMTA Bundle

In current practice, we conduct acceptance, filing, and substantive reviews for PMTAs. We use data from CTP's Office of Science to estimate the cost for each stage of review in Table 8. We derive these costs, and all the cost estimates in this section, in more detail in the technical appendix.

Table 8. Baseline Cost to Review a PMTA Bundle per Stage of Review

Product Type	Type of PMTA	Cost per Acceptance Review	Cost per Filing Review	Cost per Substantive Review
E-Liquid	Original	$465	$12,751	$580,976
	Supplemental	$465	$12,424	$569,658
E-Cigarette	Original	$465	$13,078	$592,294
	Supplemental	$440	$11,770	$539,478

During our review, we may also issue deficiency letters requesting amendments to a PMTA. In our limited history reviewing PMTAs, we estimate that we issue an average of 4 deficiency letters per bundle of PMTAs and that issuing each deficiency letter costs us an average of $21,234. Additionally, before we begin acceptance review for a PMTA bundle, we must electronically process all the submission materials. With our limited experience reviewing PMTAs, we have found that applicants often submit large amounts of raw data, which we do not require for our review. We estimate that processing unnecessary data costs us, on average, $7,518 per bundle.

In Table 9, we illustrate how the costs to review a bundle depend on a bundle's completeness. We use the same assumptions we made in the previous section and additionally assume that:

- Applicants submit unnecessary data only for initial submissions and not for follow-on submissions.
- We only issue deficiency letters during substantive review.

When applicants submit incomplete bundles, we incur the cost of acceptance review twice: once during initial review and once during follow-on review. Similarly, we incur the costs of acceptance review and filing review twice for partially complete bundles. These duplicative costs make our review less efficient.

Table 9. Incidence of Review Costs for Initial and Follow-On Reviews, by Bundle Completeness

Type of Review Cost	Complete Bundle		Partially Complete Bundle		Incomplete Bundle	
	Initial Review	Follow-On Review	Initial Review	Follow-On Review	Initial Review	Follow-On Review
Acceptance Review	X		X	X	X	X
Filing Review	X		X	X		X
Substantive Review	X			X		X
Deficiency Letters	X			X		X
Unnecessary Data	X		X		X	

We use our cost estimates for acceptance review, filing review, substantive review, deficiency letters, and unnecessary data, as well as the assumptions about the incidence of review costs from Table 9, to estimate the average cost per bundle by completeness. In Table 10, we present these estimates, discounted relative to the time of submission.

Table 10. Discounted Cost to Review a PMTA Bundle in the Baseline by Completeness ($m)

Product Type	Type of PMTA	Cost per Complete Bundle	Cost per Partially Complete Bundle	Cost per Incomplete Bundle

		7%	3%	7%	3%	7%	3%
E-Liquid	Original	$0.69	$0.69	$0.61	$0.66	$0.60	$0.65
	Supplemental	$0.67	$0.67	$0.60	$0.65	$0.59	$0.64
E-Cigarette	Original	$0.70	$0.70	$0.63	$0.67	$0.61	$0.66
	Supplemental	$0.64	$0.64	$0.58	$0.62	$0.56	$0.61

8. Average Costs per Bundle in the Baseline

We estimate that, in the baseline, 44 percent of bundles are incomplete, 6 percent of bundles are partially complete, and 50 percent of bundles are complete. Given this distribution and the estimates in Table 7 and Table 10, we estimate the costs to prepare and review a PMTA bundle, averaged over completeness, in Table 11. We will return to these estimates as we look at how the final rule changes the total cost of the PMTA pathway by improving efficiency.

Table 11. Baseline Average Discounted Cost to Prepare and Review a PMTA Bundle ($m)

Product Type	Type of PMTA	Cost to Prepare a Bundle		Cost to Review a Bundle	
		7%	3%	7%	3%
E-Liquid	Original	$1.16	$1.19	$0.64	$0.67
	Supplemental	$1.11	$1.14	$0.63	$0.65
E-Cigarette	Original	$0.80	$0.82	$0.65	$0.68
	Supplemental	$0.43	$0.44	$0.60	$0.62

9. Baseline Number of PMTA Bundles

In the Deeming Analysis, we estimated that we will receive between 1,530 and 2,850 PMTAs during the Expected Period for Existing Product Submissions and between 28 and 105 PMTAs annually thereafter in the Expected Period for Future Product Submissions. However, the market for ENDS has changed significantly since the publication of the Deeming Rule. We therefore update these estimates in this analysis based on new market data.

One source of data we could use to estimate the number of PMTA submissions is our Tobacco Registration and Listing (TRLM) data. This data includes all tobacco products listed with FDA. However, the cost of listing a product with us is low and firms may have listed new tobacco products for which they do not intend to submit PMTAs. Therefore, we expect that using this data will artificially inflate our estimate of the number of PMTAs. Instead, we use market data from RMS Nielsen (see Footnote 9), which includes product-level revenue data, to estimate the number of PMTA bundles we will receive.

To determine whether an applicant will submit a PMTA bundle for a set of currently marketed tobacco products, we compare the discounted expected profits over that bundle's lifetime to the discounted expected cost of submitting a PMTA bundle. We assume that applicants only submit PMTAs for bundles where expected profits are greater than expected costs.

In Table 12, we estimate the average number of e-liquid and electronic nicotine delivery system bundles we will receive annually over 20 years. For these estimates, we make two key additional assumptions:

- Though the Deeming Compliance Date is September 9, 2020, we receive PMTAs for currently marketed ENDS between 2020 to 2022.
- Applicants submit original PMTAs from 2020 to 2022 and supplemental PMTAs after 2022.

We derive these estimates in more detail in the technical appendix. Note that because we use a pre-statutory baseline for originally regulated products, we do not include PMTAs for originally regulated products in the baseline. That is, the number of originally regulated PMTA bundles submitted in the baseline is zero.

Table 12. Number of Bundles Submitted in the Baseline

Year	E-Liquid Bundles	E-Cigarette Bundles	Total Bundles
2020	11.5	9.2	20.7
2021	11.5	9.2	20.7
2022	11.5	9.2	20.7
Annually after 2022	6.2	3.2	9.4

E. Direct Impacts of the Final Rule on the PMTA Pathway for ENDS

The final rule will make the PMTA pathway more efficient by providing greater detail on the format and content requirements for PMTAs and creating new requirements for acceptance and filing review. The final rule also includes some new requirements for PMTAs that we did not include in the Deeming Analysis. The final rule impacts our model of the costs of the PMTA pathway in three ways:

1. Increasing the administrative effort required to organize and prepare a PMTA,
2. Reducing the cost of PMTA review, and
3. Increasing the completeness of submitted PMTAs.

In Figure 3, we illustrate how these changes impact the cost for applicants to prepare PMTAs for ENDS. Upward arrows represent increases due to rulemaking, and downward arrows represent decreases due to rulemaking. Question marks represent theoretically ambiguous impacts that depend on the magnitude of the increases and decreases of other values. The expected cost to prepare a bundle increases as the administrative costs to prepare incomplete, partially complete, and complete bundles increase. Additionally, because complete bundles are more expensive to prepare than less complete bundles (see Table 7), the expected cost to prepare a bundle also increases with the completeness of PMTAs. Complete PMTAs get marketing granted orders faster than partially complete and incomplete PMTAs, so the expected profits from submission increase with the completeness of PMTAs. While increasing the expected cost to prepare a bundle reduces the incentives for applicants to submit PMTAs, increasing the expected profits from submission increases incentives to submit PMTAs. As a result, the net impacts of the final rule on the number of submitted bundles and the total costs of the PMTA pathway to industry depends on the magnitude of these two effects.

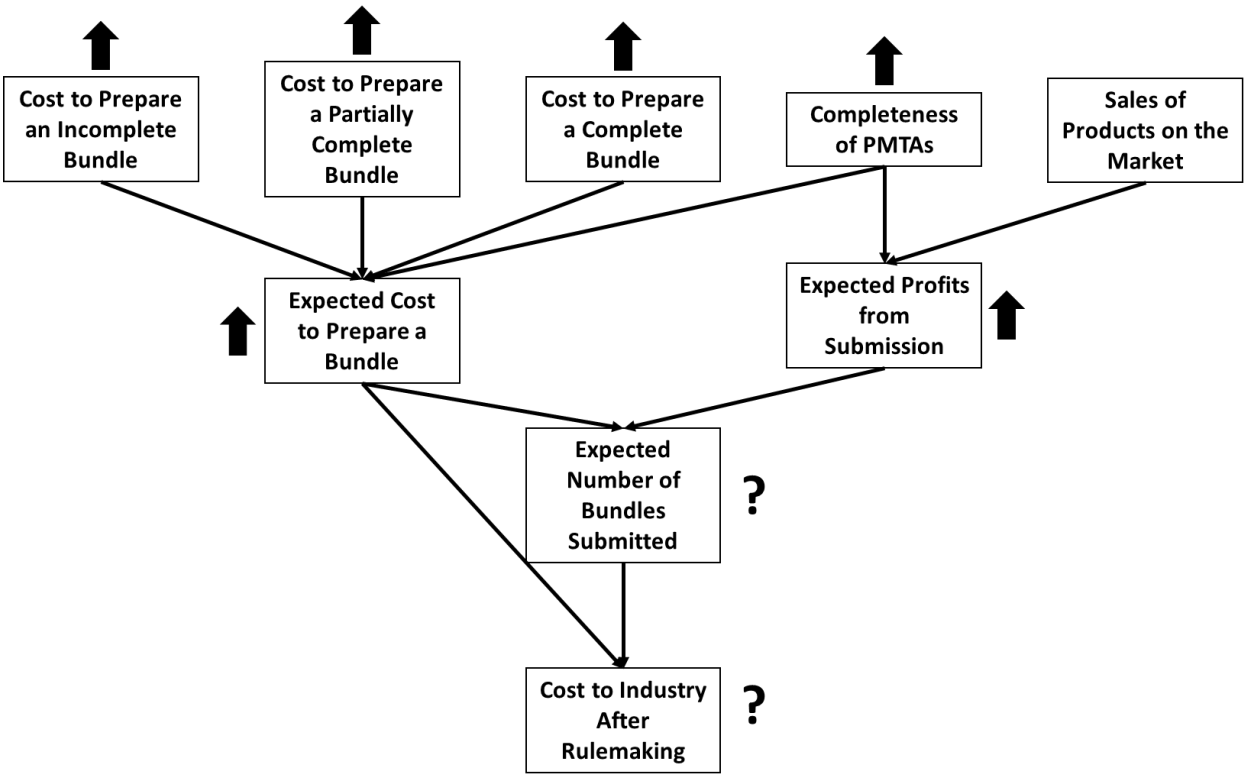

Figure 3. Impact of the Final Rule on the Cost of the PMTA Pathway to Industry

Similarly, we illustrate how the final rule will impact the costs for FDA to review PMTAs for ENDS in Figure 4. The costs to review incomplete, partially complete, and complete bundles falls with the final rule, reducing the expected cost to review a bundle. However, complete bundles are costlier to review than less complete bundles (see Table 8), so the expected cost to review a bundle increases as submissions become more complete. The net impact of the final rule on the expected cost to review a bundle depends on the magnitudes of these impacts. Because the impacts of the final rule on the expected cost to review a bundle and the expected number of bundles submitted are ambiguous, the net impact of the final rule on the cost of reviewing PMTAs could be positive or negative.

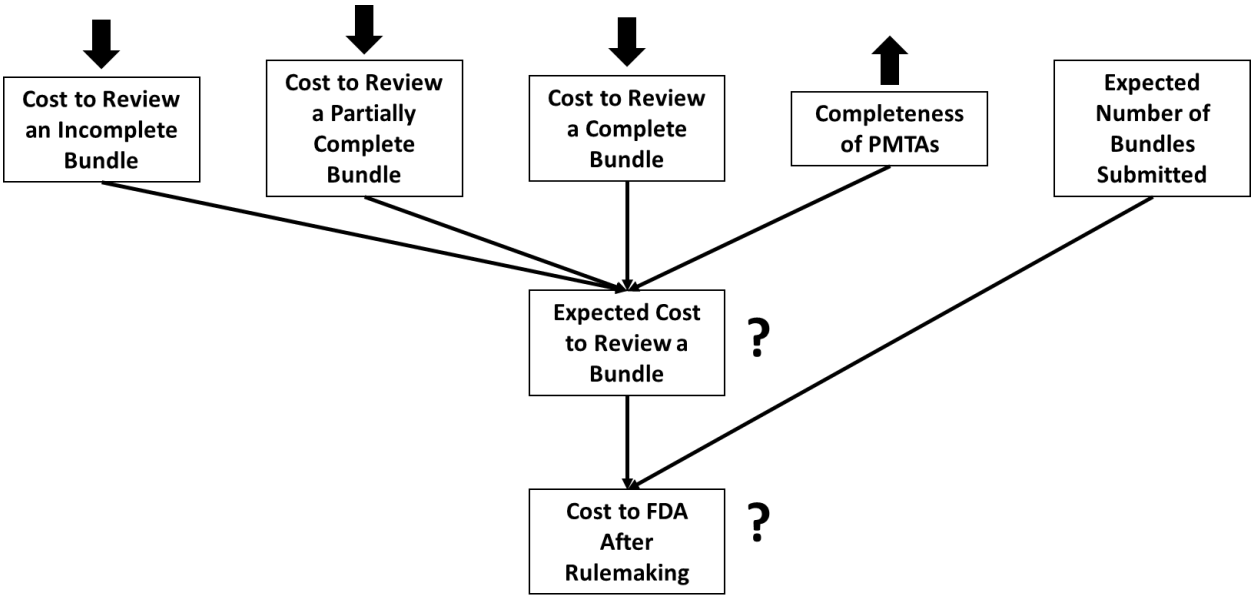

Figure 4. Impact of the Final Rule on the Cost of the PMTA Pathway to FDA

1. Increased Administrative Effort

The final rule includes some new requirements for PMTAs that were not included in the Deeming Analysis. For example, we will require applicants to provide an application summary and a description of their plans to market the new tobacco product. To account for the incremental burden of this rulemaking, we assume that the administrative cost per bundle will increase by, on average, 50 percent. Given this assumption, we present our estimates of the costs of preparing incomplete, partially complete, and complete bundles under the final rule in Table 13.

Table 13. Discounted Cost to Prepare a PMTA Bundle with Rulemaking, by Completeness ($m)

Product Type	Type of PMTA	Cost per Complete Bundle		Cost per Partially Complete Bundle		Cost per Incomplete Bundle	
		7%	3%	7%	3%	7%	3%
E-Liquid	Original	$1.22	$1.22	$1.19	$1.22	$1.14	$1.20
	Supplemental	$1.16	$1.16	$1.13	$1.16	$1.09	$1.14
E-Cigarette	Original	$0.84	$0.84	$0.81	$0.83	$0.78	$0.82
	Supplemental	$0.45	$0.45	$0.44	$0.45	$0.42	$0.44

2. Decreased Cost of PMTA Review

We expect that the final rule will encourage applicants to submit better organized and more complete PMTAs, making our review more efficient. We expect that the final rule will increase the cost per acceptance review because the final rule includes some new acceptance requirements. However, we expect that the final rule will decrease the cost per filing and substantive review as applicants submit PMTAs that better meet the content and format

requirements for PMTAs. In Table 14, we present CTP's Office of Science's estimates of the cost per acceptance, filing, and substantive review with rulemaking.

Table 14. Cost to Review a PMTA Bundle per Stage of Review, with Rulemaking

Product Type	Type of PMTA	Cost per Acceptance Review	Cost per Filing Review	Cost per Substantive Review
E-Liquid	Original	$604	$6,376	$465,913
	Supplemental	$597	$6,212	$458,367
E-Cigarette	Original	$610	$6,539	$473,458
	Supplemental	$572	$5,885	$431,959

We also expect that the cost of issuing deficiency letters and the cost of processing unnecessary data will decrease due to the final rule. We estimate that we will issue, on average, 2.5 deficiency letters for each bundle of PMTAs during substantive review. We also expect that the final rule will eliminate the submission of unnecessary data, further reducing costs to FDA. Based on these assumptions, we estimate the costs to review incomplete, partially complete, and complete bundles in Table 15.

Table 15. Discounted Cost to Review a PMTA Bundle with Rulemaking, by Completeness ($m)

Product Type	Type of PMTA	Cost per Complete Bundle		Cost per Partially Complete Bundle		Cost per Incomplete Bundle	
		7%	3%	7%	3%	7%	3%
E-Liquid	Original	$0.52	$0.52	$0.46	$0.49	$0.45	$0.49
	Supplemental	$0.51	$0.51	$0.45	$0.49	$0.44	$0.48
E-Cigarette	Original	$0.52	$0.52	$0.46	$0.50	$0.46	$0.49
	Supplemental	$0.48	$0.48	$0.43	$0.46	$0.42	$0.45

3. Increased Completeness of PMTAs

First, as described in the baseline section, most of the PMTA bundles that we have received to date have been incomplete. We expect that we would receive more complete bundles if firms had more detailed information about the format and content requirements of a PMTA. This final rule will communicate our expectations to industry. Because applicants have incentives to submit complete bundles, we expect that communicating our expectations to industry will increase the completeness of submitted bundles.

To estimate the impact of the final rule on the completeness of PMTAs, we use data from our review of Premarket Approval Applications (PMAs) for medical devices. Like CTP's review of PMTAs, the Center for Devices and Radiological Health's review of PMAs includes an acceptance review, a filing review, and a substantive review. However, unlike premarket review of tobacco products, we have conducted premarket review of medical devices for many years. We estimate that 13 percent of the PMAs we receive are incomplete, 4 percent are partially complete, and 83 percent are complete.[15]

[15] Based on a 2017 performance report, available at https://www.fda.gov/media/110947/download.

Industry experience with premarket applications may explain some of the difference in the completeness of medical device applications and tobacco product applications. We therefore expect that PMTAs will not be as complete as PMAs under the final rule. We assume that, on average, 31 percent of PMTAs will be incomplete, 5 percent will be partially complete, and 63 percent will be complete, representing the midpoint between current PMTA completeness and the completeness of PMAs.

We use the estimates in Table 14 and Table 15 and the completeness distribution of PMTAs to estimate the expected average costs to prepare and review PMTAs for ENDS as a result of rulemaking in Table 16. We find that, on average, the cost to prepare a PMTA bundle increases with rulemaking and that the cost to review a PMTA falls with rulemaking.

Table 16. Average Discounted Cost to Prepare and Review a PMTA Bundle with Rulemaking ($m)

Product Type	Type of PMTA	Cost to Prepare a Bundle		Cost to Review a Bundle	
		7%	3%	7%	3%
E-Liquid	Original	$1.19	$1.21	$0.49	$0.51
	Supplemental	$1.13	$1.15	$0.48	$0.50
E-Cigarette	Original	$0.82	$0.83	$0.50	$0.51
	Supplemental	$0.44	$0.45	$0.46	$0.47

F. Benefits of the Rule

1. Change in Incentives to Submit ENDS PMTAs

Though the average cost to submit[16] a PMTA increases with rulemaking, we find that the final rule will, on average, increase the incentives for most applicants to submit PMTAs. For existing products, firms must choose between submitting a PMTA or discontinuing marketing their product. For future products, firms must choose between submitting a PMTA or not bringing a product to market. The final rule will increase the incentives for most applicants to submit a PMTA. As discussed in the Baseline section, we assume that preparing a follow-on submission takes 2 years on average. That is, products with complete PMTAs get marketing granted orders and begin earning profits 2 years sooner than products with partially complete or incomplete PMTAs. As applications become more complete with rulemaking, the applicants receive marketing granted orders and earn profits earlier. We find that, on average, these increases in profits are higher for applicants than the increases in costs to prepare PMTAs.

However, for some applicants with lower annual revenue per bundle, the increase in the cost to prepare a PMTA from this rule is higher than the increase in profits from receiving marketing orders earlier. For these firms, the rule will decrease the incentives to submit PMTAs. In Table 17, we estimate the percent of bundles with net gains or net losses with rulemaking by the level of the gain or loss.

Table 17. Percent of ENDS Bundles by Net Changes in Profits

Net Change in Profits from Rulemaking	Percent of Bundles

[16] The cost to submit a PMTA with rulemaking in our model includes both the cost to prepare a PMTA and the lifetime costs of postmarket reporting.

	7% Discount Rate	3% Discount Rate
Losses Less than $1 million	33%	46%
Gains Less than $1 million	38%	30%
Gains between $1 and $5 million	14%	12%
Gains between $5 and $10 million	5%	4%
Gains between $10 and $50 million	7%	5%
Gains over $50 million	4%	2%

For a few bundles that applicants chose to submit in the baseline, the final rule will increase the cost to submit a PMTA by enough to make submitting the bundle unprofitable. That is, applicants will not submit these bundles with rulemaking, though they submitted them in the baseline. As a result, our model predicts a decrease in the number of ENDS PMTA bundles submitted with rulemaking. In Table 18, we estimate the number of ENDS bundles submitted with rulemaking.

Table 18. Number of ENDS Bundles Submitted with Rulemaking

Year	E-Liquid Bundles	E-Cigarette Bundles	Total ENDS Bundles
2020	11.3	9.1	20.4
2021	11.3	9.1	20.4
2022	11.3	9.1	20.4
After 2022	6.1	3.2	9.3

In Table 19, we estimate the change in the number of ENDS bundles submitted with rulemaking, given these changes in incentives to submit PMTAs. We obtain these estimates by subtracting the estimates in Table 18 from the estimates in Table 12.

Table 19. Change in the Number of ENDS Bundles Submitted with Rulemaking

Year	E-Liquid Bundles	E-Cigarette Bundles	Total ENDS Bundles
2020	-0.2	-0.1	-0.3
2021	-0.2	-0.1	-0.3
2022	-0.2	-0.1	-0.3
After 2022	-0.1	0.0	-0.1

The reduction in the number of ENDS bundles submitted with rulemaking creates cost savings for applicants and for FDA. The total cost savings from fewer submissions equals the change in the number of ENDS bundles from Table 19 times the sum of the baseline costs to prepare and review PMTAs from Table 16. In Table 20, we estimate the total cost savings from fewer ENDS bundles. We estimate that, over 20 years, the final rule will generate annualized cost savings of $0.29 million at a 7 percent discount rate and $0.28 million at a 3 percent discount rate due to the final rule's impacts on the number of ENDS bundles.

Table 20. Cost Savings from Fewer ENDS Bundles ($m)

	Cost Savings for E-Liquids	Cost Savings for E-Cigarettes	Total Cost Savings
Present Value (7%)	$2.69	$0.55	$3.25
Present Value (3%)	$3.58	$0.70	$4.28

Annualized Value (7%)	$0.24	$0.05	$0.29
Annualized Value (3%)	$0.23	$0.05	$0.28

2. Cost Savings from Review of ENDS PMTAs

In Table 21, we estimate the incremental change in the costs to review a PMTA bundle due to this rulemaking. In the first two columns, we present the baseline estimates from Table 11. In the second two columns, we present the estimates with rulemaking from Table 16. In the third two columns, we estimate the difference between the costs with rulemaking and the costs without rulemaking.

Table 21. Review Cost Savings per Bundle ($m)

Product Type	Type of PMTA	Baseline Cost to Review a Bundle		Cost to Review a Bundle with Rulemaking		Incremental Cost Savings per Bundle due to Rulemaking	
		7%	3%	7%	3%	7%	3%
E-Liquid	Original	$0.64	$0.67	$0.49	$0.51	$0.15	$0.16
	Supplemental	$0.63	$0.65	$0.48	$0.50	$0.14	$0.16
E-Cigarette	Original	$0.65	$0.68	$0.50	$0.51	$0.15	$0.16
	Supplemental	$0.60	$0.62	$0.46	$0.47	$0.14	$0.15

In Table 22, we estimate the average present and annualized value of review costs savings over 20 years, obtained by multiplying the cost savings estimates from Table 21 and the number of bundles submitted from Table 19. We estimate that, over 20 years, the final rule will generate annualized cost savings of $1.76 million at a 7 percent discount rate and $1.80 million at a 3 percent discount rate due to the final rule's impacts on the cost to review PMTAs.

Table 22. Net Impact of the Final Rule on the Costs of Reviewing ENDS PMTAs ($m)

	Cost Savings for E-Liquids	Cost Savings for E-Cigarettes	Total Cost Savings
Present Value (7%)	$12.18	$7.74	$19.92
Present Value (3%)	$17.14	$10.47	$27.61
Annualized Value (7%)	$1.07	$0.68	$1.76
Annualized Value (3%)	$1.12	$0.68	$1.80

3. Summary of Quantified Cost Savings

In Table 23, we estimate the total cost savings of the final rule over 20 years. The average present value total cost savings will equal $23.17 million at a 7 percent discount rate and $31.89 million at a 3 percent discount rate. The average annualized cost savings will equal $2.04 million at a 7 percent discount rate and $2.08 million at a 3 percent discount rate.

Table 23. Total Costs of the Final Rule over 20 Years ($m)

Type of Cost Savings	Present Value (7%)	Present Value (3%)	Annualized Value (7%)	Annualized Value (3%)
Decreased Cost to Review ENDS PMTAs	$19.92	$27.61	$1.76	$1.80
Cost Savings from Fewer ENDS PMTAs	$3.25	$4.28	$0.29	$0.28

Total Cost Savings	$23.17	$31.89	$2.04	$2.08

4. Non-Quantified Benefits of Postmarket Reporting

FDA currently monitors the continued safety of medical products like drugs, biologics, and medical devices through postmarket reporting. Though the premarket review process allows us to evaluate risks identified during clinical development, other safety issues may arise once a product enters the market. Postmarket reporting allows us to assess these new risks as they occur and to determine whether a product remains safe for consumers.

The final rule will require similar reports for tobacco products with marketing orders through the PMTA pathway. As with medical products, postmarket reporting will allow us to continually assess whether products are appropriate for the protection of public health as new information becomes available. For example, we will require a summary of U.S. sales and distribution information, to the extent that the applicant collects or receives such data, in periodic reports. We can use this information, for example, to identify adverse use behavior for a product, like youth initiation.

If postmarket data demonstrates that a product is no longer appropriate for the protection of public health, we must withdraw the marketing order. Consumers may respond by quitting tobacco use or switching to another tobacco product. If the other product is one we have deemed "appropriate for the protection of public health," then the final rule will generate public health benefits. However, given our limited experience with postmarket reporting for tobacco products, we lack data to quantify the magnitude of these public health benefits or the net consumer welfare changes associated with gross health and longevity impacts.

G. Costs of the Rule

1. One Time Costs to Read and Understand the Rule

We expect that all firms in the tobacco manufacturing industry will incur some costs to read and understand the final rule. The final rule has approximately 138,000 words. Consistent with guidelines from the Department of Health and Human Services (see Footnote 3), we assume that regulations reviewers can read an average of 228 words per minute (described in Table 36 in the Appendix).

Some firms will pay lawyers to read the final rule. We expect that 2 lawyers will read the rule at such small firms and 4 lawyers will read the rule at such large firms. However, we expect that most vape shops and specialty tobacco product manufacturers will learn about the rule from industry associations rather than paying a lawyer to read the rule. We lack information to predict the exact number of firms that will incur these costs. To account for uncertainty in the number of firms that will read and understand the rule, we use the total number of affected firms (2,567) as the upper bound number of firms. That is, we assume that all tobacco firms will read the rule in the upper bound. For the lower bound, we subtract the number of firms that only own vape shops from the total number of affected firms (2,567 – 846 = 1,721). That is, we assume that no vape shops or specialty tobacco manufacturers will read the rule in the lower bound.

We estimate that the average one-time costs will equal $7.43 million. We estimate that the annualized costs over 20 years will equal $0.66 million at a 7 percent discount rate and $0.48 million at a 3 percent discount rate.

2. Increased Costs to Prepare ENDS PMTAs

In Table 24, we estimate the incremental change in the costs to prepare a PMTA bundle due to this rulemaking. In the first two columns, we present the baseline estimates from Table 11. In the second two columns, we present the estimates with rulemaking from Table 16. In the third two columns, we estimate the difference between the costs with rulemaking and the costs without rulemaking.

Table 24. Change in Expected Costs to Prepare a Bundle ($m)

Product Type	Type of PMTA	Baseline Cost to Prepare a Bundle		Cost to Prepare a Bundle with Rulemaking		Incremental Costs per Bundle due to Rulemaking	
		7%	3%	7%	3%	7%	3%
E-Liquid	Original	$1.16	$1.19	$1.19	$1.21	$0.03	$0.02
	Supplemental	$1.11	$1.14	$1.13	$1.15	$0.03	$0.02
E-Cigarette	Original	$0.80	$0.82	$0.82	$0.83	$0.02	$0.01
	Supplemental	$0.43	$0.44	$0.44	$0.45	$0.01	$0.01

In Table 25, we estimate the average present and annualized value of the costs to prepare ENDS PMTAs over 20 years, obtained by multiplying the cost estimates from Table 24 and the number of bundles submitted from Table 19. We estimate annualized costs over 20 years of $0.26 million at a 7 percent discount rate and $0.15 million at a 3 percent discount rate due to the increased costs to prepare PMTAs.

Table 35. Net Impact of the Final Rule on the Costs of Preparing ENDS PMTAs ($m)

	Costs for E-Liquids	Costs for E-Cigarettes	Total Costs
Present Value (7%)	$2.22	$0.68	$2.90
Present Value (3%)	$1.81	$0.48	$2.29
Annualized Value (7%)	$0.20	$0.06	$0.26
Annualized Value (3%)	$0.12	$0.03	$0.15

3. Premarket Review Costs for Originally Regulated Tobacco Products

We assume a pre-statutory baseline for originally regulated tobacco products in this analysis. Therefore, we include the full costs of preparing and reviewing PMTAs for such products in our analysis of this rulemaking. However, we expect that PMTAs for originally regulated products will be rare. We assume that we will receive, on average, one bundle every two years.

Originally regulated tobacco products have been on the market for many years. We therefore expect that the burden to prepare an originally regulated PMTA bundle is lower than that of an ENDS bundle. To estimate the cost of preparing and reviewing an originally regulated PMTA bundle, we make the following assumptions:

1. The cost to prepare a bundle falls between the cost to prepare a low average cost e-cigarette bundle and the cost to prepare a low average cost e-liquid bundle.[17]
2. Applicants only submit original PMTAs for originally regulated tobacco products.
3. The cost to review a bundle equals the cost to review a low average cost bundle.

Given these assumptions, we estimate the total costs of the final rule for originally regulated tobacco products over 20 years in Table 26.

Table 46. Total Costs for Originally Regulated Tobacco Products ($m)

	Cost to Prepare PMTAs	Cost to Review PMTAs	Total Cost
Present Value (7%)	$1.44	$1.48	$2.92
Present Value (3%)	$1.98	$1.99	$3.98
Annualized Value (7%)	$0.13	$0.13	$0.26
Annualized Value (3%)	$0.13	$0.13	$0.26

4. Costs of Postmarket Reporting Requirements

To estimate the cost of postmarket reporting under the final rule, we first estimate the number of bundles on the market in each year. We assume that applicants begin marketing the products in each PMTA bundle as soon as they receive a marketing order and that they continue marketing those products until the end of their profitable life. We estimate the total number of bundles with marketing orders through the PMTA pathway in each year in Table 27.

Table 57. Number of Bundles with Active Marketing Orders through the PMTA Pathway over Time

Year	E-Liquid Bundles	E-Cigarette Bundles	Originally Regulated Bundles	Total Bundles
2020	0.0	0.0	0.0	0.0
2021	7.1	5.8	0.3	13.2
2022	15.7	12.7	0.7	29.0
2023	25.5	20.7	1.1	47.3
2024	33.5	26.0	1.6	61.2
2025	40.9	30.7	2.1	73.7
2026	47.2	34.3	2.6	84.2
2027	52.6	36.8	3.1	92.4
2028	57.3	38.7	3.5	99.5
2029	61.6	40.3	3.9	105.8
2030	65.3	41.7	4.3	111.2
2031	68.6	42.7	4.6	115.9
2032	71.5	43.6	4.9	120.0
2033	73.9	44.3	5.2	123.4
2034	75.9	44.8	5.4	126.1
2035	77.5	45.0	5.6	128.2
2036	78.6	45.0	5.8	129.5
2037	79.4	44.9	6.0	130.2

[17] We discuss bundle complexity in more detail in the technical appendix.

2038	79.6	44.4	6.1	130.2
2039	79.5	43.8	6.2	129.5

a. Cost of Periodic Reports

Under the final rule, applicants will submit periodic reports for products with marketing granted orders. In general, while we may require in a specific marketing granted order that an applicant make reports more or less frequently, initially we expect to require these periodic reports annually. For this analysis we assume that applicants will submit these reports annually for the complete duration of the products' life. By making this assumption, we likely overestimate the cost of periodic reporting.

CTP's Office of Science estimates that it will take firms an average of 50 hours to prepare periodic reports for all products in each PMTA bundle. They also estimate that it will take us an average of 289 hours to review all periodic reports within a PMTA bundle. Using the composite wage for preparing submissions and the wage for CTP staff, we estimate that it will cost applicants $4,187 to prepare a periodic report for a single bundle and it will cost us $36,294 to review each bundle. Given the number of marketed bundles in each year from Table 27, we estimate the average costs of periodic reports to applicants and to FDA in Table 28.

Table 68. Total Cost of Periodic Reporting ($m)

	Cost to Applicants	Cost to FDA	Total Cost
Present Value (7%)	$3.66	$31.81	$35.47
Present Value (3%)	$5.51	$47.84	$53.35
Annualized Value (7%)	$0.32	$2.81	$3.13
Annualized Value (3%)	$0.36	$3.12	$3.48

b. Cost of Mandatory Adverse Experience Reporting

Under the final rule, we will require applicants to submit adverse experience reports for serious and unexpected adverse experiences for tobacco products with marketing granted orders through the PMTA pathway. Currently, firms may voluntarily submit adverse experience reports through the Safety Reporting Portal using FDA Form 3800. The Information Collection Request[18] for this form estimates that mandatory reporting takes 1 hour to complete form for tobacco products. Using the composite wage from Table and assuming it will take 1 hour for tobacco products as well, we estimate that submitting an adverse experience report will cost $84.

We use the number of voluntary product problem reports we have received to estimate the number of mandatory adverse experience reports we will receive for each bundle under the final rule. We use the market for smokeless tobacco products to characterize the market for originally regulated tobacco products that use the PMTA pathway. In 2019, we received 582 product problem reports for ENDS and 3 reports for smokeless products. We identified 214 ENDS bundles and 323 smokeless bundles in FDA CTP-licensed Nielsen data (Footnote 9).

[18] Available at https://www.reginfo.gov/public/do/PRAViewICR?ref_nbr=202005-0910-005.

This data suggests that we have received approximately 2.76 product problem reports per ENDS bundle and 0.01 product problem reports per smokeless bundle.

However, voluntary adverse experience databases tend to underreport the total number of adverse experiences. Goldman et al. (1996) found that voluntary drug surveillance systems typically only report an average of 5.5 percent of adverse events.[19] Therefore, we estimate that, had adverse experience reporting been mandatory, we would have received an additional 67.38 reports for each ENDS bundle and an additional 0.23 reports for each smokeless bundle.

Using the estimated number of adverse experience reports per bundle, the cost per adverse experience report, and the number of marketed bundles from Table 27, we estimate the total cost of adverse experience reporting in Table 29.

Table 29. Total Cost of Adverse Experience Reporting ($m)

	ENDS Bundles	Originally Regulated Bundles	Total Cost
Present Value (7%)	$4.87	$0.00	$4.87
Present Value (3%)	$7.31	$0.00	$7.31
Annualized Value (7%)	$0.43	$0.00	$0.43
Annualized Value (3%)	$0.48	$0.00	$0.48

We do not include the cost to review adverse experience reports in the total cost of adverse experience reporting. We will require periodic reports to include summary information on all serious and unexpected adverse experiences. Therefore, we assume that the cost to review a periodic report includes the cost to review all serious and unexpected adverse experience reports from the year of the report.

c. Non-*Quantified Costs to Withdraw a Marketing Order*

As discussed previously, we must withdraw a product's marketing order if postmarket data demonstrates that continued marketing of the product is no longer appropriate for the protection of public health. Withdrawing a marketing order may create administrative costs for both the firm and for FDA and consumers may switch to an alternative tobacco product. However, given our limited experience with postmarket reporting for tobacco products, we lack data to quantify the magnitude of these costs.

5. Costs to Establish Records for Exemptions and Pre-Existing Tobacco Products

The final rule will require that firms maintain records related to Exemption Requests and Pre-Existing Tobacco Products. However, we expect that the cost to maintain records will be negligible once firms have established records. Firms will therefore only incur one-time costs to establish any records.

We expect that the cost of this final rule will be negligible for products with Exemption Requests. Firms will have already established the required records when submitting the

[19] https://www.nvic.org/CMSTemplates/NVIC/pdf/FDA/vaers-medwatch-1996.pdf

Exemption Request and will only incur small costs to maintain these records. Similarly, we expect the cost of this final rule to be negligible for any Pre-Existing Tobacco Products for which firms have already submitted Standalone Pre-Existing Tobacco Product Submissions, because firms will have established the required records when submitting the Standalone Pre-Existing Tobacco Product Submissions.

The final rule will only generate costs to establish records for any Pre-Existing Tobacco Products for which firms have not submitted Standalone Pre-Existing Tobacco Product Submissions. Based on our inspections of manufacturers of finished, originally regulated tobacco products, we estimate that 10 percent of originally regulated products are Pre-Existing Tobacco Products for which the manufacturer did not submit Standalone Pre-Existing Tobacco Product Submissions. Given that there are approximately 5,369 originally regulated products listed with FDA, we estimate that firms will establish records for approximately 537 products under the final rule.

We estimate that it will take administrative staff about 2 hours to collect the required records for such Pre-Existing Tobacco Products. Maintaining records will require minimal efforts once identified. Using the wage for administrative staff from Table 4, the total cost to estimate records will equal $45,916 (2 hours per product × $42.76 per hour × 537 products). We assume that firms will incur these costs by the effective date of the rule, one year after publication of the final rule. We estimate that he annualized value of these costs will equal $4.05 thousand at a 7 percent discount rate and $3.00 thousand at a 3 percent discount rate.

6. Summary of Costs

In Table 30, we estimate the total costs of the final rule over 20 years. The average present value total costs will equal $53.64 million at a 7 percent discount rate and $74.40 million at a 3 percent discount rate. The average annualized costs will equal $4.73 million at a 7 percent discount rate and $4.86 million at a 3 percent discount rate.

Table 70. Total Costs of the Final Rule over 20 Years ($m)

Type of Cost	Present Value (7%)	Present Value (3%)	Annualized Value (7%)	Annualized Value (3%)
Read and Understand the Rule	$7.43	$7.43	$0.66	$0.48
Increased Cost to Prepare ENDS PMTAs	$2.90	$2.29	$0.26	$0.15
PMTAs for Originally Regulated Products	$2.92	$3.98	$0.26	$0.26
Postmarket Reporting	$40.34	$60.66	$3.56	$3.96
Establish Records	$0.05	$0.05	$0.00	$0.00
Total Costs	$53.64	$74.40	$4.73	$4.86

H. Distributional Effects

As discussed in the benefits section, we expect that the final rule will increase incentives for applicants to submit PMTAs for ENDS. In our model, products with complete PMTAs get marketing orders and begin earning profits an average of 2 years sooner[20] than products that

[20] Our model assumes that all complete PMTAs receive orders. However, in practice, the content within a PMTA must also demonstrate that the product is appropriate for the protection of public health to receive a marketing order.

initially submit partially complete or incomplete PMTAs. As applications become more complete with rulemaking, applicants receive marketing orders and earn profits earlier.

In our model, we assume a fixed demand for tobacco products in a given period. Every product on the market captures some share of this demand. Once a product receives a marketing order, the applicant increases their share of the market for tobacco products, increasing the profits generated by that product and decreasing the profits generated by other products on the market. Because the final rule will result in products receiving marketing orders earlier, the final rule will create these between-firm transfers.

I. International Effects

The requirements of the final rule are the same for foreign and domestic firms. We find no evidence that the final rule will disproportionately affect foreign PMTA applicants.

J. Uncertainty and Sensitivity Analysis

1. Monte Carlo Simulation

We have limited experience with PMTAs. Therefore, there is significant uncertainty in our estimates of the effort needed to prepare and review PMTAs. To address this uncertainty, we use a Monte Carlo simulation to estimate the benefits and costs of this final rule. A Monte Carlo simulation is a way to incorporate uncertainty into a benefit-cost analysis.[21] In the primary analysis, we present the mean estimates from our simulation for simplicity. In the technical appendix, we describe the uncertain inputs in our model in more detail. Table 36 includes our assumptions about the distributions of these inputs.

In Table 31, we present the 5th percentile and 95th percentile estimates of the different types of benefits analysis, while in Table 32 we present the 5th percentile and 95th percentile estimates of the different types of costs in this analysis. Together, these estimates represent the 90 percent confidence interval around our estimates in the primary analysis. The estimates in these tables correspond to the low and high estimates in Table 1.

Table 81. 90 Percent Confidence Interval around Estimates of Annualized Benefits of the Final Rule over 20 Years ($m)

Type of Benefit	5th Percentile (7%)	5th Percentile (3%)	95th Percentile (7%)	95th Percentile (3%)
Decreased Cost to Review ENDS PMTAs	$1.26	$1.35	$2.33	$2.31
Cost Savings from Fewer ENDS PMTAs	$1.03	$1.00	$0.00	$0.00
Total Benefits	$1.36	$1.43	$2.85	$2.84

Note that rows do not sum to total benefits in percentile estimates from a simulation.

Table 92. 90 Percent Confidence Interval around Estimates of Annualized Costs of the Final Rule over 20 Years ($m)

[21] Palisade offers a succinct description of Monte Carlo simulations at https://www.palisade.com/risk/monte_carlo_simulation.asp. We run 10,000 iterations of our model, using an initial seed of 1.

Type of Impact	5th Percentile (7%)	5th Percentile (3%)	95th Percentile (7%)	95th Percentile (3%)
Cost to Read and Understand the Rule	$0.49	$0.36	$0.86	$0.64
Increased Cost to Prepare ENDS PMTAs	$0.07	$0.03	$0.51	$0.27
Cost of PMTAs for Originally Regulated Products	$0.19	$0.20	$0.33	$0.33
Cost of Postmarket Reporting	$1.50	$1.62	$6.23	$7.04
Cost to Establish Records	$0.00	$0.00	$0.00	$0.00
Total Costs	$2.63	$2.50	$7.45	$7.95

Note that rows do not sum to total costs in percentile estimates from a simulation.

The annualized net benefits of the final rule range from -$5.24 million to -$0.62 million at a 7 percent discount rate and from -$5.69 million to -$0.50 million at a 3 percent discount rate. Because the sum of percentiles of random variables do not equal the percentile of sums of random variables, the low and high estimates net benefits do not equal the difference between the estimates of total benefits and total costs from these tables.

2. Alternative Baseline Analysis

In the primary analysis of the final rule, we use a pre-statutory baseline for originally regulated products. Here, however, we use a post-statutory baseline for originally regulated products. That is, we use a baseline where originally regulated products are subject to premarket review through the PMTA pathway. In this alternative baseline, applicants incur costs to prepare originally regulated PMTAs and FDA incurs costs to review these PMTAs. The benefits and costs of this final rule are then the incremental impact of rulemaking on the total cost to prepare and review originally regulated PMTAs.

In Table 33, we estimate the net impacts of the final rule under this alternative baseline. We estimate that annualized cost savings would equal $1.85 million at a 7 percent discount rate and $1.95 at a 3 percent discount rate and that annualized costs would equal $4.64 at a 7 percent discount rate and $4.75 at a 3 percent discount rate. The annualized net benefits would equal -$2.63 million at a 7 percent discount rate and -$2.71 million at a 3 percent discount rate. The negative net benefits result from monetized costs of post-marketing reporting requirements, the benefits of which we do not quantify.

Table 103. Estimates of Impacts with a Post-Statutory Baseline for Originally Regulated Products over 20 Years ($m)

Type of Impact	Present Value (7%)	Present Value (3%)	Annualized Value (7%)	Annualized Value (3%)
Total Benefits	$23.82	$32.83	$2.10	$2.14
Total Costs	$53.62	$74.37	$4.73	$4.85
Total Net Benefits	($29.80)	($41.55)	($2.63)	($2.71)

K. Analysis of Regulatory Alternatives to the Final Rule

As an alternative to this final rule, we could publish the format and content requirements for PMTAs without including requirements for postmarket reporting, including periodic reporting and mandatory adverse experience reporting. In the cost section, we estimate that the annualized total costs of postmarket reporting over 20 years are $3.56 million at a 7 percent discount rate and $3.96 million at a 3 percent discount rate.[22] Eliminating the requirement for postmarket reporting would reduce the total cost to submit a PMTA bundle, eliminating the direct costs of postmarket reporting and increasing incentives for applicants to submit PMTAs for ENDS.

Although we lack information to quantify the benefits of postmarket reporting, we expect that periodic reports and mandatory adverse experience reports will provide us with important information about unexpected adverse health outcomes from marketed tobacco products. Removing postmarket reporting requirements would eliminate any potential public health benefits of postmarket reporting .

In Table 34, we estimate the impacts of the final rule in this regulatory alternative. We estimate that the annualized total benefits in this alternative over 20 years would equal $1.79 million at a 7 percent discount rate and $1.83 million at a 3 percent discount rate. The annualized costs would equal $1.19 million at a 7 percent discount rate and $0.91 million at a 3 percent discount rate.

Table 114. Estimates of Impacts in a Regulatory Alternative without Postmarket Reporting ($m)

Type of Impact	Present Value (7%)	Present Value (3%)	Annualized Value (7%)	Annualized Value (3%)
Total Benefits	$20.26	$28.07	$1.79	$1.83
Total Costs	$13.47	$13.91	$1.19	$0.91
Total Net Benefits	$6.79	$14.16	$0.60	$0.92

III. Final 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 we expect that the final rule will generate net benefits or negligible net costs for most affected small entities, we certify that the final rule will not 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 Final Regulatory Flexibility Analysis, as required under the Regulatory Flexibility Act.

A. Response to Comments by the Small Business Administration's Office of Advocacy

The Office of Advocacy submitted a comment to the docket stating that we failed to provide "an adequate factual basis to certify that the proposed rule will not have a significant economic impact on a substantial number of small entities." They argue that this rulemaking should include the full costs for industry to comply with the PMTA requirements as described in the FD&C Act. We address this argument in our response to Comment 1 on page 13.

[22] We base these estimates on an assumption that marketing products with marketing orders is profitable for between 5 and 20 years. If applicants market these products for longer than 20 years, then these costs would be higher.

The Office of Advocacy also requests that we prepare a full Initial Regulatory Flexibility Analysis, including an analysis of alternatives. Because we certify that this final rule will not have a significant economic impact on a substantial number of small entities, this rulemaking does not require a full Initial Regulatory Flexibility Analysis.

B. Description and Number of Affected Small Entities

The Small Business Administration (SBA) considers tobacco manufacturing entities with fewer than 1,500 employees as small. Data from the U.S. Census Bureau shows that SBA would consider at least 93 percent of tobacco manufacturers as small entities (Table 35). Data from Dun and Bradstreet matched to TRLM data suggests that SBA would consider an average of 88 percent of tobacco manufacturers as small entities.

Table 125. Percent of Firms and Average Annual Revenues per Firm by Employment Size, based on Census Data

Employment Size	Percent of Firms	Average Annual Revenues per Firm ($m)
0 to 19 Employees	60%	$3.09
20 to 99 Employees	24%	$26.78
100 to 499 Employees	10%	$120.69
Over 500 Employees	7%	$5,250.34
All Small[a]	93%	$3.09

[a] Census data does not include revenue information for small firms with between 500 and 1,500 employees.

Most of the impacts of this final rule will only impact those firms that remain on the market following the submission of applications for existing products. The Deeming Rule will cause many existing firms to exit the market, creating significant market consolidation. Some small firms may exit the market or merge with other firms to afford the compliance costs associated with the Deeming Rule. Other small firms may expand production and increase their market share as their competition exits the market. As stated in the Deeming Analysis, we expect the Deeming Rule to have a significant impact on a substantial number of small entities. However, those impacts are attributable to the Deeming Rule and not this final rule.

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

1. Impacts on Non-Applicants

Small tobacco manufacturers that do not submit PMTAs will only incur one-time costs to read and understand the rule of $3,107, with annualized costs of $274 at a 7 percent discount rate and $203 at a 3 percent discount rate. We base these estimates on an assumption that two lawyers will read and understand the rule at all small firms. However, we expect that most vape stores and specialty tobacco product manufacturers will learn about the rule from industry associations, rather than paying a lawyer to read the rule. Therefore, we likely overestimate the cost to read and understand the rule for many small tobacco manufacturers.

Some small manufacturers of Pre-Existing Tobacco Products without Standalone Pre-Existing Tobacco Product Determinations will incur one-time costs to estimate records of $86 per product. We do not know how many Pre-Existing Tobacco Products without Standalone

Pre-Existing Tobacco Product Determinations are from small entity manufacturers. However, if we assume that such small manufacturers would each establish records for 10 products on average, then the one-time costs per small entity to establish records will equal $855, with annualized costs of $75 at a 7 percent discount rate and $56 at a 3 percent discount rate.

2. Impacts on ENDS PMTA Applicants

We expect that most applicants that submit ENDS PMTA bundles will *benefit* from the final rule. As illustrated in Table 17, we estimate that applicants' profits will increase for 67 percent of submitted bundles at a 7 percent discount rate and 54 percent of submitted bundles at a 3 percent discount rate. Applicants' profits will decrease for the remaining submitted bundles. We estimate that the average annualized losses for these applicants will be $4,180 per bundle at a 7 percent discount rate and $5,150 per bundle at a 3 percent discount rate. These losses represent approximately 0.16 percent of annual revenue for the smallest tobacco manufacturers.

While these losses do not represent a significant cost on a substantial number of small entities, the magnitude of losses from the final rule depend on the assumptions in our model. For example, some comments to the proposed rule suggest that we underestimate the baseline cost to prepare a PMTA by using estimates from the Deeming Analysis. While we believe that the estimates from the Deeming Analysis continue to reflect the best available estimates of the baseline cost to prepare a complete PMTA, there is inherent uncertainty in these estimates because of the limited experience both we and industry have with PMTAs.

If we underestimate the baseline cost to prepare a PMTA by 50 percent, then we estimate that applicants' profits would increase from rulemaking for 71 percent of submitted bundles at a 7 percent discount rate and 59 percent at a 3 percent discount rate. For the minority of applicants that would experience losses, we estimate that applicants would experience average annualized losses for the remaining bundles of $0.06 million per bundle at a 7 percent discount rate and $0.05 million per bundle at a 3 percent discount rate, representing approximate 1.5 percent of annual revenue for the smallest tobacco manufacturers.

We note, however, that the final rule will only impact those manufacturers that remain on the market following the implementation of Deeming rule. The Deeming analysis predicts significant consolidation in the ENDS market, which will increase the size of the firms that remain on the market. We expect that most of the firms that will incur costs from this final rule will not be small entities.

3. Impacts on Originally Regulated Tobacco Product PMTA Applicants

Finally, manufacturers of some new originally regulated products will incur costs to prepare PMTAs and the costs of postmarket reporting. We estimate that, between lost profits from getting on the market later and the cost to prepare PMTAs, the total annualized losses per bundle will equal at least $0.03 million at a 7 percent discount rate and $0.02 million at a 3 percent discount rate.[23] For the smallest entities from Table 35, these costs represent 0.9 percent of annual revenue at a 7 percent discount rate and 0.7 percent of annual revenue a 3 percent

[23] We calculate the minimum loss per originally regulated bundle by assuming a bundle's annual revenue equals the annual revenue required for the applicant to be indifferent between submitting and not submitting a bundle. See the technical appendix for more details.

discount rate. While these costs are close to significant for the smallest tobacco manufacturers, we expect that such submissions will be rare. We estimate that we will receive, on average, 1 bundle every 2 years. The final rule will then impact at most 10 small entities manufacturing new originally regulated products over 20 years. While the cost may be significant for such small entities, we do not anticipate that it will affect a substantial number of small entities.

D. Alternatives to Minimize the Burden on Small Entities

In the alternatives section in the Final Regulatory Impact Analysis, we analyze the impacts issuing the final rule without postmarket reporting requirements. Eliminating the requirement for postmarket reporting would reduce the total cost to submit a PMTA bundle, eliminating the direct costs of postmarket reporting and increasing incentives for applicants to submit PMTAs for ENDS. Therefore, this alternative would reduce the burden of the final rule on small entities.

E. Conclusion

To summarize, most small entities will either benefit from the final rule or will incur small annualized costs of approximately $2,000. Some small tobacco manufacturers of bundles with low annual revenue will incur annualized losses that represent an average of 0.15 percent of annual revenue. We therefore certify that the final rule will not have a significant economic impact on a substantial number of small entities.

IV. Technical Appendix

A. Monte Carlo Simulation

As described in the Uncertainty and Sensitivity Analysis, we use a Monte Carlo simulation to address uncertainty in our analysis. In Table 36 below, we describe the assumed distributions for all the random variables used in our analysis.

Table 136. Assumptions about Random Variables in this Analysis and their Distributions

Random Variable	Distribution	Comments
Originally Regulated PMTA Cost Distance Variable	Uniform random variable with a low estimate of 0 and a high estimate of 1.	This variable represents where the cost of an originally regulated PMTA falls between the cost of an e-cigarette PMTA and the cost of an e-liquid PMTA.
Probability a Bundle is Accepted, with Rulemaking	Uniform random variable with a low estimate of 42 percent and a high estimate of 88 percent.	The low estimate is the baseline probability that we accept a PMTA bundle. The high estimate is the probability that we accept a PMA for a medical device.
Probability a Bundle is Filed Conditional on Being Accepted, with Rulemaking	Uniform random variable with a low estimate of 60 percent and a high estimate of 95 percent.	The low estimate is the baseline probability that we file a PMTA bundle that has been accepted. The high estimate is the probability that we file a PMA that has been accepted.
Definition of a Bundle	Uniform random integer with a low estimate of 0 and a high estimate of 1.	If this variable equals 0, then we use the Nielsen variable "Brand Low" to define a bundle. If this variable equals 1, then we use the variable "Brand High" to define a bundle (Footnote 9).
Weighted Average Cost of Capital for the Tobacco Industry	Triangle distributed random variable with a low estimate of 7.0 percent, a mean estimate of 8.8 percent, and a high estimate of 9.5 percent.	Low and high estimates from Finbox.[24] Mean estimate from Damadoran (2020).[25]
Length of Profitable Life for a Product with a Marketing Order	Uniform random integer with a low estimate of 5 years and a high estimate of 20 years.	
Increase in the Administrative Cost to Prepare a PMTA Bundle from the Final Rule	Uniform random variable with a low estimate of 0 percent and a high estimate of 100 percent.	
Time Between Initial Submission and Follow-On Submission	Uniform random integer with a low value of 1 year and a high value of 3 years.	

[24] https://finbox.com/NYSE:PM/explorer/wacc, retrieved February 20, 2020.
[25] http://people.stern.nyu.edu/adamodar/New_Home_Page/datafile/wacc.htm.

Random Variable	Distribution	Comments
Cost to FDA to Prepare a Deficiency Letter	Uniform random variable with a low estimate of 71 hours and a high estimate of 266 hours.	Estimate from CTP's Office of Science.
Cost to FDA to Process Unnecessary Data	Uniform random variable with a low estimate of 40 hours and a high estimate of 80 hours.	Based on discussions with CTP's Office of Science, we assume that processing unnecessary data takes between five and ten business days.
Number of Firms Reading the Final Rule	Uniform random variable with a low estimate of 1,721 firms and a high estimate of 2,567 firms.	The high estimate is the total number of firms registered with FDA. The low estimate is the total number of firms registered with FDA, excluding any firms that only own vape shops.
Percent of Firms that are Small Businesses	Uniform random variable with a low estimate of 86 percent and a high estimate of 90 percent.	The low and high estimates are based on the employment estimates and the small business indicator from Dun and Bradstreet for FDA-registered firms.
Reading Speed of English Speakers	Normal random variable with a mean of 228 words per minute and a standard deviation of 30 words per minute.	From Trauzettel-Klosinski, Dietz, and the IReST Study Group (2012).[26]
Cost to Prepare a Periodic Report	Uniform random variable with a low estimate of 20 hours and a high estimate of 80 hours.	Based on estimates of the administrative cost to prepare a PMTA for a single product from the Deeming Analysis.
Cost for FDA to Review a Periodic	Uniform random variable with a low estimate 96 hours and a high estimate of 480 hours.	Estimates from CTP's Office of Science.
Reported Adverse Experiences as a Percent of All Adverse Experiences	Uniform random variable with a low estimate of 1 percent and a high estimate of 10 percent.	Estimate from MedWatch (1996).[27]
Number of Originally Regulated Bundles Submitted in Year t	Uniform random variables between 0 and 1 for each year t.	
E-Liquids Seeking Marketing Granted Order Annually in the Expected Period for Future Product Submissions	Triangle distributed random variable with a low estimate of 56 products, a mean estimate of 127 products, and a high estimate of 225 products.	Estimates from the Deeming Analysis.
E-Cigarettes Seeking Marketing Granted Order Annually in the Expected Period for Future Product Submissions	Triangle distributed random variable with a low estimate of 17 products, a mean estimate of 28 products, and a high estimate of 42 products.	Estimates from the Deeming Analysis.

[26] https://www.ncbi.nlm.nih.gov/pubmed/22661485
[27] https://www.nvic.org/CMSTemplates/NVIC/pdf/FDA/vaers-medwatch-1996.pdf

B. Deriving the Cost to Prepare a PMTA Bundle

1. ENDS Bundles

To estimate the cost to prepare a PMTA bundle for ENDS products, we use estimates from the Deeming Analysis. The Deeming Analysis assumes that the cost to prepare a PMTA bundle includes:

- Administrative costs
- Costs of composition, design, and manufacturing studies
- Costs of human studies
- Cost of toxicological studies
- Costs of environmental assessments

The Deeming Analysis assumes that these costs depend on whether the applicant needs to conduct new studies for their application. We call bundles for which applicants do not need to conduct new studies "low average cost" bundles and we call bundles which applicants need to conduct new studies "high average cost" bundles. As in the Deeming Analysis, we expect to receive more bundles with high average costs during the Expected Period for Existing Product Submissions (called "initial" PMTAs in the Deeming Analysis) than during the Expected Period for Future Product Submissions (called "subsequent" PMTAs in the Deeming Analysis). In Table 37, we estimate the expected proportion of ENDS bundles with low, medium, and high average costs by product type and time period.

Table 147. Proportion of ENDS Bundles with Low, Medium, and High Average Costs

Product Type	Time Period	Bundles with Low Average Costs	Bundles with Medium Average Costs	Bundles with High Average Costs
E-Liquids	Initial	25%	65%	10%
	Subsequent	20%	75%	5%
E-Cigarettes	Initial	30%	55%	15%
	Subsequent	30%	65%	5%

The Deeming Analysis also assumes that in the Expected Period for Future Product Submissions, applicants can rely more on materials compiled for initial submissions, reducing the cost per bundle. In the context of this final rule, we interpret this reduction in the cost per bundle in the Expected Period for Future Product Submissions as an increased reliance on supplemental PMTAs, as described in the final rule. Therefore, we assume that all bundles submitted in the Expected Period for Existing Product Submissions are original bundles and that all bundles submitted in the Expected Period for Future Product Submissions are supplemental bundles. That is, we assume that the costs of "initial" bundles in the Deeming Analysis represent the costs of original bundles and that the costs of "subsequent" bundles in the Deeming Analysis represent the costs of supplemental bundles.

For the purposes of this analysis, we divide the costs to prepare a PMTA bundle into administrative and studies costs. In Table 38, we update the estimates of the administrative cost

per bundle from the Deeming Analysis using new market data on the average number of products per bundle and 2019 wage estimates. As explained in Table 36, we expect these costs to increase by between 0 and 100 percent as a result of this final rule.

Table 158. Updated Deeming Estimates of the Administrative Cost to Prepare a PMTA Bundle ($)

Product Type	PMTA Type	Bundles with Low Average Costs[a]	Bundles with Medium Average Costs[b]	Bundles with High Average Costs[c]	Average Administrative Cost per Bundle[d]
E-Liquids	Original	$7,660	$19,151	$30,642	$17,428
	Supplemental	$7,660	$19,151	$30,642	$17,428
E-Cigarettes	Original	$2,715	$6,788	$10,862	$6,177
	Supplemental	$2,715	$6,788	$10,862	$5,770

[a] Assumes 20 hours of administrative staff time per PMTA in the bundle.
[b] Assumes 50 hours of administrative staff time per PMTA in the bundle.
[c] Assumes 80 hours of administrative staff time per PMTA in the bundle.
[d] Weighted averages based on the proportions from Table 37.

In Table 39, we update the cost of studies from the Deeming Analysis by using new estimates of the average number of products per bundle, using 2019 wage estimates, and inflating cost estimates to 2019 dollars. The cost of studies includes the costs of composition, design, and manufacturing studies, the costs of human studies, the costs of toxicological studies, and the costs of environmental assessments. We do not expect the final rule to change these costs.

Table 39. Updated Deeming Estimates of the Cost of Studies for a PMTA Bundle ($)

Product Type	PMTA Type	Bundles with Low Average Costs[a,b,c]	Bundles with Medium Average Costs[a,c]	Bundles with High Average Costs[a,c]	Average Studies Cost per Bundle[d]
E-Liquids	Original	$344,118	$1,341,611	$2,326,033	$1,190,680
	Supplemental	$160,111	$1,312,342	$2,301,642	$1,131,361
E-Cigarettes	Original	$357,838	$523,598	$2,895,868	$829,710
	Supplemental	$56,754	$433,351	$2,866,598	$442,034

[a] Assumes environmental assessments requires 213 hours of technical labor per PMTA in the bundle, valued using the composite wage.
[b] Assumes toxicological studies require 100 hours of technical labor per bundle, valued using the composite wage.
[c] All other cost inputs inflated to 2019 dollars using the 2014 inflation factor from Table 5.
[d] Weighted averages based on the proportions from Table 37.

The Deeming Analysis did not account for incomplete or partially complete submissions, and instead implicitly assumed that all initial submissions are complete. We expect applicants to incur administrative costs every time they submit a PMTA. That is, applicants incur the full administrative costs from Table 38 at both initial and follow-on submission. We also expect applicants to distribute the costs of studies between initial and follow-on submissions for

incomplete and partially complete bundles. Applicants incur part of the costs from Table 39 at initial submission and the rest of the costs at follow-on submission. In Table 40, we summarize our assumptions about the incidence of administrative and studies costs for incomplete, partially complete, and complete bundles.

Table 160. Incidence of Preparation Costs for Initial and Follow-On Submissions, by Bundle Completeness

Completeness	Administrative Costs		Studies Costs	
	Initial Submission	Follow-On Submission	Initial Submission	Follow-On Submission
Complete	100%	0%	100%	0%
Partially Complete	100%	100%	67%	33%
Incomplete	100%	100%	33%	67%

When an applicant initially submits a PMTA, the total preparation cost equals the sum of the costs at initial submission and follow-on submission, discounted relative to the time of submission. That is, if C_0 is the cost at initial submission and C_1 is the cost at follow-on submission, then the total cost to prepare PMTA bundle C is given by:

$$C = C_0 + \frac{C_1}{(1+\delta)^t},$$

where δ is the discount rate and t is the time to follow-on submission (a random variable described in Table 36). In Table 7 and Table 13, we use this formula to estimate the discounted cost to prepare a PMTA bundle at the mean in the baseline and with rulemaking by bundle completeness. We then calculate the average discounted cost to prepare a PMTA bundle, weighted by the completeness of PMTAs in Table 11 and Table 16.

2. Originally Regulated Bundles

We assume that the cost to prepare an originally regulated bundle falls between the cost to prepare an original e-cigarette bundle with low average costs and the cost to prepare an original e-liquid bundle with low average costs. We create a random variable $\Delta \in [0,1]$ to represent the distance between the cost of an originally regulated bundle and the costs of original, low average cost, e-liquid and e-cigarette bundles. Using this distance variable allows us to assume perfect correlation between each input that determines the cost of an originally regulated bundle.

To illustrate how we use Δ to estimate each cost element,[28] consider the costs of human studies. Suppose human studies for original e-liquid bundles with low average costs cost H_{EL} while human studies for original e-cigarette bundles with low average costs cost H_{EC}. Then, the cost of human studies for originally regulated bundles, H_{OR}, is given by:

$$H_{OR} = H_{EC} + \Delta \cdot (H_{EL} - H_{EC}).$$

[28] As described in the footnotes to Table 38 and Table 39, the administrative and environmental assessment costs per bundle depend on the number of PMTAs in the bundle. For these costs, we assume that each originally regulated bundle includes only 1 PMTA rather than estimating the cost using Δ.

Based on this equation, if Δ equals 1, then H_{OR} equals H_{EL}. If Δ equals 0, then H_{OR} equals H_{EC}. If $\Delta = 0.5$, then H_{OR} is the average of H_{EC} and H_{EL}.

C. Deriving the Cost to Review a PMTA Bundle

1. ENDS Bundles

CTP's Office of Science provided estimates of the number of labor hours spent on each stage of review for a bundle (Table 41). Like the cost to prepare PMTAs, we expect that the cost of each stage of review depends on the complexity of the application. Products that require more original research likely cost more to review. Therefore, we characterize the cost of each review stage according to low, medium, and high average cost.

Table 171. Cost to Review a Bundle in Hours, by Stage of Review

Stage of Review	Baseline			Rulemaking		
	Bundles with Low Average Cost	Bundles with Medium Average Cost	Bundles with High Average Cost	Bundles with Low Average Cost	Bundles with Medium Average Cost	Bundles with High Average Cost
Acceptance	2	4	6	3	5	8
Filing	52	104	208	26	52	104
Substantive	2,400	4,800	9,000	1,800	3,900	7,200

The estimates in Table 8 and Table 14 are the average cost of each stage of review for a bundle, weighted by the proportion of bundles with low, medium, and high average cost from Table 37 and valued with the fully loaded wage for CTP Staff from Table 4. Because e-liquid and e-cigarette bundles differ in terms of the proportion with low, medium, and high average costs, the average costs per stage of review for e-liquid and e-cigarette bundles differ slightly. Average costs per stage of review differ for original and supplemental bundles for the same reason.

We assume that the cost to FDA to prepare a deficiency letter follows a uniform distribution with a low estimate of 71 hours and a high estimate of 266 hours. CTP's Office of Science does not expect the cost to prepare a deficiency letter to change as a result of this rulemaking. However, we do expect the average number of letters issued per bundle to fall. We assume that we will issue 4 letters per bundle of PMTAs in the baseline and 2 letters per bundle of PMTAs with rulemaking.

CTP's Office of Science estimates that processing unnecessary data takes between 5 and 10 business days. To convert this to an hourly cost estimate, we assume that a single staff member works full time on data processing for a given bundle, implying a cost of 40 to 80 hours per bundle.

Given the incidence of review costs for initial and follow-on reviews from Table 9, we then calculate the total cost of initial review and follow-on review for incomplete, partially complete, and complete bundles. Like with the cost to prepare PMTA bundles, we estimate the

total review cost (R) for a bundle of a given completeness by discounting the initial review (R_0) and follow-on review (R_1) costs back to the time of submission:

$$R = R_0 + \frac{R_1}{(1+\delta)^t},$$

where δ is the discount rate and t is the time to follow-on submission. Note that we assume that initial preparation and review costs occur at the time of initial submission and that follow-on preparation and review costs occur at the time of follow-on submission.

In Table 10 and Table 15, we use the above formula to estimate the discounted cost to review a PMTA bundle at the mean in the baseline and with rulemaking by bundle completeness. We then calculate the average discounted cost to prepare a PMTA bundle, weighted by the completeness of PMTAs in Table 11 and Table 16.

2. Originally Regulated Bundles

Because of the wide existing literature for originally regulated tobacco products, we assume that all originally regulated bundles are low average cost. Therefore, we use the low average cost bundle cost estimates from Table 41 to estimate the cost per stage of review for originally regulated bundles.

D. Number of PMTA Bundles

1. Data Definition of a PMTA Bundle

We define a PMTA bundle using Nielsen RMS data from January 2019 to December 2019 from the xAOC and Convenience channels, where xAOC stands for "expanded all outlets combined" (see Footnote 9). This data includes product characteristics and annual sales at the UPC-level in a national sample of retail establishments that includes:

- Food, drug, dollar, and club stores;
- Mass merchandisers;
- Military commissaries; and
- Convenience stores.

We define the set of all potential ENDS PMTAs during the submission of applications for existing Product as the set of ENDS products contained in the Nielsen RMS data. By using Nielsen RMS data, we inherently assume that applicants will not submit bundles for any tobacco products that do not appear in Nielsen data. Practically, this assumption means that we do not include any tobacco products that are exclusively sold online or in vape shops. We expect that such products have low market share in the ENDS market and that the firms manufacturing these products are not likely to have the resources necessary to prepare a PMTA bundle.

To convert UPC-level Nielsen RMS data to "bundle"-level data, we first restrict our sample to the Nielsen product category "electronic vapor products." We then classify each UPC in this category as an "e-cigarette" or an "e-liquid" based on the product type listed in Nielsen RMS data. Specifically, we define an "e-cigarette" to include disposable electronic cigarettes, cigars, hookahs, and pipes, as well as electronic cigarette batteries and kits. We define an "e-

liquid" to include liquid refills for electronic cigarettes and non-liquid refills (typically cartridges containing e-liquids) for electronic cigarettes.

Then, we collapse the data to the bundle-level, combining all UPCs with the same values of certain variables into a single observation. We use two different sets of variables to define a PMTA bundle, creating two separate sets of collapsed data. For the first bundle definition, we define a bundle in our data as a unique combination of three variables:

- Major brand, which is the major brand name listed on a product's label;
- Brand extension, which we find often identifies a specific model of a product marketed by the major brand; and
- Product type (i.e. e-liquid vs. e-cigarette).

The resulting dataset combines 1,114 UPC-level observations into 239 bundle-level observations. For the second bundle definition, we define a bundle as a unique combination of two variables:

- Major brand; and
- Product type.

The resulting dataset combines 1,114 UPC-level observations into 193 bundle-level observations.

As we combine UPCs into bundles, we sum the UPC-level sales data to estimate the expected annual revenue for all products in a bundle in distribution channels covered by Nielsen RMS data. That is, for a given bundle i, the expected annual revenue (R_i) in Nielsen distribution channels is given by:

$$R_i = \sum_{j \in B_i} r_j,$$

where j indexes the UPC, B_i is the set of all UPCs in bundle i, and r_j is the sales of UPC j.

In our Monte Carlo simulation, we randomly choose the bundle data definition. With a 50 percent probability, we define a bundle as a unique combination of the major brand, brand extension, and product type variables. The rest of the time, we define a bundle as a unique combination of the major brand and product type variables only. These two data definitions represent different degrees of market consolidation.

This data represents the set of e-liquid and e-cigarette PMTA bundles that applicants may submit during the submission of applications for existing products. To determine which bundles applicants are likely to submit, we compare the expected lifetime profits from submission, estimated using the bundle-level sales in 2019 from Nielsen RMS data, to the expected lifetime cost of submission. We assume that applicants only submit a bundle if the expected lifetime profits from submission are greater than the expected lifetime cost of submission.

2. Expected Lifetime Benefits from Submission

a. Expected Annual Profits per Bundle

The expected annual revenue (R_i) for a bundle i estimated using Nielsen data includes only revenue in Nielsen-covered channels. Using data from Euromonitor International, we estimate that the revenue for ENDS in Nielsen-covered channels represents approximately 54 percent of total ENDS revenue in the United States. We then assume that R_i also represents 54 percent of expected annual revenue for bundle i and adjust the revenue estimate upwards for each bundle.

Some of the remaining 46 percent of revenue likely comes from sales of bundles found in the Nielsen data from different distribution channels, like e-commerce or vape shops. However, this revenue also comes from bundles sold exclusively in distribution channels not covered by the Nielsen data. As discussed in the previous section, we assume that all bundles sold exclusively in non-Nielsen distribution channels will exit the market in response to the Deeming Rule. By adjusting the expected revenue for bundles in our sample upwards, we further assume that bundles found in the Nielsen data will absorb all revenue from these exiting bundles in proportion with their market share in the Nielsen sample.

Applicants make their submission decision based on annual profits, not annual revenue. To convert expected annual revenue to expected annual profits, we define the profit margins in the ENDS market (m) as a uniform random variable with a low estimate of 40 percent[29] and a high estimate of 70 percent.[30] The expected annual profits (π_i) for bundle i is then given by:

$$\pi_i = \frac{100}{54} \cdot m \cdot R_i$$

We assume that real annual profits are constant over time for each bundle. In making this assumption, we do not account for future trends in the ENDS market. Given the pending changes to the regulatory landscape for ENDS, we cannot predict how sales of individual bundles will change in the future.

b. Present Value Profits

We assume that the average life of a tobacco product with a marketing order is a uniform random integer between 5 and 20 years. Note that this assumption does not mean that we expect products with marketing orders will completely exit the market after the end of their profitable life. Instead, applicants will likely make modifications to these tobacco products to increase profitability. Under the TCA, modifications to tobacco products represent new tobacco products, and new tobacco products must follow the PMTA, SE, or Exemption pathways to obtain marketing authorization. That is, at the end of a bundle's profitable life, the applicant must again compare the expected profits from submission to the expected costs of submission to decide whether to modify their tobacco product.

The present value profits of a bundle over its life depend on the completeness of the bundle. In our model, complete bundles will receive marketing orders in the year after they are initially submitted, while partially complete or incomplete bundles won't receive marketing

[29] Based on profit margins for ENDS manufacturers in the European Union, available at https://www.retaildata.co.uk/news-updates/e-cigarettes-high-margins-high-potential/.
[30] Based on profits margins for JUUL, a leading manufacturing of ENDS products, available at https://www.axios.com/numbers-juul-investor-appeal-vaping-22c0a2f9-beb1-4a48-acee-5da64e3e2f82.html.

orders until the year after follow-on submission. We illustrate how completeness impacts the stream of profits for a bundle in Table 42 below, using an example where the average profitable life for a bundle is 5 years and the time to follow-on submission is 2 years.

Table 182. Example Stream of Profits to Submitted Bundles, by Completeness

Time	Profits for Complete Bundle[a]	Profits for Partially Complete or Incomplete Bundle[a]
0 *Year of Initial Submission*	0	0
1	π_i	0
2 *Year of Follow-On Submission*	π_i	0
3	π_i	π_i
4	π_i	π_i
5	π_i	π_i
6	0	π_i
7	0	π_i
8	0	0

[a] Where π_i is the annual profits of bundle i.

Following OMB Circular A-4 guidelines, we use discount rates of 3 and 7 percent to represent the social discount rate in our benefit cost analysis. However, firms in the tobacco industry likely make investment decisions based on the cost of capital. As described in Table 36, we assume that the cost of capital in the tobacco industry is a random variable with a mean around 8.5 percent. Given this assumption, we estimate the present value profits for complete, partially complete, and incomplete bundles for each individual bundle over its profitable life.

c. Expected Present Value Profits from Submission

Knowingly submitting a partially complete or incomplete bundle is not profit-maximizing behavior in our model for most firms. Thus, we assume that the completeness of a PMTA bundle is unknown to the applicant. This assumption is consistent with our experience with PMTA applicants to date, who frequently request more guidance on the format and content requirements for PMTAs. In addition, the net profits that an applicant can earn for a complete bundle are, in general, higher than the net profits that an applicant can earn for a partially complete or incomplete bundle.

Based on this assumption, applicants make submission decisions based on the expected present value profits from submission. Let $\Pi_i(x)$ represent the net present value profits for a bundle i with a completeness x, where x_0 denotes an incomplete bundle, x_1 denotes a partially complete bundle, and x_2 denotes a complete bundle. Then, if p_0, p_1, and p_2 denote the probability that a bundle is incomplete, partially complete, and complete, the expected present value profits from submission are given by:

$$E[\Pi_i] = p_0 \cdot \Pi_i(x_0) + p_1 \cdot \Pi_i(x_1) + p_2 \cdot \Pi_i(x_2).$$

3. Expected Lifetime Costs from Submission

In Table 11 and Table 16, we estimated the expected cost to prepare a PMTA bundle with and without rulemaking at a 7 percent discount rate and at a 3 percent discount rate. In Table 43, we use the same method to estimate the mean estimated cost to prepare a PMTA bundle with and without rulemaking, discounted accounting to the tobacco industry's cost of capital.

Table 193. Expected Cost to Prepare a PMTA Bundle with and without Rulemaking, Discounted Using the Cost of Capital ($m)

Product Type	Type of PMTA	Cost to Prepare a Bundle in the Baseline	Cost to Prepare a Bundle with Rulemaking
E-Liquid	Original	$1.15	$1.18
	Supplemental	$1.10	$1.13
E-Cigarette	Original	$0.80	$0.81
	Supplemental	$0.43	$0.44

Because firms will not submit postmarket reports in the baseline, the only costs of submitting a PMTA in the baseline are the expected costs of preparing a PMTA bundle from Table 7. However, applicants submitting bundles with rulemaking will also incur postmarket reporting costs once they receive marketing orders. We estimate the total lifetime cost of postmarket reporting for a bundle in the same way we estimated the total lifetime profits to a bundle.

The total lifetime cost of postmarket reporting depends on the completeness of the bundle. Let c_i represent the annual cost of postmarket reporting for bundle i. We illustrate the completeness impacts the stream of postmarket reporting costs for a bundle in Table 44 below, using the same example as in Table 42.

Table 204. Example Stream of Postmarket Reporting Costs for Submitted Bundles, by Completeness

Time	Postmarket Reporting Cost for Complete Bundle[a]	Postmarket Reporting Cost for Partially Complete or Incomplete Bundle[a]
0 *Year of Initial Submission*	0	0
1	c_i	0
2 *Year of Follow-On Submission*	c_i	0
3	c_i	c_i
4	c_i	c_i
5	c_i	c_i
6	0	c_i
7	0	c_i
8	0	0

[a] Where c_i is the annual cost of postmarket reporting for bundle i.

The mean present value lifetime cost of postmarket reporting for an ENDS bundle, discounted back to the time of submission using the cost of capital for the tobacco industry, equals $0.07 million per complete bundle and $0.06 million per incomplete or partially complete

bundle. Averaging over completeness, the expected total lifetime cost of postmarket reporting equals $0.07 million.

We then let $E[C_i]$ represent the expected cost to submit bundle i. In the baseline, $E[C_i]$ includes only the cost to prepare a PMTA bundle. With rulemaking, $E[C_i]$ is the sum of the cost to prepare a PMTA bundle and the lifetime cost of postmarket reporting.

4. Bundles Submitted During the Expected Period for the Existing Product Submissions

For each bundle i in the sample defined using Nielsen RMS data, we estimate $E[\Pi_i]$ and $E[C_i]$. Submitting a PMTA bundle is profit maximizing if $E[\Pi_i] \geq E[C_i]$ for that bundle. For e-liquids and e-cigarettes, we estimate the number of bundles for which submitting a PMTA bundle is profit maximizing. Then, using the estimates from Table 3, we adjust these estimates downward to account for use of other marketing pathways.[31]

Our model predicts that, on average, applicants will submit approximately 34 e-liquid bundles and 28 e-cigarette bundles for currently marketed ENDS products. We anticipate that applicants will continue to submit these bundles, which, assuming some delays in PMTA submissions following the Deeming Compliance Date, lasts in our model from 2020 to 2022. Therefore, we assume that, on average, we will receive approximately 11 e-liquid bundles and 9 e-cigarette bundles annually from 2020 to 2022.

5. Bundles Submitted During the Expected Period for Future Product Submissions

We expect that any bundles submitted during the Expected Period for Future Product Submissions represent products that are truly new to the market. Nielsen RMS data does not capture these newly developed products. We are therefore unable to apply our model to predict submissions during the Expected Period for Future Product Submissions. Instead, we use estimates from the Deeming Analysis to estimate the number of submissions from 2022 to 2039.

First, the Deeming Analysis assumed that applicants will seek marketing authorization for between 56 and 225 e-liquids annually, with a primary estimate of 127 e-liquids, and for between 17 and 42 e-cigarettes annually, with a primary estimate of 28 e-cigarettes. We use these estimates to simulate the number of e-liquids and e-cigarettes seeking marketing authorization each year. That is, we assume that the number of products seeking marketing authorization in a given year is independent of the number of products seeking marketing in all other years.

Then, we convert the number of products seeking marketing authorization to the number of bundles seeking marketing authorization. We use Nielsen RMS data to estimate the number of products within each bundle. When we collapse the UPC-level data to the bundle level, we also create a variable that counts the number of UPCs that make up that bundle. On average, e-liquid bundles include 9 UPCs and e-cigarette bundles include 3 UPCs. The number of bundles seeking marketing authorization equals the number of products seeking marketing authorization divided by the number of products per bundle.

[31] Specifically, we expect 78 percent of e-cigarette bundles to use the PMTA pathway in the Deeming compliance period.

Next, using estimates from the Deeming Analysis (Table 3), we adjust downward to account for applicants use of other marketing pathways for ENDS products. We estimate then that, based on the Deeming Analysis, applicants will submit PMTAs for 6 e-liquid bundles and 3 e-cigarette bundles. We use these estimates as the baseline number of bundles submitted annually during the Expected Period for Future Product Submissions.

To account for changes in incentives to submit PMTAs from rulemaking, we use outputs from our model of bundle submission during the Expected Period for Existing Product Submissions. We find that, on average, the number of e-liquid and e-cigarettes bundles submitted during the Deeming compliance period will fall by 2 percent as a result of rulemaking. We assume that rulemaking will have the same impact on the number of bundles submitted during the Expected Period for Future Product Submissions. That is, we estimate that, with rulemaking, applicants will submit PMTAs for an average of 6 e-liquid bundles and 3 e-cigarette bundles annually during the Expected Period for Future Product Submissions.