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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 1100, 1107, and 1114

[Docket No. FDA-2019-N-2854]

RIN 0910-AH44

Premarket Tobacco Product Applications and Recordkeeping Requirements

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA, the Agency, us, or we) is issuing a final rule that sets forth requirements for premarket tobacco product applications (PMTAs) and requires manufacturers to maintain records establishing that their tobacco products are legally marketed. The rule will help ensure that PMTAs contain sufficient information for FDA to determine whether a marketing granted order should be issued for a new tobacco product. The rule codifies the general procedures FDA will follow when evaluating PMTAs and creates postmarket reporting requirements for applicants that receive marketing granted orders. The rule also requires tobacco product manufacturers to keep records establishing that their tobacco products are legally marketed, such as documents showing that a tobacco product is not required to undergo premarket review or has received premarket authorization.

DATES: This rule is effective [INSERT DATE 30 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*].

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Executive Summary

A. Purpose of the Regulatory Action

FDA is issuing this final rule to improve the efficiency of the submission and review of PMTAs. We are finalizing this rule after reviewing comments to the proposed rule (84 FR 50566, September 25, 2019) (hereinafter referred to as the proposed rule) and are basing this rule on the experience the Agency has gained by reviewing several types of premarket applications submitted by industry, including substantial equivalence (SE) reports, requests for exemptions from the SE requirements, modified risk tobacco product applications (MRTPAs), and PMTAs. As described in the proposed rule, FDA has received thousands of premarket applications that range widely in the level of detail they contain. This rule describes and sets forth requirements related to the content and format of PMTAs and will provide applicants with a better understanding of the information a PMTA must contain. The rule requires an applicant to submit detailed information regarding the physical aspects of its new tobacco product and full reports of information regarding investigations that may show the health risks of the new tobacco product and whether it presents the same or different risks compared to other tobacco products. FDA is requiring the submission of these health risk investigations to ensure it understands the full scope of what is known about the potential health risks of a new tobacco product.

The rule also addresses issues such as the procedures by which FDA reviews a PMTA, retention of records related to a PMTA, confidentiality of application information, electronic submission of the PMTA and amendments, and postmarket reporting requirements. FDA will announce the withdrawal of its September 2011 draft guidance entitled "Applications for Premarket Review of New Tobacco Products" in the *Federal Register*. Additionally, FDA will update the guidance for industry entitled "Premarket Tobacco Product Applications for Electronic Nicotine Delivery Systems" (the ENDS PMTA Guidance)[1] to ensure the product-

[1] Available at https://www.fda.gov/tobacco-products/rules-regulations-and-guidance/guidance.

specific recommendations on preparing and submitting PMTAs for ENDS are consistent with the requirements of this rule.

Additionally, the rule creates requirements for the maintenance of records demonstrating the legal marketing status of Pre-Existing Tobacco Products (i.e., tobacco products (including those products in test markets) that were commercially marketed in the United States as of February 15, 2007) and products that are exempt from the requirements of demonstrating substantial equivalence. These recordkeeping requirements will allow FDA to more efficiently determine the legal marketing status of a tobacco product.

B. Legal Authority

This rule is being issued under FDA's authority to require premarket review of new tobacco products under section 910 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 387j), FDA's authority to require records and reports under section 909(a) of the FD&C Act (21 U.S.C. 387i(a)), FDA's authorities related to adulterated and misbranded tobacco products under sections 902 and 903 (21 U.S.C. 387b and 387c), as well as FDA's rulemaking and inspection authorities under sections 701(a) and 704 of the FD&C Act (21 U.S.C. 371(a) and 374).

C. Summary of Major Provisions

This rule describes and sets forth content and format requirements for PMTAs and includes FDA's interpretations of various provisions in section 910 of the FD&C Act. Under the rule, a PMTA must contain information necessary for FDA to determine whether it should issue a marketing granted order for a new tobacco product under section 910(c)(1)(A) of the FD&C Act. Specifically, the PMTA must enable FDA to find whether: (1) there is a showing that permitting the marketing of the new tobacco product would be appropriate for the protection of

the public health; (2) the methods used in, or the facilities and controls used for, the manufacture, processing, or packing of the product conform to the requirements of section 906(e) of the FD&C Act (21 U.S.C. 387f(e)); (3) the product labeling is not false or misleading in any particular; and (4) the product complies with any applicable product standard in effect under section 907 of the FD&C Act (21 U.S.C. 387g) or there is adequate information to justify a deviation from such standard. The rule will also allow applicants to submit a supplemental PMTA or a resubmission, which will improve the efficiency of submitting and reviewing an application in certain instances. A supplemental PMTA can be submitted in situations where an applicant is seeking authorization for a new tobacco product that is a modified version of a tobacco product for which they have already received a marketing granted order. A resubmission can be submitted to address application deficiencies following the issuance of a marketing denial order.

In addition, the rule explains how an applicant can amend or withdraw a PMTA and how an applicant may transfer ownership of a PMTA to a new owner. The rule also addresses FDA communications with applicants and identifies the actions that FDA may take after receipt of a PMTA. Where an applicant receives a marketing granted order, the rule requires the submission of postmarket reports, addresses when FDA may withdraw a marketing granted order, and explains how long an applicant will be required to maintain the records related to the PMTA and postmarket reports. The rule also sets forth FDA's disclosure procedures regarding PMTAs and requires the electronic submission of PMTAs, unless the applicant requests and obtains a waiver. Additionally, the rule requires tobacco product manufacturers to maintain records related to the legal marketing of Pre-Existing Tobacco Products and products that are exempt from the requirements of demonstrating substantial equivalence.

D. Costs and Benefits

The final rule will require manufacturers of Pre-Existing Tobacco Products and manufacturers of products that are exempt from the requirements of demonstrating SE to maintain records to demonstrate that they can legally market their products. For products that receive a 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. 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 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[2] in the final regulatory impact analysis for the deeming final rule, no regulatory impact analysis includes the costs to submit and review PMTAs for originally

[2] Note that for the purposes of this final rule, "deemed tobacco products" are those tobacco products subject to Chapter IX of the FD&C Act as a result of regulations enacted by FDA (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, 81 FR 28974, May 10, 2016 ("deeming final rule")). These products include cigars, pipe tobacco, waterpipe tobacco, electronic nicotine delivery systems (ENDS), and other novel tobacco products.

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. 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 of Abbreviations/Commonly Used Acronyms

Abbreviation/Acronym	What It Means
APPH	Appropriate for the protection of public health
CAS	Chemical Abstracts Service
CCI	Confidential commercial information
CCS	Container Closure System
CGMP	Current good manufacturing practices
CORESTA	Cooperation Centre for Scientific Research Relative to Tobacco
CTP	Center for Tobacco Products
DPF	Denier per filament
EA	Environmental assessment
ENDS	Electronic nicotine delivery systems
FDA	Food and Drug Administration
FD&C Act	Federal Food, Drug, and Cosmetic Act
FEI	Facility Establishment Identifier
FOIA	Freedom of Information Act
GLP	Good laboratory practice
HACCP	Hazard analysis and critical control point
HCI	Health Canada Intense
HHS	Department of Health and Human Services
HPHC	Harmful or potentially harmful constituent
HTP	Heated tobacco products
IUPAC	International Union of Pure and Applied Chemistry

ICH	International Council for Harmonization
IRB	Institutional Review Board
ISO	International Organization for Standardization
MDSS	Manufacturing Data Sheet Specification
mL	Milliliters
mm	Minimum and maximum diameter
MRTP	Modified risk tobacco product
MRTPA	Modified risk tobacco product application
NCI	National Cancer Institute
NEPA	National Environmental Policy Act of 1969
NNK	4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone
NNN	N-nitrosonornicotine
NTRM	Nontobacco related material
NYTS	National Youth Tobacco Survey
OMB	Office of Management and Budget
OTDN	Oral tobacco-derived nicotine
OV	Oven volatiles
PDU	Power delivery unit
PK	Pharmacokinetic
PM	Particulate matter
PMTA	Premarket tobacco product application
RIA	Regulatory Impact Analysis
RTA	Refuse to accept
RTF	Refuse to file
RYO	Roll-your-own
SAS	Statistical Analysis Software
SE	Substantial equivalence
Secretary	Secretary of Health and Human Services
SES	Socioeconomic status
STN	Submission tracking number
TAMC	Total aerobic microbial count
TPMF	Tobacco product master file
TSNA	Tobacco specific nitrosamine
TYMC	Total yeast and mold count
TPSAC	Tobacco Products Scientific Advisory Committee
UNII	Unique ingredients identifier
a_w	Water activity

I. Background

The Family Smoking Prevention and Tobacco Control Act (Tobacco Control Act) (Pub. L. 111-31) provides FDA with the authority to regulate tobacco products under the FD&C Act. The FD&C Act, as amended by the Tobacco Control Act, generally requires that a new tobacco

product undergo premarket review by FDA before it may be introduced or delivered for introduction into interstate commerce. Section 910(a)(1) of the FD&C Act defines a "new tobacco product" as: (1) any tobacco product (including those products in test markets) that was not commercially marketed in the United States as of February 15, 2007, or (2) any modification (including a change in design, any component, any part, or any constituent, including a smoke constituent, or in the content, delivery or form of nicotine, or any other additive or ingredient) of a tobacco product where the modified product was commercially marketed in the United States after February 15, 2007 (21 U.S.C. 387j(a)(1)).

The FD&C Act establishes three premarket review pathways for a new tobacco product:

- submission of a PMTA under section 910(b);
- submission of a report intended to demonstrate that the new tobacco product is substantially equivalent to a predicate tobacco product under section 905(j)(1)(A) (21 U.S.C. 387e(j)(1)(A)) (SE Report);[3] and
- submission of a request for an exemption under section 905(j)(3) (implemented at 21 CFR 1107.1) (exemption request).

Generally, if a new tobacco product is marketed without either a marketing granted order (for PMTAs), a substantially equivalent order (for SE reports), or a finding of exemption from SE (for exemption requests), it is adulterated under section 902 of the FD&C Act and misbranded under section 903 of the FD&C Act and subject to enforcement action.

[3] Additionally, section 910(a)(2)(B) of the FD&C Act also allows for the continued marketing of new tobacco products first introduced or delivered for introduction into interstate commerce for commercial distribution after February 15, 2007, and prior to March 22, 2011, for which a manufacturer submitted an SE Report prior to March 23, 2011 ("provisional tobacco products"), unless FDA issues an order that the tobacco product is not substantially equivalent.

Since 2010, FDA has received thousands of premarket applications for tobacco products, hundreds of which have been PMTAs. Of these PMTAs, FDA has completed its full substantive review and acted on several sets of bundled PMTAs, which are single submissions containing PMTAs for a number of similar or related tobacco products. To assist manufacturers in preparing PMTAs, FDA has issued guidance, conducted webinars, met with manufacturers, hosted public meetings regarding premarket submissions, and posted the technical project lead reviews (which describe the reviews completed on specific PMTAs) and marketing granted orders issued to date. FDA has also completed review and issued decisions on hundreds of exemption requests, thousands of SE reports, and thousands of voluntarily submitted requests for Pre-Existing Tobacco Product status review, which has provided FDA with information and experience to use when implementing the PMTA program and establishing recordkeeping requirements.

FDA issued the proposed rule on September 25, 2019, to set forth proposed requirements related to the PMTA premarket pathway and outline the information needed for FDA to determine whether it will issue a marketing granted order under the pathway. FDA received about 1,000 comments to the docket for the proposed rule, including comments from individuals, academia, healthcare professionals, consumer advocacy groups, industry, public health groups, and trade associations. We summarize and respond to these comments in section III of this rule. After considering these comments, FDA developed this final rule, which includes changes made in response to the comments.

II. Legal Authority

As described in the following paragraphs, FDA is describing and setting forth requirements for the content, format, submission, and review of PMTAs, as well as other

requirements related to PMTAs, including recordkeeping requirements, and postmarket reporting. FDA is also creating recordkeeping requirements regarding the legal marketing of Pre-Existing Tobacco Products and products that are exempt from the requirements of demonstrating substantial equivalence. In accordance with section 5 of the Tobacco Control Act, FDA intends that the requirements that are established by this rule be severable and that the invalidation of any provision of this rule would not affect the validity of any other part of this rule.

Section 910(a)(2) of the FD&C Act requires that a new tobacco product be the subject of a marketing granted order unless FDA has issued an order finding it to be substantially equivalent to a predicate product, or exempt from the requirements of demonstrating substantial equivalence.[4] A manufacturer may choose to submit a PMTA under section 910(b) of the FD&C Act to satisfy the requirements of premarket review. Section 910(b)(1) describes the required contents of a PMTA and, in addition to the items specified in section 910(b)(1)(A) through (F), allows FDA to require applicants to submit other information relevant to the subject matter of the application under section 910(b)(1)(G). Section 910(c)(2) of the FD&C Act requires FDA to issue an order denying a PMTA if it finds that the applicant has not made a showing that permitting the marketing of the new tobacco product would be appropriate for the protection of the public health; the methods used in, or the facilities or controls used for, the manufacture, processing, or packing of the product do not conform to the requirements of section 906(e) of the FD&C Act; the proposed labeling is false or misleading in any particular; or the product has not been shown to meet the requirements of a product standard in effect and there is a lack of adequate information to justify a deviation from the standard, if applicable.

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[4] See section I for a discussion of provisional tobacco products and their relation to the premarket review requirements.

Section 909(a) of the FD&C Act authorizes FDA to issue regulations requiring tobacco product manufacturers or importers to maintain records, make reports, and provide information as may be reasonably required to assure that their tobacco products are not adulterated or misbranded and to otherwise protect public health. Section 910(f) of the FD&C Act allows FDA to require that applicants who receive marketing granted orders establish and maintain records, and submit reports to enable FDA to determine, or facilitate a determination of, whether there are or may be grounds for withdrawing or temporarily suspending an order.

Section 910(d)(1) of the FD&C Act grants FDA authority to issue an order withdrawing a marketing granted order if FDA finds:

- that the continued marketing of such tobacco product no longer is appropriate for the protection of the public health;
- that the application contained or was accompanied by an untrue statement of a material fact;
- that the applicant:
    - has failed to establish a system for maintaining records, or has repeatedly or deliberately failed to maintain records or to make reports, required by an applicable regulation under section 909 of the FD&C Act;
    - has refused to permit access to, or copying or verification of, such records as required by section 704 of the FD&C Act; or
    - has not complied with the requirements of section 905 of the FD&C Act;
- on the basis of new information before the Secretary of Health and Human Services (the Secretary) with respect to such tobacco product, evaluated together with the evidence before the Secretary when the application was reviewed, that the methods used in, or the

facilities and controls used for, the manufacture, processing, packing, or installation of such tobacco product do not conform with the requirements of section 906(e) of the FD&C Act and were not brought into conformity with such requirements within a reasonable time after receipt of written notice from the Secretary of nonconformity;

- on the basis of new information before the Secretary, evaluated together with the evidence before the Secretary when the application was reviewed, that the labeling of such tobacco product, based on a fair evaluation of all material facts, is false or misleading in any particular and was not corrected within a reasonable time after receipt of written notice from the Secretary of such fact; or
- on the basis of new information before the Secretary, evaluated together with the evidence before the Secretary when such order was issued, that such tobacco product is not shown to conform in all respects to a tobacco product standard which is in effect under section 907 of the FD&C Act, compliance with which was a condition to the issuance of an order relating to the application, and that there is a lack of adequate information to justify the deviation from such standard, if applicable.

Under section 902(6) of the FD&C Act, a tobacco product is adulterated if it is required to have premarket review and does not have an order in effect under section 910(c)(1)(A)(i), or if it is in violation of an order under section 910(c)(1)(A) of the FD&C Act. Under section 903(a)(6) of the FD&C Act, a tobacco product is misbranded if a notice or other information respecting it was not provided as required by section 905(j) of the FD&C Act. In addition, a tobacco product is misbranded if there is a failure or refusal to furnish any material or information required under section 909 (section 903(a)(10)(B) of the FD&C Act). Section 701(a) of the FD&C Act also gives FDA general rulemaking authority to issue regulations for

the efficient enforcement of the FD&C Act and section 704 of the FD&C Act provides FDA with general inspection authority.

III. General Description of Comments on the Proposed Rule

FDA received over 1,000 comments on the proposed rule. The comments came from individuals, academia, healthcare professionals, consumer advocacy groups, industry, public health groups, and trade associations. In addition to the comments specific to this rulemaking that we address in sections IV through XVIII of this document, we received many general comments expressing support or opposition to the rule. Some of these comments express broad policy views and do not address specific points related to this rulemaking. Therefore, these general comments do not require a response. Other comments addressed topics outside the scope of this rulemaking, such as requests for product standards under section 907 of the FD&C Act, recommendations regarding the compliance date for manufacturers of deemed tobacco products to submit premarket applications, statements that ENDS and pipes should not be regulated as tobacco products, and that pipes should not be subject to the requirements of premarket review.

We describe and respond to comments in the description of the final rule in sections IV through XVIII of this document. To make it easier to identify comments and our responses, the word "Comment," in parentheses, will appear before each comment, and the word "Response," in parentheses, will appear before each response. We have numbered the comments to make it easier to distinguish between comments; the numbers are for organizational purposes only and do not reflect the order in which we received the comments or any value associated with the comment. We have combined similar comments, or comments on similar topics that can be addressed by a single response, under one numbered comment.

IV. Description of the Final Regulations for, and Comments and FDA's Responses Regarding, the Maintenance of Records Demonstrating That a Tobacco Product Was Commercially Marketed in the United States as of February 15, 2007 (Part 1100, Subpart C)

The rule adds subpart C regarding records to part 1100 of subchapter K of Title 21. Other than the comments and changes described in this section regarding the proposed definition of the term "grandfathered tobacco product," (now referred to as a "Pre-Existing Tobacco Product"), FDA received no comments regarding proposed part 1100 and FDA is finalizing the requirements as proposed without additional changes.

A. Purpose and Scope (§ 1100.200)

Subpart C of part 1100 establishes requirements for the maintenance of records by tobacco product manufacturers who introduce a Pre-Existing Tobacco Product, or deliver it for introduction, into interstate commerce. These requirements are created under the authority of section 909 of the FD&C Act, which authorizes FDA to require tobacco product manufacturers to establish and maintain records to assure that a tobacco product is not adulterated or misbranded and to otherwise protect public health. Under section 902(6)(A), a tobacco product is adulterated if it is required by section 910(a) of the FD&C Act to have premarket review and does not have an order in effect under section 910(c)(1)(A)(i). In addition, under section 903(a)(6) of the FD&C Act, a tobacco product is misbranded if a notice or other information respecting it was not provided as required by section 905(j) of the FD&C Act. The records that are required under this subpart demonstrate that a tobacco product is a Pre-Existing Tobacco Product and, therefore, not required by section 910(a) to have premarket review and not adulterated or misbranded if marketed without an FDA order. FDA is basing these requirements on its experience gained by performing thousands of Pre-Existing Tobacco Product status

reviews conducted during its review of SE reports and at manufacturers' voluntary requests. These requirements are needed because currently manufacturers do not always maintain sufficient documentation to demonstrate that their tobacco product is a Pre-Existing Tobacco Product. The records that are required under this rule will allow FDA to more quickly and efficiently determine whether a tobacco product is a Pre-Existing Tobacco Product.

B. Definitions (§ 1100.202)

Section 1100.202 sets forth the meaning of terms as they apply to part 1100:

1. Tobacco Product

The rule defines the term "tobacco product" consistent with section 201(rr)(1) of the FD&C Act (21 U.S.C. 321(rr)(1))

2. Tobacco Product Manufacturer

The rule defines the term "tobacco product manufacturer" consistent with section 900(20) of the FD&C Act (21 U.S.C. 387(20)). FDA interprets the phrase "manufactures, fabricates, assembles, processes, or labels" in the definition as including, but not being limited to: (1) repackaging or otherwise changing the container, wrapper, or labeling of any tobacco product package; (2) reconstituting tobacco leaves; or (3) applying any chemical, additive, or substance to the tobacco leaf other than potable water in the form of steam or mist. For the purposes of the definition, "finished tobacco product" means a tobacco product, including all components and parts, sealed in final packaging (e.g., filters or filter tubes sold to consumers separately or as part of kits) or in the final form in which it is intended to be sold to consumers.

3. Commercially Marketed

In the proposed rule, FDA proposed to define "commercially marketed" as "selling or offering a tobacco product for sale to consumers in all or in parts of the United States."

(Comment 1) Several comments discussed specific changes to the proposed definition of the term "commercially marketed." One comment stated that the proposed definition of commercially marketed departs from the plain meaning of the statutory language and FDA's historical approach to evaluating whether a product is a Pre-Existing Tobacco Product. Specifically, comments raised concerns that inclusion of "in all or in parts of the United States" seems to depart from the plain meaning of the statutory phrase "commercially marketed in the United States" and requires that firms demonstrate that a product was offered nationwide, in multiple regions, or even across State lines. The comments also argue that, for example, the statutory definition of "new tobacco product" does not state or imply that a product offered for sale within a particular State cannot qualify as "commercially marketed in the United States." The comments state that FDA should define "commercially marketed" as "offered for sale in the United States to any individual or entity by advertising or by any other manner used to communicate that the tobacco product is available for purchase." Another comment expressed similar concerns, stating that the definition seems to require the selling or marketing of products directly to consumers as well as offering it for sale nationwide.

(Response 1) After reviewing the comments related to commercially marketed, we have added a definition of this term to the final rule, which reflects the input we received. Given the wide variety of input we have received on this term as well as the dictionary definition, we do not believe that the term "commercially marketed" has a plain meaning. Instead, we have added a definition stating that "commercially marketed" means selling or offering for sale a tobacco product in the United States to consumers or to any person for the eventual purchase by consumers in the United States. This definition clarifies that tobacco products that are not sold or offered for sale in order to reach consumers within the United States, such as tobacco products

sold solely for export, fall outside of the definition of commercial marketing. Examples of products that may not be covered by the definition of commercially marketed include investigational tobacco products and free samples. Examples of documentation of commercial marketing may include the following items listed in § 1100.204(a): dated bills of lading, dated freight bills, dated waybills, dated invoices, dated purchase orders, dated advertisements, dated catalog pages, dated promotional material, dated trade publications, dated manufacturing documents, inventory lists, or any other document demonstrating that the product was commercially marketed in the United States as of February 15, 2007.

(Comment 2) One comment requested clarification as to whether limited edition products would be considered test marketed products or commercially marketed products.

(Response 2) "Limited edition" products are considered commercially marketed if they were sold or offered for sale in the United States to consumers or to any person for the eventual purchase by consumers in the United States--regardless of whether they were solely sold or offered for sale in a test market. Therefore, if a "limited edition" product was commercially marketed--even if only in a test market--as of February 15, 2007, it would be a Pre-Existing Tobacco Product. We note that considering test marketed products to be commercially marketed is a change in FDA's interpretation of section 910(a)(1)(A) of the FD&C Act, which is discussed further in the response to comment 3. However, a product that was solely in a test market as of February 15, 2007, cannot serve as a predicate product under section 905(j) of the FD&C Act. Test marketed products may include, for example, products that were sold or offered for sale to determine the commercial viability of a product through the collection of consumer reaction data.

4. Pre-Existing Tobacco Product

In the proposed rule, we proposed to define the term "grandfathered tobacco product" as "a tobacco product that was commercially marketed in the United States as of February 15, 2007" and does not include a tobacco product exclusively in test markets as of that date. A grandfathered tobacco product is not subject to the premarket requirements of section 910 of the FD&C Act." In the final rule, we have changed this term from "grandfathered tobacco product" to "Pre-Existing Tobacco Product" because it more appropriately describes these products by using the more precise "Pre-Existing" in place of "grandfathered." FDA received many comments regarding the definition of "Pre-Existing Tobacco Product,"[5] which are discussed as follows.

(Comment 3) Multiple comments discussed the proposed definition of the term "commercially marketed" as well as the definition of the term "test marketing" set forth in the preamble of the proposed rule as used in, or to inform, the definitions of "Pre-Existing Tobacco Product" and "new tobacco product" in the proposed rule. Some comments argued that Congress was intentional in its use of test markets in the definition of new tobacco product and, as such, a product in test market as of February 15, 2007 (if not subsequently modified within the meaning of section 910(a)(1)(B)), of the FD&C Act is not a new tobacco product and is not subject to premarket review. These comments also stated that because section 905(j)(1)(A)(i) of the FD&C Act explicitly excludes test marketed products from the commercially marketed products that may serve as valid predicate products, it demonstrates that the term "commercially marketed" encompasses products that are test marketed (i.e., if test marketed products did not constitute commercially marketed products, there would have been no need for Congress to exclude them from the types of commercially marketed products that may qualify for use as

[5] Although comments were submitted regarding the term "grandfathered tobacco product," we describe them using the new term, "Pre-Existing Tobacco Product," throughout this document for clarity.

predicate products under the substantial equivalence premarket pathway). Some comments requested FDA include the definitions as they were defined in the proposed rule, including as they relate to the definition of the term "new tobacco product" in proposed part 1114 (21 CFR part 1114). Other comments stated that the proposed definitions should not be included in the final rule because they are unnecessary, confusing, conflicting, and not useful. Specifically, some comments argued that FDA did not provide a workable or rational basis to distinguish "test marketing" from "commercially marketed" and the proposed definitions do not reflect industry realities.

(Response 3) Following our consideration of these comments, we have revised the definitions related to "Pre-Existing Tobacco Product" to remove language related to "exclusively" test marketed.

Upon reviewing comments received, we reassessed our interpretation of section 910(a)(1)(A) of the FD&C Act, and we agree with the comment indicating that a tobacco product test marketed in the United States as of February 15, 2007, is not a new tobacco product. Section 910(a)(1)(A) defines a "new tobacco product" to include "any tobacco product (including those in test markets) that was not commercially marketed in the United States as of February 15, 2007." The parenthetical "including those in test markets" in section 910(a)(1)(A) of the FD&C Act modifies the phrase directly before it--"any tobacco product"--and is intended to clarify that tobacco products commercially marketed in test markets in the United States as of February 15, 2007, should be treated the same way as any other tobacco product that was commercially marketed as of February 15, 2007, i.e., they are not "new tobacco products." We also agree that section 905 of the FD&C Act provides additional context that supports this interpretation. Section 905(j)(1)(A)(i) of the FD&C Act describes products that can serve as valid predicate

tobacco products: a tobacco product commercially marketed (other than for test marketing) in the United States as of February 15, 2007, or a tobacco product that the Secretary by delegation to FDA has previously determined, pursuant to section 910(a)(3), is substantially equivalent. Here, Congress' inclusion of the parenthetical "(other than for test marketing)" supports a reading of the term "commercially marketed" as including products that were test marketed; otherwise, there would not be the need to specifically carve out test marketed products from the commercially marketed products that can serve as valid predicate products.

In addition, in the preamble to the proposed rule, we explained that FDA was considering whether to add the following definition of test marketing: "test marketing" means distributing or offering for sale (which may be shown by advertisements, etc.) a tobacco product in the United States for the purpose of determining consumer response or other consumer reaction to the tobacco product, with or without the user knowing it is a test product, in which any of the following criteria apply: (1) offered in a limited number of regions; (2) offered for a limited time; or (3) offered to a chosen set of the population or specific demographic group (84 FR 50566 at 50571).

We agree with the commenter that further discussion of the term, test marketing, is needed to more accurately capture the scope of this term; accordingly, we are not including a definition of test marketing in the final rule.

After reviewing these comments and for the purposes of consistency, FDA is finalizing the definition of "Pre-Existing Tobacco Product" with changes to better align with the statute, first, by adding "(including those products in test markets), and, second, by removing "and does not include a tobacco product exclusively in test markets as of that date." Specifically, FDA defines a "Pre-Existing Tobacco Product" to mean a tobacco product (including those products

in test markets) that was commercially marketed in the United States as of February 15, 2007. The definition of "Pre-Existing Tobacco Product" in this rule reflects FDA's interpretation that "as of" means "on", which has been included as part of previously issued regulations and guidance.[6] For more information on this topic, see the response to comment 5 explaining FDA's interpretation that "as of" means "on." A Pre-Existing Tobacco Product is not subject to the premarket review requirements of section 910 of the FD&C Act.

C. Recordkeeping Requirements (§ 1100.204)

1. Required Records

Consistent with the authority to require recordkeeping under section 909 of the FD&C Act, § 1100.204(a) requires any tobacco product manufacturer that introduces a Pre-Existing Tobacco Product, or delivers it for introduction, into interstate commerce to maintain records and information necessary to adequately demonstrate that the tobacco product was commercially marketed in the United States as of February 15, 2007. This requirement will ensure, among other things, that records are available to FDA during an inspection. The rule does not require tobacco product manufacturers to maintain records for all of the types of information listed in § 1100.204(a); rather, the list provides examples of the types of records that may be used to demonstrate that a tobacco product was commercially marketed in the United States as of February 15, 2007.

2. Record Maintenance

[6] See the 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" (81 FR 28973 at 28978, May 10, 2016) and the guidance entitled "Establishing That a Tobacco Product Was Commercially Marketed in the United States as of February 15, 2007" (79 FR 58358, September 29, 2014). Available at https://www.fda.gov/tobacco-products/rules-regulations-and-guidance/guidance.

Section 1100.204(b) requires that all records maintained under this part be legible, in the English language, and available for inspection and copying by officers or employees duly designated by the Secretary. This section also requires documents that have been translated from another language into English to be accompanied by: (1) the original language version of the document; (2) a signed statement by an authorized representative of the manufacturer certifying that the English language translation is complete and accurate; and (3) a brief statement of the qualifications of the person who made the translation (e.g., education and experience). This information will help FDA ensure that the English language translations of documents are complete and accurately reflect the content of the original documents.

3. Record Retention

Section 1100.204(c) requires that the records and documents demonstrating that the tobacco product was commercially marketed as of February 15, 2007, be retained for a period of at least 4 years from the date that either FDA makes a Pre-Existing Tobacco Product determination or the tobacco product manufacturer permanently ceases the introduction or delivery for introduction into interstate commerce of the tobacco product, whichever occurs sooner. FDA has selected 4 years to help ensure that the records will be available for at least one biennial FDA inspection under sections 704 and 905(g) of the FD&C Act. FDA's biennial inspections under section 905(g) of the FD&C Act are required to occur at least once in every 2-year period after a manufacturer registers an establishment with FDA, which could result in inspections occurring nearly 4 years apart. Retaining records for 4 years after a manufacturer permanently ceases introduction or delivery for introduction into interstate commerce of the tobacco product will allow FDA to verify the Pre-Existing Tobacco Product status of the product during the time period in which it is offered for sale to consumers. Manufacturers that only

temporarily cease the introduction or delivery for introduction into interstate commerce of the tobacco product must retain the records to allow FDA to verify the Pre-Existing Tobacco Product status of the product when they resume marketing the product. Additionally, manufacturers might want to retain records for longer than 4 years to help establish their product is a Pre-Existing Tobacco Product and may be eligible as a predicate product in an SE Report if it was commercially marketed (other than for test marketing) in the United States as of February 15, 2007.

V. Description of the Final Regulations for, and the Comments and FDA's Responses Regarding, the Maintenance of Records Relating to Exemptions from the Requirements of Demonstrating Substantial Equivalence (§ 1107.3)

The rule adds § 1107.3 to part 1107 of subchapter K of Title 21. Other than the comments and changes described in this section regarding the proposed definition of the term "grandfathered tobacco product" (now referred to as a "Pre-Existing Tobacco Product"), FDA received no comments regarding proposed § 1107.3, FDA is finalizing the requirements as proposed with one other change; we have removed the proposed requirement to maintain product labeling a part of § 1107.3 because it is not necessary to support an abbreviated report.

Section 1107.3 establishes recordkeeping requirements related to tobacco products that are exempt from the requirements of demonstrating SE under section 910(a)(2)(A)(ii) of the FD&C Act. Consistent with the authority to require recordkeeping under section 909 of the FD&C Act, § 1107.3 requires applicants that submitted an abbreviated report under section 905(j)(1)(A)(ii) of the FD&C Act, and received a letter from FDA acknowledging the receipt of an abbreviated report, to maintain all records necessary to support the exemption for at least 4 years from the date FDA issues an acknowledgement letter in response to an abbreviated report.

The rule requires the applicant to maintain records that are legible, written in English, and available for inspection and copying by officers or employees designated by the Secretary. Applicants may want to retain the records for a longer period if, for example they intend to submit a subsequent exemption request for a modification to the tobacco product.

A. Definition

Section 1107.3(a) defines "Pre-Existing Tobacco Product"[7] as a tobacco product (including those products in test markets) that was commercially marketed in the United States as of February 15, 2007. FDA has considered the comments described in section IV and revised this term as described in the responses in that section. As described in section IV.B.4., FDA interprets the phrase "as of February 15, 2007," as meaning that the tobacco product was commercially marketed in the United States "on February 15, 2007." See the response to comment 5 explaining FDA's interpretation that "as of" means "on."

B. Record Maintenance

The rule requires applicants to maintain all documents that support their abbreviated report, which includes the documents listed in § 1107.3(b)(1). The rule does not require an applicant to create new or additional records; rather, it requires an applicant to maintain the records it has, obtains, or creates (including those created on its behalf, such as by a contract research organization) that support its abbreviated report. This includes documents that an applicant creates under other regulatory or statutory sections such as the submission of exemption requests under § 1107.1, PMTAs under part 1114, SE Reports under section 905(j) of the FD&C Act, and tobacco product manufacturing practice requirements issued under section

[7] As described in section IV.B of this document, we have changed the term "grandfathered tobacco product" to "Pre-Existing Tobacco Product."

906(e) of the FD&C Act. The records an applicant is required to maintain include, but are not limited to:

- a copy of the abbreviated report and, if applicable, the exemption request and all amendments thereto;
- a copy of the acknowledgement letter issued in response to an abbreviated report and, if applicable, a copy of the exemption order issued by FDA;
- documents related to formulation of product, product specifications, packaging, and related items. Product formulation includes, for example, items such as the types of information described in § 1114.7(i) as described in section VIII.B. of this document;
- documents showing that design specifications are consistently met. This could include, for example, information about testing procedures that are carried out before the product is released to market, such as the information described in § 1114.7(j) as described in section VIII.B. of this document;
- documents related to product packing and storage conditions;
- analytical test method records, including:
    - performance criteria;
    - validation or verification documentation; and
    - reports/results from these test methods; and
- source data and related summaries.

In addition to the documents specified in § 1107.3(b)(1), paragraphs (b)(2) through (b)(4) require tobacco product manufacturers to maintain records that support a determination that their exemption request meets the requirements of section 905(j)(3)(A)(i) of the FD&C Act that the modification to a product additive described in the exemption request was a minor modification

made to a tobacco product that can be sold under the FD&C Act. This means that applicants need to maintain records demonstrating that the modification is being made to either a Pre-Existing Tobacco Product or a new tobacco product that has satisfied the premarket review requirements of section 910(a)(2) of the FD&C Act. For abbreviated reports based on a modification to a Pre-Existing Tobacco Product, § 1107.3(b)(2) requires applicants to maintain the documentation in § 1100.204 to demonstrate that the product that is being modified is legally marketed. For abbreviated reports based on a modification to a tobacco product that has previously received an exemption order in response to a request under § 1107.1 (and for which the applicant has submitted an abbreviated report under 905(j)(1)(A)(ii)), or a substantially equivalent order or a marketing granted order from FDA, § 1107.3(b)(3) requires applicants to maintain a copy of the exemption order, substantially equivalent order, or marketing granted order to demonstrate the product being modified is legally marketed. For abbreviated reports based on a modification to a tobacco product that is being marketed pursuant to section 910(a)(2)(B) of the FD&C Act for which FDA has not issued a substantially equivalent order, an applicant must maintain all communications to and from FDA relating to the pending SE Report, such as a letter acknowledging receipt of the report.

C. Record Quality

Section 1107.3(c) requires the records to be legible, in the English language, and available for inspection and copying by officers or employees duly designated by the Secretary. FDA also requires documents that have been translated from another language into English be accompanied by: (1) the original language version of the document, (2) a signed statement by an authorized representative of the manufacturer certifying that the English language translation is complete and accurate, and (3) a brief statement of the qualifications of the person who made the

translation (e.g., education and experience). This information helps FDA ensure that the English language translations of documents are complete and accurately reflect the content of the original documents.

D. Record Retention

Section 1107.3(d) requires the records described in § 1107.3(b) to be maintained for a period of not less than 4 years from the date on which FDA issues an acknowledgement letter in response to an abbreviated report. FDA has selected 4 years as a means to help ensure that the records are available for at least one biennial FDA inspection under sections 704 and 905(g) of the FD&C Act. FDA's biennial inspections under section 905(g) of the FD&C Act are required to occur at least once in every 2-year period after a manufacturer registers an establishment with FDA, which could result in inspections occurring nearly 4 years apart.

VI. Description of the Final Regulations for, and the Comments and FDA's Responses Regarding, Premarket Tobacco Product Applications (Part 1114)

The rule adds part 1114 to subchapter K of Title 21. The requirements set forth in this part apply to PMTAs for new tobacco products. Subpart A sets out the scope and definitions that apply to this part. Subpart B sets out the criteria for PMTA submission, content and format of PMTAs, application amendments, withdrawal of an application by an applicant, supplemental PMTAs, resubmissions, and change in ownership or contact information for a PMTA. Subpart C describes FDA review and actions on applications, including provisions for withdrawal and temporary suspension of orders. Subpart D describes postmarket restrictions and reporting requirements. Subpart E sets miscellaneous requirements such as record retention, confidentiality, and electronic submission.

VII. General (Part 1114, Subpart A)

A. Scope (§ 1114.1)

Section 1114.1 describes the scope of part 1114 and its applicability to the submission and review of, and postmarket requirements related to, PMTAs. Section 1114.1 provides that part 1114 does not apply to MRTPAs, except instances where a single application is submitted to seek both a marketing granted order and a modified risk order instead of a separate PMTA and MRTPA. Under the rule, a single application seeking both a marketing granted order and a modified risk order under section 911(g) of the FD&C Act needs to meet the content and format requirements of both part 1114 and section 911 of the FD&C Act (21 U.S.C. 387k) (and any implementing regulations). This section also notes that references in the rule to regulatory sections of the Code of Federal Regulations (CFR) are to chapter I of Title 21, unless otherwise noted. Therefore, any CFR reference that begins with "part," "section," or the section symbol (§) should be read as if it were preceded by "21 CFR" (e.g., § 1114.1 refers to 21 CFR 1114.1, part 58 refers to 21 CFR part 58), unless another source is cited (e.g., the FD&C Act).

(Comment 4) Some comments requested that "premium" cigars be exempt from the PMTA premarket pathway or that a different premarket pathway be created for them. Several comments describe the difference between "premium" cigars and other products, such as cigarettes or ENDS, and argue that these differences make it more difficult for "premium" cigars to comply with PMTA requirements. These comments request that FDA exempt "premium" cigars from premarket requirements, create a different premarket pathway for "premium" cigars, or delay the effective date for submitting premarket applications.

(Response 4) FDA received a range of comments related to "premium" cigars. A recent court decision "remand[ed] the [deeming final rule] to the FDA to consider developing a streamlined substantial equivalence process for premium cigars" and "enjoin[ed] the FDA from

enforcing the premarket review requirements against premium cigars…until the agency has completed its review."[8] Under the terms of the court's order, a "premium" cigar is defined as a cigar that meets all of the following eight criteria:

- is wrapped in whole tobacco leaf;
- contains a 100 percent leaf tobacco binder;
- contains at least 50 percent (of the filler by weight) long filler tobacco (i.e., whole tobacco leaves that run the length of the cigar);
- is handmade or hand rolled[9];
- has no filter, nontobacco tip, or nontobacco mouthpiece;
- does not have a characterizing flavor other than tobacco;
- contains only tobacco, water, and vegetable gum with no other ingredients or additives; and
- weighs more than 6 pounds per 1,000 units.

As directed by the court in the *Cigar Ass'n of Am.* decision, FDA is further considering the comments submitted to the deeming final rule docket that requested FDA create a streamlined SE process for "premium" cigars. Additionally, FDA intends to undertake a research effort specific to "premium" cigars (as defined in the preceding paragraph) and their health effects, patterns of use (such as frequency of use and usage patterns among underage persons), and other factors. The results of this research will inform the Agency's regulatory policy with respect to premarket review of "premium" cigars. Although the court opinion specifically discusses considering comments on the SE pathway, FDA's research efforts may

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[8] *Cigar Ass'n of Am., et al.* v. *Food and Drug Admin., et al.*, Case No. 1:16-cv-01460 (APM), (D.D.C. August 19, 2020), Dkt. No. 214 (*Cigar Ass'n of Am.*).

[9] A product is "handmade or hand rolled" if no machinery was used apart from simple tools, such as a scissors to cut the tobacco prior to rolling.

also inform issues related to the review of applications for premium cigars under the PMTA pathway. Because these are ongoing efforts, at this time, FDA is not finalizing the proposed PMTA rule with respect to "premium" cigars. Rather, FDA will take appropriate action once it has further considered this matter, including the results from its research. As such, the codified language has been revised to exclude "premium" cigars from the scope of this final rule, and the *Cigar Ass'n of Am.* court's definition of "premium" cigars has been added to section § 1114.3.

B. Definitions (§ 1114.3)

Section 1114.3 provides the meaning of terms as they apply to part 1114:

1. Additive

As defined in section 900(1) of the FD&C Act, "additive" means any substance the intended use of which results or may reasonably be expected to result, directly or indirectly, in its becoming a component or otherwise affecting the characteristic of any tobacco product (including any substances intended for use as a flavoring or coloring or in producing, manufacturing, packing, processing, preparing, treating, packaging, transporting, or holding), except that such term does not include tobacco, or a pesticide chemical residue in or on raw tobacco, or a pesticide chemical.

An additive can be a type of ingredient in a tobacco product; an example is methyl salicylate in smokeless tobacco, which can serve as an absorption enhancer and affect the characteristics of the tobacco product by changing the rate of absorption into the body. Tobacco is not an additive.

2. Brand

As defined in section 900(2) of the FD&C Act, "brand" means a variety of tobacco product distinguished by the tobacco used, tar content, nicotine content, flavoring used, size,

filtration, packaging, logo, registered trademark, brand name(s), identifiable pattern of colors, or any combination of such attributes.

3. Characteristics

As defined in section 910(a)(3)(B) of the FD&C Act, "characteristics" means the materials, ingredients, design, composition, heating source, or other features of a tobacco product. The terms used in the definition of characteristic (materials, ingredients, design, etc.) are defined in § 1114.3.

4. Label

As defined in section 201(k) of the FD&C Act, "label" means a display of written, printed, or graphic matter upon the immediate container of any article; and a requirement made by or under authority of the FD&C Act that any word, statement, or other information appear on the label shall not be considered to be complied with unless such word, statement, or other information also appears on the outside container or wrapper, if any there be, of the retail package of such article, or is easily legible through the outside container or wrapper.

5. Labeling

As defined in section 201(m) of the FD&C Act, "labeling" means all labels and other written, printed, or graphic matter: (1) upon any article or any of its containers or wrappers or (2) accompanying such article.

6. New Tobacco Product

As defined in section 910(a)(1) of the FD&C Act, "new tobacco product" means: (1) any tobacco product (including those products in test markets) that was not commercially marketed in the United States as of February 15, 2007, or (2) any modification (including a change in design, any component, any part, or any constituent, including a smoke constituent, or in the

content, delivery or form of nicotine, or any other additive or ingredient) of a tobacco product where the modified product was commercially marketed in the United States after February 15, 2007.

FDA received many comments regarding the proposed definition of "new tobacco product," as discussed below.

(Comment 5) Multiple comments questioned FDA's interpretation of the phrase "as of February 15, 2007" as used in the definition of the terms "Pre-Existing Tobacco Product" and "new tobacco product" and stated that there is a lack of rationale for its interpretation. Comments argue that the plain meaning of the term "as of" support the interpretation that "as of" means "on or before" rather than "on". As such, a tobacco product must qualify as a Pre-Existing Tobacco Product if it was commercially marketed in the United States at any time on or before February 15, 2007.

(Response 5) As previously stated, FDA's longstanding interpretation is that the statutory phrase "as of February 15, 2007," means that the tobacco product was commercially marketed in the United States "on February 15, 2007" (see the final guidance entitled "Establishing That a Tobacco Product Was Commercially Marketed in the United States as of February 15, 2007" (79 FR 58358, September 29, 2014)). Contrary to the comments, the term "as of" does not have a clear plain meaning. The dictionary definitions of "as of" include: "on; at" (Webster's II New Riverside University Dictionary, 1988); "beginning on; on and after" (Webster's Unabridged Dictionary Random House 1997); "from, at, or until a given time" (The American Heritage Dictionary of Idioms 2003); "on, at, from--used to indicate a time or date at which something begins or ends" (Merriam Webster's Online Dictionary). As evidenced from these varying definitions (e.g., compare "until" with "from"), the term is ambiguous. Even assuming "as of"

could be interpreted as "at any time prior to and not necessarily including on the particular date" (in short referred to as the "on or before" interpretation), interpreting "as of" to mean "on" gives a firm line of demarcation that provides clarity. Additionally, reading "as of" to mean "on or before" would mean that obsolete, abandoned, or discontinued tobacco products could return to the market without any premarket review and could serve as predicates under the SE provision. It is reasonable to conclude that Congress did not intend to allow an immeasurable number of obsolete, abandoned, or discontinued products that were marketed before February 15, 2007, to return to the market without any premarket review or serve as predicates under the SE provision, but rather intended to confine this number to those products that were commercially marketed in the United States on February 15, 2007. Thus, we decline to adopt the interpretation the comments suggest.

Under section 910(a)(1) of the FD&C Act, and as reflected in the definition, new tobacco products include those that are new because they have been rendered new through any modification (including a change in design, any component, any part, or any constituent, including a smoke constituent, or in the content, delivery or form of nicotine, or any other additive or ingredient) of a tobacco product where the modified product was commercially marketed in the United States after February 15, 2007 (21 U.S.C. 387j(a)(1)(B)). For example, modifications to cigarette paper, container closure systems (e.g., change from glass to plastic e-liquid vials or from plastic to tin container closures), product quantity, or tobacco cut size would result in a new tobacco product.

(Comment 6) One comment stated that the term "co-packaging," which is included in the discussion of the definition of the term "new tobacco product," is confusing and does not provide a basis for regulating co-packaged products as part of premarket review.

(Response 6) Manufacturers sometimes co-package tobacco products, and FDA seeks to clarify what effect co-packaging tobacco products may have on whether those products are required to undergo premarket review. If there has been a change to the packaging of co-packaged tobacco products that is intended or reasonably expected to affect or alter the performance, composition, constituents, or characteristics of the tobacco product, then it is a change to the container closure system and, therefore, is a new tobacco product. Under section 910(a)(1)(B) of the FD&C Act, new tobacco products include those that are new because they have been rendered new through any modification (including a change in design, any component, any part, or any constituent, including a smoke constituent, or in the content, delivery or form of nicotine, or any other additive or ingredient) of a tobacco product where the modified product was commercially marketed in the United States after February 15, 2007. Therefore, if two or more products are co-packaged together within a container closure system, it results in a new tobacco product requiring premarket authorization. However, co-packaging two or more legally marketed tobacco products, where there are no changes, including no change to the container closure system(s), does not result in a new tobacco product.

In addition, for purposes of determining whether a tobacco product is new under section 910 of the FD&C Act, and therefore requires premarket authorization prior to marketing, a "tobacco product" encompasses the whole product (e.g., a pack of cigarettes or a tin of loose tobacco), and is not limited to a single unit or portion of the whole product (e.g., a single cigarette or a single snus pouch). See *Philip Morris USA Inc*. v. *U.S. Food & Drug Admin.*, 202 F. Supp. 3d 31, 55-57 (D.D.C. 2016). If a premarket application includes information on only a portion of a new tobacco product, FDA would have an incomplete understanding of the tobacco product (e.g., FDA may not get information on the container closure system, which could impact

the consumable product) and would not be able to determine, for example, potential impacts on initiation and cessation of tobacco.

7. Package or Packaging

As defined in section 900(13) of the FD&C Act, the term "package," also referred to in the rule as "packaging," means a pack, box, carton, or container of any kind or, if no other container, any wrapping (including cellophane), in which a tobacco product is offered for sale, sold, or otherwise distributed to consumers. A subset of package is the container closure system (also defined in this rule). For example, the carton holding multiple soft packs of cigarettes is considered the package, and each soft pack with surrounding cellophane is considered the container closure system. Packaging that constitutes the container closure system is intended or reasonably expected to affect or alter the performance, composition, constituents, or characteristics of the tobacco product (e.g., leaching substances that are then incorporated into a consumable tobacco product), but packaging that is not the container closure system is not intended or reasonably expected to affect or alter the performance, composition, constituents, or characteristics of the tobacco product and is, therefore, not a component or part of a tobacco product.

8. Tobacco Product

As defined in section 201(rr) of the FD&C Act, the term "tobacco product" means any product that is made or derived from tobacco that is intended for human consumption, including any component, part, or accessory of a tobacco product (except for raw materials other than tobacco used in manufacturing a component, part, or accessory of a tobacco product). The term "tobacco product" does not mean an article that is a drug under section 201(g)(1), a device under

section 201(h), or a combination product described in section 503(g) of the FD&C Act (21 U.S.C. 353(g)).

9. Tobacco Product Manufacturer

As defined in section 900(20) of the FD&C Act, the term "tobacco product manufacturer" means any person, including any repacker or relabeler, who: (1) manufactures, fabricates, assembles, processes, or labels a tobacco product or (2) imports a finished tobacco product for sale or distribution in the United States. FDA interprets "manufactures, fabricates, assembles, processes, or labels" as including, but not being limited to, (1) repackaging or otherwise changing the container, wrapper, or labeling of any tobacco product package; (2) reconstituting tobacco leaves; or (3) applying any chemical, additive, or substance to the tobacco leaf other than potable water in the form of steam or mist. A definition for the term "finished tobacco product" is also included in the rule.

10. Accessory

FDA defines "accessory" as any product that is intended or reasonably expected to be used with or for the human consumption of a tobacco product; does not contain tobacco and is not made or derived from tobacco; and meets either of the following:

- is not intended or reasonably expected to affect or alter the performance, composition, constituents, or characteristics of a tobacco product or
- is intended or reasonably expected to affect or maintain the performance, composition, constituents, or characteristics of a tobacco product, but:
    - solely controls moisture and/or temperature of a stored product or
    - solely provides an external heat source to initiate but not maintain combustion of a tobacco product.

This matches the definition of accessory set forth in § 1100.3. Examples of accessories are ashtrays and spittoons because they do not contain tobacco, are not derived from tobacco, and do not affect or alter the performance, composition, constituents, or characteristics of a tobacco product. Examples of accessories also include humidors or refrigerators that solely control the moisture and/or temperature of a stored product and conventional matches and lighters that solely provide an external heat source to initiate but not maintain combustion of a tobacco product.

11. Adverse Experience

FDA defines "adverse experience" as any unfavorable physical or psychological effect in a person that is temporally associated with the use of or exposure to a tobacco product, whether or not the person uses the tobacco product, and whether or not the effect is considered to be related to the use of or exposure to the tobacco product. FDA received many comments regarding this definition, as discussed below.

(Comment 7) Multiple comments requested changes to the definition of what constitutes an adverse experience. One comment requested FDA amend the definition to explicitly include increased use by youth or young adults. Another comment stated that the definition of adverse experience is too broad and subjective, and should be revised to refer to a health-related event associated with the use of or exposure to (intended or incidental) a tobacco product.

(Response 7) FDA declines to change the definition of adverse experience because this widely understood definition is generally consistent with language used throughout the Agency and is designed to capture a broad swath of information related to health effects from FDA regulated products. Due to the fact that the experience may not relate to the individual user but could also affect the general public or bystander, it is FDA's intent that the definition remain

broad to ensure we receive the potential wide variety of voluntary reports of adverse experiences involving tobacco products from investigators, consumers, healthcare professionals and concerned members of the public. Additionally, FDA declines to revise the definition to include use by youth and young adults because it constitutes a behavior, not a health effect related to an adverse experience. Increases in use by individuals under the minimum age of sale will be monitored through the review of periodic reports submitted under § 1114.41, among other means.

FDA notes that it is important to also include information regarding adverse experiences associated with use of or exposure to a product where the individual suffering the adverse experience did not use the product because it can help FDA determine health risks for nonusers, such as the effects of second-hand exposure or accidental exposure (e.g., skin burns from accidental exposure to liquid nicotine, harmful effects resulting from a child drinking an e-liquid, respiratory difficulties from second-hand exposure to an e-cigarette). Additionally, reporting information regarding all adverse experiences that are temporally associated with the use of or exposure to the product will help the applicant avoid self-selection bias of what is reported to FDA and help identify harmful effects that are not obviously attributable to the product.

12. Applicant

FDA defines "applicant" as any person that submits a PMTA to receive a marketing granted order for a new tobacco product.

13. Commercially Marketed

In the proposed rule, FDA proposed to define "commercially marketed" as "selling or offering a tobacco product for sale to consumers in all or in parts of the United States." After reviewing comments described in section IV of this document, FDA has decided to finalize the

definition of "commercially marketed" to mean selling or offering for sale a tobacco product in the United States to consumers or to any person for the eventual purchase by consumers in the United States. Examples of products that may not be covered by the definition of commercially marketed include investigational tobacco products and free samples. Examples of documentation of commercial marketing may include dated bills of lading, dated freight bills, dated waybills, dated invoices, dated purchase orders, dated advertisements, dated catalog pages, dated promotional material, dated trade publications, dated manufacturing documents, inventory lists, or any other document demonstrating that the product was commercially marketed in the United States as of February 15, 2007. See discussion in section IV.B.3 of this document.

14. Component or Part

FDA defines "component or part" as any software or assembly of materials intended or reasonably expected: (1) to alter or affect the tobacco product's performance, composition, constituents, or characteristics or (2) to be used with or for the human consumption of a tobacco product. Component or part excludes anything that is an accessory of a tobacco product. A container closure system (which is also defined in this section) is considered a component or part. With respect to these definitions, FDA notes that "component" and "part" are separate and distinct terms within chapter IX of the FD&C Act. However, for purposes of this rule, FDA is using the terms "component" and "part" interchangeably and without emphasizing a distinction between the terms. FDA may clarify the distinctions between "component" and "part" in the future. This definition matches the definition in § 1100.3.

15. Composition

FDA defines "composition" as the materials in a tobacco product, including ingredients, additives, and biological organisms. The term includes the manner in which the materials, for

example, ingredients, additives, and biological organisms, are arranged and integrated to produce a tobacco product. Composition refers primarily to the chemical and biological properties of a tobacco product, whereas design refers to the physical properties of a tobacco product. A biological organism refers to any living biological entity, such as an animal, plant, fungus, or bacterium.

16. Constituent

In this final rule, we have updated the definition of constituent on our own initiative to clarify the meaning. FDA defines "constituent" as any chemical or chemical compound in a tobacco product that is or potentially is inhaled, ingested, or absorbed into the body, any chemical or chemical compound in an emission (e.g., smoke, aerosol, droplets) from a tobacco product, that either transfers from any component or part of the tobacco product to the emission or that is formed by the product, including through combustion or heating of tobacco, additives, or other components of the tobacco product.

17. Container Closure System

FDA defines "container closure system" as any packaging materials that are a component or part of a tobacco product. FDA received several comments regarding the proposed definition, as discussed below.

(Comment 8) A few comments suggested related revisions to both the definitions of the terms "container closure system" (CCS), "packaging," and "component or part," as well as what modifications to a CCS FDA considers to result in a new tobacco product. The comments requested that the definition of CCS be limited to only the product packaging that is designed or reasonably expected to alter the product characteristics after the time of manufacture. Comments stated that failure to make such a change would be inconsistent with the court's decision in

Philip Morris v. *FDA*, 202 F. Supp. 3d 31, 51 (D.D.C. 2016). Citing this case, which in the course of distinguishing between a product and its labeling, referenced "the physical attributes of the product itself, as distinct from its label or the package in which it is contained," the comments argue that the law's requirements for new tobacco products apply only when there are changes in "the physical attributes of a tobacco product--not its labeling or packaging." *Id.* Likewise, the comments stated that modifications to the CCS should result in a new tobacco product only if modifications are intended or reasonably expected to alter the characteristics of the product. The comments maintained that if the packaging's purpose is merely to maintain or preserve the characteristics of the product, it should only be considered packaging, not a CCS.

(Response 8) As described in the rule, FDA defines "component or part" as any software or assembly of materials intended or reasonably expected: (1) to alter or affect the tobacco product's performance, composition, constituents, or characteristics or (2) to be used with or for the human consumption of a tobacco product. Contrary to the commenter's assertion, packaging that constitutes the container closure system is intended or reasonably expected to affect or alter the performance, composition, constituents, or characteristics of the tobacco product (e.g., leaching substances that are then incorporated into a tobacco product), and is thus a component or part of a tobacco product. This is consistent with the holding of *Philip Morris*, 202 F. Supp. at 51, as is its converse: Packaging that is not the container closure system and is not intended or reasonably expected to affect or alter the performance, composition, constituents, or characteristics of the tobacco product is, therefore, not a component or part of a tobacco product. As such, packaging that is, for example, the packaging around a blister pack is not part of the PMTA review process if it is not intended or reasonably expected to alter or affect the performance, composition, constituents, or characteristics of the tobacco product within the

blister pack. However, where a change in the container closure system could affect the chemistry of the product, FDA requires the applicant, where it submits a PMTA, to demonstrate that permitting marketing of the product with the change in the container closure system is appropriate for the protection of public health.

For example, packaging materials constitute a container closure system if substances within that packaging are intended or reasonably expected to affect product moisture, e.g., when the manufacturer changes the package of a moist snuff from plastic to fiberboard, which can affect microbial stability and tobacco-specific nitrosamine (TSNA) formation during storage. Another example of this is when menthol or other ingredients are applied to the inner foil to become incorporated into the consumed product (Ref. 1). Packaging materials may also be intended or reasonably expected to affect the characteristics of a tobacco product by impacting the rate of leaching into, and ultimately, the amount of substances found in, the consumable tobacco product. In fact, it has been demonstrated that compounds in packaging materials may diffuse into snuff and affect its characteristics (Ref. 2). Thus, packaging material that affects the characteristics of a tobacco product by impacting the moisture level or shelf life of a tobacco product is a container closure system (e.g., a plastic versus a metal container of smokeless tobacco). A difference in tobacco moisture is reasonably expected to affect microbial growth in the product, extraction efficiency, and total exposure to nicotine or the carcinogens *N*-nitrosonornicotine (NNN) or 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) (Ref. 3).

Considering a distinct subset of packaging (i.e., container closure system) to be a component or part is consistent with the FD&C Act and furthers the fundamental purpose of the Tobacco Control Act to protect the public health. For example, section 900(1) of the FD&C Act defines an “additive” as any substance the intended use of which results or may reasonably be

expected to result, directly or indirectly, in its becoming a component or otherwise affecting the characteristic of any tobacco product (including any substance intended for use as a flavoring or coloring or in producing, manufacturing, packing, processing, preparing, treating, packaging, transporting, or holding), except that such term does not include tobacco or a pesticide chemical residue in or on raw tobacco or a pesticide chemical. Congress specifically included a broad definition of "additive" that encompasses not just substances that do in fact have such effects but also those that may reasonably be expected to have such effects. Similarly, if FDA were to adopt a narrow construction of "tobacco product" to exclude these materials, the Agency's ability to evaluate whether permitting the marketing of the new tobacco product was appropriate for the protection of public health (APPH) would be impeded, thereby leaving the Agency unable to fully execute its mission to protect the public health. The definition of "package" in section 900(13) of the FD&C Act does not dictate a contrary result and can be reasonably interpreted to mean that a distinct subset of packaging is also a component or part of a tobacco product.

18. Design

FDA defines "design" to mean the form and structure concerning, and the manner in which components or parts, ingredients, software, and materials are integrated to produce a tobacco product. This term refers to the physical properties of a tobacco product. Examples of design parameters include ventilation, paper porosity, filter efficiency, battery voltage and current operating range, and electrical heater coil resistance. FDA received one comment on this definition, as discussed below.

(Comment 9) One comment stated that the definition of the term "design" does not take into account the inherent variability that can occur in tobacco crops over the years. The comment stated that such variability may require manufacturers to alter, in a limited capacity,

certain characteristics of the product, in order to minimize variability of constituent levels in its final aerosol. The comment concluded that the proposed definition was rather narrow and did not allow for the control of emission levels through design adjustments. The comment recommended that the definition be amended to allow applicants to adjust design features for the sole purpose of accommodating natural variability of tobacco plants, without requiring the submission of a new PMTA or a supplemental PMTA.

(Response 9) FDA declines to make changes as a result of this comment. At this time, FDA does not intend to enforce the requirement of premarket review in section 910 for tobacco blending changes required to address the natural variation of tobacco (e.g., blending changes due to variation in growing conditions) to maintain a consistent product.[10] Where an applicant changes other characteristics of a tobacco product (i.e., characteristics other than tobacco blend) to minimize variability of the product, FDA intends to enforce the premarket authorization requirements, and the PMTA must contain all appropriate information for the distinct new tobacco product that would result from such changes.

19. Finished Tobacco Product

FDA defines "finished tobacco product" to mean a tobacco product, including all components and parts, sealed in final packaging (e.g., filters or filter tubes sold to consumers separately or as part of kits, or e-liquids sealed in final packaging sold to consumers either separately or as part of kits) or in the final form in which it is intended to be sold to consumers. FDA received one comment on this definition, as discussed below.

[10] For more information on FDA's enforcement of premarket review for tobacco blending changes, see the guidance entitled "Demonstrating the Substantial Equivalence of a New Tobacco Product: Responses to Frequently Asked Questions" available at https://www.fda.gov/tobacco-products/rules-regulations-and-guidance/guidance.

(Comment 10) One comment stated that the definition of the term "finished tobacco product" should conform to the definition previously used in the registration and listing guidance, which included the phrase "intended for consumer use."

(Response 10) FDA has edited the definition of the term "finished tobacco product" to include the phrase "or in the final form in which it is intended to be sold to consumers" to help clarify the meaning of the term "finished." We believe that by including products sold in the final form in which it is intended to be sold to consumers, we are capturing a variety of products including those intended for consumer use as requested by the commenter.

20. Harmful or Potentially Harmful Constituent (HPHC)

FDA defines "harmful or potentially harmful constituent" as any chemical or chemical compound in a tobacco product or tobacco smoke or emission that: (1) is or potentially is inhaled, ingested, or absorbed into the body, including as an aerosol or any other emission and (2) causes or has the potential to cause direct or indirect harm to users or nonusers of tobacco products. This definition aligns with the definition provided for in the guidance for industry entitled "'Harmful and Potentially Harmful Constituents' in Tobacco Products as Used in Section 904(e) of the FD&C Act."

The established list of HPHCs can be found on FDA's website at https://www.fda.gov/tobacco-products/rules-regulations-and-guidance/harmful-and-potentially-harmful-constituents-tobacco-products-and-tobacco-smoke-established-list (77 FR 20034, April 3, 2012). FDA issued a notice in the *Federal Register* of August 5, 2019 (84 FR 38032), seeking public comment on the proposed addition of 19 constituents to the established list of HPHCs. FDA is proposing these additions to reflect the range of tobacco products now subject to FDA's tobacco product authorities, including deemed tobacco products such as ENDS. FDA will

finalize the addition of these HPHCs to the established list, as appropriate, after reviewing public comment and generally intends to make any future updates to the established list of HPHCs through a similar notice and comment process.

FDA received one comment on this definition, as discussed below.

(Comment 11) One comment stated that FDA should either change the definition of the term "harmful or potentially harmful constituent" (HPHC) to include a list of all HPHCs for which testing results must be submitted in a PMTA or include a list of all such HPHCs elsewhere in the rule.

(Response 11) FDA declines to revise the definition of HPHC. In defining this term, FDA is describing criteria for what constitutes an HPHC and is not attempting to identify specific constituents. In contrast, section 904 of the FD&C Act requires FDA to establish, and periodically revise, a list of HPHCs. More importantly for PMTA content, as discussed in section VIII.B.9.a.v. of this document, an application would not be required to contain testing for all HPHCs; rather, it would be required to contain testing for constituents, including HPHCs, that are contained within and can be delivered by the type of product and contain a description of why the HPHCs that were tested are appropriate for the type of product.

FDA similarly declines to set forth a list of constituents that must be tested because it would be overly broad as it pertains to most tobacco products. It is FDA's understanding that manufacturers have information concerning what constituents might be emitted from their specific tobacco products. FDA believes that allowing applicants to use this knowledge in selecting the appropriate constituents for testing would result in a more efficient process for preparing PMTAs than requiring manufacturers to test for each constituent in a broad list, including HPHCs that might not pertain to the applicant's specific product.

21. Heating Source

FDA defines "heating source" as the source of energy used to burn or heat the tobacco product. Examples of a heating source include a flame or a rechargeable battery.

22. Ingredient

FDA defines "ingredient" as tobacco, substances, compounds, or additives added to the tobacco, paper, filter, or any other component or part of a tobacco product, including substances and compounds reasonably expected to be formed through a chemical reaction during tobacco product manufacturing. For example, an ingredient may be a single chemical substance, leaf tobacco, or the product of a reaction, such as a chemical reaction, in manufacturing. Examples of substances and compounds (ingredients) reasonably expected to be formed through a chemical reaction during tobacco product manufacturing include the following:

- the reaction of sugars with amines to form families of compounds with new carbon-nitrogen bonds, including Maillard reaction products and Amadori compounds;
- the reaction of sodium hydroxide with citric acid to form sodium citrate;
- the production of ethyl alcohol, a residual solvent, from ethyl acetate during production of tipping paper adhesive;
- products of thermolytic reactions, such as the production of carboxylic acids from sugar esters;
- products of enzymatically or nonenzymatically catalyzed reactions, such as the hydrolytic production of flavor or aroma precursors from nonvolatile glucosides; and
- products of acid-base reactions, such as removal of a proton from protonated nicotine to generate the basic form of nicotine ("free" nicotine).

23. Line Data

FDA defines "line data" to mean an analyzable dataset of observations for each individual study participant, laboratory animal, or test replicate. Line data typically provides information that is more useful to FDA's review of an application than data in its more "raw" forms because it allows information about time, people, and places involved in investigations to be organized and reviewed quickly, and it facilitates tracking of different categories of cases. FDA is requiring an applicant to submit line data rather than source data (also referred to as raw data) to allow for a more efficient review process. As described in § 1114.45, applicants are required to retain all source data in the event that FDA needs to inspect the data as part of its application review.

24. Material

FDA defines "material" to mean an assembly of ingredients. Materials are assembled to form a tobacco product, or components or parts of tobacco product. For example, material includes the glue or paper pulp for a cigarette where the paper pulp includes multiple ingredients (e.g., multiple types of tobacco, water, and flavors) assembled into the paper (or pulp depending on the water content). Another example of a material is a plastic composed of chemical substances that houses electrical components.

25. Marketing Granted Order

FDA defines "marketing granted order" to mean the order described in section 910(c)(1)(A)(i) of the FD&C Act that authorizes the new tobacco product to be introduced or delivered for introduction into interstate commerce.

26. Marketing Denial Order

FDA defines "marketing denial order" to mean the order described in section 910(c)(1)(A)(ii) of the FD&C Act that the product may not be introduced or delivered for introduction into interstate commerce.

27. Other Features

FDA defines "other features" to mean any distinguishing qualities of a tobacco product similar to those specifically enumerated in section 910(a)(3)(B) of the FD&C Act. The definition includes: (1) HPHCs (the definition of new tobacco product includes any modification to any constituents, including smoke constituents; section 910(a)(1)(B) of the FD&C Act) and (2) any other product characteristics that relate to the chemical, biological, or physical properties of the tobacco product. The term "other features" also encompasses other product characteristics that relate to the chemical, biological, and physical properties of the product that would not be included as a material, ingredient, design, composition, or heating source.

28. Premarket Tobacco Product Application or PMTA

FDA defines "premarket tobacco product application" or "PMTA" to mean the application described in section 910(b) of the FD&C Act. This term includes the initial premarket tobacco product application and all subsequent amendments.

29. "Premium" Cigar

As discussed in section VI.A. of this document, we are adding the *Cigar Ass'n of Am.* court's definition of "premium" cigars to § 1114.3. "Premium" cigars means a type of cigar that: (1) is wrapped in whole tobacco leaf; (2) contains a 100 percent leaf tobacco binder; (3) contains at least 50 percent (of the filler by weight) long filler tobacco (i.e., whole tobacco leaves that run the length of the cigar); (4) is handmade or hand rolled (i.e., no machinery was used apart from simple tools, such as scissors to cut the tobacco prior to rolling); (5) has no filter, nontobacco tip,

or nontobacco mouthpiece; (6) does not have a characterizing flavor other than tobacco; (7) contains only tobacco, water, and vegetable gum with no other ingredients or additives; and (8) weighs more than 6 pounds per 1,000 units.

30. Serious Adverse Experience

FDA defines "serious adverse experience" to mean an adverse experience that results in any of the following outcomes: (1) death; (2) a life-threatening condition or illness; (3) inpatient hospitalization or prolongation of existing hospitalization; (4) a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions (e.g., seizures that do not result in hospitalization, burns that result in damage to a limb or nerve damage); (5) a congenital anomaly/birth defect; or (6) any other adverse experience that, based upon appropriate medical judgment, may jeopardize the health of a person and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition. This could include, for example, carbon monoxide poisoning, which if left untreated, could result in long term and possibly delayed brain damage or heart damage.

FDA received one comment on this definition, as discussed below.

(Comment 12) One comment stated that the definition of the term "serious adverse experience" needs to be clarified, recommending that it be aligned with a similar definition used by FDA for drugs. Specifically, the comment requested that FDA further define the term "life-threatening condition or illness" in paragraph (b) of the definition to mean, as it does in the drug context, any adverse experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse experience as it occurred, i.e., it does not include an adverse experience that, had it occurred in a more severe form, might have caused death. The comment also requested that FDA restrict the "catch-all" in paragraph (f) of the definition so that

it focuses on "important medical events," similar to the definition for drugs, rather than "adverse experiences" as the definition currently does.

(Response 12) FDA declines to revise the definition of serious adverse experience because it captures the events for which FDA would need prompt notification once a product is on the market. Through paragraph (b) of the definition of "serious adverse experience," FDA is seeking information about adverse experiences carrying an immediate risk of death. In contrast, through paragraph (f) of the definition of "serious adverse experience," FDA is interested in receiving prompt notification of a condition that could have delayed consequences, for example, one that that could cause death or severe organ damage if left untreated, or immediate death had it occurred in a more severe form so we can investigate whether the condition could occur in a more severe form and cause death in different individuals. We believe that having paragraph (f) focus on adverse experiences appropriately captures this scope. Applicants with questions regarding whether an adverse experience qualifies as a serious adverse experience are encouraged to promptly contact FDA.

31. Submission tracking number or STN

FDA defines "submission tracking number" or "STN" to mean the number that FDA assigns to submissions that are received from an applicant, such as a PMTA and a supplemental PMTA. FDA has added this definition to the final rule on its own initiative to help clarify requirements to specify submission tracking numbers.

32. Unexpected Adverse Experience

FDA defines "unexpected adverse experience" to mean an adverse experience occurring in one or more persons in which the nature, severity, or frequency of the experience is not consistent with: (1) the known or foreseeable risks associated with the use or exposure to the

tobacco product as described in the PMTA (including the results of human subject investigations) and other relevant sources of information, such as the product labeling and postmarket reports; (2) the expected natural progression of any underlying disease, disorder, or condition of the persons(s) experiencing the adverse experience and the person's predisposing risk factor profile for the adverse experience; or (3) the results of nonclinical investigations.

FDA received one comment regarding this definition, as discussed below.

(Comment 13) One comment stated that the definition of unexpected adverse experience is unnecessarily complex and would likely lead to unduly burdensome reporting. The comment noted potential difficulties with assessing what constitutes a "foreseeable" risk and expressed a belief that the definition should be aligned with those found in other product groups that focus on unexpected adverse experiences being those that are not currently listed on product packaging and not previously observed.

(Response 13) FDA declines to revise the definition of unexpected adverse experience because it captures the events and information that should be disclosed. This information is important to FDA's ongoing monitoring of a tobacco product because it would alert the Agency to the potential scope and frequency for health risks that were not previously considered as part of application review and may inform a determination of whether the marketing granted order should be withdrawn or temporarily suspended. Foreseeable risks are harms that could reasonably be predicted based upon the content of the PMTA and other available sources of information and is largely based on mechanism of action or composition of the tobacco product.

33. Vulnerable populations

The proposed rule did not expressly discuss vulnerable populations. However, FDA received several comments regarding this issue, as discussed below.

(Comment 14) Multiple comments raised concerns related to the lack of reference to vulnerable populations in the proposed rule. One comment stated that the tobacco industry has a history of marketing its products to individuals with specific characteristics, including, but not limited to veterans, individuals with a low socioeconomic status (SES), and vulnerable populations. The comment requested that FDA require applicants to specify detailed demographic information in their marketing plans, including the targeting of its marketing by SES as part of a PMTA. Another comment stated that a definition of vulnerable populations should be included in the final rule. In addition, multiple comments requested FDA require PMTAs to contain a consideration of the effects of permitting the marketing of the new tobacco product on vulnerable or sensitive subpopulations (e.g., individuals whose health has been compromised).

(Response 14) FDA agrees that consideration of vulnerable populations is an important part of determining whether permitting the marketing of a new tobacco product would be APPH. As discussed in section IX.D.1., FDA considers many factors when making its APPH determination, including the likelihood that existing users of tobacco products will stop using such products and the likelihood that nonusers of tobacco products will start using. This could include information regarding the marketing of a new tobacco product that may produce a positive effect for some subpopulations while producing differential effects for other subpopulations. For example, a non-combusted tobacco product that may help current adult smokers transition away from cigarettes may appeal to and lead to tobacco product initiation among youth and young adults who have never used tobacco products.

To ensure FDA understands the full health impact of the product, it is important for FDA to consider vulnerable populations and how the marketing of the new tobacco product can impact

the likelihood that existing users of tobacco products will stop using such products and the likelihood that nonusers will start using the product. FDA has revised the rule to emphasize the importance of considering the effect of marketing a new tobacco product would have on vulnerable populations as well defined the term "vulnerable populations" in § 1114.3 to mean groups that are susceptible to tobacco product risk and harm due to disproportionate rates of tobacco product initiation, use, burden of tobacco-related diseases, or decreased cessation. Relevant vulnerable populations will vary depending on the type of tobacco product and may change over time, and can include, but are not limited to, youth and young adults, those who are of low SES, certain racial or ethnic populations, underserved rural populations, people with co-morbid mental health conditions or substance use disorders, military or veteran populations, people who are pregnant or are trying to become pregnant, and sexual or gender minorities (Refs. 4-9). Also note that section VIII.B.6.b. includes SES as an example demographic characteristic to clarify the range of potential characteristics that may be included in descriptions of marketing plans.

VIII. Premarket Tobacco Product Applications (Part 1114, Subpart B)

A. Application Submission (§ 1114.5)

As described in § 1114.5, if an applicant seeks a marketing granted order under the PMTA pathway for its new tobacco product, it would be required to submit a PMTA to FDA and receive a marketing granted order before the tobacco product may be introduced or delivered for introduction into interstate commerce. An applicant submitting a PMTA to FDA should include all information required to be in a PMTA as part of its initial submission, including all sections specified in § 1114.7(a), except for product samples which, if required, must be submitted after a PMTA is accepted for review as described in the discussion § 1114.7(e) in section VII.B.5 of this

document. Submitting a complete application as part of an initial submission is important because, as explained in the discussion of § 1114.27 in section VIII.B, FDA may refuse to accept or file an incomplete application for review.

FDA received several comments regarding the scope of products required to submit a PMTA.

(Comment 15) Some comments request that certain tobacco products, such as ENDS and oral tobacco derived nicotine, be exempt from the PMTA premarket pathway or that a different premarket pathway be created for them. The comments described certain products as significantly less harmful than other products, which they contended justifies either an exemption from the requirements of the PMTA pathway or a creation of a streamlined pathway under which products can be authorized based upon a few approaches, such as the submission of significantly less information that would be required under this rule. Other comments requested a similar streamlined pathway for small businesses due to the cost of preparing a PMTA.

(Response 15) As described in detail throughout this rule, the information required by part 1114 is necessary to ensure FDA has sufficient information to consider, as required by section 910(c) of the FD&C Act, the potential risks and benefits of a new tobacco product to the health of the population as a whole in determining whether the marketing of that product would be appropriate for the protection of public health. FDA declines to create a streamlined pathway for certain tobacco product categories or manufacturers that permits the submission of significantly less information than required by this rule because it would result in FDA having insufficient information to make its statutorily required determinations under section 910(c) of the FD&C Act. Consistent with the deeming final rule,[11] we also decline the request to exempt

[11] See the deeming final rule (81 FR 28974) for responses to similar comments requesting alternative or abbreviated PMTA pathways and exemptions from the requirements of premarket review.

products from the requirements of PMTA or from premarket review more broadly. Section 910 of the FD&C Act establishes the procedures that must be followed before a new tobacco product can be authorized for marketing and it applies to all new tobacco products.

B. Required Content and Format (§ 1114.7)

1. General

As explained in § 1114.7(a), the rule requires each PMTA to contain sufficient information necessary for FDA to determine whether the grounds for denial of an application listed in section 910(c)(2) of the FD&C Act apply to the PMTA, which includes the following sections:

- general information (as described in § 1114.7(c));
- descriptive information (as described in § 1114.7(d));
- product samples (as described in § 1114.7(e));
- labeling (as described in § 1114.7(f));
- statement of compliance with part 25 (21 CFR part 25) (as described in § 1114.7(g));
- summary (as described in § 1114.7(h));
- product formulation (as described in § 1114.7(i));
- manufacturing (as described in § 1114.7(j));
- health risk investigations (as described in § 1114.7(k));
- the effect on the population as a whole (as described in § 1114.7(l)); and
- certification statement (as described in § 1114.7(m)).

As described in section VIII.B of this document, if the application does not appear to contain these sections and the information required therein (except for product samples), the Agency may refuse to accept the application for review under § 1114.27(a)(1). As described in

section VIII.B, if a PMTA does not contain sufficient information required by these sections to permit a substantive review, including substantive information regarding broad areas of scientific information noted where appropriate in this document, FDA may refuse to file the application under § 1114.27(b)(1).

2. Format

Section 1114.7(b) provides the general requirements for the format of the application and would require the applicant to submit the application with the appropriate FDA form(s) (i.e., Form FDA 4057 (Ref. 10) and Form FDA 4057b (Ref. 11)). Section § 1114.7(b)(1) would require the application and any amendments to contain a comprehensive index and table of contents and be well organized, legible, and written in the English language. The comprehensive index would include the listing of files and data associated with those files (e.g., for an application that is electronically submitted, the comprehensive index would include the listing of files and associated metadata). FDA is also requiring that documents that have been translated from another language into English must be accompanied by the original language version of the document, a signed statement by an authorized representative of the manufacturer certifying that the English language translation is complete and accurate, and a brief statement of the qualifications of the person who made the translation (e.g., education and experience). This information would help FDA ensure that the English language translations of documents are complete and accurately reflect the content of the original documents.

As described in § 1114.49, FDA is requiring that the PMTA and all supporting documents be submitted to FDA in an electronic format that the Agency can process, review, and archive, unless the Agency has previously granted a waiver from these requirements. An application would not be considered received until CTP's Document Control Center has received

an application that the Agency can process, review, and archive. Applicants that are unable to submit their applications in electronic format may seek a waiver from the electronic filing requirement, in accordance with § 1114.49.

FDA received several comments regarding PMTA format, as discussed below.

(Comment 16) One comment stated that FDA must address inconsistencies between the ENDS PMTA Guidance and the PMTA Proposed Rule, citing differences such as marketing plans and application organization.

(Response 16) FDA will update the ENDS PMTA Guidance to ensure it is consistent with the requirements and recommendations in this rulemaking. When updated, the ENDS PMTA Guidance will provide updated important product-specific recommendations for applicants submitting PMTAs for ENDS. In addition, if applicants wish to discuss the development of a PMTA, the applicant may request a meeting as set forth in the guidance for industry and investigators entitled "Meetings with Industry and Investigators on the Research and Development of Tobacco Products."[12]

(Comment 17) One commenter stated that while the proposed rule notes FDA's intent to provide information regarding acceptable technical specifications for electronic submissions, it was not aware of FDA having done so and requested that the final rule contain clear and consistent expectations for electronic submissions so that industry can properly plan and prepare applications in advance of submission.

(Response 17) Applicants can visit FDA's webpage for more information on electronic submission, including electronic submission file formats and specifications. As of the date of the publication of this rule, this information is located at: https://www.fda.gov/industry/fda-

[12] Available at https://www.fda.gov/tobacco-products/rules-regulations-and-guidance/guidance

esubmitter/using-esubmitter-prepare-tobacco-product-submissions. This webpage also contains a link to the document "Electronic Submission File Formats and Specifications," which provides additional helpful information. As mentioned in the proposed rule, FDA intends to update this information as needed to accommodate changes in technology.

FDA has created these format requirements using its authority under sections 701 and 910 of the FD&C Act to efficiently enforce premarket review requirements. The requirements in § 1114.7(b) are intended to address some of the problems we have seen with applications to date. For example, some applications have been submitted to FDA in a proprietary or password protected format without providing FDA access or password information. Following up with an applicant to obtain access or password information takes time and contributes to delays. In addition, some electronic submission files have not been of a static format, and thus, the pages reformat, repaginate, rebullet, or redate each time the document is accessed. For example, Microsoft Word files can change upon opening by FDA reviewers, while PDF files remain as the applicant intended. Receiving applications with these issues affects our ability to cross-reference, share (internally), and efficiently evaluate information. Also, FDA is required under regulations governing Federal records to maintain many files long-term, and in a "sustainable" format (for more information on sustainable formats, please refer to National Archives and Records Administration Bulletin 2014-04, https://www.archives.gov/records-mgmt/bulletins/2014/2014-04.html), § 1114.7(b) will ensure that these files can be managed, opened, and read by the Agency for the duration of the retention period.

Finally, § 1114.7(b)(2) will allow an applicant to include content in a PMTA by cross-reference to a tobacco product master file (TPMF) or a pending MRTPA for the same tobacco product submitted under section 911 of the FD&C Act. A TPMF is a file that is voluntarily

submitted to CTP that contains trade secret and/or confidential commercial information about a tobacco product or component that the owner does not want to share with other persons. TPMFs are a beneficial tool for manufacturers, component suppliers, and ingredient suppliers, and can assist the tobacco product submission process. TPMFs allow individuals to rely on the information contained in a TPMF in a submission to FDA without the TPMF owner having to disclose the information to those individuals. TPMFs are typically used to prevent the disclosure of information that contains trade secrets or confidential commercial information. One situation in which TPMFs might be useful in submitting a PMTA is where an applicant is seeking marketing authorization for a new tobacco product that is made using a component or part, or ingredient that is purchased from another tobacco product manufacturer (e.g., blended tobacco or an e-liquid). Applicants must demonstrate they have the right to reference the TPMF to be able to include content by cross-reference, such as by having the master file holder provide a letter of authorization. Applicants must specify the master file number and clearly identify the specific content that it is incorporating into its PMTA. For FDA's current thinking on the use of TPMFs, please consult the guidance for industry entitled "Tobacco Product Master Files."[13]

(Comment 18) A number of comments submitted similar concerns about the lack of data standardization, stating that FDA should standardize the data required to be submitted and allow companies to rely on the same pool of standardized data where it applies to similar aspects of their new tobacco product, such as submitting the same ingredients, to improve the efficiency for both application submission and review.

(Response 18) When companies want to rely on the same pool of data, FDA encourages the use of shared resources, such as tobacco product master files, where appropriate.

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[13] Available at: https://www.fda.gov/tobacco-products/rules-regulations-and-guidance/guidance.

Applicants may also include content in a PMTA by cross-reference to a pending MRTPA for the same tobacco product.[14] FDA recommends that applicants seeking to market a new tobacco product that has not previously received marketing authorization as a modified risk tobacco product (MRTP) submit a single application to seek both a marketing granted order and a modified risk granted order (i.e., a combined PMTA and MRTPA); however, where an applicant chooses to submit a separate PMTA and MRTPA, FDA recommends that an applicant submit the full text of any common content (e.g., the manufacturing or product formulation sections) in a PMTA and include it in the MRTPA by cross-reference. This approach would prevent any transcription errors and would allow for a more effective review by FDA because the content would only need to be reviewed once to be considered as part of both applications.

Under this rule, except as described in subpart B, FDA will not consider content included by cross-reference to any other sources of information outside of a submission. An applicant may use internal cross-references for any content that would need to be referenced in multiple sections of a PMTA (i.e., include the full text of the content in one section and use cross-references to the content in other sections), rather than including the full text of the same information multiple times. If an applicant wishes to include information it has previously submitted to FDA other than a master file or a pending MRTPA (e.g., portions of an SE Report or previously submitted PMTA for a different product), the applicant must include the full text of such information in its PMTA. FDA is implementing this restriction because cross-referencing

[14] FDA has not included MRTPAs that resulted in a modified risk order in the list of documents that an applicant may cross-reference as part of a PMTA. Because a new tobacco product must receive premarket authorization under section 910 of the FD&C to be introduced or delivered for introduction into interstate commerce, FDA does not intend to act on a MRTPA unless the product has a pending application seeking, or has already received, marketing authorization under section 910, or is a Pre-Existing Tobacco Product. Such an approach will allow FDA to efficiently enforce section 911 of the FD&C Act by focusing its efforts on only those applications that could potentially result in a tobacco product being introduced to the market.

information from other types of applications (e.g., SE Reports, previously submitted PMTAs for different products) can make review difficult and contribute to delays in the review process.

(Comment 19) One comment stated that FDA should amend the application format requirements so that it allows PMTAs to include information by cross-reference to parts of previously filed PMTAs for different products that contain studies applicable to the new tobacco product.

(Response 19) The format requirements of § 1114.7(b) permit an applicant to cross-reference a tobacco product master file or a pending MRTPA for the same tobacco product. FDA declines to revise § 1114.7(b) to broadly allow an applicant to cross-reference information contained in any previously filed PMTA because it could result in a process in which FDA would have to pull information from a variety of sources to have a complete PMTA for review, which would increase the potential for error and decrease the efficiency of FDA's review. Additionally, permitting an applicant to broadly cross-reference information presented for different products would not necessarily result in a more efficient review process. FDA is limiting the ability of applicants to cross-reference content from previously reviewed PMTAs to specific circumstances set forth in §§ 1114.15 and 1114.17 where it would facilitate application review. Where an applicant intends to submit the same information in multiple applications submitted at different periods in time, FDA recommends establishing a TPMF containing the information so that it could be included by cross-reference in each application.

An applicant may also submit a single premarket submission for multiple products (i.e., a bundled PMTA) and a single, combined cover letter and table of contents across all products; however, when FDA receives a premarket submission that covers multiple new tobacco

products, we intend to consider information on each product as a separate, individual PMTA and it is important to identify the content that pertains to each product.

(Comment 20) Multiple comments requested additional information regarding how they should bundle multiple PMTAs for related or similar tobacco products into a single submission. One comment requested that FDA formally clarify whether e-liquid manufacturers and manufacturers of closed-system devices may bundle applications for multiple flavors of e-liquid that share common nicotine strengths, package sizes, propylene glycol/vegetable glycerin ratios, or other characteristics. Another comment requested information regarding how a manufacturer should submit PMTAs for products that are used together but may be sold separately (e.g., closed e-liquids, such as cartridges or pods that are not intended to be refillable, and the e-cigarette with which the e-liquids would be used).

(Response 20) FDA recommends that an applicant group PMTAs for products in the same subcategory (see § 1114.7(c)) that are produced by the same manufacturer into a single submission because they will likely share a significant amount of application content. An applicant grouping PMTAs together by subcategory would be required to use Form FDA 4057b to identify the products that are contained in the grouped submission. Additionally, FDA recommends an applicant group PMTAs for a new tobacco product and its components or parts into a single submission where an applicant seeks to sell the components or parts separately. As discussed in section VIII.B.3. of this document, FDA generally considers an open e-cigarette, also referred to as a refillable e-cigarette, to be an e-cigarette that includes a reservoir that a user can refill with an e-liquid of their choosing. A closed e-cigarette is an e-cigarette that includes an e-liquid reservoir that is not refillable, such as a disposable cigalike, or that uses e-liquid contained in replaceable cartridges or pods that are not intended to be refillable. For example, if

a manufacturer wanted to sell a closed e-cigarette and the closed e-liquids (e.g., nonrefillable cartridges or pods) that could be used with the e-cigarette separately, it should group a PMTA for the e-cigarette and PMTAs for each of the e-liquids into a single submission. FDA does not recommend grouping open e-liquids and open ENDS devices that will be sold separately in a single submission except for instances where the applicant is seeking a marketing granted order for the e-liquids that have been designed by the manufacturer to be used solely in a particular open ENDS device. FDA reminds applicants that we intend to consider information on each product as a separate, individual PMTA, so it is important to identify the content that pertains to each product. If an applicant does not clearly identify the content in the submission that makes up the PMTA for each product, FDA may refuse to accept or refuse to file the submission.

3. General Information

Section 1114.7(c), including table 1, lists the information that must be included in the general information section of the PMTA. This information consists of general administrative information that includes the type of submission, the new tobacco product with unique identifiers, and contact information. Specifically, table 1 to § 1114.7(c)(3)(iii) provides for the information needed to help ensure that we are able to identify and evaluate each product more accurately and efficiently. This table includes, among other categories, requirements to submit general information related to ENDS product category and several subcategories of ENDS. FDA generally considers ENDS to be electronic nicotine delivery systems that deliver aerosolized e-liquid when inhaled. The term "e-cigarette" refers to an electronic device that delivers e-liquid in aerosol form into the mouth and lungs when inhaled; it is also sometimes referred to as an aerosolizing apparatus. An open e-cigarette, also referred to as a refillable e-cigarette, is an e-cigarette that includes a reservoir that a user can refill with an e-liquid of their choosing. A

closed e-cigarette is an e-cigarette that includes an e-liquid reservoir that is not refillable, such as a disposable cigalike, or that uses e-liquid contained in replaceable cartridges or pods that are not intended to be refillable. For additional information on ENDS, consult the ENDS PMTA Guidance.

In this final rule, we have revised table 1 to § 1114.7(c)(3)(iii) to help ensure that FDA is able to identify and evaluate each product more accurately and efficiently. For example, the table includes a waterpipe head as a subcategory of waterpipe. A waterpipe head is a container that is typically made of materials like clay, marble, or glass and is used to contain coal and tobacco during a waterpipe smoking session.

Additionally, the cigarette product category no longer lists noncombusted cigarettes as a subcategory. Instead, for purposes of PMTA review, a "heated tobacco product" category has been added to the identification tables. Under this revised taxonomy, some tobacco products may fit under more than one category. This PMTA review category should be used for (among others) tobacco products that meet the definition of a cigarette but are not combusted (products that do not exceed 350 ^{o}C). Heated tobacco products (HTP) can be used with e-liquids, other types of tobacco filler, or consumable (e.g., wax, oils). If, however, a tobacco product can only be used with e-liquids, it should be captured under "ENDS" and not the HTP category. To ensure we have all the information we need to efficiently and effectively review your application, if the product that is the subject of your application is a heated tobacco product and is not an ENDS product, you should submit information under § 1114.7(c)(3)(iii) under the heated tobacco product category and comply with the design parameter requirements for HTPs in

table 22 to § 1114.7(i)(2)(ii).[15] FDA believes these product categorizations will help ensure that applications include the most relevant information for their product, which in turn will facilitate FDA's review and ability to reach an authorization decision.

Other changes to table 1 to § 1114.7(c)(3)(iii) include FDA's clarification under the "cigar" category to designate "leaf-wrapped" cigars as *unfiltered* to more accurately describe the product category, as "leaf-wrapped" cigars typically do not include filters; under the "waterpipe" category, "waterpipe" diameter has been added to distinguish between waterpipes of different sizes (width/diameter and height) where all other uniquely identifying information is the same; and under the "pipe tobacco filler" category, "tobacco cut style" has been added to distinguish between different cut pipe tobacco filler, e.g., standard cut, such as shag cut, bugler cut, loose cut, etc.; or a pressed cut, such as flake, cube cut, roll cake, etc. or a mixture. Additionally, FDA has removed the requirement to provide tobacco cut size from the unique identification requirements for smokeless tobacco and cigar tobacco filler. A specific numerical value for this field is not necessary to uniquely identify the specific product to which the PMTA pertains, as it can be described further through identification of additional properties (e.g., fine cut, long cut). However, to fully characterize the tobacco product and evaluate its health effects, information to determine tobacco cut size is required under § 1114.7(i)(2)(ii) for the product categories specified in that section.

Additionally, across all product categories, the subcategory of "co-package" has been removed from § 1114.7(c). If an applicant submits a PMTA for a co-packaged tobacco product,

[15] Note that the purpose of the unique identification tables in § 1114.7(c)(3)(iii) is to explain what information we need to identify and evaluate different types of products, and § 1114.7(i)(2)(ii) explains the design parameters needed for product characterization (see discussion below). The categorization of HTPs in § 1114.7(c)(3)(iii) and (i)(2)(ii) does not extend to other legal requirements beyond those associated with unique identification and product characterization for premarket review.

the unique identification of this co-packaged product would require the specific items needed to identify each product within the co-package. For example, if the co-package is a pouch of roll-your-own (RYO) tobacco filler that contains rolling papers inside the pouch, the applicant would identify the tobacco product as a co-packaged product and provide the unique identification for both the RYO tobacco filler and the rolling papers.

The PMTA must contain the following information using the FDA-provided form(s) (i.e., Form FDA 4057 (Ref. 10) and Form FDA 4057b (Ref. 11)), as appropriate:

- applicant name, address, and contact information;
- the name, address, and contact information for the authorized representative or U.S. agent (for a foreign applicant). As required by § 1105.10(a)(5) for application acceptance, a foreign applicant must identify a U.S. agent (i.e., an individual located in the United States who is authorized to act on behalf of the applicant for the submission) to help FDA ensure adequate notice is provided to applicants for official Agency communications, assist FDA in communicating with the foreign applicant, and help the Agency to efficiently process applications and avoid delays; and
- information to uniquely identify the product. Providing unique identifying information is important to aid in FDA's review because it ensures FDA has information readily available to distinguish the tobacco product from other tobacco products, including additional new tobacco products in a bundled submission (i.e., more than one application contained in a single submission), and assists FDA in performing its acceptance and filing reviews. The required unique identifying information includes:
    - the manufacturer;

- product name(s), including the brand and subbrand (or other commercial name(s) used in commercial distribution); and
- product category; product subcategory; and product properties, as provided by the table in § 1114.7(c). The applicant must select and provide the appropriate category, subcategory, and product properties for the new tobacco product. As discussed previously, if an applicant submits a PMTA for a co-packaged tobacco product, the unique identification of this co-packaged product must include the specific items needed to identify each product within the co-package. For example, if the co-package is a pouch of RYO tobacco filler that contains rolling papers inside the pouch, the applicant must identify the tobacco product as a co-packaged product and provide the unique identification for both the RYO tobacco filler and the rolling papers. This product-specific information is required under sections 910(b)(1)(B) and (G) of the FD&C Act and this rule requires its inclusion in the general information section of the submission to help FDA quickly check whether the product is within CTP's purview and identify the specific product that is the subject of the submission. For more information regarding product properties and why specific properties are a required part of an application, see the discussion of § 1114.7(i)(1) in section VIII.B.9. It is important to note that for the characterizing flavor product property, the applicant must state "none" if it does not consider the product to have a characterizing flavor. FDA encourages applicants that have questions regarding how to describe their product's characterizing flavor to contact FDA prior to submission.

For each type of tobacco product, the applicant should also include any additional properties to fully identify the tobacco product, if applicable. For example, use of product

descriptors such as “extra-long” should be identified. While failure to include such additional properties to help uniquely identify the tobacco product would not serve as the basis for FDA refusing to accept an application under § 1114.27(a)(1), it would likely slow down the substantive review process.

FDA received a few comments regarding § 1114.7(c)(3), as discussed below.

(Comment 21) One comment stated that § 1114.7(c)(3)(iii) should be amended to require disclosure of all flavoring agents regardless of whether they constitute characterizing flavors and all solvents rather than just propylene glycol and glycerin in all new tobacco products.

(Response 21) We decline to make this proposed edit, because such information is already required as part of the full listing of all of the product’s ingredients, additives, and constituents in § 1114.7(i)(1)(ii). Section 1114.7(c)(3)(iii), entitled “general information,” is intended to allow FDA to quickly determine whether the product is under CTP’s jurisdiction and readily identify the specific product that is the subject of the application. A complete listing of all flavoring agents and solvents in this section would not further the purpose of this section.

(Comment 22) One comment requested that FDA amend § 1114.7(c)(3)(iii) to remove the “dissolvable” tobacco product subcategory and replace it with design parameters for an “oral tobacco-derived nicotine (OTDN)” subcategory. The comment stated that not only does ”dissolvable” more appropriately describe a product trait, dissolvable products are less prevalent on the market today than OTDN products.

(Response 22) FDA declines to remove the “dissolvable” tobacco product subcategory and replace it with “oral tobacco-derived nicotine (OTDN).” In 2009, the Family Smoking Prevention and Tobacco Control Act authorized FDA to regulate, among other things, smokeless tobacco products, the definition of which includes some dissolvables that contain finely ground

tobacco. While design parameters of the dissolvable tobacco products may resemble those of OTDN, the OTDN subcategory could imply that such products only contain nicotine that is derived from tobacco, and not finely ground tobacco. This narrow definition would exclude dissolvable tobacco products that contain finely ground tobacco. As discussed in section VIII.B.3. of this document, applicants are required to identify the product category and subcategory in a PMTA to help FDA quickly check whether the product is within CTP's purview and identify the specific product that is the subject of the submission. Where an applicant believes its new tobacco product, such as OTDN, does not fit within a product category set forth in the rule, it should identify the product category as "other."

(Comment 23) One comment stated that FDA should remove the requirement to identify the category and subcategory of the tobacco product in § 1114.7(c)(3), because applications should compare their products to all other tobacco products and product categories are not contemplated under section 910(b) of the FD&C Act. The comment also stated that there is no justification to support the potential for users to switch between products within categories when real-world evidence shows that current users may switch to products from different categories.

(Response 23) FDA declines to remove the requirement to identify a product's category and subcategory. Not only does this information allow FDA to identify the product, it provides important context for information contained in the application, including but not limited to health risks associated with product design and its constituents, product and packaging design risks and misuse hazards, principles of operation, and warning statement requirements. Specifically, identifying a product's category and subcategory ensures that FDA is able to distinguish between products that have the same brand and subbrand, but a different category or subcategory, which may be associated with different health risks, design risks or even have different warning

statement requirements. For example, if an applicant submits a PMTA for a product that has the same brand and subbrand as another product but has been identified as smokeless tobacco, FDA will review the product labeling to ensure it complies with category specific applicable requirements such as the Comprehensive Smokeless Tobacco Health and Education Act. Additionally, understanding the category will allow FDA to determine whether the application meets the requirement in § 1114.27(b)(1)(ii)(B) to compare the health risks of the new tobacco product to the health risks of products in the same product category and products in at least one different product category.

Section 1114.7(c) also includes the following requirements:

- the type of PMTA. The applicant is required to state the type of PMTA the applicant is submitting (i.e., PMTA, supplemental PMTA, or resubmission);
- whether the applicant requests that FDA refer the PMTA to the Tobacco Products Scientific Advisory Committee (TPSAC). An applicant should briefly describe its justification for a request to refer the PMTA to TPSAC. FDA retains the discretion to refer an application to TPSAC but will consider an applicant's request as part of its determination;
- identifying information regarding any prior submissions relating to the new tobacco product, including STNs, where applicable. The types of prior submissions include premarket applications, such as PMTAs, SE Reports, and exemption requests, as well as other submissions to FDA including MRTPAs and submissions related to investigational tobacco products. The regulatory history of a tobacco product can provide useful context for FDA's review of a submission;
- dates and purpose of any prior meetings with FDA regarding the new tobacco product;

- if the tobacco product has previously been commercially marketed[16] in the U.S., the dates during which the tobacco product was marketed;
- address and the Facility Establishment Identifier (FEI) number(s), if available, of the establishment(s) involved in the manufacturer of the new tobacco product. This information will assist the Agency with environmental impact considerations and determinations under part 25 by helping FDA understand the location of manufacturing and scale of products that would be manufactured. Additionally, it helps FDA schedule and conduct facility inspections;
- a brief statement regarding how the PMTA satisfies the content requirements of section 910(b)(1) of the FD&C Act. This could consist of a table reproducing the section 910(b)(1) requirements and listing the sections or page numbers of the PMTA that satisfy the requirements. FDA is requiring this brief statement under authority of sections 701(a) and 910(b)(1)(G) of the FD&C Act, which will allow FDA to more quickly locate application content necessary to determine whether a PMTA should be accepted and filed for further review under § 1114.27;
- a brief description of how permitting the marketing of the new tobacco product is expected to be appropriate for the APPH. This description should be no more than a sentence or two that highlights the key product characteristics and study results the applicant believes would make the marketing of the product APPH (e.g., the product delivers significantly lower levels of a specific HPHCs to users than the tobacco products they are currently consuming, which studies indicate may result in decreased morbidity and mortality); and

[16] As described in Section IV.B.4. of this document, this includes products that were commercially marketed in test markets.

- a list identifying all enclosures, labels, and labeling being submitted with the application. This list will help FDA identify application content and ensure a PMTA contains all the information the applicant intended to submit.

FDA received several comments regarding these requirements (§ 1114.7(c)(4) through (12)), as discussed below:

(Comment 24) One comment stated that FDA should refer all PMTAs to TPSAC and should make all PMTAs available for public comment. The comment stated that if referring all applications to TPSAC is unfeasible, FDA should at least refer applications from major tobacco companies and representative applications from smaller companies.

(Response 24) We decline to take the comment's suggestion. Under section 910(b)(2) of the FD&C Act, FDA has the discretion, on its own initiative or upon the request of an applicant, to refer a PMTA to TPSAC for reference and for submission of a report and recommendation respecting the application. Referring an application to TPSAC is a lengthy process that requires extensive time and resources, including the significant back-and-forth process with an applicant to redact trade secrets and confidential commercial information in an application before it can be made publicly available. Receiving and reviewing public comments also requires significant time and resources. It would not be feasible to redact all PMTAs, receive and consider public comments, and receive and consider TPSAC's report and recommendations prior to acting on the expected high volume of applications the comment is suggesting go to TPSAC within the 180-day review period required by section 910(c) of the FD&C Act.

(Comment 25) Multiple comments stated that FDA should require applicants to specify whether the new tobacco product is a deemed tobacco product that has been on the market prior to the deadline for submitting a PMTA and, if so, require the submission of information

regarding the marketing of the product prior to application submission, including items such as prior sales, labeling, advertising, and marketing strategy. One comment also requested that FDA require an applicant describe whether the prior marketing of its product has been APPH and deny applications where this has not been the case.

(Response 25) FDA has amended the rule to require a PMTA to specify the prior dates, if any, during which the tobacco product was initially marketed. Additionally, the requirement in § 1114.7(k) to submit full reports of investigations that are published or known to, or which should reasonably be known to, an applicant includes the time period during which an applicant previously marketed a deemed tobacco product. While information relating to the prior marketing of a tobacco product may inform FDA review of a PMTA, FDA declines to require an applicant to describe whether it believed its prior marketing of a product was APPH, or necessarily deny an application where prior marketing was not APPH. FDA will make its own determination as to whether permitting the marketing of the new tobacco product is APPH based on all of the contents of the application. In addition, FDA has authority to include postmarket requirements to help ensure that marketing of the product after authorization continues to be APPH.

4. Descriptive Information

Section 1114.7(d) requires applicants to provide descriptive information that outlines the major aspects of the new tobacco product, which is required to be submitted under section 910(b)(1)(A), (D), and (G) of the FD&C Act. This information includes:

- a concise description of the new tobacco product (e.g., the product is a portioned smokeless tobacco product made using a blend of burley and bright tobacco);

- a statement identifying all tobacco product standards issued under section 907 of the FD&C Act that are applicable to the new tobacco product and a brief description of how the new tobacco product fully meets the identified tobacco product standard(s). If the new tobacco product deviates from such standard(s), if applicable, the rule requires the application to include adequate information to identify and justify those deviations;
- the product name(s) as designated on the product's label;
- a description of problems identified in prototypes that are the subject of studies contained in the application, or previous or similar versions of the new tobacco product that were marketed, if any. This includes information regarding any health risks such as overheating, fires, or explosions as well any information regarding manufacturing issues related to the product, such as packaging defects that could pose a health risk. If there are previous or similar versions that were marketed or that are the subject of studies in the application, the rule requires the applicant to include a bibliography of all reports regarding the previous or similar version of the product, whether adverse or supportive. FDA requires this information under section 910(b)(1)(A) and (G) of the FD&C Act to assess whether any known issues with a predecessor product that could affect the health risks of the new tobacco product have been addressed; and
- any restrictions on the sale, distribution, advertising, or promotion of the new tobacco product (as described in section 910(c)(1)(B) of the FD&C Act) that the applicant proposes to be included as part of a marketing granted order, if issued. The applicant may choose to propose restrictions on the sales and distribution of the tobacco product to help support a showing that the marketing of the product is appropriate for the protection of the public health (e.g., a restriction that decreases the likelihood that those who do not

currently use tobacco products will initiate tobacco product use with the new tobacco product). If an applicant does not wish to propose any additional restrictions, it must explicitly state that it proposes no restrictions. As described in § 1114.31, FDA may consider these proposed restrictions during its review of the PMTA and, where appropriate, include applicant proposed restrictions in the marketing granted order for the product together with any additional restrictions FDA may require.

FDA received many comments regarding the descriptive information requirements, as discussed below.

(Comment 26) Multiple comments requested that FDA revise the requirement in § 1114.7(d)(4). One comment stated that section 910(b)(1)(B) of the FD&C Act limits review to the new tobacco product that is the subject of the application and does not permit review of other products. The comments also stated that the terms "previous or similar version," "prototype," and "problem" are so vague that they would leave applicants guessing at what information must be included. The comments concluded by stating that a product's effects on public health should be determined based on data about the product in its current form.

(Response 26) FDA disagrees with the comments statement that FDA cannot require this information or consider it during product review. FDA is requiring the submission of information regarding prototypes and previous or similar versions of the tobacco product to assess whether an applicant has addressed any known issues with a predecessor product that could affect the health risks of the new tobacco product. The terms "previous or similar version," or "prototype," mean any previous generation, model, or version of a tobacco product that has undergone testing or was on the market in other countries, such as first-generation ENDS products that underwent aerosols or battery testing, and was subsequently modified as a

result of testing, adverse experiences, or other design concerns that could impact the public health. Rather than using section 910(b)(1)(B) of the FD&C Act, as cited by the comments as authority for this requirement, FDA bases its authority for this provision on section 910(b)(1)(G) of the FD&C Act, which requires applicants to submit other information relevant to the subject matter of the application as the Secretary may require.

The information required in § 1114.7(d)(4) will allow FDA to review information regarding risks present in closely related products and determine whether the applicant has addressed such risks in the development of the product that is the subject of the PMTA. FDA declines to adopt the comments' proposed approach that would require FDA to ignore information about known problems and related health risks that could be present in the tobacco product under review. We note that information about known problems and related health risks (e.g., product class effects such as mouth ulcers in moist tobacco) would be informative and could be used to bridge health effect information. Specifically, this information could help FDA to determine the validity and applicability of the studies that relied on a prototype.

5. Samples of New Tobacco Products and Components or Parts

Section 910(b)(1)(E) of the FD&C Act requires an applicant to submit samples of a tobacco product and its components as FDA may reasonably require. After FDA accepts a submission, FDA will determine whether it will require product samples and, if so, issue instructions on how and where to submit the samples, and the number of samples that are required. Section 1114.7(e) requires an applicant to submit samples of the finished tobacco product and its components in accordance with instructions issued to the applicant after a PMTA is accepted for review, as well as to submit additional samples if required by FDA during application review. FDA generally expects that product samples will be a required part of a

PMTA and that an applicant should be prepared to submit them in accordance with FDA instructions within 30 days after submitting a PMTA. There may be situations in which sample submission may not be necessary, including, in some circumstances, PMTAs that are resubmitted for the same product after a marketing denial order (such as resubmissions as described in § 1114.17) or PMTAs submitted for modifications to an authorized product where the modifications do not require review of new samples as part of the PMTA evaluation process. Presubmission meetings with FDA may help provide additional information about whether product samples will need to be included in a PMTA; however, in most situations, FDA will only be able to determine the need for product samples after a PMTA is accepted for review.

FDA received many comments regarding product samples, as discussed below.

(Comment 27) One comment agreed that requesting samples after a PMTA submission has been accepted makes sense; however, it stated that providing information regarding the quantity and type of samples that will be required for submission in advance is important to ensure that the samples FDA requires are actually available at the time of request.

(Response 27) As described in section VIII.B.5 of this document, FDA generally expects that product samples will be a required part of a PMTA and that an applicant should be prepared to submit them in accordance with FDA instructions within 30 days after submitting a PMTA. Because the quantity and type of samples need for testing may vary based upon a number of factors including product category and specific product characteristics, FDA intends to determine the quantity and type that will be required after application acceptance. However, as noted in section VIII.B.5., presubmission meetings with FDA may help provide additional information about whether product samples will need to be included in a PMTA.

(Comment 28) We received multiple comments regarding FDA's proposal to require an applicant to submit product samples only after an application is accepted for review. One comment stated that the start of FDA's 180-day review period should not be postponed until samples are received and should instead begin at the time the application is otherwise complete except for samples. Another comment requested that FDA amend the rule to allow applicants to submit product samples as part of its initial PMTA to avoid delays. The comment stated that the costs of the delaying the start of substantive review outweigh any minor savings gained by postponing inevitable product sample submission. The comment also noted that under FDA's proposed approach, FDA could indefinitely delay filing an application for review by not requesting product samples after application acceptance.

(Response 28) We decline to make the requested revisions. FDA will have applicants submit samples (if required by FDA) after acceptance of an application rather than as part of an initial submission. This timing will help FDA to determine the need for samples, allow the samples to be tracked and identified as part of the correct application, and facilitate the submission of samples to testing facilities that are adequately prepared to accept them (e.g., one that has a refrigerated unit if the product needs to be stored at a certain temperature). Additionally, by having applicants submit samples after FDA accepts an application, applicants will be able to avoid the effort and expense of submitting samples if the application is not accepted for review or if samples are not required. It will also allow FDA to avoid similar concerns with respect to storage and the return of samples for applications where FDA refuses to accept a PMTA. As described in § 1114.27, if required by FDA, product samples will be necessary for application filing and FDA intends to refuse to file a PMTA for a lack of product

samples if the applicant has not submitted samples in accordance with FDA's instructions by the time FDA is prepared to make its filing determination.

FDA intends to notify an applicant if it determines after PMTA acceptance that product samples are not required for PMTA filing; however, even in such a situation, FDA may request product samples during substantive review after an application is filed, as needed. FDA generally expects that, where required, samples will be requested within 30 days after application submission. Applicants may discuss the need for product samples during a presubmission meeting with FDA, which may speed up the sample submission process.

6. Labeling and Description of Marketing Plans

Section 1114.7(f) of the rule requires that a PMTA contain specimens of labeling and describe the applicant's marketing plans for the new tobacco product.

a. *Labeling*. Section 910(b)(1)(F) of the FD&C Act requires that a PMTA contain specimens of the proposed labeling to be used for the tobacco product. Section 1114.7(f)(1) elaborates on this requirement and requires the application to contain specimens of all proposed labeling for the new tobacco product, including labels, inserts, onserts, instructions, and other accompanying information.

FDA received comments regarding the submission of labeling, as described below.

(Comment 29) One comment stated that FDA's proposal to require "specimens of all proposed labeling" in § 1114.7(f)(1) is outside the scope of its authority under section 910 of the FD&C Act and requested that FDA remove the word "all" from the requirement. The comment stated that the statute requires the submission of specimens proposed to be used, which connotes a typical example of a larger whole and, as such, is not compatible with the requirement to provide "all" proposed labeling.

(Response 29) FDA disagrees with the assertion that § 1114.7(f)(1) is outside of its authority and declines to interpret the term "specimens" as used in section 910(b)(1)(F) of the FD&C Act to mean a representative sample. FDA's interpretation of section 910(b)(1)(F) in § 1114.7(f)(1) is consistent with how it interprets similar statutory requirements to submit specimens of labeling for both new drug applications and premarket approval applications for medical devices.[17] Not only did FDA's interpretation of these requirements for drugs and devices exist when Congress enacted the same requirement in the Tobacco Control Act, section 905(i)(1)(B) of the FD&C Act demonstrates Congress understands how to require a representative sample when it intends to do so. It did not do so here. Furthermore, requiring specimens of all proposed labeling is important to FDA's review of an application, because FDA must deny a PMTA under section 910(c)(2)(C) of the FD&C Act where it finds, based on a fair evaluation of all material facts, the proposed labeling is false or misleading in any particular. This requirement to deny a PMTA based upon any particular of the proposed labeling is at odds with the comment's suggestion that Congress intended FDA to review only a general representation of what an applicant proposes to use.

The labeling specimens are required to include all panels and reflect the actual size and color proposed to be used for such tobacco product. The labels must include any warning statements required by statute or regulation, such as the Federal Cigarette Labeling and Advertising Act, the Comprehensive Smokeless Tobacco Health and Education Act, or the minimum required warning statements contained in 21 CFR part 1143. For products that are

[17] See the interpretation of section 505(b)(1)(F) of the FD&C Act (21 U.S.C. 355(b)(1)) in 21 CFR 314.50(e)(2)(ii) (50 FR 7493, February 22, 1985) for new drug application, and the interpretation of 515(c)(1)(F) (21 U.S.C. 360e(c)(1)(F)) in 21 CFR 814.20(b)(10) for premarket approval applications for medical devices.

required to provide rotational warning statements, the applicant should submit labeling with each of the required warnings in the rotation.[18]

As described in § 1114.33, product labeling is an important part of FDA's review of an application, because FDA must deny a PMTA under section 910(c)(2)(C) of the FD&C Act where it finds, based on a fair evaluation of all material facts, the proposed labeling is false or misleading in any particular. Additionally, product labeling can be an important part of FDA's determination under section 910(c)(2)(A) of the FD&C Act of whether there is a showing that permitting the marketing of the product would be APPH because it can be used to help show perception of the risks of the product and the ability of individuals to understand the labeling, including any instructions for use, as described in § 1114.7(k)(1)(iv).

b. *Description of Marketing Plans.*--i. General. In the proposed rule, the marketing plans provision in proposed § 1114.7(f)(2) would have required an applicant to submit detailed information about all plans it had developed to market its new tobacco product. In response to comments and on FDA's own initiative, we have revised the requirement to submit information concerning the applicant's plans to market the new tobacco product. Rather than requiring all of the detailed information required in proposed § 1114.7(f)(2), FDA has revised this section to require only a high-level description of several key aspects of these plans that directly inform FDA's APPH determination. FDA's discussion of the comments is included below.

(Comment 30) One comment stated that FDA should clarify the scope of marketing information it expects to see in a PMTA and explain how it plans to engage in a science-based review of labeling and marketing plans, noting that the rule provides little detail as to what specific marketing information the Agency expects to see. The comment stated that it is unclear

[18] For more information on rotational warning statement requirements, see https://www.fda.gov/tobacco-products/products-guidance-regulations/labeling-and-warning-statements-tobacco-products.

whether FDA is proposing to require submission of information about top-line product messaging or specific pieces of the advertising and marketing strategies for their use. The comment noted that it is also unclear to what extent FDA expects to see results of consumer research. In addition, the comment stated that it remains unknown how the Agency plans to review labeling and marketing plans and what specific considerations or methodologies will guide assessment of consumer risk perception, comprehension, and use intentions.

(Response 30) FDA has revised § 1114.7(f)(2) to require only high-level marketing plan information that it generally expects applicants will have developed prior to seeking marketing authorization for their products. The description of marketing plans now required by § 1114.7(f)(2)--including intended audience, how the applicant would target the intended audience and what other groups would foreseeably be exposed, and how exposure would be limited for individuals below the minimum age of sale--seeks information necessary for FDA to properly evaluate the extent of youth exposure to marketing materials for the product and youth access to the product. Discussion of these items will not require applicants to conduct consumer research; however, where an applicant had undertaken such research, the results of such research will be required by § 1114.7(f)(2) or (k)(1)(iv). As discussed in section VIII.B.6.b., this information will allow FDA to consider whether an applicant has addressed potential concerns about the marketing of its product, such as tobacco product use initiation by individuals under the minimum age of sale, and will help FDA to assess whether the plans to market the product are consistent with the applicant's discussion of the likelihood of changes in tobacco product use behavior in the application. These considerations will help FDA to determine whether there is a showing that permitting the tobacco product to be marketed is appropriate for the protection of public health.

(Comment 31) One comment stated that the marketing plan requirements seem to be based on the premise that companies will have developed marketing plans by the time of application submission, which fails to account for the small vape shops that currently serve as both retailers and manufacturers who are unlikely to have undertaken consumer research. The comment requested that FDA edit the marketing plan requirements to apply only "as applicable" to companies that have conducted such research.

(Response 31) The requirement to provide descriptions of marketing plans does not require applicants to undertake market or consumer research. Rather, § 1114.7(f)(2) requires PMTAs to contain a discussion of several key high-level aspects of the applicant's plans to market the product. The discussion of these items will not require consumer research; however, be aware that § 1114.7(k)(1)(iv) requires applicants to submit reports of all information published or known to, or which should reasonably be known to, the applicant concerning investigations regarding the impact of the product and its label, labeling, and advertising, to the extent that advertising has been studied, on individuals' perception of the product and use intentions. This will include any consumer research that the applicant has undertaken or used to develop the aspects of its marketing plan identified in § 1114.7(f)(2).

(Comment 32) One comment stated that FDA should amend the marketing plan requirements in § 1114.7(f)(2) to include specific language about dual use because the reality is that most adult users of tobacco products become dual users.

(Response 32) We have edited § 1114.7(f)(2) to include polyuse as an example tobacco use behavior that descriptions of marketing plans may address in describing target audiences. FDA requires descriptions of marketing plans to inform our determination of whether the new product is appropriate for the protection of public health. As part of FDA's determination of the

risks and benefits to the health of the population as a whole (which includes youth, young adults, and other vulnerable populations), FDA will consider the potential for long-term dual use among current users. FDA reviews the descriptions of marketing plans in conjunction with the other submitted information, which can include tobacco product perception and use intention studies and actual use studies to assess the likelihood that current users will switch completely to the new product or become a dual or polyuser of tobacco products. To the extent that the description of marketing plans contains information about the target audience by psychographic characteristics including tobacco use patterns, FDA will consider whether dual use is likely given the description of the marketing plans and the other submitted information.

(Comment 33) One commenter stated that the marketing plan requirements are outside of what the FD&C Act allows FDA to review as part of a PMTA. The commenter stated that the structure of the FD&C Act shows that Congress did not intend for FDA to review marketing plan information as part of a PMTA because where Congress found such information to be relevant to FDA's analysis, it expressly added such a requirement to the statute (e.g., section 905(i)(1) of the FD&C Act). The commenter stated that in contrast, in section 910 of the FD&C Act Congress required that PMTAs must contain only "specimens of the proposed labeling to be used for [the] tobacco product." The commenter concluded that the fact that Congress omitted a broader requirement for advertisements in section 910 of the FD&C Act but included the requirement for only "specimens" of labeling shows that Congress did not consider broader information relevant to FDA's evaluation of a PMTA. The commenter also states that FDA's claim of authority under section 910(b)(1)(G) is ineffective because it does not grant FDA the limitless authority to require content; rather, FDA only has the authority to require information under 910(b)(1)(G) of

the FD&C Act that is reasonable and reasonably explained, which the commenter maintains that FDA has failed to do here.

(Response 33) As discussed in Response 30, FDA has revised § 1114.7(f)(2) to require only high-level marketing plan information that it generally expects applicants will have developed prior to seeking marketing authorization for their products. But even so, we disagree with the commenter's position that FDA lacks statutory authority to require marketing plans as part of a PMTA. In describing the required contents of a PMTA in section 910(b)(1)(G), Congress explicitly authorized FDA to require "such other information relevant to the subject matter of the application." This provision demonstrates that Congress intended for FDA to apply its expertise with respect to review of scientific applications and the overall administration of the Tobacco Control Act to determine what additional information would be "relevant" to whether the application meets the requirements to receive marketing authorization.

We have determined that the description of marketing plans required by § 1114.7(f)(2) is relevant to the subject matter of a PMTA. To issue a marketing granted order for a new tobacco product, FDA must determine that permitting such tobacco product to be marketed would be APPH, which requires FDA to consider the likelihood that those who do not use tobacco products, including youth, will start using them. Determining the extent to which youth will be exposed to marketing materials for the product is critical to that consideration. As explained by Congress in enacting the Tobacco Control Act, tobacco advertising, marketing, and promotion substantially contribute to youth trial and uptake of tobacco use. See, e.g., Tobacco Control Act section 2(5) (tobacco advertising and marketing contribute significantly to the use of tobacco products by adolescents.); *id.* section 2(15) (advertising, marketing and promotion of tobacco products have resulted in increased use of such products by youth.); *id.* section 2(20) (children

are exposed to substantial and unavoidable tobacco advertising that increases the number of young people who begin to use tobacco); *id.* section 2(22) (tobacco advertising expands the size of the tobacco market by increasing consumption of tobacco products including tobacco use by young people). Congress enacted the Tobacco Control Act against the backdrop of years of litigation exposing previous tobacco product marketing campaigns in which companies successfully targeted and recruited new youth smokers. See, e.g., *United States* v. *Philip Morris USA, Inc.*, 449 F. Supp. 2d 1, 616 (D.D.C. 2006) ("As the following evidence demonstrates, Defendants have utilized the vast amount of research and tracking data they accumulated on youth smoking initiation, tastes and preferences by employing themes which resonate with youth in their marketing campaigns. Defendants have focused their attention on young people under the age of twenty-one in order to recruit replacement smokers and have emphasized the popularity, physical attractiveness, and 'coolness' of their youth brands. Above all, Defendants have burnished the image of their youth brands to convey rugged independence, rebelliousness, love of life, adventurousness, confidence, self-assurance, and belonging to the 'in' crowd." (internal citation omitted)), *aff'd in part, rev'd in part on other grounds*, 566 F.3d 1095 (D.C. Cir. 2009); see also 449 F. Supp. 2d at 616-39.

A well-established body of scientific evidence confirms the continuing impact of tobacco product marketing on initiation and use by individuals under the minimum age of sale. See, e.g., Dep't of Health & Human Servs., *E-Cigarette Use Among Youth and Young Adults: A Report of the Surgeon General* 170 (2016) ("An analysis of the 2011 National Youth Tobacco Survey found that adolescents who reported frequent exposure to protobacco advertising at the point of sale and on the Internet (e.g., seeing ads most of the time or always) had significantly higher odds of ever using e-cigarettes, and there was a dose-response association between the number of

marketing channels to which they were exposed and ever use[.]"); Dep't of Health & Human Servs., *Preventing Tobacco Use Among Youth and Young Adults: A Report of the Surgeon General* 598 (2012) ("[T]here is strong empirical evidence, along with the tobacco industry's own internal documents and trial testimony, as well as widely accepted principles of advertising and marketing that support the conclusion that tobacco manufacturers' advertising, marketing, and promotions recruit new users as youth and continue to reinforce use among young adults[.]"). Companies marketing newer forms of tobacco products have employed some of the same techniques, as well as newer innovations, to attract the youth market. For example, ENDS manufacturers have used social media, including influencers, to help create an image for their products as being cool and having sex appeal, sponsored music festivals, and created products with youth-appealing cartoon images (see, e.g., Refs. 12 through 15).

The descriptions of marketing plans required by § 1114.7(f)(2)--including intended audience, how the applicant would target the intended audience and what other groups would foreseeably be exposed, and how exposure would be limited for individuals below the minimum age of sale (e.g., avoiding online social media without access restrictions)--seeks information necessary for FDA to properly evaluate the extent of youth exposure to marketing materials for the product and youth access to the product. Accordingly, this information is directly relevant to the subject matter of a PMTA, including FDA's consideration of the likelihood that youth will use the tobacco product and its determination that permitting the product to be marketed would be APPH.

Because Congress clearly and unambiguously authorized FDA to require additional relevant information, that should be "the end of [the] analysis." *Zuni Pub. Sch. Dist. No. 89* v. *Dep't of Educ.*, 550 U.S. 81, 93 (2007) (citing *Chevron, U.S.A., Inc.* v. *Natural Res. Def.*

Council, Inc., 467 U.S. 837 (1984)). But even if Congress has not "directly" addressed "the precise question at issue," FDA's interpretation is a "permissible construction of the statute," *Chevron*, 467 U.S. 837 at 843, on a matter where the Agency's expertise plays a significant role in resolving important questions related to the administration of the statute. *Barnhart* v. *Walton*, 535 U.S. 212, 222 (2002).

In determining to require the submission of descriptions of marketing plans as part of a PMTA, FDA considered the information it needed to be able to evaluate whether the statutory requirements for PMTA authorization are met, as well as the context and purpose of the PMTA requirement. As discussed above, a well-established body of historical and scientific evidence and Congress's own findings in enacting the Tobacco Control Act support FDA's reasonable conclusion that potential exposure to tobacco product advertising, marketing, and promotion is relevant to, and indeed a critical factor in, FDA's statutorily required determination of the likelihood that nonusers, including youth, will use a new tobacco product. Moreover, based on this evidence, as well as the expertise it has developed regarding tobacco product marketing over more than a decade of administering the Tobacco Control Act, FDA has rationally concluded that the required descriptions of marketing plans will directly inform its assessment of who may be exposed to the applicant's labeling, advertising, marketing, and promotion and, as a result, its consideration of the potential impact on youth initiation and use. FDA's assessment of who may be exposed to tobacco product marketing materials and activities will include individuals below the minimum age of sale, recently raised from 18 to 21 years. For example, information regarding how the applicant will target the intended audience, such as the marketing channels and tactics an applicant expects to use, will permit FDA to determine the extent to which youth would be exposed to and influenced by marketing for the product. (See, e.g., Refs. 13, 16, and

17) As another example, a description of the ways in which an applicant would limit exposure to tobacco product marketing materials and activities for individuals below the minimum age of sale will inform FDA's assessment of the potential for youth exposure to these materials and activities.

Submission of descriptions of marketing plans also supports the Tobacco Control Act's mandate that FDA protect youth from the dangers of tobacco use. See, e.g., Tobacco Control Act section 3(2), (7) (purposes of the Tobacco Control Act include to ensure that FDA has authority to address issues of particular concern to public health officials, especially the use of tobacco by young people, and to ensure that tobacco products are not sold or accessible to underage purchasers). In enacting the Tobacco Control Act and giving FDA this mandate, Congress recognized the substantial impact of exposure to tobacco product advertising, marketing, and promotion on youth tobacco use. See, e.g., Tobacco Control Act section 2(15) (advertising, marketing and promotion of tobacco products have resulted in increased use of such products by youth.). Based on this context and the ample scientific evidence supporting the powerful impact of marketing on youth tobacco use, FDA reasonably concluded that determining the extent to which youth may be exposed to marketing materials for a new tobacco product is critical to its evaluation of the potential for youth to use the new tobacco product and to its ability to fulfill its mandate to protect youth from the dangers of tobacco use. To that end, the requirement for descriptions of marketing plans seeks information that directly informs FDA's assessment of the extent to which youth may be exposed to marketing materials for the new tobacco product, as well as information to help FDA determine whether any concerns about youth use of the product and the corresponding increases in health risks would be mitigated, such

as information regarding the extent to which an applicant would restrict access to the tobacco product for individuals below the minimum age of sale.

Contrary to the comment, Congress's inclusion of an advertising requirement in non-PMTA-related sections of the FD&C Act, such as section 905(i)(1), and omission of the requirement in section 910(b)(1)(F) of the FD&C Act, does not demonstrate Congress's intent to exclude description of marketing plans from PMTAs. Congress's explicit authorization in 910(b)(1)(G) of the FD&C Act that FDA may require "such other information relevant to the subject matter of the application" defeats the commenter's inference by omission argument. See *Adirondack Med. Ctr.* v. *Sebelius*, 740 F.3d 692, 697 (D.C. Cir. 2014) (the "*expressio unius* canon" is a "poor indicator of Congress' intent" where there is a "broad grant of authority" to the Agency; instead, " 'Congress is presumed to have left to reasonable agency discretion questions that it has not directly resolved' " (quoting *Cheney R.R. Co.* v. *I.C.C.*, 902 F.2d 66, 68–69 (D.C. Cir. 1990)). Indeed, Congress did not "omit" an advertising requirement from section 910(b)(1) but rather left its inclusion to FDA's discretion and judgment. As explained above, FDA has reasonably exercised its discretion in construing section 910(b)(1)(G) of the FD&C Act to require descriptions of marketing plans based on the Tobacco Control Act's context and purpose, ample scientific evidence, and the Agency's own expertise developed over a decade of administering the statute.

(Comment 34) The commenter also stated that the marketing plans requirement potentially limits speech, raising First Amendment concerns. The commenter stated that the requirement places more than an incidental burden on protected expression, and the government cannot show it directly advances a substantial government interest that is drawn narrowly to achieve that interest. In terms of the alleged burden, the commenter stated that the requirement

would distract and deter manufacturers from the focused development and implementation of robust marketing plans--ultimately burdening the right of consumers to receive, and manufacturers to provide, information about products determined by FDA to be appropriate for the protection of the public health. Additionally, the commenter asserted that the requirement would significantly chill protected speech due to the threat that FDA might disclose information about applicants' marketing plans to TPSAC or the public and thereby compromise an applicant's competitive strategy.

The commenter also asserted that the proposed requirement for manufacturers to report "total dollar amount(s) of media buys and marketing and promotional activities" would have been particularly burdensome and lacked justification. It stated that there was no evidence in the record that reporting such information for truthful advertising and marketing of a product with a PMTA order would directly advance the government's interest. The commenter also asserted that FDA's proposed request for marketing plans would not yield meaningful information given the amount of time it could take for FDA to review an application, the evolving tobacco product landscape, and the likelihood that the applicant's marketing plans would change.

In arguing that the government has not justified these burdens, the commenter asserts that the marketing plans requirement is a content-based burden on speech in that it applies only to applicants who wish to engage in the marketing of tobacco products, and therefore the government's justification is subject to strict scrutiny under *Reed* v. *Town of Gilbert*, 135 S. Ct. 2218, 2226 (2015), or at least heightened scrutiny under *Sorrell* v. *IMS Health Inc.*, 564 U.S. 552 (2011). The commenter states that FDA's required marketing disclosures are not narrowly tailored nor do they directly advance a compelling government interest, so they cannot meet the higher standard for content-based restrictions.

(Response 34) As discussed in Response 30, FDA has revised § 1114.7(f)(2) to require only high-level marketing plan information that it generally expects applicants will have developed prior to seeking marketing authorization for their products. That noted, we do not agree that the requirement for descriptions of marketing plans raises First Amendment concerns for several reasons. First, we disagree that the requirement to submit descriptions of marketing plans burdens speech. Federal Agencies routinely require regulated industry to disclose information to the government. The FD&C Act contains several premarket authorization requirements, including for drugs and devices, which have existed for decades, and whose constitutionality is not seriously questioned. Indeed, in the proliferation of lawsuits challenging various aspects of the Tobacco Control Act, there have been few direct challenges to the PMTA requirements, and any related challenges have been resolved in the government's favor. See *Nicopure Labs., LLC* v. *FDA*, 266 F. Supp. 3d 360, 391-95, 409 (D.D.C. 2017) (upholding FDA's decision to apply PMTA requirements to deemed tobacco products as permissible under the Administrative Procedure Act, and upholding the statutory PMTA requirement under the Due Process clause of the Constitution), *aff'd on other grounds,* 944 F.3d 267 (D.C. Cir. 2019) (PMTA rulings were not appealed); see also, e.g., *Nicopure Labs.*, 944 F.3d at 284–90 (D.C. Cir. 2019) (rejecting First Amendment challenge to the Tobacco Control Act requirement that manufacturers obtain premarket review of MRTPs).

To the extent that the commenter contends that the requirement to provide a description of its marketing plans to FDA would impinge on an applicant's ability to market its tobacco products, FDA is not aware of any evidence to support that contention (and the commenter cites none). The comment's assertion that the requirement would distract and deter manufacturers from the focused development and implementation of robust marketing plans strains credulity

given tobacco manufacturers' incentives to market their products and the significant resources tobacco product manufacturers commit to marketing their products each year. S*ee Edenfield* v. *Fane*, 507 U.S. 761, 766 (1993) ("A seller has a strong financial incentive to educate the market and stimulate demand for his product or service."). The Federal Trade Commission reported that advertising and promotional expenditures by major cigarette manufacturers totaled $8.401 billion in 2018 (Ref. 18).

FDA has considered the comment's position regarding the proposed § 1114.7(f)(2) requirement that applicants provide "total dollar amount(s) of media buys and marketing and promotional activities." FDA has revised § 1114.7(f)(2) to no longer require total dollar amounts of media buys and marketing and promotional activities. In addition, FDA has revised this section to require only high-level information that it expects applicants will generally have developed prior to seeking marketing authorization for their products. For example, revised § 1114.7(f)(2)(i) and (ii) require an applicant to provide a discussion of the intended audience for the marketing materials and activities for the tobacco product and how the applicant would target those marketing materials and activities to the intended audience. Based on its experience, FDA expects that an applicant will generally have considered its intended audience and how it will target its marketing materials and activities to that audience by the time it submits its PMTA. Discussion of these items will not require applicants to conduct consumer research; however, where an applicant has undertaken such research, such as conducting tobacco product perception and intention studies, it will be required to be included in the PMTA as set forth in § 1114.7(k)(1)(iii), where applicable. Applicants will be required to provide the descriptions of marketing plans identified in this section based on the plans they have developed as of the time

of submitting their PMTA, and where an applicant has not developed plans relating to one or more items in § 1114.7(f)(2), they would be required to state that in their application.

The comment's concern that commercial speech would be chilled due to the perceived risk that FDA would disclose an applicant's description of its marketing plans to TPSAC or the public and thereby compromise confidential commercial information (CCI) in those marketing plans is unwarranted. FDA generally may not make information in an application publicly available to the extent that the information constitutes trade secrets or CCI. See 5 U.S.C. 552(b)(4); 18 U.S.C. 1905; 21 U.S.C. 387f(c); 21 CFR 20.61(c); *id.* § 1114.47(a) (FDA will determine the public availability of any part of a PMTA under this section and part 20 (21 CFR part 20)). The Tobacco Control Act does not require FDA to refer PMTAs (or any information contained therein) to TPSAC, instead committing that decision to the Secretary's discretion. See 21 U.S.C. 387j(b)(2) (providing that the Secretary "may" refer PMTAs to TPSAC "on the Secretary's own initiative; or…upon the request of an applicant"). If the Secretary finds it appropriate to consult the TPSAC on an issue that requires consideration of CCI contained in the description of marketing plans, FDA may share that information only with TPSAC members who are subject to the same restrictions with respect to disclosure of CCI as any other FDA employee. See 21 CFR 20.84; *id.* 21 CFR 14.86(a)(2). Additionally, if the Secretary refers a PMTA to TPSAC, § 1114.47(b)(4) of this rule provides that CCI contained in the application generally will not be available for public disclosure. FDA may close a portion of a TPSAC meeting to allow discussion of an applicant's CCI to take place without disclosing the CCI to the public. See 21 CFR 14.27(b)(3) (allowing portions of an advisory committee meeting to be closed if they concern the review of trade secrets and CCI).

FDA also disagrees with the commenter's assertion that FDA's requirement for marketing plans as originally proposed would not yield meaningful information given the amount of time it might take for FDA to review an application, the evolving tobacco product landscape, and the likelihood that the applicant's marketing plans would change. Because we have revised § 1114.7(f)(2) to require a discussion of high-level items, rather than the submission of details that are more subject to change (e.g., media buys, dollar amount, specific tactics), we generally do not expect the information contained in the applicant's description of marketing plans to change significantly after the submission of the application. However, under § 1114.9, FDA may request, or an applicant may submit on its own initiative, an amendment to its PMTA containing information that is necessary for FDA to complete its review of the application, including information regarding any alterations or updates to the required description of marketing plans. As described in section VIII.C., so long as such an amendment does not require significant review time, it will not be considered a major amendment for which the review period will be extended by up to 180 days and even where such an amendment is major amendment, FDA anticipates it would generally take less than 180 days to complete review thereof.

Second, even if the requirements of § 1114.7(f)(2) restricted speech, they would readily pass muster under the intermediate scrutiny test for commercial speech articulated in *Central Hudson Gas & Elec. Corp.* v. *Pub. Serv. Comm'n*, 447 U.S. 557 (1980). Under that test, Agencies may regulate speech where the regulation advances a substantial government interest and the regulation is no more extensive than necessary to serve that interest.

It is well established that FDA has a substantial interest in protecting youth from tobacco products. See *Lorillard Tobacco Co.* v. *Reilly*, 533 U.S. 525, 564-66 (2001); see also *Discount Tobacco City & Lottery*, *Inc.* v. *United States*, 674 F.3d 509, 519-20, 541 (6th Cir. 2012). Youth

are a significant population of concern for reasons that have been extensively documented in scientific research and in the Tobacco Control Act. For example, youth are especially susceptible to addiction due to their ongoing and incomplete brain development. See 2012 Surgeon General's Report. In addition, most tobacco use is established in adolescence and age of initiation plays a significant role in the progression from tobacco experimentation to regular use. See *id.*; see also, e.g., Tobacco Control Act section 2(1) ("The use of tobacco products by the Nation's children is a pediatric disease of considerable proportions that results in new generations of tobacco-dependent children and adults."); *id.* section 2(4) ("Virtually all new users of tobacco products are under the minimum legal age to purchase such products."). FDA has a statutory mandate to protect youth from these dangers of tobacco product use. See, e.g., Tobacco Control Act section 3(2), (7) (purposes of the Tobacco Control Act include to ensure that FDA has authority to address issues of particular concern to public health officials, especially the use of tobacco by young people, and to ensure that (tobacco products) are not sold or accessible to underage purchasers).

The requirement for applications to contain descriptions of marketing plans clearly and directly advances FDA's substantial interest in protecting youth from the dangers of tobacco product use. As explained in section VIII.B.6.b, it is well established that exposure to tobacco product labeling, advertising, marketing, and promotion has a direct and powerful impact on youth trial and uptake of tobacco product use. See, e.g., Tobacco Control Act section 2(5) ("Tobacco advertising and marketing contribute significantly to the use of nicotine-containing tobacco products by adolescents."); 2016 Surgeon General's Report at 170 ("An analysis of the 2011 National Youth Tobacco Survey found that adolescents who reported frequent exposure to protobacco advertising at the point of sale and on the Internet (e.g., seeing ads most of the time

or always) had significantly higher odds of ever using e-cigarettes, and there was a dose-response association between the number of marketing channels to which they were exposed and ever use[.]"); 2012 Surgeon General's Report at 598 ("[T]here is strong empirical evidence, along with the tobacco industry's own internal documents and trial testimony, as well as widely accepted principles of advertising and marketing that support the conclusion that tobacco manufacturers' advertising, marketing, and promotions recruit new users as youth and continue to reinforce use among young adults[.]").

Accordingly, determining the extent to which youth may be exposed to marketing materials for a new tobacco product is critical to FDA's evaluation of the potential for youth use of the new tobacco product. The requirement for descriptions of marketing plans seeks information that directly informs the extent to which youth may be exposed to these marketing materials, including information regarding the intended audience for the materials, how the applicant plans to target the materials to that audience and what other groups would foreseeably be exposed to those materials, and how the applicant plans to limit youth exposure to the materials. In addition, the requirement seeks information to help FDA determine whether any concerns about youth use of the product and the corresponding increases in health risks may be mitigated, such as information regarding how the applicant plans to limit youth access to the product. Moreover, the requirement for descriptions of marketing plans is no more extensive than necessary to permit FDA to make these determinations, as it requires minimal, high-level information that FDA expects an applicant to have at the time of submitting its application.

In addition, the requirement for descriptions of marketing plans clearly and directly advances FDA's substantial government interest in ensuring that permitting the marketing of new tobacco products would be APPH. Under section 910(c)(2)(4) of the FD&C Act, a key

consideration of the APPH determination is whether permitting the marketing of the product would increase or decrease the likelihood that those who do not use tobacco products, including youth, will start using them. Among nonusers, youth are a significant population of concern for the reasons already explained above. Determining the extent to which youth would be exposed to marketing materials for the product is therefore critical to FDA's evaluation of the likelihood that youth will initiate tobacco use with the new tobacco product. Accordingly, by providing FDA with certain high-level information necessary to help determine potential youth exposure to marketing materials for a new tobacco product, the requirement for descriptions of marketing plans directly advances and is reasonably tailored to FDA's substantial interest in ensuring that permitting the marketing of the new tobacco product is APPH.

Finally, we disagree with the commenter's assertion that § 1114.7(f)(2)'s disclosure requirements are subject to strict scrutiny under *Reed* v. *Town of Gilbert*, 135 S. Ct. 2218, 2226 (2015), or at least heightened scrutiny under *Sorrell* v. *IMS Health Inc.*, 564 U.S. 552 (2011). In *Reed* v. *Town of Gilbert*, the Court applied strict scrutiny to content-based restrictions on noncommercial speech in public fora. *Reed* had nothing to do with commercial speech doctrines, see 135 S. Ct. at 2224-25, and it has not been understood to alter the applicability of *Central Hudson*. Likewise, *Sorrell* "did not mark a fundamental departure from *Central Hudson*'s four-factor test, and *Central Hudson* continues to apply" to regulations of commercial speech, regardless of whether they are content based. *Retail Digital Network*, *LLC* v. *Prieto*, 861 F.3d 839, 846 (9th Cir. 2017) (en banc); *accord Vugo*, *Inc.* v. *City of New York*, 931 F.3d 42, 50 (2d Cir. 2019), *cert. denied*, 140 S. Ct. 2717 (2020) ("No Court of Appeals has concluded that *Sorrell* overturned *Central Hudson*. We agree with our sister circuits that have held that *Sorrell* leaves the *Central Hudson* regime in place, and accordingly we assess the constitutionality of the

City's ban under the *Central Hudson* standard."); *Missouri Broad. Ass'n* v. *Lacy*, 846 F.3d 295, 300 n.5 (8th Cir. 2017) ("The upshot [of *Sorrell*] is that when a court determines commercial speech restrictions are content- or speaker-based, it should then assess their constitutionality under *Central Hudson*.") (quotation marks omitted; alteration in original); *Nicopure Labs.*, *LLC* v. *FDA*, 266 F. Supp. 3d 360, 411 (D.D.C. 2017) ("[T]he *Sorrell* opinion did not alter or replace the *Central Hudson* intermediate scrutiny standard to be applied to commercial speech."), *aff'd*, 944 F.3d 267, 290 (D.C. Cir. 2019) ("*Sorrell*'s concerns about suppression of advertising messages in the marketplace of ideas are inapposite here.").

(Comment 35) Multiple comments expressed concerns about the difficulty of creating marketing plans for the first year of product marketing given that the time it has taken FDA to review PMTAs to date has been unpredictable. Specifically, comments stated that the requirement for marketing plans in proposed § 1114.7(f)(2) did not take into account the considerable external variables that inform marketing plan decisions including competitor activities, FDA actions and State or Federal legislation. Comments noted that FDA's evaluation of the IQOS PMTA, for example, stretched over 2 years. The comments requested more flexibility in their marketing plans, including the potential to amend their plans during application review, to avoid being locked into outdated plans that do not account for the use of new technology or to allow for adjustment.

(Response 35) FDA has revised and narrowed the scope of § 1114.7(f)(2) to require an applicant's description of its marketing plans to discuss certain key, high-level aspects of its plans to market the product for the first year after receiving a marketing granted order. FDA notes that the applicant's description of its marketing plans does not by itself create rigid requirements regarding the way in which an applicant must market its new tobacco product;

however, where an applicant proposes a specific restriction on its marketing of the new tobacco product to support an APPH finding as part of its description of its marketing plans (e.g., avoiding online social media without access restrictions), FDA might incorporate such proposals into the restrictions on the sales and distribution of a new tobacco product in a marketing granted order as set forth in § 1114.31(b). Additionally, FDA will monitor an applicant's implementation of its marketing plans as described in the application to ensure the marketing of the new tobacco product continues to be APPH. Applicants are required to report information about the marketing of their product under § 1114.41(a)(1)(xi), and FDA may require submission of marketing plan changes in advance of implementation under § 1114.31(b)(3).

An applicant may alter or update its description of its marketing plans during the course of application review by submitting an amendment; however, as described in the response to comment 34, we generally do not expect an applicant's approach to the high-level items in § 1114.7(f)(2) to change significantly after the submission of an application. As described in section VIII.C. of this document, where such an amendment requires significant review time (e.g., significant changes to the intended audience(s) and how the marketing material and tactics would be targeted thereto), it will be considered a major amendment for which the review period will be extended by up to 180 days; however, FDA will review such amendments promptly and generally expects review of such changes will require fewer than 180 days.

ii. Requirements for description of marketing plans. Section 1114.7(f)(2) requires a PMTA to contain a description of the applicant's plans to market the new tobacco product, for at least the first year the product would be marketed after receiving a marketing granted order, in a way that permits FDA to determine whether this information is consistent with the applicant's discussion of the increased or decreased likelihood of changes in tobacco product use behavior,

including switching, initiation, cessation, and polyuse, under § 1114.7(l), and whether permitting the new tobacco product to be marketed would be APPH. This section requires descriptions of actions to market the new tobacco product that would be taken by the applicant, on behalf of the applicant, or at the applicant's direction, and of any restrictions on the sales and distribution of the new tobacco product that the applicant is proposing to be included in the marketing granted order under section 910(c)(1)(B) of the FD&C Act. As set forth below, the description of an applicant's plans to market a product will contain information that is important to FDA's consideration of the likelihood of changes in tobacco product use behavior (including initiation and cessation) under section 910(c)(4) of the FD&C Act. The described changes in tobacco product use behavior, when considered as part of FDA's determination of the risks and benefits of the new tobacco product to the population as a whole under section 910(c)(4) of the FD&C Act, form part of the basis upon which FDA must make its finding of whether there is a showing that permitting the marketing of the new tobacco product would be APPH under section 910(c)(2)(A) of the FD&C Act. While the criteria for FDA to accept and file the application in § 1114.27 can be satisfied with only some discussion of the four items in § 1114.7(f)(2)(i) through (iv), FDA encourages applicants to provide more detailed information to help inform FDA's substantive APPH determination.

An understanding of how an applicant plans to market a new tobacco product for at least an initial period of time will help FDA determine the potential for increases in health risks related to marketing of the new tobacco product, such as the potential for youth initiation. If FDA determines that the potential increases in health risks outweigh the potential benefits, FDA would not be able to determine that the marketing of the new tobacco product would be APPH and would issue a marketing denial order.

Section 1114.7(f)(2)(i) requires a PMTA to contain a description of the specific group(s) to which the labeling, advertising, marketing, promotion, and other consumer-directed activities for the new tobacco product would be targeted (i.e., the intended audience(s)). As used in § 1114.7(f)(2), the term "other consumer-directed activities" includes any other types of action regarding the new tobacco product taken by the applicant, on behalf of the applicant, or at the applicant's direction that may directly or indirectly impact information about the tobacco product that reaches consumers (e.g., use of third parties or social media influencers to reach consumers). Additionally, the labeling, advertising, marketing, promotion, and other consumer-directed activities for a new tobacco product are collectively referred to as "marketing materials and activities" in this document for ease of reference. An applicant would need to provide the characteristics it has used to identify the specific group(s) to which its marketing materials and activities would be targeted, such as age-range(s) (including young adult audiences ages 21 to 24 years, if applicable) and other demographic characteristics, details of tobacco use behaviors (e.g., dual use), and psychographic characteristics. Examples of other demographic characteristics include, but are not limited to, race, ethnicity, socioeconomic status and geographic location (e.g., urban, rural). Such information will be informative to FDA in identifying potential impacts of marketing on specific populations, including vulnerable populations. Examples of types of psychographic characteristics include, but are not limited to, hobbies, interests, risk-taking behaviors, purchase behaviors, and online search behaviors. Based on our experience, FDA generally expects that applicants will have conducted or otherwise obtained market or consumer research to determine its intended audience(s). Where an applicant has conducted such research and has used the results to determine its intended audience, FDA recommends an applicant discuss such information in this section.

As a general example, the description of the intended audience(s) could include, for example, a statement that the applicant would target its marketing materials and activities for the new tobacco product to all current adult cigarette smokers, with a focus on cigarette smokers aged 26 to 54 years who are seeking alternatives to combustible cigarettes.

Section 1114.7(f)(2)(ii) requires the applicant's description of its marketing plans to contain a discussion of the ways in which the applicant would target its marketing materials and activities for the new tobacco product to reach the intended audience(s) described in paragraph (i) and what other group(s) would foreseeably be exposed to the marketing materials and activities as a result. A discussion of these aspects of the plans can provide information that is important to FDA's evaluation of the increased or decreased likelihood of changes in tobacco product use behavior under section 910(c)(4) of the FD&C Act. Describing how an applicant would target the marketing materials and activities for the new tobacco product to intended audiences could help FDA determine whether the applicant's descriptions of its marketing plans are consistent with information in the application regarding the likelihood of changes in tobacco product use behaviors, such as current tobacco product users switching to the new tobacco product.

A discussion of the ways in which the applicant would target the marketing materials and activities for a new tobacco product to reach the intended audience(s) can include items such as: how the applicant would use key insights about its intended audience(s) to tailor its marketing approach; the types and sources of data, technologies, and methodologies the applicant would use to develop, implement, and track targeted paid media plans (e.g., first and second-party age-verified data, public records, industry-standard syndicated research services, and embedded

tracking pixels in digital advertising); and the marketing channels and tactics an applicant expects to use.

Additionally, this information will help FDA determine whether the identified audiences and not other audiences, such as individuals below the minimum age of sale, would be exposed to the marketing materials and activities for the new tobacco product. Describing the other groups that would foreseeably be exposed to the marketing materials and activities for the new tobacco product will help FDA understand the potential for other groups to be affected by the plans to market the new tobacco product. For example, where an applicant's plans to target its marketing materials and activities to an intended audience of adult consumers has the potential to reach individuals below the minimum age of sale, an applicant would have to note that potential and describe whether the potential would be limited under paragraph (iii). FDA is requiring a discussion of an applicant's plans to target its marketing materials and activities to the intended audience(s) and the other groups that could foreseeably be exposed to those materials as a result of such targeting because, as discussed in the following paragraphs, there is a well-established body of scientific evidence regarding the effect of advertising and marketing on tobacco product behavior (see e.g., Refs. 19-22).

Section 1114.7(f)(2)(iii) requires the applicant's description of its marketing plans to contain a discussion of the ways in which, for individuals below the minimum age of sale, access to the new tobacco product would be restricted and exposure to the marketing materials and activities for the new tobacco product would be limited. Describing the ways in which an applicant would restrict access to the new tobacco product by individuals below the minimum age of sale would be an important part of FDA's consideration under section 910(c)(4) of the FD&C Act regarding the increased or decreased likelihood that persons who do not use tobacco

products will start using the tobacco product that is the subject of the application. Limiting the potential for youth to access the new tobacco product is one way to help mitigate the potential for youth initiation with the new tobacco product (Refs. 23 and 24). For example, an applicant could propose to restrict the sale and distribution of its new tobacco product to adult-only facilities and limit the quantity of its product that an adult customer (other than scientific researchers or research institutions) may purchase within a given period of time to limit the potential for resale to youth.

Describing the ways in which an applicant would plan to limit the exposure of individuals below the minimum age of sale to the marketing materials and activities for the new tobacco product would also help FDA assess the potential for initiation with the new tobacco product by this group. Examples of how applicants could limit the exposure of individuals below the minimum age of sale to the marketing materials and activities could include actions such as utilizing services that compare consumer information against independent, competent, and reliable data sources, such as public records, before granting users access to the applicant's tobacco product website(s), using only first- or second-party age-verified data to target paid digital advertising, and limiting sales to adult-only stores. Applicants could also restrict or avoid the use of marketing practices that are not or cannot be targeted in ways that would limit exposure of individuals below the minimum age of sale and choose tactics more narrowly targeted to current adult users of tobacco products, such as avoiding online social media without access restrictions to promote the tobacco product and, instead, choose actions such as paper or electronic mail directed only to current smokers at or above the minimum age of sale.

FDA is requiring the description of an applicant's plans to market the new tobacco product to contain a discussion of an applicant's plans to target the marketing materials and

activities to reach the intended audience(s) and limit the exposure of individuals below the minimum age of sale to such materials and activities, because there is a well-established body of scientific evidence regarding their effect on tobacco product use behavior (see e.g., Refs. 19-22). The impact of tobacco marketing tactics on youth and young adult tobacco use behavior in particular has been well documented. The 2012 Surgeon General's report entitled "Preventing Tobacco Use Among Youth and Young Adults," (the 2012 SGR) synthesizes more than 30 years of research on the topic and outlines the findings demonstrating that product labeling, advertising, marketing, and promotion influence youth tobacco use by shaping attitudes, beliefs, and risk perceptions, and promoting pro-tobacco social and cultural norms (Ref. 9). The 2012 SGR states that the strong empirical evidence, along with the tobacco industry's own internal documents and trial testimony, as well as widely accepted principles of advertising and marketing, support the conclusion that tobacco manufacturers' advertising, marketing, and promotions recruit new users as youth and continue to reinforce use among young adults (Ref. 9). The 2012 SGR states that this evidence is sufficient to conclude that marketing efforts and promotion by tobacco companies show a consistent dose-response relationship in the initiation and progression of tobacco use among young people (Ref. 9). The 2012 SGR also states that research conducted by the tobacco industry consistently demonstrates that the brand imagery portrayed on packages is particularly influential during youth and young adulthood--the period in which smoking behavior and brand preferences develop. The 2016 Surgeon General's report entitled, "E-Cigarette Use Among Youth and Young Adults," similarly synthesizes research on e-cigarettes and concluded that e-cigarette manufacturers used tactics similar to those used to market conventional cigarettes to youth and young adults (Ref. 15).

The National Cancer Institute (NCI) made a similar conclusion in its monograph, "The Role of the Media in Promoting and Reducing Tobacco Use," that the total weight of evidence--from multiple types of studies, conducted by investigators from different disciplines, and using data from many countries--demonstrates a causal relationship between tobacco advertising and promotion and increased tobacco use (Ref. 20). As such, the direct role of tobacco product marketing and related activities in increasing tobacco use in the United States, especially among youth, and the high rates of youth-exposure to tobacco marketing due to its ubiquity, are two key rationales cited by NCI for restricting tobacco product marketing and related activities (Ref. 20). A variety of research has found that exposure to advertising is associated with susceptibility to use tobacco products and the actual use of tobacco products (see e.g., Refs. 25-33). For example, research has found that the use of certain kinds of imagery, such as logos and cartoons, have an impact on youth tobacco initiation (see, e.g., Refs. 34-36) and that a key tactic of tobacco companies seeking to attract and recruit youth users is to use advertising and marketing with aspirational imagery and themes known to resonate with younger audiences, such as independence, popularity, rebelliousness, attractiveness, and being cool (Ref. 9).

An analysis of the 2011 National Youth Tobacco Survey (NYTS) found that adolescents who reported frequent exposure to tobacco advertising at the point of sale and on the internet had significantly higher odds of ever using e-cigarettes and that there was a dose-response association between the number of marketing channels to which they were exposed and whether they used tobacco products (Refs. 15 and 33). An analysis of 2014 NYTS data assessing exposure to e-cigarette advertising in different channels (i.e., internet, print, television and movies, retail stores) found that as the number of channels of e-cigarette marketing exposure increased, the likelihood of use and susceptibility also increased (Refs. 15, 37, and 38). Thus,

providing information regarding the ways in which an applicant would target the marketing materials and activities for the new tobacco product to reach the intended audience(s) and limit the exposure of individuals below the minimum age of sale to such items can provide valuable insight into the potential that youth would initiate tobacco product use.

Finally, § 1114.7(f)(2)(iv) requires the description of an applicant's marketing plans to contain a concluding summary discussing how the applicant's plans for marketing the new tobacco product are consistent with the applicant's discussion regarding the increased or decreased likelihood of changes in tobacco product use behavior (including switching, initiation, cessation, and polyuse) under § 1114.7(l) and permits FDA to determine whether permitting the marketing of the new tobacco product would be APPH. This section requires an application to contain a discussion of how each of the items in § 1114.7(f)(2)(i) through (iii) are consistent with the applicant's discussion regarding the increased or decreased likelihood of changes in tobacco product use behavior by both current users and nonusers of tobacco products. This includes, but is not limited to: how the planned targeting of intended audience(s) is consistent with discussions regarding the likelihood of changes in tobacco product use behavior such as by current adult users, including switching, quitting, and polyuse; and how, for individuals below the minimum age of sale, restrictions on access to the new tobacco product and limitations on exposure to the marketing materials and activities for the new tobacco product are consistent with discussions regarding the likelihood of tobacco product use initiation, including among youth. For example, where an applicant expects current adult cigarette smokers to use its new tobacco product, the applicant would be required to explain its basis for concluding that its planned marketing is consistent with that expectation, such as providing an explanation of how the applicant determined its selected marketing channels and tactics would reasonably reach its intended users.

Similarly, if an applicant claims its marketing plans would adequately prevent or reduce youth initiation, the applicant would be required to explain its basis for such a conclusion by providing explanations of any measures or controls the applicant would use to restrict youth access to the product (e.g., selling the product only in brick-mortar retail locations), using competent and reliable third-party services to verify the age and identity of product purchasers, implementing purchase quantity limits) and limit youth exposure to the product's marketing materials and activities (e.g., restricting its marketing to channels and tactics where it is possible to target delivery of advertising to only age-verified adults).

An applicant can use this portion of the summary as an opportunity to help show the description of its marketing plans are consistent with its expectations for the potential initiation by current nonusers of tobacco products. For example, where conclusions drawn from tobacco product perception and use intention studies contained in a PMTA show the potential for current nonusers to initiate tobacco product use with the new tobacco product, an applicant could discuss how its plans to market the tobacco product, such as advertising at only point-of-sale locations for tobacco products or sending direct mail marketing to individuals of legal purchasing age who have opted-in to such communications, would mitigate the potential for initiation by nonusers and aligns with the applicant's discussion of such potential under § 1114.7(l).

In addition to the basic requirements of § 1114.7(f)(2), to help inform FDA's APPH determination, applicants may develop and submit more detailed plans to implement specific marketing campaigns. Not only would this provide an applicant the opportunity to further address any concerns about the potential for youth to initiate tobacco product use with the new tobacco product, it would be an opportunity for an applicant to more concretely show how it would target its marketing materials and activities to reach the intended audience(s).

The types of more detailed marketing plan information an applicant could develop and submit as part of a PMTA include materials such as strategic creative briefs, media and distribution channels, specific tactics, and the intended scope of each marketing activity (e.g., information such as the expected reach and frequency of audience exposures to the marketing, and timing and duration of the marketing activities), and the information described in the items listed below. These details, if provided, should be provided as part of the appropriate discussion under § 1114.7(f)(2) (if applicable) and can include:

- a description of specific insights about the intended audience(s) (e.g., findings from consumer research) that have informed the applicant's marketing plans, including its strategic approach, key messages and themes, creative direction, and potential tactics or marketing channels. This could include product-specific insights (e.g., an audience's impressions of one product being just as harmful as another, preference of a certain brand), as well as other beliefs, interests, motivations, or behaviors that can be used to tailor an applicant's approach to marketing the product. This could also include information regarding where the intended audience(s) tends to consume marketing and advertising (e.g., television programs the intended audience(s) watches, social media influencers the intended audience(s) follows, websites and retail locations the intended audience(s) frequents) that can be used to tailor an applicant's approach, select relevant marketing tactics, and use relevant marketing channels. The applicant should describe such insights in either paragraph (i) or (ii), as appropriate, and state the source of such data;
- plans to use owned, earned, shared, or paid media to create labeling for, advertise, market, or promote the tobacco product. While media categories overlap, owned media

typically consists of a company's own media properties and content they control, such as the company's product-branded website or mobile application. Earned media typically consists of unpaid media publicity or coverage of a company's brand or product that the company did not commission or pay for, such as a news article about the product or an influencer talking about a company's product without compensation. Examples of plans to use earned media can include, but are not limited to, pitching articles to news outlets, using unsolicited consumer reviews or testimonials to promote the product, and inviting influencers or reporters to attend a product launch event. Shared media typically consists of social media properties, such as a company's social media accounts and content, including interactions with other social media users and their content, such as comments, "likes," and responses to comments. Paid media typically consists of content that a company pays to place and promote in media properties it does not own, such as advertising appearing on television and radio, in and around retail stores, and in digital media, including content shared by a celebrity who a company pays to promote the tobacco product;

- plans to use (or not use) partners, influencers (e.g., celebrities, cultural icons, individuals with substantial followers on social media), bloggers, or brand ambassadors to create labeling for, advertise, market, or promote the tobacco product;
- plans to conduct (or not conduct) consumer engagements, including events at which the tobacco product will be demonstrated; and
- plans to use public relations or other communications outreach to promote the tobacco product. Public relations could consist of actions such as using a public relations firm to

promote the tobacco product. Other communications to promote the product could consist of actions such as direct mail to consumers.

7. Statement of Compliance With Part 25

A PMTA must contain an environmental assessment (EA) prepared in accordance with § 25.40 or a valid claim of a categorical exclusion, if applicable. Pursuant to § 25.15(a), all submissions requesting FDA action require the submission of either a claim of categorical exclusion or an EA. In accordance with § 25.40(a), an environmental assessment must include, at a minimum, brief discussions of: the need for the proposed action; alternatives to the proposed action as required by section 102(2)(E) of the National Environmental Policy Act of 1969 (NEPA); the environmental impacts of the proposed action and alternatives; the Agencies and persons consulted during the preparation of the EA; and the relevant environmental issues relating to the use and disposal of the tobacco product. Although applicants may wish to review the categorical exclusions specific to tobacco product applications at § 25.35, the only categorical exclusion currently available for a marketing order is for provisional SE reports that receive an SE order in the SE premarket pathway, not for PMTAs. If the applicant believes the action would qualify for an available categorical exclusion, the applicant must state under § 25.15(a) and (d) that the action qualifies for a categorical exclusion, cite to the claimed exclusion, and state that to the applicant's knowledge no extraordinary circumstances exist under § 25.21.

Failure to include an EA in a PMTA is grounds for FDA to refuse to accept an application and failure to include an adequate EA is sufficient grounds under § 25.15 for FDA to refuse to file the PMTA or refuse to issue a marketing granted order. (See the discussion of §§ 1114.27 and 1114.29 in section IX of this document.)

8. Summary

Section 1114.7(h) requires the application to contain a summary of the application contents in sufficient detail to provide FDA with an adequate understanding of the data and information in the application. FDA requires the summary under authority of sections 701(a) and 910(b)(1)(G) of the FD&C Act because it provides FDA with an understanding of the information contained in the PMTA and allows FDA to plan and conduct a more efficient review of the detailed technical information the summary describes. The summary also helps reviewers understand the product and the accompanying scientific data more quickly and allows applicants to highlight information they believe demonstrates their product should receive a marketing granted order.

The summary should discuss all aspects of the PMTA and synthesize the application in a well-structured, unified manner. The summary should serve as a briefing document that highlights the most important aspects of the application, with each section of the summary consisting of a brief explanation of information that the applicant believes contributes to a finding that permitting the marketing of the product would be APPH. The applicant must summarize the content included in the PMTA in a manner that describes the operation of the product, the health risks of the new tobacco product, the product's effect on tobacco use behavior of current users, the product's effect on tobacco use initiation by nonusers, and the product's effect on the population as a whole. The summary must describe the new tobacco product's potential effects on youth, young adults, and other relevant vulnerable populations. After reviewing comments on the proposed rule, FDA has added vulnerable populations to this requirement in the final rule to ensure the summary specifically accounts for those groups that

may be disproportionately affected or more likely to use the new tobacco product. The summary must contain the following items, where applicable:

- a summary of the product formulation section of the application. This section should provide a high-level description of the product formulation section of the application, highlighting information such as key ingredients, constituent levels, and design aspects of the product. See the discussion of § 1114.7(i) in section VIII.B.9 of this document;
- a summary of the manufacturing section of the application. This section should provide an overview of the manufacturing section of the application, including activities at each facility, and highlight information such as major aspects of the manufacturing and controls, especially those that the applicant believes contribute to a finding that permitting the marketing of the product would be APPH (e.g., an aspect of the manufacturing process that results in lower levels of HPHCs than other tobacco products in the same category). See the discussion of § 1114.7(j) in section VIII.B.12 of this document;
- a summary of the health risk investigations section of the application. This section should briefly describe and synthesize the findings of each investigation describing the following items, and explicitly identify areas in which there is a lack of information, if any:
    - the health risks of the tobacco product to both users and nonusers of the product (including youth, young adults, and other relevant vulnerable populations) and whether the tobacco product presents less health risk than other tobacco products, such as the risk of cancers (e.g., lung, mouth, pancreatic), heart disease, stroke, or lung disease, compared to other categories of tobacco products and other tobacco

products within the category, if known. See the discussion of § 1114.7(k)(1)(i) in section VIII.B.13.a.iii. of this document;

- the impact the product and its marketing will have on the likelihood of changes in tobacco use behavior of tobacco product users (including youth, young adults, and other relevant vulnerable populations), including cessation, switching (i.e., to a different tobacco product), and polyuse (i.e., using the new tobacco product in conjunction with one or more other tobacco products). See the discussion of § 1114.7(k)(1)(ii) in section VIII.B.13.a.iv. of this document;
- the impact the product and its marketing will have on the likelihood of tobacco use initiation by tobacco products nonusers, especially youth, young adults, and other relevant vulnerable populations, including among never users and former users, and the likelihood of polyuse and switching behaviors. See the discussion of § 1114.7(k)(1)(iii) in section VIII.B.13.a.v. of this document;
- How users and nonusers perceive the risk of the tobacco product based upon label, labeling, and advertising (if any has been studied). This includes how the label, labeling, and advertising affect use intentions. See the discussion of § 1114.7(k)(1)(iv) in section VIII.B.13.a.vi. of this document;
- whether users are able to understand the labeling and instructions for use, and use the product in accordance with those instructions. See the discussion of § 1114.7(k)(1)(iv) in section VIII.B.13.a.vi. of this document; and
- the impact of human factors on the health risks to product users and nonusers including, for example, how various use and misuse scenarios may impact the health

risks posed by the product. See the discussion of § 1114.7(k)(1)(v)) in section VIII.B.13.a.vii. of this document.

The rule also requires the summary to contain a concluding discussion demonstrating how the data and information contained in the PMTA both constitute valid scientific evidence and establish that permitting the marketing of the new tobacco product would be APPH as determined with respect to the risks and benefits to the population as a whole, including users and nonusers of the tobacco product. The rule also requires the summary to identify any key or pivotal studies on which an applicant is relying to establish that permitting the marketing of the new tobacco product would be APPH. FDA recommends that this discussion include estimates of the effect that the new tobacco product may have on the health of the population as a whole, such as effects on tobacco use initiation switching and cessation, and reductions in premature mortality, or increases in life-years lived. The estimates should integrate all of the information in the PMTA regarding the product and its potential effects on health, including, but not limited to adverse experiences, tobacco use behavior, and tobacco use initiation to provide an overall assessment of the potential effect that permitting the product to be marketed has or may have on overall tobacco-related morbidity and mortality.

As an illustration, an applicant may make an overall assessment of whether the product will likely have a net benefit on population health by accounting for potential reductions in disease risk (compared to other tobacco products) and the potential for current tobacco users to switch to the new tobacco product, and weighing that against the potential for nontobacco users to use the tobacco product and the accompanying potential increases in disease risks among those new tobacco product users. An applicant should provide quantitative assessments in the concluding discussion wherever possible; however, an applicant may provide qualitative

assessments where appropriate for the type of investigation(s) on which the assessment is based (e.g., focus group or interview-type studies).

The summary's concluding discussion must also briefly describe why the data and scientific information on which the applicant relies in concluding that permitting the marketing of the product would be APPH constitute valid scientific evidence. Section 910(c)(5)(A) of the FD&C Act requires FDA to make its determination of whether permitting the marketing of a new tobacco product would be APPH, where appropriate, on the basis of well-controlled investigations; however, under section 910(c)(5)(B) of the FD&C Act, where FDA determines that there exists valid scientific evidence other than well-controlled investigations that is sufficient to evaluate the product, FDA may use such evidence. As discussed in more detail in section IX.D of this document regarding § 1114.31, FDA considers valid scientific evidence to be evidence gathered using well-established or standardized methodologies from which it can be concluded by qualified experts that there is reasonable assurance of the reliability of its findings. Thus, if an application contains information regarding another tobacco product (e.g., published literature, marketing information) with appropriate bridging studies and describes the relationship to the product that is the subject of the application, FDA will review that information to determine whether it is valid scientific evidence sufficient to demonstrate that permitting the marketing of a product would be APPH.

9. Product Formulation

Section 910(b)(1)(B) of the FD&C Act requires that a PMTA contain a full statement of the components, ingredients, additives, and properties, and of the principle or principles of operation, of such tobacco product. Section 1114.7(i) implements FDA's interpretation of this

statutory requirement, together with its authority under section 910(b)(1)(G) of the FD&C Act, by requiring a PMTA to contain the following information:

a. Components or parts, materials, ingredients, additives, and constituents. Under the rule, the application is required to contain a full statement (i.e., a listing) of the product components or parts, materials, ingredients other than tobacco, tobacco ingredients, HPHCs, and the container closure system.

i. Components or parts. Section 1114.7(i)(1)(i) requires the application to state the quantity, function, and purpose of, and where applicable, target specifications of each component or part in the product. This information should also include an explanation of how each component or part is, or can be, integrated into the product design, and the purpose and function of each component or part. Where the tobacco product contains software components, the rule requires:

- a description of the software or technology (e.g., Bluetooth);
- a description of the purpose of the software or technology, such as monitoring where the tobacco product is located, activated, or used;
- a description of the data collected by the software and how this information will be used by the applicant.

FDA received comments regarding this section, as discussed below.

(Comment 36) One comment stated that the rule should be amended to state that FDA will issue a marketing denial order if the application does not include specific assurances and evidence that there will be no communication between the device and any external source, and that the software would not be programmed to increase consumption.

(Response 36) We agree that understanding how any software in a product may function is important to the review of an application. For example, software used in or with some consumer products may have functions and purposes that are not immediately clear, such as use monitoring and location tracking functions, and may be able to function in conjunction with other electronic devices, such as a smart phone. We decline to prohibit all communication between a new tobacco product and external sources as part of this rulemaking because product standards are outside the scope of this rulemaking; however, we will consider information regarding software (if applicable) as part of substantive review. For example, if the product has software features that could help prevent youth use of the tobacco product, FDA would review this information as part of the determination of whether permitting the marketing of the new tobacco product would be APPH. This information is especially important as it may not be readily apparent from a component or part's identity what function and purpose it may serve.

(Comment 37) One comment stated that FDA should amend § 1114.7(i)(3)(ii) to also require specification of software or other controls in an e-cigarette to limit the intensity of use, including minimum inter-puff interval and maximum number of puffs per hour that the device will deliver because, unlike with combusted cigarettes, there are no obvious indicators for consumers of how quickly they are consuming the product.

(Response 37) As discussed in section VIII.B.10., FDA requires the PMTA to contain a full narrative description of the way in which a typical consumer will use the new tobacco product. This includes, for example, a description of how a consumer operates the product, where applicable, whether and how a consumer can change the product design and add or subtract ingredients, the length of time it takes for a user to consume a single unit of the product, and whether the product incorporates a heating source and, if it does, a description of the heating

source. As described above, the presence of software or other controls in an e-cigarette to limit the intensity of use would be relevant to FDA's review of an application and a required part of a PMTA submission under § 1114.7.(i)(1)(i); however, FDA declines to require such controls in all e-cigarettes as part of this rule because it would constitute a product standard that is outside the scope of this rule.

ii. Materials. Section 1114.7(i)(1)(ii) requires the application to contain information for each material in the product because materials can affect the performance of the product. FDA considers materials to be part of "components" under section 910(b)(1)(B) and the required materials information is relevant to the subject matter of a PMTA under section 910(b)(1)(G) because it is needed to fully characterize the tobacco product and understand its health risks. For example, in portioned smokeless tobacco products, the materials used in the pouch can affect the rate at which nicotine is released and specifications such as pouch fabric air permeability can provide information about how quickly nicotine can be delivered to the consumer. For ENDS, the material used in the construction of an electrical heater coil influences its resistance and the temperature reached by the coil, which in turn may affect the type and amount of HPHCs produced in aerosol. The rule requires a PMTA to contain:

- the material name and common name (if applicable);
- the component or part of the tobacco product where the material is located;
- the subcomponent or subpart where the material is located (if applicable);
- the function of the material;
- quantities (including ranges or means and acceptance limits) of the materials(s) in the new tobacco product;

- specifications (including quality, grades, and suppliers) of the materials used for the new tobacco product (including any specification variations, if applicable); and
- any other material properties that fully characterize the new tobacco product, such as pouch material porosity or air permeability for portioned smokeless products. While failure to include additional material properties to fully characterize the tobacco product would not serve as the basis for FDA refusing to accept or file an application under § 1114.27(a)(1), it may slow down the substantive review process.

FDA received comments regarding this section, as described below.

(Comment 38) One comment requested that FDA clarify the scope of the materials that an applicant would have to describe in a PMTA, specifically requesting that FDA require PMTAs for e-cigarettes to contain information on only those materials that are reasonably expected to have contact with the e-liquid and not materials found in items such as the exterior plastic casing, electronic circuitry, and batteries. The comment stated that this would align with FDA's current approach set forth in the guidance entitled "Listing of Ingredients in Tobacco Products."[19]

(Response 38) FDA declines to limit the scope of the materials in an ENDS for which an applicant would have to provide information in a PMTA to only those materials that are reasonably expected to have contact with the e-liquid. As discussed in section § 1114.3, FDA defines material to mean an assembly of ingredients. Materials are assembled to form the tobacco product, or components or parts of the tobacco product. This includes both those materials that are in contact with the e-liquid as well as any other materials in the product, such as those used in the exterior plastic casing, electronic circuitry, and batteries. FDA declines to

[19] Available at https://www.fda.gov/tobacco-products/rules-regulations-and-guidance/guidance.

limit the scope of materials for ENDS because they are components or parts with the potential to introduce, diffuse, leach or extract to become part of the e-liquid formulation or constituents during storage and use. For example, batteries and solder joints of the product have been shown to be the potential source of metals contamination in e-liquid or aerosol (Ref. 39). Furthermore, defective or damaged batteries on their own may lead to battery failure or overheating, resulting in thermal runaway; thermal runaway has been identified as an immediate threat in e-cigarettes, particularly due to the metal enclosure of the e-cigarette batteries that allow the dangerous build-up of gasses (Ref. 40). In addition, the guidance for industry, entitled "Listing of Ingredients in Tobacco Products," discusses FDA's current enforcement policy for ingredient listing submission requirements under section 904(a)(1) of the FD&C Act. While FDA does not intend to enforce ingredient listing requirements for component and parts such as electrical components, batteries, and electronic circuitry, FDA recognizes that the ingredients of these other components and parts can also be important in determining the public health impact of tobacco products. As the guidance states, FDA will receive ingredient information for these other components and parts during our premarket review of new tobacco products. This is consistent with the rule's requirement to include information on materials in a PMTA.

iii. Ingredients other than tobacco. Section 1114.7(i)(1)(iii) requires that the application contain information on ingredients other than tobacco (tobacco ingredients are addressed in § 1114.7(i)(1)(iv)). The application must contain:

- International Union of Pure and Applied Chemistry (IUPAC) chemical name and common name (if applicable);
- Chemical Abstracts Service (CAS) number or FDA Unique Ingredients Identifier (UNII). Both the IUPAC and CAS or UNII are required to ensure FDA has the relevant

information associated with each identifier and to allow FDA to efficiently differentiate between similar ingredients;

- the function of the ingredient;
- the quantity of the ingredient in the tobacco product, with the unit of measure (including ranges or means, and acceptance limits) reported as mass per gram of tobacco for nonportioned tobacco products and as mass per portion for portioned tobacco products (with any specification variation, if applicable);
- the specifications (including purity or grade and supplier); and
- for complex purchased ingredients, each single chemical substance reported separately.

Additionally, FDA recommends that an application contain any other ingredient information to fully characterize the new tobacco product, as applicable. While failure to include other ingredient information to fully characterize the tobacco product would not serve as the basis for FDA refusing to accept or file an application under § 1114.27(a)(1), it may slow down the substantive review process.

iv. Tobacco ingredients. Section 1114.7(i)(1)(iv) requires information regarding tobacco ingredients, including:

- the type(s) of tobacco (e.g., Bright, Burley, reconstituted). This information is important to determining the public health impact of the products because different types of tobacco have different constituent profiles. In the proposed rule, we also included a requirement to specify the grade(s) of the tobacco and we have removed this due to the general lack of standardized grading systems.
- the quantity, with the unit of measure (including ranges or means, and acceptance limits), of each tobacco ingredient in the new tobacco product reported as mass per gram of

tobacco for nonportioned tobacco products and as mass per portion for portioned tobacco products (with any specification variation, if applicable);

- the specification(s) of tobacco used for the new tobacco product (with any specification variation, if applicable); and
- a description of any genetic engineering that impacts characteristics of the tobacco product, such as the constituent profile.

Additionally, FDA recommends a PMTA contain any other information about tobacco ingredients to fully characterize the new tobacco product, as applicable, such as country of origin, which can reflect different constituent levels (Ref. 41). While failure to include other information about tobacco ingredients to fully characterize the tobacco product would not serve as the basis for FDA refusing to accept or file an application under § 1114.27(a)(1), it may slow down the substantive review process. If the new tobacco product does not contain tobacco (e.g., rolling paper or tipping paper), this section of the application must specifically state that the product does not contain tobacco.

FDA requires in § 1114.7(i)(1) that ingredient quantities be reported as mass per gram of tobacco for nonportioned tobacco products and as mass per portion for portioned tobacco products. These specific measurements provide consistent, complete information that allows FDA to understand the ingredient quantities. In contrast, if ingredient quantities were reported as percentages, FDA would have to make assumptions about the denominator used to calculate the percentage. For example, if xylitol were reported as 10 percent of a portioned moist snuff, FDA would not able to determine if xylitol was 10 percent of the mass of the tobacco filler or of the entire product (containing filler, paper, etc.). For more information on uniquely identifying

components, ingredients, and additives and reporting their quantities, please refer to FDA's guidance for industry entitled "Listing of Ingredients in Tobacco Products."

v. Constituents. Section 1114.7(i)(1)(v) requires a full statement of the constituents, including HPHCs and other constituents, contained within, or emitted from (including its smoke or aerosol), the product, including any reaction products from leaching or aging. FDA considers constituents to be properties of the new tobacco product, a full statement of which is required to be in a PMTA by section 910(b)(1)(B) of the FD&C Act. The constituents contained within, and delivered from, the product can be detected through constituent testing on the product. The constituent testing should reflect the various conditions under which consumers may use the product (e.g., light use, typical use, and heavy use) and the types of products that consumers are likely to use in conjunction with the product. For example, an open (refillable) e-cigarette should be tested with a variety of e-liquids that consumers are likely to consume using the e-cigarette. The reports of constituent testing must be conducted in the manner required by, and include all information that is specified in, § 1114.7(i)(1)(v), including the full test data.

FDA published an initial list of the constituents that it has identified as HPHCs in the *Federal Register* of April 3, 2012, which it intends to update periodically by providing the public with notice and the opportunity to submit comments. FDA recently proposed the addition of 19 constituents to the established list of HPHCs.[20]

The constituent testing data FDA requires for all products include:

- the constituent names in alphabetical order;
- the common name(s);
- the CAS number;

[20] 84 FR 38032 (August 5, 2019).

- the mean quantity and variance with unit of measure;
- the number of samples and measurement replicates for each sample. As stated in § 1114.7(i)(4)(iv), the testing must be conducted using a sufficient sample size and number of replicates to substantiate the results of the type of testing conducted;
- a description of method procedure, method validation information, and rationale for selecting each test method (as required by § 1114.7(i)(4)(v));
- the name and location of the testing laboratory or laboratories and documentation showing that the laboratory or laboratories is (or are) accredited by a nationally or internationally recognized external accreditation organization (as required by § 1114.7(i)(4)(i));
- the length of time between dates of manufacture and date(s) of testing (as required by § 1114.7(i)(4)(ii));
- storage conditions of the tobacco product before it was tested. It is important for FDA to understand the storage conditions before testing because they could affect the quantity of volatile organic compounds or promote microbial growth in the tobacco product (as required by § 1114.7(i)(4)(iii));
- reports of constituent testing that include test protocols, any deviation(s) from the test protocols, quantitative acceptance (pass/fail) criteria, line data, and a summary of the results, for each applicable parameter (as required by § 1114.7(i)(4)(vi)); and
- complete descriptions of any smoking or aerosol generating regimens used for analytical testing that are not standardized or widely accepted by the scientific community, if applicable (as required by § 1114.7(i)(4)(vii)).

Multiple comments provided feedback or requested clarification related to these provisions, as discussed below.

(Comment 39) One comment requested additional clarification regarding the HPHCs for which an applicant must conduct testing when submitting a PMTA for an ENDS. The comment noted the proposed addition of 19 constituents to the established list of HPHCs and sought further information regarding what must be submitted in a PMTA.

(Response 39) The rule requires each applicant to submit information regarding all constituents contained in and emitted from the product, which could include both constituents that are contained within the established list of HPHCs and those that are not on the list. FDA's recommendations regarding constituents in an ENDS for which a prospective applicant might want to consider testing, as appropriate for its specific product, are discussed elsewhere in this document (see Response 35).

(Comment 40) One comment stated that while consideration of the constituents on FDA's list of HPHCs is important, FDA should not give it undue emphasis because there are other toxins in tobacco products that are not on this list. The comment stated an application's exposure assessment should cover the full range of exposures generated by the new product and that FDA should revise the rule to clearly state that evidence of biological and clinical effects of the product will be given more weight than measures of exposure.

Another comment stated that the definitions of the terms "constituent" and "HPHC" are so broad that the requirement in § 1114.7(i)(1)(v) to report all constituents contained within or emitted from the product could be difficult for applicants. The comment stated that there are practical constraints on the number, capacity, and capability of laboratories equipped to conduct the testing. The comment also expressed concern that FDA could potentially refuse to file an

application in which an applicant omitted a constituent. The comment suggested that FDA revise the rule so that an application would be required to contain only information for "relevant" constituents and HPHCs, rather than all constituents. Specifically, the comment recommended that the inclusion of constituent and HPHC information should be based on a comprehensive risk assessment of the particular product.

(Response 40) FDA declines to make revisions in response to these comments. An application is not required to contain testing for all HPHCs on the initial list; rather, it must contain testing for HPHCs that are contained within and can be delivered by the type of product and contain a description of why the HPHCs that were tested are appropriate for the type of product. FDA declines to limit the scope of the constituents that must be reported in a PMTA to only those that an applicant considers to be relevant because it may impair FDA's ability to determine the health risks of a new tobacco product. As discussed in the rule, the constituents contained within and delivered from a tobacco product directly relate to its health risks. The HPHC list can be helpful to applicants in preparing a description of why the HPHCs for which it tested are appropriate for the product type, including, where appropriate, why an applicant did not test for certain HPHCs. For example, a PMTA for a smokeless tobacco product would not be required to contain testing results for HPHCs that are a byproduct of combustion (e.g., carbon monoxide) where the product does not contain or deliver such constituents. However, a PMTA for an inhaled tobacco product that an applicant claims aerosolizes a substance but does not combust it, such as an e-cigarette or heated tobacco product, should provide evidence, such as testing for HPHCs that result from complete or incomplete combustion, to demonstrate that the product is not combusted. For recommendations on constituent testing for ENDS products, please see the ENDS PMTA Guidance.

Additionally, FDA declines to revise the rule to assign weight to different types of evidence. Finding that there is a showing that permitting the marketing of a new tobacco product would be APPH is a complex determination that must be made with respect to risks and benefits to the population as a whole, considering the likelihood of changes in tobacco product use behavior (including initiation and cessation) caused by the marketing of the new tobacco product. When determining whether the marketing of a particular new tobacco product would be APPH, FDA will evaluate the factors in light of available information regarding the existing tobacco product market, tobacco use behaviors, and the associated health risks at the time of review.

(Comment 41) One comment requested FDA provide greater detail regarding the ranges of constituents that would be acceptable in a PMTA.

(Response 41) FDA does not set limits for what constitutes acceptable ranges for constituents as a part of this rulemaking. FDA's APPH determination will include a consideration of constituent levels and their resulting health risks; however, FDA must also consider of a variety of information related to health risk and tobacco product use behaviors. FDA recommends that applicants take all the necessary steps in controlling and mitigating any circumstances that may affect the constituent yields generated from a new tobacco product as this may impact the risks and benefits associated with the new tobacco product on the population health as a whole, when compared to other products on the market.

(Comment 42) One comment stated the final rule must provide greater detail regarding the appropriate validated methodologies or regimens required for testing.

(Response 42) As discussed in § 1114.7(i)(1)(v), for combusted or inhaled tobacco products, constituent smoke or aerosol yields from the new product must be determined using

intense and nonintense smoking or aerosol-generating regimens, where established. Two smoking or aerosol-generating regimens are required, where established, to understand the way that constituent yields delivered by a tobacco product can change over a range of different smoking conditions. If constituent yields were only reported from a single smoking or aerosol-generating regimen, FDA would have limited and potentially misleading information about constituent yields produced by a given tobacco product. Many studies demonstrate that different smoking regimens result in different constituent yields from the same product (Refs. 42 and 43). By requiring both an intense and a nonintense smoking or aerosol generating regimen, where established, FDA will have a better understanding of quantities of each constituent that may be produced by the tobacco product when used under different conditions. If no intense and nonintense smoking or aerosol-generating regimens (e.g., International Organization for Standardization (ISO) and Health Canada Intense (HCI) regimens for cigarettes, Cooperation Centre for Scientific Research Relative to Tobacco (CORESTA) regimens for cigars) have been established and an applicant must use an alternative regimen, an applicant should provide an explanation as to why the alternative regimen provides comparable results. For ENDS products, for example, where intense and nonintense regimens may have not been established, the application must contain an explanation of why the alternative regimen provides comparable results to the intense and nonintense regimens.

(Comment 43) One comment stated that manufacturers of premium cigars should not be required to submit information regarding HPHCs and other constituents. The comment stated that not only is there a lack of testing standards, the variability inherent in premium cigars would render the results of any constituent testing worthless for assessing a product.

(Response 43) As stated in § 1114.1(d) and described in section VII.A. of this document, this rule does not apply to "premium" cigars. To the extent this comment is applicable to products other than "premium" cigars, such as large cigars that do not meet the definition of "premium" cigar, FDA disagrees with this comment. Each applicant that submits a PMTA is required by § 1114.7(i)(1)(v) to conduct constituent testing and submit the results as part of their application. Understanding the constituents contained within and emitted from a tobacco product is a crucial component of being able to determine its health effects, which is why FDA will refuse to accept a PMTA (under § 1114.27(a)(1)), as appropriate, where it lacks constituent testing information required by § 1114.7(i)(1)(v). Where a product's ingredients have natural variability that could affect constituent testing results, FDA recommends an applicant submit scientific evidence justifying why the results reflect the natural variability of the ingredients in the new tobacco product. This evidence could include items such as scientific literature establishing the variability of the product, information related to international or national testing standards, or data from an investigation with sufficient sample size to demonstrate attributes affecting variability of the test results (e.g., weight, smoke efficiency, crop year to crop year, region to region). Additionally, CORESTA[21] have established and published methods on how to generate cigar smoke to quantitatively compare HPHCs found in cigar smoke.

vi. Container closure system. Section 1114.7(i)(1)(vi) requires that the application contain a description of the container closure system for the new tobacco product, if applicable,

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[21] CORESTA standards that applicants might consider include CORESTA Reference Method (CRM) 46: Atmosphere for Conditioning and Testing Cigars of all Sizes and Shapes; CRM 47: Cigars--Sampling; CRM 64: Routine Analytical Cigar-Smoking Machine--Specifications, Definitions and Standard Conditions; CRM 65: Determination of Total and Nicotine-Free Dry Particulate Matter using a Routine Analytical Cigar-Smoking Machine--Determination of Total Particulate Matter and Preparation for Water and Nicotine Measurements; CRM 66: Determination of Nicotine in the Mainstream Smoke of Cigars by Gas Chromatographic Analysis; CRM 67: Determination of Water in the Mainstream Smoke of Cigars by Gas Chromatographic Analysis; CRM 68: Determination of Carbon Monoxide in the Mainstream Smoke of Cigars by Non-Dispersive Infrared Analysis.

including information describing how the container closure system protects and preserves the product from damage during transport, environmental contaminants, and leaching and migration of constituents into the new tobacco product. The description must also contain information describing design features developed to prevent the risk of accidental exposure, if any (e.g., child resistant packaging for e-liquids). These descriptions are important to FDA's review of the product because they help demonstrate that the product used by consumers is in the same condition as that described in the application and manufactured by the applicant and provide information regarding whether the container closure system has any features that could prevent accidental exposure.

Additionally, evidence demonstrates that the container closure system used can change the characteristics of the product. For example, substances within the packaging materials can affect product moisture (e.g., when the manufacturer changes the container closure system of a moist snuff from plastic to fiberboard), which can affect microbial stability and TSNA formation during storage (Ref. 44). Another example is when menthol or other ingredients are applied to the inner foil of a cigarette package to become incorporated into the consumed product (Ref. 1). The container closure system may also be intended or reasonably expected to affect the characteristics of a tobacco product by impacting the rate of leaching into, and ultimately, the amount of substances found in, the consumable tobacco product. In fact, it has been demonstrated that compounds in the container closure system may diffuse into snuff and affect its characteristics (Ref. 2). Thus, for example, packaging material that affects the characteristics of a tobacco product by impacting the moisture level or shelf life of a tobacco product is a container closure system (e.g., a plastic container compared to a metal container of smokeless tobacco) because a difference in tobacco moisture is reasonably expected to affect microbial

growth in the product, extraction efficiency, and total exposure to nicotine or the carcinogens NNN or NNK. For additional examples of container closure systems, see the ENDS PMTA Guidance.

vii. Statement of tobacco blending, reconstitution, and manipulation. Finally, the rule requires a PMTA to contain a full statement of the tobacco blending, reconstitution, or manipulation, where applicable. This may include manufacturer specifications, and tobacco types, and quantities. This information is important because it helps FDA understand the characteristics of the tobacco product. Information on tobacco types and quantities used by an applicant (where applicable) will help FDA understand the composition of tobacco used, which can provide important information since the tobacco types and quantities may impact the tobacco chemistry (e.g., the nicotine content) and, thereby, the chemical composition of the tobacco product (Ref. 45).

b. Other properties. Section 1114.7(i)(2) describes additional parts of FDA's interpretation of the requirement in section 910(b)(1)(B) of the FD&C Act to provide a full statement of the product properties and, together with FDA's authority under section 910(b)(1)(G), requires the applicant to provide a full description of the properties of the tobacco product that includes:

i. Product dimensions and construction. The product dimensions and the overall construction of the product using a diagram or schematic drawing that clearly depicts the finished product and its components with dimensions, operating parameters, and materials. Under the definition of finished tobacco product (which includes all components and parts, sealed in final packaging), the dimensions and schematic drawings are required to include the final packaging. The diagram or schematic is an annotated graphical representation that will

help FDA understand the applicant's nomenclature, how the components and parts function together, and the overall principles of operation of the finished tobacco product.

ii. Design parameters and test data. All design parameters of the product and test data, specifying nominal values or the explicit range of values as well as the design tolerance (i.e., upper and lower range limits), where appropriate. Changes in design parameters can change the health impact of the tobacco product by affecting the level of constituents that reach the user or nonuser and are also necessary to fully characterize a tobacco product. Given the potential health impacts associated with changes in design parameters as well as the importance of design parameters in fully characterizing a product, the PMTA review process does not simply note or link these parameters to the product and any associated constituents. Instead, during PMTA review, FDA evaluates how products are manufactured, and the controls put in place during production. For the PMTA pathway, FDA reviews whether each design parameter meets its specification through test data, determining whether each parameter is adequately controlled via documented processes, determining whether safeguards are in place against hazards and foreseeable misuse, and assessing how the applicant deals with nonconforming products. FDA believes it is necessary to review sufficient information to ensure that products marketed under the PMTA pathway have the necessary manufacturing and control processes in place. Tables 1 through 22 in § 1114.7(i)(2)(ii)(B) provide the parameters that are required for different categories of tobacco products. As part of the full description of the properties of the tobacco product, the rule also requires, as included in the tables, a quantitative description of the performance criteria, including test protocols, test data, and a summary of the results, for each applicable design parameter and manufacturing step. The test data is a required part of the PMTA to demonstrate the product consistently meets the nominal values or range of values as

well as the design tolerance. While test data is a required part of the PMTA, FDA does not require test data for all the parameters for which it requires target and range. For example, for parameters that are observational (e.g., number of waterpipe holes), FDA would not seek test data on that parameter. Also, some design parameters are machine settings (e.g., tobacco cut size), calculated (e.g., denier per filament (DPF)), provided by suppliers (e.g., certificate of analysis for base paper porosity), or can be extrapolated from other design parameter test data (e.g., filter pressure drop test data is more informative than filter length test data). Test data would not be needed for such parameters. In addition, in tables 1 through 22, FDA has clarified alternative terminology for "porosity" understanding that applicants may refer to this term as "permeability" for several design parameters as well as adding units of measure for several design parameters. The design parameters, their importance to understanding their impact on public health, and methods for applicants to provide this information are described below.

One way an applicant can provide the information needed for a product's required design parameters is with a Manufacturing Data Sheet Specification (MDSS) document. The MDSS is a document typically maintained by manufacturers, describing all the parameters that are controlled by the manufacturer during manufacture of their tobacco products. There will be cases where the design parameters on the MDSS will not directly translate into one of the product-specific design parameters in section 1114.7(i)(2)(ii). In these cases, additional information would need to be submitted to provide the complete characterization necessary. There may also be instances (e.g., for novel tobacco products in one of the categories described in table 1 to § 1114.7(c)(3)(iii)) where one or more of the required design parameters do not apply to the tobacco product described in the PMTA. In these instances, an applicant must justify why the required design parameter does not apply or how an alternative design

parameter(s) would satisfy one or more of the required design parameters. Similarly, for test data, an applicant must justify why the required test data does not apply or how alternative test data should be considered by FDA in lieu of the required test data. Further, there may be instances where the tobacco product may not fit into any of the categories described in table 1 to § 1114.7(c)(3)(iii). In these instances, the applicant must provide design parameters that would fully characterize their product. Additionally, if there are design parameters beyond what FDA is requiring that would characterize the tobacco product, applicants should provide those to aid in FDA's scientific review. While failure to include additional design parameters to fully characterize the tobacco product beyond what FDA is requiring under this rule would not serve as the basis for FDA refusing to accept or file an application under § 1114.27(a)(1), it may slow down the substantive review process.

Applicants should also state whether the ranges or tolerances associated with each design parameter correspond to product or process controls, and what actions the applicant takes when test data falls outside of these specified ranges. As an example of product and process controls, a smokeless tobacco product may have set design parameters (also known as product specifications) for pH and oven volatiles (OV). The applicant may establish process controls for the fermentation process by setting lower and upper temperature and humidity limits for specified time durations. At the end of the fermentation process, a sample may be tested to verify that the tobacco product meets the established pH and OV design parameter limits. For any design parameters that are provided that are not included in the tables to § 1114.7(i)(2)(ii)(B), applicants must provide test data or process information to demonstrate that these parameters or their associated processes are adequately controlled.

Table 1 to § 1114.7(i)(2)(ii)(B) describes the design parameters and information on performance criteria that must be contained in a PMTA for cigarettes. In this final rule we have revised table 1 to § 1114.7(i)(2)(ii)(B) to help ensure that FDA is able to identify and evaluate each product more accurately and efficiently. These changes include: (1) removal of the proposed requirement for applicants to provide cigarette draw resistance, as FDA determined that requiring this parameter was unnecessary and not as informative as pressure drop as draw resistance could be modified by the user by puffing more or less intensely; (2) removal of cigarette paper base paper basis weight and tipping paper basis weight, as they are not as informative as other design parameters, such as cigarette paper base paper porosity; (3) removal of plug wrap parameters, as the effects of plug wrap are not as informative as cigarette paper parameters; (4) removal of cigarette mass, paper width, filter diameter, tipping paper width, and tobacco rod length, as these parameters can be either calculated from other required design parameters or are not as informative as other required parameters; (5) removal of filter mass and filter tow crimp index, as these parameters have less of an impact on the filter efficiency than other required design parameters that will affect the smoke constituents that are exposed to users and nonusers; (6) removal of filter ventilation position of holes, filter ventilation number of holes, and filter ventilation number of rows as filter ventilation, which is still required, is affected by these parameters; (7) the inclusion of filter efficiency as an alternative to DPF, total denier, or filter density, if available, as these parameter have a direct effect on filter efficiency and vice versa; (8) the option to provide cigarette diameter as an alternative to cigarette circumference as FDA is able to calculate the necessary information based on either one; and (9) the option for the applicant to provide cigarette paper band diffusivity in lieu of cigarette paper band porosity, if applicable (also described as permeability). FDA has clarified terminology for cigarette paper

band porosity, as applicants may refer to this term as permeability, and also provided an alternative to providing cigarette paper band porosity or permeability--band diffusivity, while not preferred, is an acceptable alternative if it is currently not part of an applicant's practice to specify cigarette paper band porosity. While there are minor differences (porosity is more relevant during active puffing, whereas diffusivity is more relevant during smoldering), the addition of diffusivity as an alternative parameter allows flexibility to applicants who do not directly measure porosity or permeability (see Ref. 46).

Additionally, FDA has revised certain proposed parameters for test data, which includes: (1) removal of puff count as this was duplicative of information that an applicant would submit with smoke constituent data since puff count is determined in a smoking machine using either the ISO or HCI smoking regimen or other applicable regimen; (2) removal of cigarette draw resistance, as explained above; (3) removal of cigarette mass, cigarette paper base paper and tipping paper basis weight, as explained above; (4) removal of plug wrap parameters, as explained above; (5) removal of tipping paper width and tipping paper perforation, as explained above; (6) removal of tipping paper length and width, tobacco rod length, cigarette paper length and width, cigarette length, cigarette diameter, cigarette paper band width, cigarette paper band space, filter diameter and length as these are measured parameters, that are not needed as test data; (7) removal of filter tow crimping index and filter mass, as explained above. The finalized parameters listed in table 1 to § 1114.7(i)(2)(ii)(B) are a necessary part of the application because they are needed to fully characterize the product and changes in these parameters may affect the cigarette's impact on the public health, as described below:

- cigarette length may alter tobacco biomarker levels (Ref. 47);

- cigarette circumference or diameter may affect filter efficiency and, in turn, smoke constituent yields (Ref. 48); puff count can directly affect smoke constituent yields (Ref. 49);
- tobacco filler mass may affect smoke constituent yields (Ref. 50);
- tobacco rod density may modify burn properties and smoke constituent yields (Refs. 51 and 52);
- tobacco cut size alters the size of the tobacco pieces, which may result in more particulate matter (Ref. 53);
- tobacco moisture may affect puff count (Ref. 54);
- cigarette paper base paper basis weight may affect puff count and smoke constituent yields (Ref. 55);
- cigarette paper base paper porosity or permeability may affect smoke constituent yields (Ref. 55);
- cigarette paper band porosity or permeability may affect smoke constituent yields because band porosity allows for the overall assessment of the weighted change in air flow through the cigarette paper during active puffing (Ref. 56);
- cigarette paper band diffusivity may affect smoke constituent yields because it mimics air flow during smoldering (Ref. 57);
- cigarette paper band width may affect ventilation and, in turn, smoke constituent yields (Ref. 58);
- cigarette paper band space may affect ignition propensity and, in turn, puff count (Ref. 59);
- filter efficiency may affect smoke constituent yields (Ref. 58);

- filter DPF, total denier, filter density, and filter length may affect filter efficiency and, in turn, smoke constituent yields (Ref. 60);
- filter pressure drop may affect smoke constituent yields (Ref. 61);
- tipping paper, including length, may affect smoke constituent yields (Ref. 62); and
- filter ventilation may affect smoke constituent yields (Ref. 48).

Table 2 to § 1114.7(i)(2)(ii)(B) describes the design parameters and information on performance criteria that must be contained in a PMTA for portioned and nonportioned smokeless tobacco products. We have revised table 2 to § 1114.7(i)(2)(ii)(B) to help ensure that FDA is able to identify and evaluate each product more accurately and efficiently. These changes include: (1) removal of portion thickness, as it is an unnecessary parameter because it is the pouch effective area that may result in an increase of the release level of nicotine, unprotonated nicotine, and could affect TSNA levels, and the pouch effective area can be calculated from other required design parameters, i.e., pouch length and pouch width; (2) removal of pouch material nicotine dissolution extent, as nicotine dissolution rate provides the nicotine exposure to the user over time, and therefore was considered redundant and unnecessary; (3) addition of pouch material thickness as this parameter influences the release level of nicotine and can affect TSNA levels[22]; (4) option to provide tobacco particle size in lieu of tobacco cut size, as tobacco particle size can impact the use profile of the product and thereby affect the rate and total delivery of HPHCs similar to tobacco cut size. FDA has revised certain proposed parameters for test data, which includes the removal the portion length, width, portion

[22] See, e.g., Gale, N., G. Errington, and K. McAdam, Group Research & Development, British American Tobacco, "Effects of Product Format on Nicotine and TSNA Extraction from Snus Pouches," Presentation at the 67th Tobacco Science Research Conference, Williamsburg, VA, September 15-18, 2013. Available at: https://www.researchgate.net/publication/299854728_Effects_of_Product_Format_on_Nicotine_and_TSNA_Extraction_from_Snus_Pouches.

thickness, and material thickness, as these are measured design parameters that can be obtained from the supplier of the portion or pouch, and (5) clarification of requiring certain parameters "if applicable" for portioned product properties. While these parameters are needed for all portioned smokeless products, not all portioned products are pouched, so the pouch-specific properties should only be reported if applicable, and thus FDA has added "if applicable" to pouch material porosity or permeability and pouch material basis weight.

The finalized parameters in table 2 to § 1114.7(i)(2)(ii)(B) are a necessary part of the applications because they are needed to fully characterize the product and changes in these parameters may affect the smokeless tobacco product's impact on public health, as described below:

- tobacco cut size may alter the particle surface area and accessibility of saliva to get to the surfaces of the tobacco, thereby affecting the amount and rate of constituents released from the product (Ref. 63);
- tobacco moisture may affect microbial growth in the product, extraction efficiency, and total exposure to nicotine, NNN, and NNK (Refs. 3 and 64);
- portion mass may affect user exposure to a tobacco product and, in turn, HPHCs contained in each portion (Ref. 65);
- portion length may affect the constituents in each portion (Ref. 65);
- portion width may result in a surface area difference, which is proportional to the amount and rate of constituents released from the product (Ref. 66);
- pouch material basis weight, pouch material air permeability, and pouch material thickness influences the interactions between the tobacco and oral cavity, thereby

potentially affecting the amount and rate of constituents released from the product (Refs. 67, 141, and 142[23]); and

- nicotine dissolution rate is a function of tobacco cut size and pouch materials, thereby potentially affecting the amount and rate of constituents released from the product (Ref. 68).

Table 3 to § 1114.7(i)(2)(ii)(B) describes the design parameters and information on performance criteria that must be contained in a PMTA for RYO tobacco rolling paper products. In this final rule, we have revised table 3 to § 1114.7(i)(2)(ii)(B) to help ensure that FDA is able to identify and evaluate each product more accurately and efficiently. These changes include the option to provide RYO paper band diffusivity in lieu of RYO paper band porosity (also described as permeability). FDA has clarified terminology for RYO paper band porosity, as applicants may refer to this term as permeability, and also provided an alternative to providing cigarette paper band porosity or permeability--band diffusivity, while not preferred, is an acceptable alternative if it is currently not part of an applicant's practice to specify cigarette paper band porosity. While there are minor differences (porosity is more relevant during active puffing, whereas diffusivity is more relevant during smoldering), the addition of diffusivity as an alternative parameter allows flexibility to applicants who do not directly measure porosity or permeability (see Ref. 46). Additionally, FDA has revised certain proposed parameters for test data, which includes the removal the paper length, width, band space, and band width as these are measured design parameters that are not needed as test data.

[23] See response 45 for additional information.

The finalized parameters listed in table 3 to § 1114.7(i)(2)(ii)(B) are a necessary part of the application because they are needed to fully characterize the product and changes in these parameters may affect the rolling paper's impact on public health, as described below:

- RYO paper length and RYO paper width may alter the surface area that is available for tobacco packing, thereby affecting the smoke constituent yields (Ref. 61);
- RYO mass per paper may be a result of a surface area or basis weight difference and, in turn, may affect puff count and smoke constituent yields (Refs. 55 and 61);
- RYO paper base paper basis weight may affect puff count and smoke constituent yields (Ref. 55);
- RYO paper base paper porosity may affect smoke constituent yields (Ref. 55);
- RYO paper band porosity may affect smoke constituent yields because band porosity allows for the overall assessment of the weighted change in air flow through the cigarette paper during active puffing (Ref. 56);
- RYO paper band diffusivity may affect smoke constituent yields because it mimics air flow during smoldering (Ref. 57);
- RYO paper band width may affect ventilation and, in turn, smoke constituent yields (Ref. 58); and
- RYO paper band space may affect ignition propensity and, in turn, puff count (Ref. 59).

Table 4 to § 1114.7(i)(2)(ii)(B) describes the design parameters and information on performance criteria that must be contained in a PMTA for RYO tobacco tubes. We have revised table 4 to § 1114.7(i)(2)(ii)(B) to help ensure that FDA is able to identify and evaluate each product more accurately and efficiently. These changes include the addition of: (1) the option to provide tube diameter as an alternative to tube circumference, as FDA is able to

calculate the information necessary based on either one and (2) the option for the applicant to provide tube paper band diffusivity in lieu of tube paper band porosity or permeability, if applicable. FDA has clarified terminology for RYO paper band porosity, as applicants may refer to this term as permeability, and also provided an alternative to providing cigarette paper band porosity or permeability--band diffusivity, while not preferred, is an acceptable alternative if it is currently not part of an applicant's practice to specify cigarette paper band porosity. While there are minor differences (porosity is more relevant during active puffing, whereas diffusivity is more relevant during smoldering), the addition of diffusivity as an alternative parameter allows flexibility to applicants who do not directly measure porosity or permeability (see Ref. 46). FDA has revised certain proposed parameters for test data, which includes the removal of tube length, tube paper width, tube circumference, tube paper band width, and tube paper band space, as these are measured design parameters.

The finalized parameters listed in table 4 to § 1114.7(i)(2)(ii)(B) are a necessary part of the application because they are needed to fully characterize the product and changes in these parameters may affect the RYO tube's impact on public health, as described below:

- tube mass may affect smoke constituent yields (Ref. 50);
- tube length may alter tobacco biomarker levels (Ref. 47);
- tube circumference or diameter may affect filter efficiency and, in turn, smoke constituent yields (Ref. 48);
- tube paper width may affect smoke constituent yields (Ref. 50);
- tube paper base paper basis weight may affect puff count and smoke constituent yields (Ref. 55);
- tube paper base paper porosity may affect smoke constituent yields (Ref. 55);

- tube paper band porosity may affect smoke constituent yields since band porosity allows for the overall assessment of the weighted change in air flow through the cigarette paper during active puffing (Ref. 56);
- tube paper band diffusivity may affect smoke constituent yields because it mimics air flow during smoldering (Ref. 57);
- tube paper band width may affect ventilation and, in turn, smoke constituent yields (Ref. 58); and
- tube paper band space may affect ignition propensity and, in turn, puff count (Ref. 59).

Table 5 to § 1114.7(i)(2)(ii)(B) describes the design parameters and information on performance criteria that must be contained in a PMTA for RYO tobacco filtered tubes. In this final rule we have revised table 5 to § 1114.7(i)(2)(ii)(B) to help ensure that FDA is able to identify and evaluate each product more accurately and efficiently. These changes include: (1) the option to provide tube diameter as an alternative to tube circumference, as FDA is able to obtain the information necessary from calculations based on what the applicant submits; (2) the option for the applicant to provide filter efficiency as an alternative to DPF, total denier, or filter density (Ref. 60); (3) the option for the applicant to provide diffusivity in lieu of paper band porosity or permeability, as described in previous design parameter sections, is an acceptable alternative if it is currently not part of an applicant's practice to specify paper band porosity; (4) removal of filter mass, filter diameter, and filter tow crimping index as these parameters are considered as not as important as other parameters such as DPF and total denier, and therefore deemed unnecessary; (5) removal of plug wrap length, width, basis weight, and porosity as plug wrap parameters contribute to ventilation; however, filter ventilation and paper porosity have more of an effect on ventilation and therefore, plug wrap parameters were considered

unnecessary; (6) removal of tipping paper width, basis weight, and perforation are considered unnecessary because they have little effect on the airflow and are not combusted during use; and (7) removal of filter ventilation position of holes, filter ventilation number of holes, and filter ventilation number of rows as these parameters are considered redundant because the filter ventilation is affected by these parameters. The alternatives (filter efficiency and diffusivity) are also provided under test data for this product category. Further, FDA has revised certain parameters for test data that were previously proposed in the PMTA rule, which include: (1) removal of the tube mass, tube length, tube diameter, tube paper length, nonfilter tube length, tube width, tube paper band width and space, filter length, filter mass, and filter diameter as these are measured design parameters and (2) removal of filter tow index, plug wrap length, plug wrap width, and tipping paper basis weight for reasons described above.

The finalized parameters listed in table 5 to § 1114.7(i)(2)(ii)(B) are a necessary part of the application because they are needed to fully characterize the product and changes in these parameters may affect the filtered tube's impact on public health, as described below:

- tube mass may affect smoke constituent yields (Ref. 50);
- tube length may alter tobacco biomarker levels (Ref. 47);
- tube circumference or diameter may affect filter efficiency and, in turn, smoke constituent yields (Ref. 48);
- tube paper length directly correlates to non-filter tube length, which may affect smoke constituent yields (Ref. 50);
- tube paper width may affect smoke constituent yields (Ref. 50);
- tube paper base paper basis weight may affect puff count and smoke constituent yields (Ref. 55);

- tube paper base paper porosity may affect smoke constituent yields (Ref. 55);
- tube paper band porosity may affect smoke constituent yields since band porosity allows for the overall assessment of the weighted change in air flow through the cigarette paper during active puffing (Ref. 56);
- tube paper band diffusivity may affect smoke constituent yields because it mimics air flow during smoldering (Ref. 57);
- tube paper band width may affect ventilation and, in turn, smoke constituent yields (Ref. 58);
- tube paper band space may affect ignition propensity and, in turn, puff count (Ref. 59);
- filter efficiency may affect smoke constituent yields (Ref. 58);
- filter DPF may affect filter efficiency and, in turn, smoke constituent yields (Ref. 60);
- total denier, filter density, and filter length may affect filter efficiency and, in turn, smoke constituent yields (Ref. 43);
- filter pressure drop may affect smoke constituent yields (Ref. 61);
- tipping paper length may affect smoke constituent yields (Ref. 62); and
- filter ventilation may affect smoke constituent yields (Ref. 48).

Table 6 to § 1114.7(i)(2)(ii)(B) describes the design parameters and information on performance criteria that must be contained in a PMTA for RYO tobacco. In this final rule, we have revised table 6 to § 1114.7(i)(2)(ii)(B) to help ensure that FDA is able to identify and evaluate each product more accurately and efficiently. This change includes the removal of the requirement for the applicant to provide filler mass as this is provided as part of unique identification of the tobacco product under § 1114.7(c).

The finalized parameters listed in table 6 to § 1114.7(i)(2)(ii)(B) are a necessary part of the application because they are needed to fully characterize the product and changes in these parameters may affect the RYO tobacco's impact on public health, as described below:

- tobacco cut size alters the size of the tobacco pieces, which may result in more particulate matter (Ref. 53) and
- tobacco moisture may affect puff count when used with rolling paper (Ref. 54).

Table 7 to § 1114.7(i)(2)(ii)(B) describes the design parameters and information on performance criteria that must be contained in a PMTA for RYO tobacco paper tips. In this final rule, we have revised table 7 to § 1114.7(i)(2)(ii)(B) to help ensure that FDA is able to identify and evaluate each product more accurately and efficiently. This includes the replacement of the requirement for the applicant to provide RYO paper base paper perforation, and instead provide RYO paper porosity. RYO porosity was found to directly convey the smoke constituent exposure to users, while paper perforation was less indicative of the exposure of smoke constituents when accounting for additional design parameters. FDA has also revised certain parameters for test data that were proposed previously in the PMTA rule, which include: (1) removal of the tip length and width and tip mass as these are measured design parameters; and (2) replacement of paper perforation to paper porosity, as described above.

The finalized parameters listed in table 7 to § 1114.7(i)(2)(ii)(B) are a necessary part of the application because they are needed to fully characterize the product and changes may affect the paper tip's impact on public health, as described below:

- RYO paper tip length and RYO paper tip width may alter the surface area that is available for tobacco packing, thereby affecting the smoke constituent yields (Ref. 61);

- RYO paper tip mass may be a result of a surface area or basis weight difference and, in turn, may affect puff count and smoke constituent yields (Refs. 55 and 61);
- RYO paper base paper basis weight may affect puff count and smoke constituent yields (Ref. 55);
- RYO paper base paper porosity may affect smoke constituent yields (Ref. 55); and
- RYO paper tip ventilation may affect smoke constituent yields (Ref. 48).

Tables 8 through 12 to § 1114.7(i)(2)(ii)(B) describe the design parameters and information on performance criteria that must be contained in a PMTA for products categorized as cigars. Cigarettes (outside the category of heated tobacco products) and cigars are similar , as they are both cylinders filled with a blend of processed tobacco that is generally smoked. Both are generally lit with a fire source, which burns the tobacco as the user inhales at one end; thus, they are consumed and deliver nicotine in a similar manner. A main difference between cigarettes and cigars is that cigars are either wrapped in a tobacco leaf (wrapper and binder) or a material containing tobacco, whereas non-HTP cigarettes are wrapped in paper (cigarette paper) or a material that does not contain tobacco. Additionally, cigars come in a wider variety of sizes and some types of cigars may be thicker in diameter and contain more tobacco filler than cigarettes. Despite these differences, for both types of tobacco products, no matter the size, air is pulled through the tobacco column, which aids in tobacco combustion and nicotine delivery. Cigarette paper commonly has an established porosity (permeability), that is set during manufacturing, while cigar wrapper properties are based on the tobacco used as the wrapper. Although cigars and cigarettes are wrapped in different materials, both cigar wrappers and binders, as well as cigarette papers, have inherent permeabilities/porosities, which may affect smoke constituent yields. Cigars may be filtered (containing filter tow or other materials),

unfiltered, or unfiltered with tips made of wood or plastic, while most cigarettes have filters (containing filter tow) and do not contain tips. If a cigar does contain a filter, it will be similar to cigarette filters and contain tow. Based on FDA's experience with cigarettes under the SE pathway, as well as the similarities between the two products, FDA has used established design parameter information from cigarettes to develop some of the design parameter requirements for cigars. Tables 8 through 12 to § 1114.7(i)(2)(ii)(B) describe in more detail the parameters for each subcategory of cigars.

Table 8 to § 1114.7(i)(2)(ii)(B) describes the design parameters and information on performance criteria that must be contained in a PMTA for filtered, sheet-wrapped cigars. In this final rule we have revised table 8 to § 1114.7(i)(2)(ii)(B) to help ensure that FDA is able to identify and evaluate each product more accurately and efficiently. These changes include (1) the addition of cigar wrapper and binder band space, as these parameters affect smoke constituents; (2) the addition of cigar minimum and maximum diameter (mm), as the shape of cigars can differ, with the tips being narrower than the center of the cigar, affecting the rod density, which in turn modifies the burn properties and smoke yields; (3) providing applicants the option to provide oven volatiles as an alternative to tobacco moisture, as well as the option to provide oven volatiles instead of moisture, as this provides similar information to FDA[24] and allows the applicant flexibility to provide either parameter based on the specific manufacturing processes they employ; and (4) removing cigar length, cigar diameter, filter diameter, filter

[24] Please note that the term "moisture," has widely varying and conflicting definitions and terminology in use within the tobacco industry. It is common for "moisture" or "moisture content" to be used to refer to water content of a material but in relation to the tobacco industry it is necessary to differentiate between "moisture" as water content and "moisture" as oven volatiles. https://www.coresta.org/sites/default/files/technical_documents/main/PTM-CTR_MoistureWaterOvenVolatiles_July2014%282%29.pdf.

length as requirements for test data as these are measured design parameters that are not needed as test data.

Additionally, based on FDA's understanding of machine-made cigars and their similarity to cigarettes, we have also included design requirements previously recommended in the proposed PMTA rule. These design parameters include (1) cigar mass, wrapper and binder basis weight, cigar binder and wrapper length and width, cigar wrapper and binder band porosity, and cigar wrapper and binder width, as these design parameters may affect smoke constituent yields and (2) the option for the applicant to provide filter efficiency, if available, as an alternative to DPF, total denier, or filter density. We have also included test data requirements for cigar mass, puff count, wrapper and binder basis weight, and cigar minimum and maximum diameter for reasons previously discussed.

The finalized parameters listed in table 8 to § 1114.7(i)(2)(ii)(B) are a necessary part of the application because they are needed to fully characterize the product and changes may affect the cigar's impact on public health, as described below:

- cigar mass reflects the amount of tobacco in a cigar, which may affect smoke constituent yields (Ref. 69);
- cigar puff count can directly affect smoke constituent yields (Ref. 69);
- cigar length and diameter can directly affect the amount of tobacco that is burned and, in turn, affect smoke constituent yields (Ref. 70);
- tobacco filler mass may affect smoke constituent yields (Ref. 71);
- for cigarettes, the cigarette paper basis weight may affect puff count and smoke constituents (Ref. 71). Similarly, for cigars, the cigar wrapper and binder basis weight may affect puff count and smoke constituent yields;

- for cigarettes, the paper length and width may affect puff count and smoke constituents (Ref. 71). Similarly, for cigars, the cigar wrapper and binder length and width may directly influence the area through which air is permitted to enter the tobacco column, which, in turn, may affect puff count and smoke constituent yields;
- cigar wrapper porosity may affect smoke constituent yields (Refs. 72 and 73);
- for cigarettes, tobacco rod density may modify burn properties and smoke constituent yields (Refs. 51 and 52). Similarly, for cigars, tobacco rod density may modify burn properties and smoke constituent yields;
- for cigarettes, the tobacco moisture or oven volatiles may affect puff count (Ref. 54). Similarly, for cigars, the tobacco moisture may affect puff count (Ref. 54);
- for cigarettes, the tobacco cut size may result in more particulate matter (Ref. 53). Similarly, for cigars, the tobacco cut size alters the size of the tobacco pieces, which may result in more particulate matter;
- for cigarettes, the band porosity may affect smoke constituent yields (Ref. 56). Similarly, for cigars, the band porosity or permeability may affect smoke constituent yields because band porosity allows for the overall assessment of the weighted change in air flow through the cigarette paper during active puffing;
- for cigarettes, the band width may affect smoke yields (Ref. 58). Similarly, for cigars, the wrapper band width and binder band width may affect ventilation and, in turn, smoke constituent yield;
- for cigarettes, the band space may affect puff count (Ref. 59). Similarly, for cigars, the wrapper band space and binder space may affect ignition propensity and, in turn, puff count;

- for cigarettes, the filter parameters can impact smoke yields (Ref. 60). Similarly, for cigars, the filter diameter, filter mass, filter tow crimping index, DPF, total denier, filter density, and filter length may affect filter efficiency and, in turn, smoke constituent yields;
- For cigarettes, the filter pressure drop affects smoke yields (Ref. 61). Similarly, for cigars, the filter pressure drop may affect smoke constituent yields.
- for cigarettes, tipping paper length may affect smoke constituent yields (Ref. 62). Similarly, for cigars, the tipping paper, including width, and basis weight, may affect smoke constituent yields; and
- ventilation may affect smoke constituent yields (Ref. 69).

Table 9 to § 1114.7(i)(2)(ii)(B) describes the design parameters and information on performance criteria that must be provided for unfiltered, sheet-wrapped cigars. In this final rule, we have revised table 9 to § 1114.7(i)(2)(ii)(B) to help ensure that FDA is able to identify and evaluate each product more accurately and efficiently. These changes include: (1) the addition of overall diameter because cigar diameter can directly affect the amount of tobacco that is burned and, in turn, affect smoke constituent yields; (2) the removal of cigar tip width (mm); (3) the option for applicants to provide oven volatiles in lieu of tobacco moisture, as this provides similar information to FDA[25] and allows the applicant flexibility to provide either parameter based on the specific manufacturing processes they employ. In addition, as compared to the proposed PMTA rule, FDA has removed certain parameters for test data, including the removal of cigar length, cigar tip length, cigar tip diameter, and cigar tip width, as FDA has determined that these parameters are not necessary as test data. Additionally, based on FDA's

[25] See footnote 21.

understanding of cigars and their similarity to cigarettes, we have also included all the design requirements previously recommended in the proposed PMTA rule except cigar burn rate and cigar draw resistance. We have also included the following test data: puff count, tobacco rod density, tobacco cut size, cigar wrapper and binder basis weight, binder porosity, and cigar tip mass.

The finalized parameters listed in table 9 to § 1114.7(i)(2)(ii)(B) are a necessary part of the application because they are needed to fully characterize the product and changes may affect the cigar's impact on public health, as described below:

- cigar mass reflects the amount of tobacco in a cigar, which may affect smoke constituent yields (Ref. 69);
- cigar puff count can directly affect smoke constituent yields (Ref. 69);
- cigar length and diameter can directly affect the amount of tobacco that is burned and, in turn, affect smoke constituent yields (Ref. 70);
- tobacco filler mass may affect smoke constituent yields (Ref. 69);
- for cigarettes, the cigarette paper basis weight may affect puff count and smoke constituents (Ref. 71). Similarly, for cigars, the cigar wrapper and binder basis weight may affect puff count and smoke constituent yields;
- for cigarettes, the paper length and width may affect puff count and smoke constituents (Ref. 71). Similarly, for cigars, the cigar wrapper length and width and binder width may directly influence the area through which air is permitted to enter the tobacco column, which, in turn, may affect puff count and smoke constituent yields;
- cigar wrapper porosity may affect smoke constituent yields (Refs. 72 and 73).

- for cigarettes, tobacco rod density may modify burn properties and smoke constituent yields (Refs. 51 and 52). Similarly, for cigars, the tobacco rod density may modify burn properties and smoke constituent yields;
- for cigarettes, the tobacco moisture or oven volatiles may affect puff count (Ref. 54). Similarly, for cigars, the tobacco moisture may affect puff count;
- for cigarettes, the tobacco cut size may result in more particulate matter (Ref. 53). Similarly, for cigars, the tobacco cut size alters the size of the tobacco pieces, which may result in more particulate matter;
- for cigarettes, the band porosity may affect smoke constituent yields (Ref. 56). Similarly, for cigars, the wrapper and binder band porosity or permeability may affect smoke constituent yields because band porosity allows for the overall assessment of the weighted change in air flow through the cigarette paper during active puffing;
- for cigarettes, the band width may affect smoke yields (Ref. 58). Similarly, for cigars, the wrapper and binder band width may affect ventilation and, in turn, smoke constituent yields;
- for cigarettes, the band space may affect puff count (Ref. 59). Similarly, for cigars, the wrapper and binder band space may affect ignition propensity and, in turn, puff count; and
- cigar tip dimensions directly influence the overall cigar draw resistance and in turn, puff count (Ref. 74).

Table 10 to § 1114.7(i)(2)(ii)(B) describes the design parameters and information on performance criteria that must be provided for leaf-wrapped cigars. In this final rule, we have revised table 10 to § 1114.7(i)(2)(ii)(B) to help ensure that FDA is able to identify and evaluate

each product more accurately and efficiently. These changes include the option to provide oven volatiles instead of moisture, as this provides similar information to FDA[26] and allows the applicant flexibility to provide either parameter based on the specific manufacturing processes they employ. FDA has also revised certain parameters for test data previously discussed in the proposed PMTA rule. Specifically, FDA has removed cigar length as this is a measured design parameter for which we do not need test data. Additionally, based on FDA's understanding of leaf-wrapped cigars and their similarity to cigarettes, we have included the design requirements that were previously recommended in the proposed PMTA rule except cigar draw resistance, wrapper and binder porosity, and cigar burn rate. We have also included the following parameters for test data that were previously recommended in the proposed PMTA rule: puff count, tobacco rod density, tobacco filler mass, tobacco cut size, and wrapper and binder basis weight.

FDA has also included: (1) the overall diameter as a design parameter because cigar diameter can directly affect the amount of tobacco that is burned and, in turn, affect smoke constituent yields and (2) tobacco cut size as a design parameter as it can alter the size of tobacco pieces, which may result in more particulate matter.

The finalized parameters listed in table 10 to § 1114.7(i)(2)(ii)(B) are a necessary part of the application because they are needed to fully characterize the product and changes may affect the cigar's impact on public health, as described below:

- cigar mass reflects the amount of tobacco in a cigar, which may affect smoke constituent yields (Ref. 69);
- cigar puff count can directly affect smoke constituent yields (Ref. 69);

[26] See footnote 21.

- for cigarettes, the paper length and width may affect puff count and smoke constituents (Ref. 71). Similarly, for cigars, the cigar wrapper length and width and binder width may directly influence the area through which air is permitted to enter the tobacco column, which, in turn, may affect puff count and smoke constituent yields;
- cigar length and diameter can directly affect the amount of tobacco that is burned and, in turn, affect smoke constituent yields (Ref. 70);
- for cigarettes, the tobacco moisture or oven volatiles may affect puff count (Ref. 54). Similarly, for cigars, the tobacco moisture may affect puff count;
- for cigarettes, the cigarette paper basis weight may affect puff count and smoke constituents (Ref. 71). Similarly, for cigars, the cigar wrapper and binder basis weight may affect puff count and smoke constituent yields;
- for cigarettes, tobacco rod density may modify burn properties and smoke constituent yields (Refs. 51 and 52). Similarly, for cigars the tobacco rod density may modify burn properties and smoke constituent yields; and
- for cigarettes, the tobacco cut size may result in more particulate matter (Ref. 53). Similarly, for cigars, the tobacco cut size alters the size of the tobacco pieces, which may result in more particulate matter.

Table 11 to § 1114.7(i)(2)(ii)(B) describes the design parameters and information on performance criteria that must be provided for cigar tobacco. In this final rule, we have revised table 11 to § 1114.7(i)(2)(ii)(B) to help ensure that FDA is able to identify and evaluate each product more accurately and efficiently. These changes include the option to provide oven volatiles instead of moisture, as this provides similar information to FDA[27] and allows the

[27] See footnote 21

applicant flexibility to provide either parameter based on the specific manufacturing processes they employ. FDA has also revised certain proposed parameters for test data, which includes the option to provide oven volatiles instead of moisture, as described above. In the proposed rule, we proposed a recommended design parameter for cigar tobacco, filler mass. Based on FDA's understanding of cigar tobacco, we have decided not to include filler mass (mg) as a required design parameter. FDA has concluded that the amount of tobacco added to a cigar is generally user-dependent and so, the filler mass of the cigar tobacco as packaged does not have a direct effect on the smoke constituents.

The finalized parameters listed in table 11 to § 1114.7(i)(2)(ii)(B) are a necessary part of the application because they are needed to fully characterize the product and changes may affect its impact on public health, as described below:

- for cigarettes, the tobacco cut size may result in more particulate matter (Ref. 53). Similarly, for cigars, the tobacco cut size alters the size of the tobacco pieces, which may result in more particulate matter and
- for cigarettes, the tobacco moisture or oven volatiles may affect puff count (Ref. 54). Similarly, for cigars, the tobacco moisture may affect puff count.

Table 12 to § 1114.7(i)(2)(ii)(B) describes the design parameters and information on performance criteria that must be provided for a cigar wrapper. In this final rule, we have revised table 12 to § 1114.7(i)(2)(ii)(B) to help ensure that FDA is able to identify and evaluate each product more accurately and efficiently. These changes include, for both target specification and test data, the replacement of cigar maximum and minimum width with wrapper width, as not all cigar wrappers have a maximum and minimum width; additionally, in the proposed rule, we discussed recommended design parameters for cigar wrappers. Based on

FDA's understanding of cigar wrappers, and because cigar wrapper basis weight affects smoke constituents as well as puff count, we have included cigar wrapper basis weight in the final rule. For test data that was previously recommended in the proposed rule, FDA has included cigar wrapper basis weight as a requirement and replaced cigar minimum and maximum wrapper width with wrapper width for the reasons discussed previously.

The finalized parameters listed in table 12 to § 1114.7(i)(2)(ii)(B) are a necessary part of the application because they are needed to fully characterize the product and changes may affect its impact on public health, as described below:

- for cigarettes, the paper length and width may affect puff count and smoke constituents (Ref. 71). Similarly, for cigars, the cigar wrapper length and width may directly influence the area through which air is permitted to enter the tobacco column, which, in turn, may affect puff count and smoke constituent yields and
- for cigarettes, the cigarette paper basis weight may affect puff count and smoke constituents (Refs. 71 and 72). Similarly, for cigars, the cigar wrapper and binder basis weight may affect puff count and smoke constituent yields.

Table 13 to § 1114.7(i)(2)(ii)(B) describes the design parameters and information on performance criteria that must be provided for a waterpipe. Cigarette tobacco and waterpipe tobacco are similar, as they are both processed tobacco that is cut, milled, and sifted before ingredients are added to control for tobacco moisture and taste. Therefore, tobacco parameters for a cigarette can be extrapolated to tobacco parameters for a waterpipe. Additionally, the waterpipe length of the waterpipe stem causes affects the pressure drop in the waterpipe in a similar way as to the length of the cigarette filter and filter tow causes a filter pressure drop in a cigarette: both determines the amount of suction a smoker needs to apply to the tobacco product

to draw smoke through. Therefore, filter pressure drop for a cigarette can be extrapolated to the pressure drop of a waterpipe. The parameters included in table 13 apply to waterpipes generally. For products that contain a heating source or waterpipe tobacco, applications should specify information regarding the heating source and waterpipe tobacco as described in tables 14 and 15.

In this final rule, we have revised table 13 to § 1114.7(i)(2)(ii)(B) to help ensure that FDA is able to identify and evaluate each product more accurately and efficiently. These changes include: (1) the removal of number of hoses as the number of hoses can vary during smoking session and (2) the change in terminology from "bowl" to "base." Additionally, in the proposed rule, we recommended design parameters for waterpipes. Based on FDA's understanding of waterpipes, we have required the following design parameters: (1) hose length, hose material, and hose internal diameter, which are directly proportional to air infiltration and affects toxicant yields; (2) stem length and stem internal diameter, which impacts puffing behavior and toxicant exposure; (3) pressure drop, which affects smoke constituent yields; (4) water filter efficiency, which is directly proportional to mainstream smoke and can increase exposure to HPHCs; and (5) hose air permeability and heating source type, as theses parameters have a direct correlation with toxicants and smoke constituents exposed to users and nonusers. For test data that was previously recommended in the proposed rule, FDA is requiring all the parameters except foil length, foil width, and ventilation.

Further, based on FDA's understanding of waterpipes, we have also included the following required design parameters: base diameter, base volume, base shape, head height, head top diameter, head bottom diameter, number of holes, head volume, and head material. The shape and size of the base can affect the pressure drop or difficulty of pulling air through the waterpipe hose, while the head dimensions affect how long a smoke session lasts by controlling

how much tobacco can be used during a session. Head dimensions can also affect airflow beneath and through the tobacco to make heat transfer more effective, prolonging smoking sessions. FDA has also included the following required parameter for test data: head height, head top diameter, head bottom diameter, and head volume.

The finalized parameters listed in table 13 to § 1114.7(i)(2)(ii)(B) are a necessary part of the application because they are needed to fully characterize the product and changes may affect its impact on public health, as described below:

- hose dimensions (length and diameter) are directly proportional to air infiltration and affects toxicant yields (Ref. 75);
- hose material may affect hose permeability, which may affect smoke constituent yields (Ref. 75);
- stem length influences draw resistance, which can in turn impact nicotine and other toxicant delivery to the user (Ref. 76);
- stem internal diameter can impact puffing behavior and toxicant exposure, and in turn, smoke constituent yields (Ref. 76);
- for cigarettes, the pressure drop effect smoke constituent yields (Ref. 71). For waterpipes the base diameter and base volume impact how much water the base can hold and how much water the user can add to the base and the volume of water impacts the pressure drop or the difficulty of pulling air through the waterpipe hose. Similarly, for waterpipes, the pressure drop may result in differences in the difficulty of pulling air through the waterpipe and, in turn, affect smoke constituent yields (Ref. 71);
- head dimensions affect how long a smoke session lasts by controlling how much tobacco can be used during a session. Head dimensions can also affect airflow beneath and

through the tobacco to make heat transfer more effective, prolonging smoking sessions. With a wider surface area, there is more room for the head to more evenly distribute heat to the tobacco. A shallower bowl makes tobacco at the bottom of the head more accessible to heat and allows for heat to be more evenly distributed to the tobacco. The more holes in the head, the more airflow, which affects the tobacco temperature. All of this causes the tobacco to reach different temperatures that affects smoke yields (Ref. 75);

- water filtering efficiency is directly proportional to mainstream smoke and can increase exposure to HPHCs (Ref. 77);
- for cigarettes, the filter pressure drop affects smoke yields (Ref. 71). Similarly, for waterpipes, the pressure drop may result in differences in the difficulty of pulling air through the waterpipe and, in turn, affect smoke constituent yields;
- heating source type affects tobacco temperature, which in turn, may affect smoke constituent yields (Ref. 78); and
- head material could aid in heat transfer, prolonging the heating of the tobacco and causing the tobacco to reach temperatures that affect smoke yields.

Table 14 in § 1114.7(i)(2)(ii)(B) describes the design parameters and information on performance criteria that must be provided for waterpipe tobacco. In this final rule, we have revised table 14 to § 1114.7(i)(2)(ii)(B) to help ensure that FDA is able to identify and evaluate each product more accurately and efficiently. These changes include the option for the applicant to provide oven volatiles as an alternative to tobacco filler moisture. We have provided this alternative because it will allow the applicant to provide information needed to evaluate the product without conducting additional testing as this alternative may satisfy these requirements. Additionally, in the proposed rule, we recommended a design parameter for waterpipe tobacco,

filler mass. Based on FDA's understanding of waterpipe tobacco, we have decided not to include filler mass as a required design parameter for waterpipe tobacco. FDA concluded that the amount of tobacco added during a given smoking session is user-dependent and so, filler mass of the waterpipe tobacco as packaged does not have a direct impact on smoke constituents.

The finalized parameters listed in table 14 to § 1114.7(i)(2)(ii)(B) are necessary to fully characterize the product and changes may affect its impact on public health as follows:

- for cigarettes, the tobacco cut size may result in more particulate matter (Refs. 53 and 54). Similarly, for waterpipe tobacco, the tobacco cut size alters the size of the tobacco pieces, which may result in more particulate matter. Finer tobacco cut size may result in a decrease in filling power and in turn, a larger amount of tobacco in the bowl (Refs. 53 and 54) and
- for cigarettes, the tobacco moisture or oven volatiles may affect puff count (Ref. 54). Similarly, for waterpipe tobacco, the tobacco moisture may affect puff count. Moisture contributes to packing density, thus decreasing void volume (Ref. 54).

Table 15 to § 1114.7(i)(2)(ii)(B) describes the design parameters and information on performance criteria that must be provided for a waterpipe heating source. In this final rule, we have revised table 15 to § 1114.7(i)(2)(ii)(B) to help ensure that FDA is able to identify and evaluate each product more accurately and efficiently. These changes include: (1) the removal of heating source type. As there are multiple types of heating source for waterpipe, instead of asking for the source type, FDA has changed the terminology and considered all heating sources as the heating element and (2) the removal of charcoal temperature and coil temperature range, as described above, FDA considers all heating sources the heating element; therefore, the charcoal and coil temperature have been removed and replaced with "heating element

temperature." FDA has also revised the test data and removed test data for charcoal temperature range and coil temperature range, for reasons previously described.

Additionally, in the proposed rule, we recommended design parameters for waterpipe heating source. Based on FDA's understanding of waterpipe heating sources, we have included some of these design parameters, including those related to batteries and power delivery units (PDU). The finalized parameters listed in table 15 to § 1114.7(i)(2)(ii)(B) are necessary to fully characterize the product and changes may affect its impact on public health as follows:

- when combusted, heating sources such as charcoal or wood cinders expose the user to high yields of toxicants such as carbon monoxide and polycyclic aromatic hydrocarbons. Therefore, the heating source mass, density, and temperature may affect smoke constituent yields (Ref. 78);
- for ENDS, the number of elements affects resistance and distribution of heat dissipation (Ref. 79). Similarly, for waterpipe heating source, the number of heating elements can affect resistance and distribution of heat dissipation;
- for ENDS, the heating element configuration effect affect toxicant emissions and nicotine delivery (Refs. 80-84). Similarly, for waterpipe heating source, the eating element configuration may affect overall heating element resistance, thereby influencing heating element temperature. The heating element temperature may affect toxicant emissions and nicotine delivery;
- for ENDS, the heating element diameter may affect toxicant emissions and nicotine delivery (Refs. 80-84). Similarly, for waterpipe heating source, the diameter of the heating element affects its resistance. Heating element resistance may influence heating element temperature, which in turn affects toxicant emissions and nicotine delivery;

- for ENDS, an increase in battery capacity (mAh rating) can increase the number of puffs the e-cigarette can deliver per vaping session. Longer vaping sessions may lead to greater exposure to toxicant emissions (Ref. 83). Similarly, for waterpipe heating source the battery mAh ratings is a measure of the average amount of current the battery releases over time under normal. Current may influence the heating element temperature, which in turn affects toxicant emissions and nicotine delivery. In addition, provides understanding how long a battery will last and thus the product stability;
- for ENDS, the battery and PDU voltage impacts the amount of e-liquid consumed, the vapor temperature, and the total emissions of volatile aldehydes (Ref. 85). Similarly for waterpipe heating sources, the battery voltage operating range and PDU voltage operating range (volts) impact the amount of e-liquid consumed, the vapor temperature, and the total emissions of volatile aldehydes;
- for ENDS, the battery type, battery current operating range, battery failure safety features, battery conformance to standards, and PDU current operating range are necessary for evaluating battery and PDU safety. Risks of e-cigarette battery explosion, leakage, fire, or overheating are a safety concern (Refs. 58 and 86). Similarly, for waterpipe heating source, the battery current operating range is a measure of the current batteries put out to heat the heating element of the product. The battery should have a normal operating range as to not overheat the product and cause it to become a hazard to the user. In addition, this current range has a direct impact on the heating element, which in turn affects the smoke constituent yields;
- for ENDS, the battery and PDU voltage impacts the amount of e-liquid consumed, the vapor temperature, and the total emissions of volatile aldehydes (Ref. 85). Similarly for

waterpipe heating source the PDU voltage operating range impacts the amount of e-liquid consumed, the vapor temperature, and the total emissions of volatile aldehydes;

- for ENDS, the battery type, battery current operating range, battery failure safety features, battery conformance to standards, and PDU current operating range are necessary for evaluating battery and PDU safety. Risks of e-cigarette battery explosion, leakage, fire, or overheating are a safety concern (Refs. 58 and 86). Similarly for waterpipe heating source, the PDU current operating range is a measure of the current output to heat the heating element of the product, which, if not adequately controlled can lead to overheating the product subsequently may harm the user. In addition, this current range has a direct impact on the heating element, which in turn affects the smoke constituent yields; and
- for ENDS, PDU current operating range and wattage range are necessary for evaluating battery and PDU safety. Risks of e-cigarette battery explosion, leakage, fire, or overheating are a safety concern (Refs. 80 and 86). Similarly, for waterpipe heating source the PDU wattage operating range determines the amount of heat produced. PDU wattage or wattage operating range may affect the heating element temperature, thereby affecting toxicant emissions.

Table 16 to § 1114.7(i)(2)(ii)(B) describes the design parameters and information on performance criteria that must be provided for waterpipe foil. In this final rule, we have revised table 16 to § 1114.7(i)(2)(ii)(B) to help ensure that FDA is able to identify and evaluate each product more accurately and efficiently. Specifically, in the proposed rule, we recommended design parameters for waterpipe foil. Based on FDA's understanding of waterpipe foil, we have included the following design parameter requirements: foil diameter, foil thickness, number of

holes, and diameter of holes. We have added these parameters because foil parameters affect smoke constituent yields, and ultimately, the user's exposure to toxicants and HPHCs. FDA has also revised the required test data to include the following parameters for the reasons detailed previously: foil diameter, foil thickness, and diameter of the holes. Waterpipe foil length and width were erroneously listed both as required parameters (in table 16) and as recommended parameters in table 16a. FDA notes that waterpipe foil length and width are included in the final rule required parameters.

The finalized parameters listed in table 16 to § 1114.7(i)(2)(ii)(B) are necessary to fully characterize the product and changes may affect its impact on public health as follows.

- waterpipe foil length, diameter, and width are necessary because they impact the user's puffing behavior and toxicant exposure. Therefore, the foil dimensions may affect smoke constituent yields (Ref. 76);
- waterpipe foil thickness influences the distribution of heat to the tobacco, affecting tobacco temperatures and therefore smoke constituent yields (Ref. 76); and
- the number and diameter of holes impacts the path of hot gases through the tobacco mixture, which may affect smoke constituent yields (Ref. 76).

Table 17 to § 1114.7(i)(2)(ii)(B) describes the design parameters and information on performance criteria that must be provided for a waterpipe head. These parameters are a necessary part of the application because they are needed to fully characterize the product and changes may affect the waterpipe head's impact on public health, as described below:

- head dimensions (height, top diameter, bottom diameter), including number of holes, and head volume, affect how long a smoke session lasts, as well as how much tobacco is used. Head dimensions can also affect airflow beneath and through the tobacco in the

head, affecting heat transfer to the tobacco. The temperatures reached during smoking affect smoke yields, and user exposure to these smoke yields and

- the head material could aid in heat transfer, prolonging the heating of the tobacco and causing the tobacco to reach temperatures that affect smoke yields.

Table 18 to § 1114.7(i)(2)(ii)(B) describes the design parameters and information on performance criteria that must be provided for a pipe. The design parameters described in table 18 to § 1114.7(i)(2)(ii)(B) are a necessary part of the application because they are needed to fully characterize the product and changes that may affect the pipe's impact on public health. In this final rule, we have revised the design parameters related to pipes to help ensure that FDA is able to identify and evaluate each product more accurately and efficiently. These changes include the removal of: bore minimum diameter, bore maximum diameter, bit length, and bit diameter. We have removed these parameters because they were found to be equal to the stem and shank diameter should be equal to the bore diameter, and in addition, the length of the bit can vary and have little effect on the user's exposure to toxicants. FDA has also revised the parameters for test data to include the removal of: bore minimum diameter, bore maximum diameter, bit length, and bit diameter for the reasons described previously. Additionally, in the proposed rule, we recommended design parameters for pipes. Based on FDA's understanding of pipes, we have added design parameters related to the bowl chamber (bowl chamber cover outer diameter, bowl chamber cover inner diameter, bowl chamber hole shape, and bowl chamber volume), shank (length and diameter), draught hole (draught hole diameter, draught hole shape, draught hole location, and draught hole dimension), screen, airway and pressure drop, and filter (filter efficiency, pressure drop, and length). These parameters are a necessary part of the application

because they are needed to fully characterize the product and changes may affect the pipe's impact on public health, as described below:

- pipe screens are used in pipes to filter and stop hot embers and tobacco from traveling up the pipe to the user;
- the bowl chamber inner and outer diameters allow FDA to calculate the chamber wall thickness. A thicker wall will lead to a cooler smoke and makes it less likely the user will burn themselves when holding the chamber. Additionally, the chamber inner diameter will affect temperature and tobacco capacity, meaning the greater the pipe surface area, the more leaf can be burned at once, and with increased temperature, this will affect smoke constituents;
- the bowl chamber hole shape is important to characterize the pipe as this may affect the airflow and tobacco temperatures, which in turn affects the burn rate and smoke constituents delivered;
- the bowl chamber volume affects the burn rate and temperature, which in turn, dictates the smoke constituents delivered to users.
- the draught hole allows the user to pull air through the tobacco to their mouth. The diameter of the draught holes affects the resistance to draw, which can impact nicotine and other toxicant delivery to the user;
- the draught hole dimensions and geometry may affect the airflow and oxygen available at the burning tobacco for the chemical reaction and thus affect smoke constituent yields;
- the draught hole location should enter the bowl directly centered and at the very bottom of the bowl. The location can affect airflow and tobacco temperatures, which in turn, affects the burn rate and smoke constituents delivered;

- the stem of a pipe delivers smoke from the bowl to the user's mouth. The length of the stem may affect the smoke temperature, which may affect how the product is consumed, while the diameter of the stem may affect resistance to draw which can impact nicotine and other toxicant delivery to the user;
- the shank of a pipe may affect the smoke temperature (length) and resistance to draw (diameter);
- for cigarettes, the filter pressure drop affects smoke yields (Ref. 62). Similarly, for pipes, the pressure drop through the air valve can affect nicotine and other toxicant delivery to the user. Air flow through an air valve can affect tobacco burn rate and tobacco temperatures which in turn, may affect smoke constituent delivery to the user. Some pipes may come with a filter; and
- for cigarettes, filter diameter, DPF, total denier, filter density, and filter length may affect filter efficiency and, in turn, smoke constituent yields (Ref. 60). Similarly, for pipes, the filter efficiency, filter pressure drop, and filter length may affect smoke constituent yields.

Table 19 to § 1114.7(i)(2)(ii)(B) describes the design parameters and information on performance criteria that must be provided for pipe tobacco. In this final rule, we have revised table 19 (formerly table 18 in the proposed PMTA rule) to § 1114.7(i)(2)(ii)(B) to help ensure that FDA is able to identify and evaluate each product more accurately and efficiently. These changes include allowing applicants to provide oven volatiles (%) as an alternative for tobacco moisture. We have provided these alternatives because it will allow the applicant to provide information needed to evaluate the product without conducting additional testing as these alternatives may satisfy the requirements. Additionally, in the proposed rule, we recommended

design parameters for pipe tobacco. Based on FDA's understanding of pipe tobacco, we have decided not to include filler mass (mg) as a design parameter.

The finalized parameters listed in table 19 to § 1114.7(i)(2)(ii)(B) are required as part of the application because they are necessary to fully characterize the product and changes may affect its impact on public health:

- for cigarettes, the tobacco cut size may result in more particulate matter (Ref. 53). Similarly, for pipes, the tobacco cut size alters the size of the tobacco pieces, which may result in more particulate matter and
- for cigarettes, the tobacco moisture or oven volatiles may affect puff count (Ref. 54). Similarly, for pipes, the tobacco moisture or oven volatiles may affect puff count.

While demonstrating compliance with voluntary standards can provide information that is important to FDA's review, this alone would neither fulfill the reporting requirements for battery design parameters under § 1114.7(i)(2)(ii) nor render further of the battery review superfluous. As described elsewhere in this section, FDA needs a full characterization of the tobacco product--including the battery, where applicable--to complete its review. FDA provides information regarding the health impacts for each design parameter for products categorized as ENDS, as discussed elsewhere in this section.

Table 20 to § 1114.7(i)(2)(ii)(B) describes the design parameters and information on performance criteria that must be provided for an ENDS. In this final rule, we have revised table 20 (formerly table 19 in the proposed PMTA rule) to § 1114.7(i)(2)(ii)(B) to help ensure that FDA is able to identify and evaluate each product more accurately and efficiently. These changes include (1) the removal of overall atomizer resistance (ohms), wick ignition temperature, coil temperature cut-off, and coil temperature range. We have removed these

parameters because, current cut-off and heating element temperature range are now required; as such, the inclusion of these parameters would be considered redundant. We have removed wicking ignition because not all wicking materials have an ignition temperature, nor do all ENDS products have an overall atomizer resistance; (2) change in language instead of "coil" the phrase "heating element" is used to include all heating elements that may not be considered a coil; and (3) the inclusion of ventilation. Additionally, in the proposed rule, we recommended design parameters for ENDS. Based on FDA's evolving understanding of ENDS products, we have included the following previously recommended design parameters, as required: draw resistance puff count, atomizer tank/cartridge volume, number of heating elements, heating elements length and diameter, heating element configuration, battery voltage operating range, battery current operating range, battery nominal voltage, battery current rating, battery charging temperature limits, battery discharge temperature limits, battery end of discharge voltage, battery maximum charging current, battery maximum discharging current, battery upper limits charging voltage, PDU voltage operating range, and PDU current operating range. FDA has also revised the test data to include these parameters, as these parameters affect the heating element temperature which in turn effects the smoke constituents exposed to the users and nonusers.

The finalized parameters listed in table 20 to § 1114.7(i)(2)(ii)(B) are a necessary part of the application because they are needed to fully characterize the product and changes may affect its impact on public health, as described below.

- the air flow rate of the ENDS can affect the coil/heating element temperature, e-liquid consumption, and aerosol characteristics such as particle number concentration, count median diameter, and PM2.5, which impact aerosol exposure (Ref. 87);

- coil/heating element resistance may affect overall heating element resistance, thereby influencing heating element temperature. The coil/heating element's resistance, material and the voltage[28] determine the current flow and heating element temperature. The heating element temperature and temperature duration may affect toxicant emissions and nicotine delivery (Refs. 80-84);
- coil/heating element resistance and battery output voltage determine PDU wattage. PDU wattage determines the amount of heat produced by the atomizer. PDU wattage or wattage operating range may affect the heating element temperature, thereby affecting toxicant emissions and nicotine delivery (Refs. 82 and 84);
- an increase in battery capacity (mAh rating) can increase the number of puffs the e-cigarette can deliver per vaping session. Longer vaping sessions may lead to greater exposure to toxicant emissions (Ref. 83);
- the temperature of the coil/heating element can affect the chemical and physical characteristics of the aerosol delivered to the user. An increase in coil/heating element temperature can increase HPHC levels in the aerosol, therefore, maximum coil/heating element temperature and temperature control deviation from this maximum coil/heating element temperature can affect toxicant emissions and nicotine delivery (Refs. 80-84);
- number of coils/heating element present can affect overall atomizer resistance and distribution of heat dissipation (Ref. 79);
- the position of the coil/heating element can increase the possibility of dry puff conditions and subsequent increased toxicant emissions (Ref. 82);

[28] Voltage, current, and resistance are used to ensure the battery and the ENDS are operating within the "normal operating range." The battery manufacturer sets the normal range of the voltage and current. Understanding the resistance allows FDA to assess whether the coil is drawing more current than the battery is designed for.

- atomizer and cartridge components of e-cigarettes may be heated repeatedly and aerosolized and can contribute to increased toxicant emissions (Ref. 80);
- puff count can differ depending on other puff topography (e.g., puff duration and puff flow rate), e-cigarette and atomizer design, and e-liquid parameters. Puff count can also affect total puff volume, which in turn can affect total toxicant emissions (Ref. 88). In addition, information on the puff count of ENDS can help FDA assess the health risks of the product, including how it compares to other products;
- e-liquid capacity of the atomizer tank/cartridge can affect total puff volume, which in turn can affect total toxicant emissions (Refs. 88 and 89);
- battery/PDU voltage or voltage operating range may affect the heating element temperature, thereby affecting toxicant emissions and nicotine delivery (Refs. 81-84);
- battery wattage or wattage operating range may affect the heating element temperature, thereby affecting toxicant emissions (Refs. 82 and 84);
- coil/heating element resistance and battery output voltage determine PDU wattage. PDU wattage determines the amount of heat produced by the atomizer. PDU wattage or wattage operating range may affect the heating element temperature, thereby affecting toxicant emissions (Refs. 82 and 84);
- PDU wattage deviation may influence heating element temperature, thereby affecting toxicant emissions (Refs. 82 and 84).
- the temperature of the coil/heating element can affect the chemical and physical characteristics of the aerosol delivered to the user. An increase in coil/heating element temperature can increase HPHC levels in the aerosol, therefore, maximum coil/heating

element temperature and temperature control deviation from this maximum coil/heating element temperature can affect toxicant emissions and nicotine delivery (Refs. 81-84);

- coil/heating element resistance, number of coils/heating element, coil/heating element gauge, and coil/heating element configuration may affect overall heating element resistance, thereby influencing heating element temperature. The heating element temperature may affect toxicant emissions and nicotine delivery (Refs. 81-84);
- battery type, battery current operating range, battery failure safety features, battery conformance to standards, and PDU current operating range are necessary for evaluating battery and PDU safety. Risks of e-cigarette battery explosion, leakage, fire, or overheating are a safety concern (Refs. 80 and 86);
- battery power impacts the delivery of nicotine and the total emissions of volatile aldehydes (Refs. 85 and 90);
- battery and PDU voltage impact the amount of e-liquid consumed, the vapor temperature, and the total emissions of volatile aldehydes (Ref. 85);
- the draw resistance of the ENDS impacts the ease of drawing air into the ENDS to produce aerosol, which can affect nicotine and other toxicant delivery to the user (Ref. 91). For cigarettes, we evaluate filter pressure drop since it is more informative than draw resistance; however, for ENDS, there is no filter pressure drop or other similar parameter that could be used in place of draw resistance;
- inhaled aerosol temperatures can be damaging or uncomfortable to users who inhale aerosol above a certain temperature (Ref. 92); and
- ventilation may affect smoke constituent yields (Ref. 69).

Table 21 to § 1114.7(i)(2)(ii)(B) describes the design parameters and information on performance criteria that must be provided for an e-liquid. In this final rule, we have revised Table 21 (formerly Table 20 in the proposed PMTA rule) to § 1114.7(i)(2)(ii)(B) to help ensure that FDA is able to identify and evaluate each product more accurately and efficiently. Specifically, we removed the requirement to provide the e-liquid boiling point as a required design parameter because the information it would provide is sufficiently captured by coil temperature and e-liquid composition.

The finalized parameters listed in table 21 to § 1114.7(i)(2)(ii)(B) are a necessary part of the application because they are needed to fully characterize the product and changes may affect its impact on public health, as described below:

- the e-liquid volume can affect the delivery of nicotine and other toxicants to the user (Refs. 88 and 89);
- aerosol parameters such as particle number concentration, count median diameter, and PM2.5 are used to characterize the amount and size of particles to which the user is exposed. Epidemiological and clinical studies have shown that exposure to large amounts of small particles can impair lung function and is correlated with cardiovascular disease (Refs. 93 and 94);
- e-liquid viscosity impact the proportion of nicotine that is aerosolized (Ref. 95). Also, the e-liquid viscosity can affect the electronic cigarette nicotine and other toxicant delivery to the user (Refs. 79 and 88); and
- the e-liquid volume can affect the delivery of nicotine and other toxicants to the user (Refs. 88 and 89).

Table 22 to § 1114.7(i)(2)(ii)(B) describes the design parameters and information on performance criteria that must be provided for heated tobacco products (HTPs). HTPs currently sold in global markets can function in ways that are similar to products in other product categories. For example, some HTPs can function like ENDS products by aerosolizing e-liquids or using a battery and PDU to power the product. Other HTPs can contain tobacco filler, like a cigarette or cigar, but are heated instead of combusted. For these reasons, the properties of HTPs vary widely, but are comparable to the properties of other tobacco product categories. As such, based on FDA's experience with other similarly characterized tobacco products, the information needed from a design parameter standpoint perspective for HTPs overlaps with that of products in other categories. The parameters listed in table 22 to § 1114.7(i)(2)(ii)(B) are a necessary part of the application because they are needed to fully characterize the product and changes may affect its impact on public health, as described below:

- for cigarettes, the length, diameter, and mass can affect smoke constituent yields (Ref. 70). Similarly, for HTPs, dimensions (mass, length, width, height, and diameter) can directly affect the amount of tobacco that is heated and, in turn, affect smoke constituent yields;
- for ENDS products, the draw resistance can affect nicotine and other toxicant delivery to the user (Ref. 91). Similarly, for HTPs, the draw resistance can impact the ease of drawing air into the product to produce aerosol, which can affect smoke constituent yields;
- for ENDS, puff count can affect total toxicants emissions (Refs. 88). Similarly, for HTPs, the puff count can affect puff volume, which in turn can affect total toxicant emissions;

- for ENDS, e-liquid capacity of the atomizer tank / cartridge can affect total toxicant emissions (Refs. 88 and 89). Similarly, for HTPs, the product volume (capacity of the cartridge) can affect total puff volume, which in turn can affect total toxicant emissions;
- for ENDS, airflow rate can impact aerosol exposure (Ref. 87). Similarly, for HTPs, the airflow rate allows air to flow from the heating element to the user's mouth; some products allow the user to manually change the airflow while others have a minimum airflow that activates the product;
- for cigars, ventilation may affect smoke constituents yields. Similarly, for HTPs, ventilation may affect smoke constituent yields (Ref. 69);
- for ENDS, the battery and PDU voltage may affect the heating element, thereby affecting toxicant emissions and nicotine delivery (Refs. 81-84). Similarly, for HTPs, the battery and PDU voltage impact the amount of e-liquid consumed, the vapor temperature, and the total emissions of volatile aldehydes (Ref. 85). In addition, it gives an idea of the temperature users will encounter;
- for ENDs, the battery type, failure safety features, and battery conformance to standards are necessary for evaluating battery and PDU safety. Risks of e-cigarette battery explosion, leakage, fire, or overheating are a safety concern (Refs. 60 and 86). Similarly, for HTPs the temperature sensor is a safety feature that allows the product power to be cut off to ensure the product does not get too hot, causing the battery to vent or harm the user;
- for cigarettes, wrapper length and width may affect puff count and smoke constituents yields (Ref. 71). Similarly, for HTPS material wrapper length and width may directly

influence the area through which the air is permitted to enter the tobacco column, which, in turn, may affect puff count and smoke constituent yields (Ref. 71);

- for cigarettes, wrapper basis weight may affect puff count and smoke constituents (Ref. 71 and 72). Similarly, for HTPs, the material wrapper basis weight may affect puff count and smoke constituent yields;
- for cigars, the cigar wrapper porosity may affect smoke constituent yields (Refs. 72 and 73). Similarly, for HTPs, the material porosity may affect smoke constituent yields;
- for waterpipe, the heating source may affect smoke constituent yields. Similarly for HTPs, the heating element source (or a description of the type or approach) provides information on the type of heated tobacco product, such as a coil applied to the product;
- for ENDS, the temperature of the heating element can affect the chemical and physical characteristics of the aerosol delivered to the user (Refs. 81-84). Similarly for HTPs, the temperature of the heating element (heating element temperature range, operational temperature, maximum temperature) can affect the chemical and physical characteristics of the aerosol delivered to the user. An increase in heating element temperature can increase HPHC levels in the aerosol; therefore, maximum heating element temperature and temperature control deviation from this maximum heating element temperature can affect toxicant emissions and nicotine delivery;
- for ENDS, the heating element temperature may affect toxicant emissions and nicotine delivery (Ref. 84). Similarly, for HTPs, the heating element material can have a direct effect on the heat transfer to the e-liquid or tobacco, and in turn, affect the smoke constituent yields;

- for ENDS, the heating element configuration may affect toxicant emissions and nicotine delivery (Refs. 80-84). Similarly, for HTPs, the heating element configuration may affect overall heating element resistance, thereby influencing heating element temperature. The heating element temperature may affect toxicant emissions and nicotine delivery;
- for ENDS, the heating element dimensions may affect toxicant emissions and nicotine delivery (Refs. 80-84). Similarly, for HTPs, the heating element dimensions such as length influences the overall surface area, which affects heating element resistance, which influences the heating element temperature;
- for ENDS, the heating element mass may affect toxicant emissions and nicotine delivery (Refs. 80-84). Similarly, for HTPs, the heating element mass influences the power delivery of the battery, and in turn, the heat applied to the e-liquid or tobacco, which affects the smoke constituent yields and in turn, affects the smoke constituent yields;
- for ENDS, the heating element location may affect toxicant emissions and nicotine delivery (Refs. 80-84). Similarly, for HTPs, the heating element location can affect nicotine emissions;
- for ENDS, the number of heating elements may influence the heating element temperature thereby affecting toxicant exposure and nicotine delivery (Ref. 79). Similarly, for HTPs, the number of coils/heating element present can affect overall resistance and distribution of heat dissipation;
- for ENDS, the heating element diameter or gauge may affect toxicant emissions and nicotine delivery (Refs. 80-84). Similarly, for HTPs, the bigger the diameter of the heating element, the lower its resistance, and vice versa. Heating element resistance may

influence heating element temperature. The heating element temperature may affect toxicant emissions and nicotine delivery;

- for ENDS, the heating element resistance may affect toxicant emissions and nicotine delivery (Refs. 80-84). Similarly, for HTPs, the heating element resistance may affect overall heating element resistance, thereby influencing heating element temperature. The heating element temperature may affect toxicant emissions and nicotine delivery;
- for cigars, tobacco filler mass may affect smoke constituent yields (Ref. 69). Similarly, for HTPs, the tobacco filler mass may affect smoke constituent yields;
- for cigarettes, tobacco rod density may modify burn properties and smoke constituent yields (Refs. 51 and 52). Similarly, for HTPs, the tobacco rod density may modify burn properties and smoke constituent yields;
- for cigarettes, the tobacco moisture or oven volatiles may affect puff count (Ref. 54). Similarly, for HTPs, tobacco moisture or oven volatiles may affect puff count.
- for cigarettes, tobacco cut size alters the size of the tobacco pieces, which may result in more particulate matter (Ref. 53). Similarly, for HTPs, tobacco cut size alters the size of the tobacco pieces, which may result in more particulate matter (Ref. 53);
- for e-liquids, the e-liquid volume can affect the delivery of nicotine and other toxicants to the user (Refs. 88 and 89). Similarly, for HTPs, the e-liquid volume can affect the delivery of nicotine and other toxicants to the user;
- for e-liquids, the e-liquid viscosity can affect the electronic cigarette nicotine and other toxicant delivery to the user (Refs. 79 and 88). Similarly, for HTPs e-liquid viscosity impact the proportion of nicotine that is aerosolized. The e-liquid viscosity can affect the nicotine and other toxicant delivery to the user (Refs. 79 and 88);

- for ENDS, an increase in battery capacity (mAh rating) can increase the number of puffs the e-cigarette can deliver per vaping session. Longer vaping sessions may lead to greater exposure to toxicant emissions (Ref. 83). Similarly, for HTPs the battery capacity is a measure of the charge stored by the battery. The higher the mAh rating, the higher the capacity of the battery and the longer it will last between charges. The longer the battery lasts, the more the user can inhale smoke constituents;
- for ENDS, the battery voltage operating range and PDU voltage operating range impact the amount of e-liquid consumed, the vapor temperature, and the total emissions of volatile aldehydes (Ref. 85). Similarly, for HTPs, the battery and PDU voltage operating range or wattage impact the amount of e-liquid consumed, the vapor temperature, and the total emissions of volatile aldehydes;
- for ENDS, the battery type, battery current operating range, battery failure safety features, battery conformance to standards, and PDU current operating range are necessary for evaluating battery and PDU safety. Risks of e-cigarette battery explosion, leakage, fire, or overheating are a safety concern (Refs. 58 and 86). Similarly, for HTPs, the battery current range gives an indication of the safe zone for the battery to charge and what is considered its normal operating region; if the battery levels go beyond the safe zone while charging, the battery could be damaged, which could cause harm to the user;
- for ENDS, the battery and PDU voltage impacts the amount of e-liquid consumed, the vapor temperature, and the total emissions of volatile aldehydes (Ref. 85). Similarly for HTPs, the battery nominal voltage indicates how much current the battery can send out to the heating element. For the same resistance, a higher voltage will send more current (and more watts) to the heating element and it will produce more vapor. There is a link

between voltage and capacity because vaping at a higher wattage will produce a higher current and that will reduce the amount of time you can vape between charges;

- for ENDS, an increase in battery capacity (mAh rating) can increase the number of puffs the e-cigarette can deliver per vaping session. Longer vaping sessions may lead to greater exposure to toxicant emissions (Ref. 83). Similarly, for HTPs, the battery rating is a measure of the average amount of current the battery releases over time under normal use. Current may influence the heating element temperature, which in turn affects toxicant emissions and nicotine delivery. In addition, battery mAh rating provides an understanding of how long a battery will last and thus the product stability;
- for ENDS, the battery type, failure safety features, and battery conformance to standards are necessary for evaluating battery and PDU safety. Risks of e-cigarette battery explosion, leakage, fire, or overheating are a safety concern (Refs. 58 and 86). Similarly for HTPs, the battery charging temperature limits gives insight on the safe range for battery charging temperatures and testing will show if the software of the battery can keep the battery in the safe zone;
- for ENDS, the battery type, failure safety features, and battery conformance to standards are necessary for evaluating battery and PDU safety. Risks of e-cigarette battery explosion, leakage, fire, or overheating are a safety concern (Refs. 58 and 86). Similarly, for HTPs, battery discharge temperature limits give insight on the safe range for battery discharging temperatures and testing will show if the software of the battery can keep the battery in the safe zone;
- for ENDS, the battery type, failure safety features, and battery conformance to standards are necessary for evaluating battery and PDU safety. Risks of e-cigarette battery

explosion, leakage, fire, or overheating are a safety concern (Refs. 58 and 86). Similarly, for HTPs, the end of discharge voltage is the level to which the battery voltage or cell voltage can fall to before affecting the load. This helps to establish the life cycle of the battery;

- for ENDS, the battery type, failure safety features, and battery conformance to standards are necessary for evaluating battery and PDU safety. Risks of e-cigarette battery explosion, leakage, fire, or overheating are a safety concern (Refs. 58 and 86). Similarly, for HTPs, the battery maximum charging current at which the battery can be charged continuously is usually defined by the battery manufacturer in order to prevent excessive charge rates that would damage the battery or reduce its capacity. Damage to batteries is a hazard to users;
- for ENDS, the battery type, failure safety features, and battery conformance to standards are necessary for evaluating battery and PDU safety. Risks of e-cigarette battery explosion, leakage, fire, or overheating are a safety concern (Refs. 58 and 86). Similarly, for HTPs, the battery maximum discharge current at which the battery can be discharged continuously is usually defined by the battery manufacturer in order to prevent excessive discharge rates that would damage the battery or reduce its capacity. Damage to batteries is a hazard to users;
- for ENDS, the battery type, failure safety features, and battery conformance to standards are necessary for evaluating battery and PDU safety. Risks of e-cigarette battery explosion, leakage, fire, or overheating are a safety concern (Refs. 58 and 86). Similarly, for HTPs, the battery upper limits charging voltage is important to limit the maximum

battery voltage during charging to prevent damage to the battery, which is a hazard to users;

- for ENDS, battery and PDU voltage can impact the total emissions of volatile aldehydes (Ref. 85). Similarly, for HTPs, the battery and PDU voltage impact the amount of e-liquid consumed, the vapor temperature, and the total emissions of volatile aldehydes (Ref. 85);
- for ENDS, PDU current operating range and wattage range are necessary for evaluating battery and PDU safety. Risks of e-cigarette battery explosion, leakage, fire, or overheating are a safety concern (Refs. 80 and 86). Similarly, for HTPS, PDU current operating range and wattage operating range may influence the heating element temperature thereby affecting toxicant emissions;
- for ENDS, the battery type, failure safety features, and battery conformance to standards are necessary for evaluating battery and PDU safety. Risks of e-cigarette battery explosion, leakage, fire, or overheating are a safety concern (Refs. 58 and 86). Similarly, for HTPs, the PDU temperature cutoff is an electrical safety product that interrupts electric current when heated to a specific temperature to protect the user;
- for ENDS, the battery type, failure safety features, and battery conformance to standards are necessary for evaluating battery and PDU safety. Risks of e-cigarette battery explosion, leakage, fire, or overheating are a safety concern (Refs. 58 and 86). Similarly, for HTPs, the current cutoff is an electrical cutoff, which is an electrical safety product that interrupts electric current when a specific condition is met (i.e., temperature, current, etc.) to protect the user;

- for ENDS, the battery and PDU current operating range may influence the toxicant emissions (Refs. 82 and 84). Similarly, for HTPs, the batteries and PDU should have a normal current operating range so as to not overheat the product and cause it to become a hazard to the user. In addition, this current range has a direct impact on the heating element, which in turn affects the smoke constituent yields;
- inhaled aerosol temperatures can be damaging or uncomfortable to users who inhale aerosol above a certain temperature;
- for e-liquids, aerosol parameters such as particle number concentration, count median diameter, and particulate matter (PM)2.5 are used to characterize the amount and size of particles to which the user is exposed (Refs. 93 and 94). Similarly, for HTPs, aerosol parameters such as particle number concentration, count median diameter, and PM2.5 are used to characterize the amount and size of particles to which the user is exposed. Clinical studies have shown that exposure to large amounts of small particles can impair lung function and is correlated with cardiovascular disease;
- for cigarettes, filter efficiency may affect smoke constituent yields (Ref. 60). Similarly, for HTPs, filter efficiency effect smoke constituent yields;
- for cigarettes, filter pressure drop may affect smoke constituent yields (Ref. 61). Similarly, for HTPs, filter pressure drop may affect smoke constituent yields; and
- for cigarettes, filter diameter, DPF, total denier, filter density, and filter length may affect filter efficiency and, in turn, smoke constituent yields (Ref. 60). Similarly, for the HTPs, the filter diameter, DPF, total denier, filter density, and filter length, may affect filter efficiency and, in turn, smoke constituent yields (Ref. 60).

FDA received comments regarding design parameters and test data, as required by § 1114.7(i)(2)(ii) and associated tables, as discussed below.

(Comment 44) One comment stated that the lists of product design parameters in § 1114.7(i)(2)(ii) do not reflect the subcategories of innovative tobacco products or nicotine delivery systems that exist in some of the product categories and that by requiring all parameters, FDA would have some applicants generate parameters that are not relevant to their particular subcategory. The comment suggested that FDA make the design parameters in these tables recommendations rather than required parameters.

(Response 44) FDA declines to make this change to the rule. FDA believes that design parameters are necessary to fully characterize a tobacco product and are an important consideration in determining its health effects. FDA agrees that the required lists of product design parameters in § 1114.7(i)(2)(ii) are not necessarily reflective of all subcategories of innovative tobacco products or nicotine delivery systems. However, table 1 to § 1114.7(c)(3)(iii) includes a list of tobacco product categories and subcategories, which should help the applicant to determine whether the rule includes an appropriate category and subcategory for its new tobacco product and the corresponding design parameters that must be submitted, where applicable.

(Comment 45) One comment stated that FDA should not require testing for nicotine dissolution in portioned smokeless tobacco because it does not represent the potential rate or amount of exposure. The comment also stated that because the pouch material for smokeless tobacco does not have nicotine, applicants should not be required to provide pouch material information.

(Response 45) FDA believes that nicotine dissolution testing is an effective mechanism for FDA to gain insight into product performance and relative differences in the likely experience of users. In addition, changes in pouch materials of portioned smokeless tobacco products may change the permeability of the pouch and the rate at which nicotine is released, which can affect the overall performance of the product, including the rate at which nicotine is released to consumers (Ref. 67). Additionally, a study using nicotine tablets with different polymer content shows that nicotine release can be affected by thickness and pore size of the material that encloses nicotine (Ref. 67). In this study, upon hydration, polymer in tablet formulations swells, forming a polymer gel layer and effectively acting as a permeable membrane. The tablets released nicotine at a rate controlled by swelling of the polymer followed by the diffusion through the swollen polymer gel layer. Polymer network gel swelling can affect material layer thickness (Ref. 141) and pore size (Ref. 142) which in turn can affect diffusion across the layer. Pouch materials are characterized by basis weight, air permeability, and thickness. Therefore, pouch material properties such as basis weight, air permeability and thickness are required to evaluate nicotine release from pouched smokeless tobacco products. Given the important information that nicotine dissolution testing and pouch material provide to FDA's review, FDA declines to remove the requirements for reporting pouch material information and nicotine dissolution testing in this PMTA rule.

(Comment 46) One comment stated that FDA needs to remove the proposed design parameters for cigars in § 1114.7(i)(2)(ii) from the rule and reassess its thinking as to the design parameters it requires and recommends for premarket review for cigars. The comment stated that the current proposed parameters for each type of cigar specified do not correspond to the actual design parameters that cigar manufacturers can or do use or test for and, therefore, it

would be impossible for applicants to provide the proposed parameters to FDA. The comment recommended that FDA require the reporting of design parameters only for cigar length, ring gauge, weight, and filter ventilation.

(Response 46) FDA declines to remove the design parameters for cigars. As described below, design parameters are needed to fully characterize the product and assess its impact on public health. Because these design parameters are an important component of being able to determine a product's health effects, FDA may refuse to accept or refuse to file a PMTA if it lacks design parameters information required by § 1114.7(i)(2)(ii). To ensure that FDA is able to fully determine the precise product being reviewed, FDA requires applicants provide all design parameters specific to the new product tobacco category. In an event that an applicant is unable to provide a design parameter listed in § 1114.7(i)(2)(ii) for the new tobacco product, the applicant must provide a justification and scientific evidence for why those design parameters are not relevant and do not raise public health concerns.

(Comment 47) One comment stated that it would be arbitrary and capricious to require manufacturers to submit the design parameters for pipes because the terms used are ones that pipe manufacturers neither know nor could they test for in pipes.

(Response 47) FDA disagrees with the suggestion that requiring pipe manufacturers to submit design parameters for their new tobacco products in PMTAs would be arbitrary and capricious. FDA believes that these design parameters are needed to fully characterize the product and assess its impact on public health. Because these design parameters are an important component of being able to determine a product's health effects, FDA may refuse to accept or refuse to file a PMTA if it lacks design parameters information required by § 1114.7(i)(2)(ii). For FDA to fully determine the precise product being reviewed and understand the potential

health effects associated with the product, we are requiring that applicants provide all design parameters specific to the new product tobacco category. The design parameters required for pipes are measurable, and therefore test data should be easily obtained. Even if the design parameter names were not familiar to manufacturers, the manufacturers could supplement design parameter information by providing labeled images of their product that associate each component with the design parameter name used by the applicant or as discussed above, provide the information needed is with an MDSS document. FDA believes with the information provided in this rule, manufacturers should now be familiar with the required design parameters and can provide the necessary data. If FDA did not have the design parameters for the product it was reviewing, it would be unable to determine the precise product being reviewed, let alone whether the data and information contained in a PMTA are applicable.

(Comment 48) One comment stated that many of the items listed in the ENDS design parameters section apply to components or parts that do not provide a direct correlation to aerosol emissions when evaluated independently or individually. The comment suggested that measuring HPHCs is a better way to assess the product than by reviewing these design parameters.

(Response 48) Sections 1114.7(i)(1)(v) and (i)(2)(ii) require a PMTA to include both a full statement of the constituents, including HPHCs and other constituents, and of the design parameters for the new tobacco product because both provide information that is important for FDA's review. The design parameters are necessary to fully characterize the new tobacco product, which is important to FDA's accurately identifying and understanding of the product under review. As described elsewhere in this document, these design parameters can also affect the health risks of the new tobacco product. Information regarding the constituents contained in

and delivered from the new tobacco product is also important because, as described in section VIII.B.13.a.iii, it directly correlates to the health risks of the new tobacco product.

(Comment 49) One comment stated that the costs associated with generating design parameter data exceeds the potential marginal benefit of the data to FDA's overall determination of whether permitting the marketing of the new tobacco product would be APPH. The comment stated that rather than providing information regarding a product's battery, it should just be able to provide a certificate of compliance with the Underwriters Laboratories 8139 standard, which would render further review of the battery by FDA superfluous. The comment also stated that even though information regarding the particles in the aerosol produced by e-cigarettes is relevant to lung and cardiovascular function, FDA does not need it to determine whether permitting the marketing of e-cigarettes would be APPH because they are far less harmful than combusted cigarettes.

(Response 49) FDA disagrees with the comment's suggestion that FDA should not require design parameters for ENDS. While FDA acknowledges there is cost associated with generating design parameter data, the design parameters of the product can change the health impact of the tobacco product by affecting the level of constituents that reach tobacco product users or nonusers and as such are an important part of the APPH determination. This information is also necessary to fully characterize a tobacco product. The differences in health risks that a new tobacco product may present compared to one other product category such as cigarettes is not, by itself, sufficient to demonstrate that permitting the marketing of a new tobacco product would be APPH. As explained in section IX.D. of this document, FDA interprets the APPH standard in 910(c)(2)(A) to require a showing that permitting the marketing of a new tobacco product would likely have at least a net benefit to public health based upon the

risks and benefits to the population as a whole (which includes youth, young adults, and other vulnerable populations). Comparative health risk information is just one factor FDA may consider in making this determination. Additionally, a comparison to just one other product category may not be sufficient when current users of more than one product category may begin using the new tobacco product.

iii. Function. The rule requires the application to contain a description of how the product is intended to function. For example, this could include a description of how the energy or heating source is used in or with the product, and how the delivery of the product's output (e.g., smoke, aerosol, nicotine) is controlled. This information can be critical to FDA's review of a tobacco product, including whether the product functions as intended and whether the application contains data and information that is relevant to the way in which it is intended to function. For example, if an applicant states that a product heats or aerosolizes, but does not combust tobacco or an e-liquid, it would assist FDA in determining whether the information in the PMTA shows the product functions as intended and whether the application contains appropriate information regarding this function (e.g., data regarding relevant HPHCs).

iv. pH of product and nicotine formulation. The rule requires the PMTA to specify the pH of the product. The pH of the product is important for FDA to review as part of a PMTA because it can affect the amount of unprotonated nicotine delivered to the user (Refs. 96 and 97).

The rule also requires the PMTA to specify the formulation of the nicotine in the product. The nicotine formulation information is required to state the type(s) and quantity of nicotine in the product. Type(s) of nicotine include, but are not limited to, unprotonated nicotine and nicotine salts (e.g., nicotine lactate, nicotine benzoate, nicotine pyruvate). The quantity of unprotonated nicotine is important for FDA to review because the amount and speed of nicotine

delivered by a tobacco product is related to the proportion of nicotine in a tobacco product that is unprotonated (Refs. 98 and 99). The types and quantities of nicotine salts in the product are important for FDA to review because nicotine salt complexes can substantially increase nicotine delivery relative to free-base nicotine in ENDS products (Refs. 100-102)

v. Fermentation process. For smokeless tobacco products and tobacco products that contain fermented tobacco (including naturally fermented tobacco), the rule requires an application to contain information on the fermentation process. The rule requires this information because the fermentation process can result in different degrees of change in the chemical constituents of the tobacco (Refs. 103-105) and affect the type and number of microorganisms in the final tobacco product, (Refs. 106-108) which could potentially affect the levels of TSNAs and stability of the tobacco products during storage. In addition, the type and amount of the fermentation inoculum can change the product as a result of directed fermentation (Ref. 109). Therefore, the application must contain the following information regarding the fermentation process:

- a description of the fermentation process;
- composition of the inoculum (starter culture) with genus and species name(s) and concentration(s) (if applicable);
- any step(s) taken to reduce microbes already present during product processing (e.g., cleaning of product contact surfaces);
- specifications and test data for pH, temperature, and moisture content, or water activity;
- frequency of aeration or turning (if applicable);
- duration of fermentation;
- added ingredients;

- method used to stabilize or stop fermentation. If the applicant uses heat treatment, then it must provide the information specified in the following subsection. If an applicant uses a method other than heat treatment, it must provide the parameters of the method (e.g., length of treatment, temperature) and method validation data; and
- storage conditions of the fermented tobacco prior to further processing or packaging and duration of storage (if applicable).

vi. Heat treatment process. In final rule, we have added a requirement for information on the heat treatment process, if applicable. For tobacco products that are heat treated, the rule requires an application to contain information on the heat treatment process. We have included this requirement for information because the heat treatment process can potentially reduce the microbial load, resulting in lower levels of carcinogenic TSNAs thereby altering product composition (i.e., product characteristics) (Refs. 110-112). Therefore, the application must contain the following information regarding the heat treatment process:

- a description of the heat treatment process;
- the type of heat treatment;
- the conditions of heat treatment, including time, temperature, and moisture; and
- method validation data, including microbial loads (including bacteria, spores, yeast, and fungi) and TSNAs before and after heat treatment.

vii. Shelf life and stability information. In the proposed rule, § 1114.7(i)(2)(vii) would have required a PMTA for any category of tobacco product to contain tobacco product storage and stability information that establishes the microbial and chemical stability of the tobacco product throughout the stated shelf life. Upon review of public comments and further

consideration, we are finalizing these requirements (with specified changes) for products other than cigarettes and RYO tobacco as explained in this section.

Shelf life and stability information is important for FDA's review of many tobacco products because bacterial communities and constituents in tobacco products can change over time (Refs. 107, 108, 113 and 114). Stability information is a particular concern with smokeless tobacco products and other tobacco products that contain fermented tobacco (including naturally fermented tobacco) because the characteristics of these products can be affected by the manufacturing process, storage conditions, and length of time on a shelf. Carcinogenic TSNA production is critically influenced by the microbial communities associated with the tobacco (Refs. 113 and 105). TSNA content in the finished tobacco products is greatly affected by a variety of factors, such as tobacco processing method(s) (e.g., curing, aging, sweating, fermentation, and heat treatment), chemical additives added to control microbial activity (e.g., humectants or preservatives), water activity (a_w) of the product, container closure system, and product storage conditions (e.g., temperature, humidity), all of which could potentially alter microbial activity and, in turn, affect the stability of the tobacco products over the shelf life (Refs. 107, 108, 110, 113, 114, 115-120). Furthermore, some tobacco products such as smokeless tobacco products and e-liquids, have been shown to contain microbial cell wall constituents ([1→3]-β-D-glucan) and/or microbial toxins, such as aflatoxins and endotoxins (Refs. 121 and 122). These microbial components or toxins may result in increased risk to public health because they are either carcinogenic in nature or associated with the development of respiratory symptoms, reduced lung function, inflammation and asthma (Refs. 121 and 122). In addition, based on our experience, HTPs can contain high levels of humectants, which can affect product stability; therefore shelf life and stability information is required to support an

application for HTPs. Humectants function to keep a product moist, thereby impacting the moisture content and water activity of the product, which in turn may impact microbial growth and product stability (Ref. 116). Thus, for many tobacco products, information obtained through stability testing and shelf life is important for FDA to consider during its review to ensure that the tobacco products are microbiologically and chemically stable during the storage and do not result in an increased risk to public health as the product sits in storage.

Under the final rule, applicants submitting a PMTA for cigarettes[29] and RYO tobacco products do not need to provide the shelf life and stability information under § 1114.7(i)(2)(vii). In our review experience, we have found that since the vast majority of cigarettes and RYO tobacco products do not contain fermented tobacco, these products generally do not present the same stability concerns as other tobacco products. Thus, after further consideration, FDA is not finalizing the shelf life and stability information requirements for these products based upon its review experience with the product categories under the SE pathway. However, since we lack similar experience with novel tobacco products, such as ENDS and HTPs, we need stability information for these types of products to determine whether there is a difference in microbial factors or HPHC quantities over time. Given the Agency's lack of experience reviewing applications for novel tobacco products, at this time FDA believes information regarding these products' shelf life and stability over time is needed to ensure FDA fully understands the microbial and chemical stability of the tobacco products throughout their stated shelf life.

In addition, after review of available scientific information regarding stability testing as well as consideration of comments received in responses to the proposed rule, the stability testing requirements have been updated including changes such as the removal of identification

[29] See the discussion in section VIII.B.3. of this document about how products should be categorized for purposes of PMTA review.

of microbiological organisms by genus and species and removal of testing for pH, moisture content, nitrate and nitrite levels, and preservatives and microbial metabolic inhibitors. Specifically, the final rule requires an application to contain the following shelf life and stability information:

- the length of the shelf life, a description of how the shelf life is determined and a description of how shelf life is indicated on the tobacco product, if applicable. The rule would not require a tobacco product to indicate the product's shelf life; however, if it is indicated on the product, the PMTA must describe how it is determined. For example, if the tobacco product labeling has a "use by," "best by," or expiration date, a PMTA must contain a description of how the date is determined (e.g., a certain number of days after packaging);
- stability date assessed at the beginning (zero time), middle, and end of the expected shelf life. If a tobacco product does not have a defined shelf life, provide stability data over a specified amount of time and a justification for why that time period is appropriate. For example, if an applicant believes that 2 years after the date of product manufacture is an appropriate shelf life, the applicant should provide clear justification to support this time. Stability testing must be performed for the chemical and microbial endpoints for the following items:
    - microbial content data, including total aerobic microbial count and total yeast and mold count;
    - water activity (a_w);
    - TSNA yields (total N-nitrosonornicotine [NNN], and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone [NNK]); and

- preservative content (if applicable).

If microbial activity during the product shelf life is detected, further information, such as endotoxin or aflatoxin levels, should be included in the PMTA.

Accelerated studies for chemical endpoints, combined with basic stability information on the components or parts and container closure system (separately), or the tobacco product (as a whole) may be used to support chemical stability of the tobacco product provided full shelf life studies are not available and are being conducted. Where data from accelerated studies are used to project a tentative shelf life that is beyond a date supported by actual shelf life studies, stability studies must be conducted under nonaccelerated conditions at appropriate intervals, until the tentative expiration date is verified or the appropriate expiration date is determined.

As required by § 1114.7(i)(4), the reported stability testing must be performed on test samples that reflect the final tobacco product composition and design (including the container closure system) and be conducted using a sufficient sample size and number of replicates to substantiate the results of the type of testing conducted. Section 1114.7(i)(4) also requires the application to contain the following information regarding stability testing:

- the mean quantity and variance with unit of measure;
- the number of samples and measurement replicates for each sample;
- the methods used, associated reference(s) including a deviation(s) from the methods, and full validation reports for each method;
- the name and location of the testing laboratory or laboratories and documentation showing that the laboratory or laboratories is (or are) accredited by a nationally or internationally recognized external accreditation organization;
- the length of time between dates of tobacco product manufacture and date(s) of testing;

- the length of time between date of tobacco product manufacture and date(s) of testing;
- the storage conditions of the tobacco product before it was tested;
- a statement that the testing was performed on a tobacco product in the same container closure system in which the tobacco product is intended to be marketed; and
- full test data (including quantitative acceptance (pass/fail) criteria, complete data sets, and a summary of the results) for all stability testing performed.

FDA received several comments regarding shelf life and stability information, as discussed below.

(Comment 50) One comment requested that FDA clarify, with regard to shelf life and stability testing, whether changes to the product over time will form the basis of FDA's decision to issue a marketing denial order for a new tobacco product.

(Response 50) Product stability information is important for FDA to consider during its review because if a product changes over time, it may affect the health risks presented by the new tobacco product. As described in section IX.D, the health risks of a new tobacco product forms part of the basis for FDA's determination of whether it should issue a marketing granted order for the new tobacco product. This may include the health risks of a new tobacco product as it changes over time. For example, a product with a 24-month expiration date whose stability testing data demonstrates that the product may be unstable after manufacturing, with the levels of TSNAs (NNN and NNK) increasing significantly over the 24-month period shelf life above what is reasonably expected for similar products on the market, may raise additional health risks. Because NNN and NNK are carcinogenic to humans with no safe level of exposure, the increased levels of TSNAs may increase the health risks to the users. Therefore, this type of stability testing information is important for FDA to consider during its review to ensure that the

tobacco products are microbiologically and chemically stable, and the product remains APPH, over the product's shelf life.

(Comment 51) One comment stated that where a product does not have an established shelf life, the rule should require an applicant to report stability data using the upper bound length of time the product will remain in storage, such as the upper 95 percent confidence interval, rather than relying on the typical period of time in which a product is sold to consumers, which it interprets to be the median time. The comment also stated that the rule should be amended to require applicants to provide regular postmarket reports on how much product has been removed because it was in storage for too long and how that product was disposed of.

(Response 51) FDA disagrees with this comment. As discussed elsewhere in this document, a PMTA is required to contain product storage and stability information that establishes the microbial and chemical stability of the product throughout the product's shelf life. For tobacco products with no established or defined shelf life, FDA recommends that applicants provide details of stability over a specified amount of time and justify why that time period is appropriate. This time period should correspond to the expected storage time of the tobacco product after the date of manufacture of the product until it is sold to consumers, as determined by the applicant. This information is product-specific, and the burden is on the applicant to show that the product is stable for the entire duration determined by the applicant. Since the expected storage time is product-specific, FDA declines to establish requirements for postmarket reports regarding product removal or disposal for all products. FDA will monitor the marketing of the product, including review of periodic reports required under § 1114.41, to determine whether there are product stability issues that were not addressed in the PMTA.

(Comment 52) One comment stated that FDA's approach for stability testing for microbiological endpoints in the form of total aerobic microbial count (TAMC), total yeast and mold count (TYMC), and testing for specific microbial organisms is not aligned with current scientific approaches. The comment also noted that the proposed testing requirements are not aligned with the current scientific approaches in addressing microbiological quality in various industries (e.g., pharmaceuticals), which take into consideration the importance of water for microbiological proliferation. The comment suggested that applicants should be allowed to adopt a risk-impact assessment-based approach, whereby results of a toxicological assessment of the product taking into account its composition, manufacturing process, and typical supply chain conditions shall be used by the applicant to define and execute a stability program appropriate for the product category. The comment stated that in particular, with regards to risks associated with potential microbiological activity, scientifically justified surrogate factors can be employed such as water activity (a_w). The comment concluded by stating that FDA should not employ a one-size fits all approach for different categories of tobacco products.

(Response 52) FDA disagrees with this comment. During review of a PMTA, FDA evaluates stability of the finished tobacco product during storage. To determine the microbial and chemical stability of a tobacco product during the expected storage period, FDA evaluates the cumulative effect of all factors, such as tobacco processing (e.g., fermentation, heat-treatment, curing), product composition (e.g., humectants, preservatives, certain flavor compounds, metabolic inhibitors), a_w of the finished tobacco product, container closure system, and product storage conditions (e.g., temperature, humidity), that could potentially affect the stability of the product during storage. A_w is a measure of the amount of water that is available for microbial growth in a product. Therefore, it only provides information on the potential of a

product to support growth of microbes present in the product. Fresh tobacco leaves are colonized by a variety of microorganisms. Additionally, microbial contamination could potentially occur during tobacco processing, finished tobacco product manufacture, and/or storage. Some tobacco products such as smokeless tobacco products and e-liquids, have been shown to contain microbial cell wall constituents ([1→3]-β-D-glucan) or microbial toxins, such as aflatoxins and endotoxins (Refs. 121 and 122). These microbial components or toxins may result in increased risk to public health because they are either carcinogenic in nature or associated with the development of respiratory symptoms, reduced lung function, inflammation and asthma. Therefore, TAMC and TYMC data provide crucial information on the microbial load in the finished tobacco product and serve as an indicator for the potential of presence or absence of microbial toxins in the product. Additionally, a_w levels are influenced by several factors (e.g., humectant levels, container closure system, storage conditions) and could potentially change during storage. TAMC and TYMC data are important to corroborate changes in a_w during storage and therefore crucial in evaluating the stability of the finished tobacco product during storage. FDA will evaluate shelf life and stability information of each tobacco product as part of its APPH determination.

(Comment 53) Two comments expressed additional concerns about the breadth of information required to be submitted regarding the stability of smokeless tobacco products. One comment disagreed with the proposed requirement to include analytical measurements of pH, moisture content, a_w, TAMC, TYMC, nitrate, nitrite, preservatives, and microbial metabolic inhibitors in stability studies for new smokeless tobacco products. The comment stated that because the ultimate endpoint of stability testing is to determine whether TSNA formation occurs over time, assessment of these additional parameters is burdensome, resource intensive, and

unnecessary. The comment noted that not only would they have to develop validated methodologies and find laboratories to conduct the testing, the analysis of the proposed parameters would only indicate favorable conditions for increases of TSNAs and would not yield a change in total TSNAs, which are also being measured. Another comment expressed similar concerns and disagreed with the requirement to provide microbial content data that identifies detected microbiological organisms by genus and species names because it would be costly and time intensive, yield highly variable results depending on the method used, and would not alter the presence of TSNAs in the tobacco product as measured at each stability timepoint.

(Response 53) FDA has revised section § 1114.7(i)(2)(vii) of the codified to include a_w, preservative content, TSNAs (reported as separate amounts for the total TSNAs, NNN, NNK) and microbial content data including TAMC and TYMC along with identification of microbiological organisms by genus and species names. FDA disagrees with the statement that the parameters would only indicate favorable conditions for increases of TSNAs and would not yield a change in total TSNAs. Microbial-mediated reduction of nitrate results in production of nitrite, which further reacts with alkaloids present in tobacco to produce carcinogenic TSNAs (Refs. 107 and 113). Microbial-mediated nitrite production is a key determinant of TSNA levels in the final tobacco product. Several nitrate-reducing bacterial species (e.g., *Bacillus*, *Enterobacter*, *Staphylococcus*, *Corynebacterium*, *Escherichia*) and fungal species (e.g., *Candida*, *Fusarium*, *Aspergillus*, *Alternaria*) that are active across a wide temperature and pH range have been identified in smokeless tobacco products (Refs. 107, 113, and 123). During tobacco processing and storage, these nitrate-reducing microbial species could potentially convert nitrate to nitrite resulting in increases in TSNA levels thereby affecting product stability during storage. It is important for FDA to evaluate all of the factors that affect microbial growth and determine if

any increases in TSNAs over tobacco product storage are microbial-mediated. This information ensures that the tobacco product is microbiologically and chemically stable during the expected storage period and does not result in an increased risk to public health as the product sits in storage.

viii. Product and packaging design risks and misuse hazards. This section of an applicant's PMTA is required to contain a review and assessment of reasonably foreseeable risks associated with the design of the tobacco product and its packaging that may occur during normal use of the tobacco product or during any foreseeable misuse of the product, including user error, which may cause illness, injury, or death not normally associated with the use of the tobacco product. The review and assessment must identify the measures taken to reduce or eliminate each risk associated with the design of the tobacco product and packaging. Examples of these design risks include, but are not limited to: (1) defects in the air permeability of fire standards compliant banding on cigarette paper that is intended to allow cigarettes to self-extinguish when left unattended; (2) software errors or flaws (i.e., bugs) that occasionally result in the product performing differently than designed; (3) failure of a safety switch to shutoff a product if it exceeds a certain temperature; and (4) the failure of a battery design feature to prevent battery from overcharging. The PMTA must contain a review and assessment of each defect, describing the potential to cause illness, injury, or death and the measures taken to reduce or eliminate the defects and their potential impact. FDA is requiring this information under section 910(b)(1)(G) of the FD&C Act, because the potential for the product design or foreseeable misuse to cause illness, injury, or death provides information that informs FDA's determination of whether permitting the marketing of the product would be APPH.

FDA received one comment regarding product and packaging design risks and misuse hazards, as discussed below.

(Comment 54) One comment stated that applicants should not be required to report or assess the ways in which a tobacco product could be misused because requiring companies to do so would require judgments that are so wildly subjective that the results are unlikely to be valid or relevant.

(Response 54) FDA disagrees with this comment. As discussed above, a PMTA would not be required to contain information regarding all potential misuses; rather it would be required to contain an identification and assessment of foreseeable misuses. Prospective applicants should review section VII.13.a, which explains the ways in which applicants can include this type of information, including information bridged from investigations on similar products.

10. Principles of Operation

Section 1114.7(i)(3) describes FDA's interpretation of the full statement of the principle or principles of operation required by section 910(b)(1)(B) of the FD&C Act and requires the PMTA to contain full narrative descriptions of:

- the way in which a typical consumer will use the new tobacco product. This includes a description of how a consumer operates the product, how long a single unit of the product is expected to last (e.g., total length of time of use to consume a unit, number of use sessions expected per unit), and where applicable, whether and how a consumer can change the product design and add or subtract ingredients, such as:
    - e-cigarettes that allow users to change performance features, such as the temperature, voltage, or wattage;

- e-cigarettes that allow users to add or subtract e-liquid ingredients, such as liquid nicotine and flavoring, including instances where such manipulation is not intended by the manufacturer (e.g., ways to misuse the product);
- e-cigarettes that allow users to add, subtract, or substitute components or parts other than identical replacement parts; and
- waterpipes that allow users to add, subtract, or substitute components or parts other than identical replacement parts, such as stems and hoses;

- a justification for an applicant's determination of what constitutes a single unit of product as described in the PMTA; and
- whether the product incorporates a heating source and, if it does, a description of the heating source.

FDA received several comments regarding these provisions, as discussed below.

(Comment 55) FDA received multiple comments in response to its request for comment regarding how the rule should require measurement of the length of time it takes a user to consume a single unit of the product. One comment stated that FDA should not require any such measurements with respect to e-cigarettes because it is the overall exposures to HPHCs from repeated use of a product that informs health risks, not the use of a single unit. Another comment had specific suggestions as they relate to ENDS, stating that for a closed ENDS, a single unit should be the amount of e-liquid in the closed ENDS; for an open ENDS, a single unit should be the amount of liquid required to fill the reservoir; and for open e-liquids, a single unit should be 2 milliliters (mL) of e-liquid regardless of the container size.

(Response 55) FDA agrees that the overall exposures to HPHCs from repeated use of a product provide the most relevant information about health risk. However, because the overall

exposures come from an accumulation of individual use sessions over time, it is important for FDA to understand how the new tobacco product is likely to be used by a typical consumer in an individual use session as well as how frequently they use the product (including variable use behaviors within sessions and over time). It is also important to fully characterize the product so that FDA can determine the differences in health risks between the new tobacco product and other similar products on the market. Therefore, FDA declines to exempt e-cigarettes from reporting the length of time it takes for a user to consume a single unit of product.

In terms of what should constitute a single unit for an ENDS, FDA agrees with the comment's suggestions and recommends that applicants consider a closed e-cigarette, such as a prefilled disposable cigalike, or closed e-liquids, like cartridges or pods that are not intended to be refillable, to constitute a single unit. For an open e-cigarette, applicants consider a single unit to be the amount of e-liquid required to fill the reservoir. FDA believes these measurements of a single unit are appropriate because they are a consistent unit of measure set by the manufacturer that could be useful in providing meaningful information about product use; however, for open e-liquids, differences in how consumers use the product may make a different unit of measure more appropriate. Therefore, for open e-liquids, it may be more appropriate to consider the volume of e-liquid required to fill the container to be a single unit, rather than 2 mL of e-liquids. Due to product variability and associated differences on what may be appropriate as a single unit of a tobacco product, FDA declines to set a required unit size and requires applicants to provide a scientific justification for why the single unit used for the new tobacco product is appropriate.

11. Product Testing and Analysis Information

Section 1114.7(i)(4) requires that all testing and analyses of the tobacco product required in § 1114.7(i) be performed on test samples that reflect the final tobacco product composition

and design, and that they be conducted using a sufficient sample size and number of replicates to substantiate the results of the type of testing conducted. This is required under FDA's authority in section 910(b)(1)(G), because the testing requirements are relevant to the subject matter of the application in that they help FDA determine whether the product testing and analyses are accurate and reliable. If the product that is the subject of the PMTA is a component or part, testing and analyses of the product should be performed with a range of other components or parts with which a consumer is expected to use the product (e.g., an e-liquid should be tested in a representative sample of e-cigarettes in which it is may be used).

Additionally, the applicant must provide the following information about the testing and analysis:

- the name and location of the testing laboratory or laboratories and documentation showing that the laboratory is (or laboratories are) accredited by a nationally or internationally recognized external accreditation organization;
- the length of time between dates of manufacture and date(s) of testing;
- the storage conditions of the tobacco product before it was tested;
- the number of samples and measurement replicates for each sample;
- description of method procedure, method validation information and rationale for selecting each test method, including relevant voluntary testing standards;
- reports of all product formulation testing, including line data, test protocols, quantitative acceptance criteria, and a summary of the results, for each applicable parameter. Please note that an applicant must retain source data under § 1114.45; and
- complete descriptions of any smoking or aerosol-generating regimens used for analytical testing that are not standardized or widely accepted by the scientific community, if

applicable. Where the applicant is not using a widely recognized and standardized regimen, such as the ISO or HCI regimens, the PMTA must contain a complete description of the regimen.

FDA received one comment regarding constituents and stability testing, as discussed below.

(Comment 56) One comment stated that the final rule must provide greater detail regarding method validation and the number of samples and measurement replicates required for constituent and stability testing.

(Response 56) FDA declines to set requirements for a specific number of samples and replicates because the type of product and methodology of testing will vary for a PMTA and the sample size and number of replicates necessary to substantiate the type of testing may vary. Thus, FDA does not find it appropriate to establish specific requirements for testing in terms of validation methodologies, and the number of samples and replicates at this time. While FDA generally recommends testing across three batches with seven replicates per batch as advised in the ENDS PMTA Guidance, varying numbers of batches and replicates may be required to substantiate the results of testing. FDA recommends that the validation report include sufficient information to demonstrate method efficiency, specificity, sensitivity, accuracy, and precision needed for the intended purpose. In addition, FDA recommends that a PMTA contain an explanation of why the information used for testing is sufficient to support the reliability of the results, representative of their products, and does not cause public health concerns.

12. Manufacturing

Section 910(b)(1)(C) of the FD&C Act requires a PMTA to contain full descriptions of the methods used in, and the facilities and controls used for, the manufacture, processing, and,

when relevant, packing and installation of, the tobacco product. Section 1114.7(j) provides FDA's interpretation of this requirement, together with its authority under section 910(b)(1)(G) of the FD&C Act, stating that these descriptions must include information regarding all manufacturing facilities, include descriptions of design controls, and be sufficiently detailed to demonstrate that the product meets manufacturing specifications and can be manufactured in a manner consistent with the information submitted in the PMTA.

Additionally, because FDA must, under section 910(c)(2)(B) of the FD&C Act, deny a PMTA that does not demonstrate compliance with regulations issued under section 906(e) of the FD&C Act, the descriptions contained in the manufacturing section must demonstrate the means by which the processes comply with any applicable tobacco product manufacturing practices regulation issued under section 906(e). FDA has not yet issued a regulation under section 906(e) of the FD&C Act, so demonstrating compliance with such regulations is not currently required; however, FDA intends to issue regulations under section 906(e), and once such regulations are effective, applicants must demonstrate that their methods, facilities, and controls comply with that rule to receive a marketing granted order under section 910(c)(1)(i)(A) of the FD&C Act.[30] Until a final rule issued under section 906(e) of the FD&C Act is effective, FDA will evaluate the manufacturing process information and consider whether the product can be manufactured in a manner consistent with the information submitted within the application as part of its determination of whether the marketing of the new tobacco product would be APPH. As part of

[30] In establishing the effective date of a regulation under section 906 of the FD&C Act, FDA must provide for a "reasonable period of time for … manufacturers to conform to good manufacturing practices," and small tobacco product manufacturers will have at least 4 additional years to comply. See section 906(e)(1)(B) of the FD&C Act. FDA anticipates that manufacturers preparing PMTA applications before any regulation under 906(e) is finalized will have sufficient time to prepare applications that demonstrate that their methods, facilities, and controls comply with such a rule before the applicable effective date. For PMTA applications submitted before any regulation under 906(e) is finalized, FDA generally expects the review of such applications will be concluded prior to the effective date.

this evaluation, FDA may conduct inspections as described in § 1114.27 to verify the information and data submitted in the application.

FDA received one comment regarding this issue, as discussed below.

(Comment 57) One comment stated that the proposed manufacturing information requirements in § 1114.7(j) exceed FDA's statutory authority because they constitute the equivalent of a current good manufacturing practice that must be issued in accordance with the process specified in section 906(e) of the FD&C Act. The comment further stated that FDA would, in effect, be requiring that applicants demonstrate to its satisfaction that a new tobacco product conforms with manufacturing criteria as precondition to placing that product on the market. The comment requested that FDA significantly revise § 1114.7(j) and establish regulations in accordance with section 906(e) of the FD&C Act.

(Response 57) FDA disagrees with the comment's conclusory assertion that requiring the submission of information regarding whether an applicant can manufacture the product described in its application constitutes manufacturing practice requirements. Section 906(e) requires that FDA, in applying manufacturing restrictions to tobacco, follow a prescribed process to require manufacturers to conform to current good manufacturing practices (CGMP) or hazard analysis and critical control point (HACCP) methodology. In issuing section § 1114.7(j), FDA has neither created a requirement to conform to a CGMP or HACCP methodology, nor set forth any manufacturing practice requirements; rather, FDA has created a requirement to submit information about the manufacturing process and has identified the level of detail of such information that must be submitted in the application. Drawing upon its experience with CGMP and HACCP regulations for other regulated products, such as medical devices, FDA has embraced a similar flexible approach that does not prescribe in detail how a manufacturer must

produce a specific tobacco product but rather provides a framework to provide detailed information regarding the manufacturing of a specific product.[31] As described in the following paragraphs, the process by which a tobacco product is manufactured is important to FDA's determination of whether a new tobacco product is APPH because it demonstrates the likelihood that the tobacco product that will ultimately be used by consumers meets the specifications set forth in the PMTA.

The information required under § 1114.7(j) is based on FDA's interpretation of the manufacturing information required by section 910(b)(1)(C) of the FD&C Act as supplemented by FDA's section 910(b)(1)(G) authority. The statutory requirement to submit manufacturing information under section 910(b)(1)(C) of the FD&C Act exists independently of the requirements in section 906(e) of the FD&C Act and FDA is in no way required to create a rule under section 906(e) before requiring the submission of manufacturing information and reviewing it as part of a PMTA. Only once FDA issues a regulation under section 906(e) of the FD&C Act would an applicant have to demonstrate it complies with any manufacturing practice requirements established by FDA.

The process by which a tobacco product is manufactured is important to FDA's determination of whether a new tobacco product is APPH because it demonstrates the likelihood that a tobacco product will be manufactured in accordance with the specifications set forth in the PMTA. A tobacco product that fails to conform to the PMTA's specifications, referred to as a "nonconforming tobacco product," could result in a defective product and increase the product's risk compared to what would normally be expected from use of the product as characterized in the PMTA. Additionally, a nonconforming tobacco product constitutes a different tobacco

[31] See e.g., Medical Devices; Current Good Manufacturing Practice (CGMP); Final Rule, 61 FR 52601 (October 7, 1996).

product than the one authorized in the marketing granted order, which would render a nonconforming tobacco product adulterated under section 902(6)(B) of the FD&C Act. A nonconforming tobacco product can be the result of a number of issues, including design defects, failures of or problems with purchasing controls, inadequate process controls, improper facilities or equipment, inadequate training, inadequate manufacturing methods and procedures, or improper handling of the tobacco product.

Nonconforming tobacco products have been highlighted in the news. For example, in 2017, a manufacturer of smokeless tobacco products issued a voluntary recall of certain products after receiving complaints of foreign metal material, including sharp metal objects, in its smokeless tobacco products. After the recall, the manufacturer investigated whether the contamination was a result of the manufacturing practice or a deliberate act by an individual to contaminate the product. FDA is also aware of other instances where smokeless tobacco products contained rocks or metal shavings as well as other nontobacco related materials (NTRMs) (e.g., glass, nails, pins, wood, dirt, sand, fabric, cloth, and plastics) in finished tobacco products. These NTRMs can cause cuts or lacerations to the lips and gums or result in broken teeth.

FDA also has observed during inspections that tobacco product manufacturers have received complaints regarding nonconforming tobacco products that contain contaminants and hazards such as biological materials (e.g., mold, mildew, hair, fingernails) and chemical hazards (e.g., ammonia, cleaning agents, and kerosene). Caustic cleaning chemicals may cause the consumer to experience adverse health effects not normally associated with tobacco use, such as vomiting, nausea, allergic reactions, dizziness, numbness, or headaches.

Nonconforming tobacco products may also contain higher levels of a constituent than the consumer is expecting and that the product is supposed to have as characterized by the PMTA, which may result in increased risks to health. For example, FDA is aware of the variability of nicotine among certain ENDS products and that the labeling may not accurately reflect the actual levels of nicotine in those products. In one study, researchers found that actual nicotine amounts differed from labeled amounts by more than 20 percent in 9 out of 20 original e-cigarette cartridges tested, and in 3 out of 15 refill cartridges tested (Ref. 124). FDA has observed on inspections that some e-liquid manufacturers do not have established procedures to conduct activities or maintain records of their manufacturing processes, including but not limited to calibration of equipment, documenting the identity or purity of their ingredients, and testing final product to confirm that it meets established specifications such as the concentration of nicotine. A finished ENDS product that contains a nicotine concentration higher than the established specification can be more addictive (Refs. 125 and 126). Similarly, a cigarette that does not conform to its pH specification can deliver nicotine in a different speed and amount to the user which can impact the tobacco product's toxicity and addictiveness (Ref. 59). Exposure to nonconforming products in this circumstance can result in user exposure to increased levels of nicotine, which can lead to increased addictiveness.

Nonconforming products may also contain defects that can cause the tobacco product to be more harmful. For example, an ENDS product may have a defect that contributes to an increased risk of fire and/or explosion. The ENDS product, during use or foreseeable misuse, can expose consumers to increased harm if the device catches fire or explodes resulting in serious burns that would not be expected from use of the product (e.g., Ref. 127).

Given the dangers associated with nonconforming (including contaminated) tobacco products, FDA will evaluate an applicant's manufacturing process information to help determine whether the marketing of a new tobacco product would be APPH, specifically considering whether the manufacturer explains controls it would establish and maintain to prevent the manufacture and distribution of nonconforming products that may have an adverse effect on public health.

The manufacturing section of a PMTA must contain the following information in the manufacturing section to meet the requirements of § 1114.7(j) and to help FDA determine if it conforms to the requirements of section 906(e) of the FD&C Act, when regulations are in effect:

- a listing of all manufacturing, packaging, storage, and control facilities for the product, including the name, address, and FEI number for each facility, if applicable, and a contact name and telephone number for a representative from each facility;
- a narrative description, accompanied by a list and summary of all standard operating procedures (SOPs) and examples of relevant forms and records for the following categories of information for all manufacturing, design controls, packing, and storage for the tobacco product:
    - manufacturing and production process activities at each establishment, including a description of each establishment, all production steps, process controls, process specifications with relevant acceptance criteria, and monitoring and acceptance activities;
    - managerial oversight and employee training related to the manufacture, processing, packing, and installation of the tobacco product, as applicable;

- monitoring procedures and manufacturing controls for product design, product characteristics, and changes in products, specifications, methods, processes, or procedures, including a hazard analysis that details the correlation of the product design attributes with public health risk, as well as any mitigation strategies implemented;
- activities related to identifying and monitoring suppliers and the products supplied (including, for example, purchase controls and product acceptance activities);
- handling of complaints, nonconforming products and processes, and corrective and preventative actions;
- testing procedures carried out before the product is released to market, including:
    - a list and summary of any standards used for all testing methods;
    - validation or verification activities for all test methods used to ensure that the tobacco product meets specifications;
    - documentation of accreditation information for all testing laboratories;
    - complete description of smoking or aerosol-generating regimes used for analytical testing, if any;
    - tobacco product specifications (including any physical, chemical, and biological specifications) and acceptance criteria for those specifications; and
    - reports of release testing performed on finished products to demonstrate conformity with established specifications, including test protocols, line data, and a summary of the results for each applicable testing.

13. Health Risk Investigations

Under section 910(b)(1)(A) of the FD&C Act, a PMTA must contain full reports of all information, published or known to, or which should be reasonably known to, the applicant concerning investigations which have been made to show the health risks of the tobacco product and whether the tobacco products present less risk than other tobacco products. Section 1114.7(k) sets forth FDA's interpretation of this requirement, together with its authority in section 910(b)(1)(G), in three parts: (1) the types of investigations that are considered investigations into the health risks of the product and whether the tobacco product presents less risk than other products; (2) the documentation an application must contain to demonstrate that the application contains all published investigations; and (3) the information that constitutes a full report of an investigation.

a. Types of investigations and analyses.

i. Interpretation of statutory language. FDA interprets the information required under section 910(b)(1)(A) of the FD&C Act, together with its authority under section 910(b)(1)(G) of the FD&C Act, to include the health risk investigations specified in § 1114.7(k)(1). Under the rule, applicants must submit full reports (as described in § 1114.7(k)(3)) of all information, both favorable and unfavorable, published or known to, or which should reasonably be known to, the applicant regarding the types of investigations described in § 1114.7(k)(1). Applicants are required to submit full reports of these investigations, regardless of whether they support or are adverse to the application, or are conducted within or outside the United States.

Section 1114.7(k)(1) requires an application to contain health risk investigations that are published, known to, or should reasonably be known to an applicant. This requirement ensures that FDA understands the full scope of the health risk investigations for a new tobacco product.

Section 1114.7(k) interprets section 910(b)(1)(A) of the FD&C Act broadly to ensure FDA has a complete understanding of the existing information about a new tobacco product; it does not set requirements for specific studies that must be contained in every single PMTA. The description of the issuance of marketing denial orders (§ 1114.33), discussed in section VIII.E, describes circumstances where FDA intends to issue a marketing denial order. The description of the issuance of marketing order (§ 1114.31) in section VIII.D contains information regarding FDA's determination of whether there is a showing that the marketing of a new tobacco product would be APPH.

FDA received many comments regarding this provision, as discussed below.

(Comment 58) Multiple comments expressed concerns about what they consider to be the breadth of the information required by proposed § 1114.7(k)(1). One comment stated that FDA should define the scope of health risk investigations that must be submitted in every PMTA so that applicants know exactly what to present in a PMTA and to reduce potential burdens on both applicants and FDA. Another comment interpreted the proposed rule as requiring information regarding investigations for each of the topics described in § 1114.7(k)(1) and requested that FDA provide information about the expected design of these studies as well as details regarding the ranges of acceptable approaches to provide consistency and reliability to the PMTA review process.

(Response 58) FDA has made edits to the codified to further clarify that FDA is not requiring an applicant to conduct an investigation into each individual topic in § 1114.7(k)(1). As described throughout this document, a PMTA must contain at least some amount of substantive information regarding each of the topic areas in § 1114.27(b)(1)(ii) to be filed for substantive review. Additionally, a PMTA must contain full reports of all investigations that are

published or known to, or which should reasonably be known to an applicant, concerning the topics in § 1114.7(k)(1) to be filed for substantive review. FDA generally expects that applicants will be able to meet the substantive information requirement in § 1114.27(b)(1)(ii) by submitting investigations that are published or known to, or which should reasonably be known to, an applicant under § 1114.7(k)(1); however, in the event an application is lacking required substantive information, an applicant may need to conduct its own investigation to meet the filing requirements.

(Comment 59) Other comments stated that FDA is providing too much flexibility for applicants and should instead require applicants conduct specific types of studies, allowing for exceptions only where an applicant can demonstrate that a specific type of information is not applicable.

(Response 59) We decline to require that an applicant conduct a list of new studies as part of every application under this rule because there may be other ways in which an applicant can provide scientific information to inform FDA's review (e.g., bridging, published literature). Additionally, while a PMTA must contain substantive information regarding certain categories of information set forth in § 1114.27(b)(i)(ii) to be filed by FDA as described in section VIII.B of this document, an applicant has some flexibility in determining how to use existing information to support a PMTA for their product and what types of additional investigations it may need to conduct to provide FDA with information that demonstrates that permitting the marketing of its new tobacco product would be APPH. For example, information about known problems and risks related to mouth ulcers in moist tobacco products would be informative and could be used to extrapolate known health risk information for a related type of product that is the subject of the PMTA submitted to FDA. Applicants may want to review the areas of

scientific investigation listed in § 1114.31 to determine whether there are gaps in the existing scientific information regarding its product that it may need to fill by conducting a new study regarding its tobacco product. As discussed in the description of § 1114.31 in section VIII.D, acceptance and filing of a PMTA does not mean that it has sufficient scientific information necessary to obtain a marketing granted order.

(Comment 60) Another comment stated that FDA's interpretation of section 910(b)(1)(A) of the FD&C Act set forth in § 1114.7(k) is both unclear and is potentially limitless in scope. The comment noted that the requirements in § 1114.7(k)(1) go far beyond the information that is required to be submitted for other products regulated by FDA, such as the requirements for new drug applications. The comment recommended that rather than requiring information concerning the product under the range of conditions under which the product might be used, FDA should revise the rule to focus on normal, customary, and ordinary conditions of use and permit the use of customary scientific methods, such as bracketing and dose response curves, to provide such information to FDA.

(Response 60) FDA declines to revise § 1114.7(k) in response to the comment and disagrees with the claim that it is potentially limitless in scope. Unlike the premarket approval standard for drugs or devices, which requires the submission of information to show whether a drug or device is safe and effective, section 910(b)(1)(A) of the FD&C Act requires applications to include information regarding the health risk of the tobacco product and whether the product presents less risk than other tobacco products. As discussed in section VIII.B.13.a, FDA interprets the information required under section 910(b)(1)(A) of the FD&C Act, together with its authority under section 910(b)(1)(G) of the FD&C Act, to include the health risk investigations specified in § 1114.7(k)(1). This requirement ensures that FDA understands the

full scope of the health risk investigations for a new tobacco product as well as provides FDA with crucial information when determining whether permitting the marketing of the new tobacco product is APPH.

FDA also declines to limit the required submission of information to just what the applicant considers to be normal, customary, and ordinary conditions of use because understanding the full range of conditions under which a product may be used, including the potential for misuse, is important to determining the health risks posed by a new tobacco product. For example, in ENDS products, the heating element configurations and the number of heating elements have been known to be modified. Another misuse that has occurred includes modifying the wicking materials and the amount of wicking materials in the ENDS product. Information such as whether an applicant's product design reduces the possibility that the product will be misused or used outside of ordinary conditions of use are an important part of demonstrating that the new tobacco product would be APPH.

(Comment 61) Another comment requested clarification regarding what constitutes information that is "known to or which should reasonably be known to an applicant," suggesting that documentation of a search of its own files and a survey of its scientific staff should be sufficient. Multiple comments also requested that FDA amend § 1114.7(k)(2) to require that an applicant impose a reasonable time limit on searches of its own files and available literature, such as a limitation to what is currently available or what has recently been published (e.g., within a specified time period).

(Response 61) FDA declines to adopt an interpretation of documents that should reasonably be known to an applicant as part of this rulemaking because it is likely to be a fact specific determination. FDA also declines to set a time limit for the literature search requirement

because there is no such limitation in the statutory requirement to submit full reports of published investigations. Under § 1114.7(k)(2), the application must contain a description of the literature search performed, including the databases searched and the date searched, search terms, reasons for inclusion or exclusion of documents, and the strategy for study quality assessment. If, for example, an applicant limits the literature search to a certain time period, the applicant must include the reason for such limitation in their description of the literature search.

ii. General recommendations related to health investigations. The rule does not require an applicant to conduct any of its own studies for the purposes of the application acceptance and filing requirements in § 1114.27, except as necessary to meet the filing requirements of § 1114.27(b)(2)(ii). Should an applicant choose to do so, FDA is providing recommendations for consideration throughout this section of the preamble. In addition to recommendations for specific types of studies that follow, FDA is making recommendations for three general topics related to health risk investigations that may help an applicant prepare a PMTA in some instances: (1) bridging data from an investigation conducted using a different product to the product that is the subject of the application; (2) choosing appropriate comparison products; and (3) using foreign data.

(Comment 62) One comment stated that because FDA is acknowledging the acceptability of "bridging," "comparison products," and "foreign data," it should define these terms in the final rule, stating that it is not sufficient to just mention these terms in passing.

(Response 62) FDA declines to define the terms in the final rule. We believe the discussion of these topics and the associated recommendations that follow provide sufficient information to be useful to applicants in preparing PMTAs.

- *Bridging*

FDA recognizes that in preparing the health risk investigations section of a PMTA, an applicant may choose to use data from a study conducted using a different tobacco product in an attempt to demonstrate the health risks of the product that is the subject of the application. The submission of studies using different products is optional. Ideally, a PMTA will contain studies conducted with respect to the new tobacco product itself, but the bridging of data from a different product to the new tobacco product that is the subject of the application may be feasible for a subset of products or for certain types of studies. If an applicant lacks data on the product from one or more of the types of studies listed in this section, the applicant could bridge data regarding another product, or an earlier version of the product where appropriate. For example, "X-flavor" e-liquids with nicotine concentrations ranging from 1 milligram per milliliter (mg/mL) to 24 mg/mL may be able to show the health risks of each of the e-liquids without having to conduct a unique study for each nicotine concentration of the "X-flavor" product if data from a subset of nicotine concentrations (e.g., low, middle, high) of "X-flavor" products may be bridged to other nicotine concentrations of "X-flavor" products. Other examples where data from studies on a smaller number of products could potentially be bridged to a larger number of products include smokeless tobacco products available in various pouch sizes or e-liquids available in various container volumes.

FDA received multiple comments regarding bridging information in a PMTA, as discussed below.

(Comment 63) Multiple comments expressed concerns related to the use of bridging in a PMTA. One comment requested that FDA prohibit the use of bridging information from an investigation conducted using a different tobacco product to the new tobacco product that is the subject of the PMTA. The comment stated that specifically with regard to ENDS, even minor

variations in e-liquids and battery outputs affect the production of toxicants. Another comment stated that the health effects of a given product can differ dramatically because of individual differences among consumers. Both comments suggested instead that FDA require applicants to conduct product-specific research. Another comment stated that FDA should issue a marketing granted order for a PMTA based on bridged data only where FDA concludes that there is compelling evidence that the differences between the product studied and the new tobacco product that is the subject of the application are immaterial to FDA's review of the application.

(Response 63) FDA declines to prohibit the use of bridging in a PMTA because it can be used to provide information that is relevant to FDA's review of a PMTA. Where an applicant chooses to bridge to data from a general study or a study conducted using a different tobacco product, it would need to provide a scientific rationale to justify why the study findings apply to its new tobacco product and any study limitations that may be relevant. Failure to provide a sufficient justification that such data can be used to evaluate the new tobacco product would result in FDA being unable to rely upon it in evaluating the PMTA. There may be circumstances when an applicant would need to submit additional substantive information, including bridging studies, as appropriate, to justify that the results of a general study or a study using a different tobacco product is relevant to evaluation of its new tobacco product. Where an applicant seeks to use information from a study conducted using a different tobacco product in the same product category, it may need to provide comparative product information or potentially a bridging study to show the results apply to its specific new tobacco product. For instance, if an applicant wants to use the results of an abuse liability study that was conducted on a different product, an applicant should justify how key similarities between the products (e.g., product design, nicotine formulation and content) demonstrate the results of the study apply to its tobacco product. As

another example, national surveys, such as the NYTS, provide information about trends in tobacco product use by youth and typically do so for product categories as a whole, rather than specific products. If an applicant intends to use such survey data to help show the likelihood of youth initiation with its product, it would need to explain why results about a product category in general apply to its specific product.

Another example of when a justification or a bridging study may be needed is when the location or region of a study differs from the intended locations or regions where the product will be used, which is further described in the foreign data section.

- *Comparison Products*

As part of FDA's consideration under 910(c)(4) of the FD&C Act of the risks and benefits of permitting the marketing of the new tobacco product to the population as a whole, including users and nonusers of tobacco products, FDA reviews the health risks associated with changes in tobacco product use behavior (e.g., initiation, switching, polyuse, cessation) that may occur with the marketing of the new tobacco product. Applicants must compare the health risks of its product to both products within the same category and subcategory, as well as products in different categories as appropriate. Additionally, as likely users of a new tobacco product will vary dependent on the type of product, and product use patterns vary across different populations, the appropriate comparison product(s) may vary. When identifying the likely users of the product and appropriate comparator products, FDA recommends that applicants specifically consider product use patterns in youth, young adults, and other relevant vulnerable populations. It is helpful for FDA to understand the applicant's rationale and justification for comparators chosen whether within the same category or different categories of tobacco products. This comparative health risk data is an important part of the evaluation of the health

effects of product switching. As set forth in § 1114.27(b)(1)(ii), a PMTA must contain substantive information regarding comparative health risks to be filed for review.

Information about tobacco products in the same category or subcategory is important to FDA's evaluation of a tobacco product's potential effect on public health because current users may switch to other products within the same category. When determining an appropriate comparison product within the same category or subcategory of product, FDA recommends applicants consider products consumers are most likely to consider interchangeable with the new tobacco product and other similar products. For example, for a PMTA for an e-liquid, FDA recommends the product be compared to other e-liquids used in a similar manner. This comparison is not meant to be a 1 to 1 comparison as in a SE report under section 905(j); rather, it is meant to demonstrate how the new tobacco product may be evaluated in relation to similar products.

Information about tobacco products in different categories is important to FDA's evaluations because it can help demonstrate the changes in health risks current tobacco users could face if they switched to the new tobacco product or use it in conjunction with their current tobacco product. For tobacco products that are not in the same tobacco product category, but that may be appropriate for examining health risk, FDA recommends determining the likely users of the new tobacco product to justify appropriate comparison products. For example, if an applicant submitting a PMTA for an ENDS believes that current users of cigarettes and ENDS will use its product, it would be appropriate to compare the health risks of the ENDS to both cigarettes and other similar ENDS products. Polytobacco use risks should also be considered.

FDA received many comments regarding comparison products, as discussed below.

(Comments 64) Multiple comments discussed comparison products. One comment stated that the rule should specifically require PMTAs to compare the health risks of new tobacco products to the health risks of all other tobacco products on the market. Another comment stated that § 1114.7(k)(1)(i) is unclear regarding the tobacco products to which an applicant must compare the new tobacco product that is the subject of an application and stated that requiring a comparison to just cigarettes could disincentivize the development of new, lower risk e-cigarettes., not just to combustible cigarettes.

(Responses 64) As described in the preceding paragraphs, comparative health risk information is an important part of FDA's review of a PMTA because it can demonstrate the potential risks and benefits that current tobacco users could face if they switched to the new tobacco product or used it in conjunction with their current tobacco product. As required by § 1114.27(b)(1)(ii)(B), applicants must compare the health risks of its product to both products within the same category and subcategory, as well as products in at least one different category that are used by the consumers an applicant expects will use its new tobacco product. FDA declines to require comparisons to all other products in every instance because not every application will necessarily require comparisons to all other categories and the determination of which comparison products are necessary to consider in determining the risks and benefits to the health of the population as a whole is more appropriately considered during substantive review. We also disagree with the suggestion that the comparative health risk information requirements in the rule would disincentivize development of lower risk products because FDA requires each PMTA to compare the health risk of its product to other tobacco products in the same product category. Because FDA's APPH determination considers changes in health risks to users of other products in the same category that switch to the new tobacco product, applicants have an

incentive to ensure its product does not pose greater health risks than other products in the same category.

(Comment 65) One comment stated that section 910 of the FD&C Act does not permit FDA to require a PMTA to contain a comparison to other products in the same product category and, as a result, FDA should remove the requirement to do so in § 1114.27(b)(2)(ii)(B). The comment stated that interpreting the phrase "other tobacco products" in section 910(b)(1)(A) to include products in the same category would defeat the congressional intent of the APPH standard, which the comment, citing a statement from a 1998 Senate committee report, argues is to ensure FDA issues PMTA marketing orders for only those products that do not introduce more risk than conventional tobacco products.

(Response 65) FDA disagrees with this comment. The determination of whether the marketing of a new product would be APPH under section 910(c) of the FD&C Act is required to be based on the risks and benefits to the health of the population as a whole, and not limited to a determination of on whether a new tobacco product presents less risk than conventional tobacco products. As described in this section, information about tobacco products in the same category or subcategory is important to FDA's evaluation of a tobacco product's potential effect on public health because current users may switch to other products within the same category. Not only does this constitute information regarding "other tobacco product" that falls under section 910(b)(1)(A), it is relevant to the subject matter under 910(b)(1)(G) of the FD&C Act because it informs FDA's consideration of the risks and benefits of the product to the health of the population as a whole.

- *Foreign Data*

Foreign clinical studies should be performed by clinical investigators so that the rights, safety, and welfare of human subjects are protected in accordance with ethical principles acceptable to the international community, such as those reflected in the International Council for Harmonisation (ICH) Good Clinical Practice standards.

An application may be required to contain full reports of foreign investigations even if they do not meet these criteria because of the requirements of § 1114.7(k) that an application contain all published studies regarding the health risks of a new tobacco product and other topics. This could include, for example, a published health risk investigation regarding the product conducted outside the United States by someone other than the applicant. Where data do not meet the recommendations described in the preceding paragraph, an application should contain a description of the ways in which the foreign data fails to meet those criteria and, if applicable, describe whether FDA should still consider the data to be valid.

FDA received one comment regarding foreign data, as discussed below.

(Comment 66) One comment stated that FDA should be required to provide its own rationale as to why any foreign data in an application are relevant to the U.S. population and why FDA concluded that specific data from U.S. studies are not required. The comment stated that FDA should not assume that consumers in the U.S. market will respond the same way as consumers in a different country.

(Response 66) FDA declines to make the requested revision. An application may contain health risk investigations conducted outside of the United States. If the study data concern a demographic that is different from the United States, the burden is on the applicant to provide a scientific rationale for why the results of the study can be generalized to other demographic

groups that are representative of the U.S. population as whole.[32] This could include a discussion of the factors that would be expected to influence study findings and whether they vary significantly across the U.S. population. The applicant should also clearly describe any reasons why study findings may not be generalized to the broader U.S. population.

iii. Health risks of the product. Section 1114.7(k)(1)(i) requires a PMTA to contain full reports of all investigations, published or known to, or which should reasonably be known to, the applicant regarding the potential health effects of their product. This includes full reports of investigations on the constituents, including HPHCs, in the specific product or formed during use of the product, and at the quantitative levels that would be delivered to both users and nonusers under the range of conditions under which the specific product may be used. FDA includes these investigations under its interpretation of the requirements of section 910(b)(1)(A) of the FD&C Act, because the health effects of constituents at the levels delivered to both users and nonusers help demonstrate the overall health risks of the product. Types of investigations into the health effects of constituents that applicants must submit as part of a PMTA if published or known to, or which should reasonably be known to an applicant include human exposure studies, in silico computational toxicology techniques, risk assessments, in vitro toxicology studies, published reports of in vivo toxicology studies, and, if necessary, new in vivo toxicology studies.

As set forth in § 1114.27(b)(1)(ii) and described in section VIII.B, an application must contain substantive information regarding the health risks of the new tobacco product as described in either § 1114.7(k)(1)(i)(A), (B), or (C) as well as substantive information regarding the health risks of the new tobacco product compared to the health risks generally presented by

[32] For a discussion of both intrinsic and extrinsic factors in foreign data that might need to be addressed, please see the International Council for Harmonisation (ICH) E5 guidance: "Ethnic Factors in the Acceptability of Foreign Clinical Data."

products in the same category as described in § 1114.7(1)(i)(D). While the rule does not require an applicant to conduct any particular type of studies regarding the health risks of the constituents for the purposes of application acceptance and filing, the applicant would be required to do so where it is not aware of existing studies that could be used to support the application or where additional information is necessary to ensure the application contains substantive information regarding the health risks of the new tobacco product. Where an applicant chooses to, or must, conduct its own investigations, FDA is providing the following discussion of nonbinding recommendations for consideration. The adequacy of the studies provided and whether they help demonstrate that a product is APPH will be determined during FDA's review of the application. The study recommendations, provided here and throughout this document, are intended to help an applicant develop a more robust application, which would facilitate FDA making a determination as to whether the product is APPH.

The health effect evaluation of tobacco constituents, including HPHCs, in a PMTA should begin with an assessment of human exposure. For tobacco product users, this assessment should include direct measurements of exposure, estimates of exposure from analytical studies of the tobacco product and its smoke or aerosol, or investigations that combine both approaches. For nonusers of the tobacco product, exposure estimates would include analytical studies. One source of this information can be the HPHC data required by § 1114.7(i)(1)(v). FDA recommends that these investigations specifically assess the levels of each HPHC to which users and nonusers could be exposed and that direct measurements or estimates of exposure use the same route of administration (e.g., inhalation, ingestion, dermal contact) as the tobacco product they evaluate. Other aspects of the exposure that FDA recommends applicants define in the

tobacco constituent exposure assessment include exposure duration, inhalation rate, consumption rate, body mass, and other similar relevant measures.

Study reports regarding the health effects of product constituents at both the exposure ranges estimated for user and nonuser exposure and higher exposures are important in the toxicological evaluation of a PMTA because it allows for a more thorough dose-response assessment. Higher exposures may provide indication of toxicity potential from lower exposure levels over longer exposure times. FDA recommends including dose-response assessments across a range of exposures. For noncarcinogenic constituents, FDA recommends including study reports that define the threshold of toxicity, especially those that identify the no-observable-adverse effect level and lowest-observable-adverse-effects-level. For carcinogenic constituents, if only high-exposure studies are available, an assumption of linearity should be made for low-dose extrapolation. For both carcinogenic and noncarcinogenic constituents, user and nonuser exposures should be compared to available dose response information.

FDA received several comments regarding this issue, as discussed below.

(Comment 67) One comment stated that because FDA notes that clinical studies would typically be a necessary part of a PMTA, FDA should not allow applicants to conduct animal studies, which the comment states are unethical.

(Response 67) Restrictions on the types of investigations that an applicant is allowed to conduct are outside the scope of this rule. FDA supports reducing the reliance on animal testing where adequate and scientifically valid nonanimal alternatives can be substituted. FDA encourages sponsors to meet with CTP early in the development process to discuss what, if any, animal testing is appropriate and the suitability and acceptability of nonanimal tests for their specific new tobacco product. When animal-based nonclinical laboratory studies are conducted,

investigators should use appropriate animal models and adhere to the best practices of refinement, reduction, and replacement of animals in research and to applicable laws, regulations, and policies governing animal testing, such as the Animal Welfare Act (7 U.S.C. 2131 *et seq*.) and the Public Health Service Policy of Humane Care and Use of Laboratory Animals (available at https://olaw.nih.gov/policies-laws/phs-policy.htm).

Under § 1114.7(k)(1)(i)(B), a PMTA must contain all investigations, published or known to, or which should reasonably be known to, the applicant regarding the toxicological profile of the new tobacco product related to the route of administration, including, but not limited to, the genotoxicity, carcinogenicity, respiratory toxicity, cardiac toxicity, reproductive and developmental toxicity, and chronic (repeat dose) toxicity of the new tobacco product relative to other tobacco products.

(Comment 68) One comment stated that FDA should revise all of the PMTA requirements to give more prominence to heart and lung disease effects and in particular, § 1114.7(k)(1)(i)(B) should be amended to require applicants to prioritize submission of information regarding the cardiovascular and respiratory effects of the new tobacco product, and additionally include effects on blood and intergenerational health effects caused by epigenetic changes.

(Response 68) FDA agrees that heart and lung disease effects are important considerations, which is why they are part of the information required by § 1114.7(k)(1)(i)(B). However, the rule does not set forth requirements in order of importance and moving a particular item would not affect the importance of any requirements.

The toxicological profile also includes information regarding the ingredients, additives, and HPHCs, relative to the route of administration and the range of the potential levels of

exposure resulting from the use of or other exposure to the product. While FDA is aware of the risk of harm posed by HPHCs generally, understanding the toxicological effects of HPHCs in the product is important to FDA's review because the levels and combinations of HPHCs to which a consumer may be exposed can determine whether, and the severity with which, a user may experience harm. For example, some constituents may only cause harm above certain levels of exposure, while others may have no safe level of exposure. Additionally, since there are potential complex interactions between HPHCs and each tobacco product can produce a different mixture of these HPHCs, FDA needs to determine the toxicity of the specific mixture of HPHCs in a tobacco product in order to compare that tobacco product to other similar products on the market and to use this comparison in its determination of whether permitting the marketing of the product would be APPH. The toxicological profile investigations covered by the rule also includes studies that discuss the toxicological effects of any leachables and extractables from the container closure system and the ingredient mixture, such as additive or synergistic effects.

FDA includes the toxicological profile of the tobacco product as part of its interpretation of the health risk investigations required under section 910(b)(1)(A) of the FD&C Act, where published, known to, or which should reasonably be known to an applicant, because it identifies the hazardous or harmful effects of product constituents and allows for product comparisons that estimate the impact of the assessed tobacco product on the health of both users and nonusers of the tobacco product.

The types of toxicological information or data regarding a tobacco product that a PMTA must contain if published or known to, or should reasonably be known to, an applicant generally include the characterization of toxic effects of HPHCs to which users and nonusers may be exposed. This evaluation can include identification of the organs affected by constituents; the

cancer and noncancer effects of the constituents; dose response relationships between exposure to constituents and health effects; and, when appropriate, threshold levels of exposure above which noncancer effects occur. The toxicological assessment of the product that is the subject of a PMTA should focus on the HPHCs reported in § 1114.7(i)(1)(v), the constituent reporting section. The types of studies or information required by the rule, if published or known to, or should reasonably be known to an applicant, include toxicological assessments conducted in terms of both the whole tobacco product and the individual HPHCs that the product contains or delivers to users and nonusers.

Because different tobacco products contain different ingredients and additives, they may also have different HPHC yields. A tobacco product that would result in increased exposure to a potent HPHC or set of HPHCs, for example, may present higher health risks to users. However, important aspects such as dose-response and whether the end organ toxicity is carcinogenic or noncarcinogenic in nature could affect whether this higher exposure results in an estimate of increased risk. The information generated from the toxicological assessment of tobacco products is part of the information that the applicant should use in product comparisons to estimate the impact of the assessed tobacco product on the public health.

The types of toxicological information that the applicant must include in a PMTA if published or known to, or should reasonably be known to, the applicant include information about, or investigations into, the potential for a tobacco product or its constituents to cause toxicity. For the specific toxicological profile of a new tobacco product or constituents in or formed during use of the new tobacco product, the applicant should address known tobacco target organs of toxicity, as appropriate for the product and/or route of administration. The

profile should include data and thorough literature reviews of the following health effects known to be caused by tobacco products as applicable such as:

- genotoxicity (the ability of a chemical agent to damage DNA within a cell, causing mutations that may lead to cancer);
- carcinogenicity (the ability of a chemical agent to directly cause cancer in humans or animals after exposure);
- cardiovascular toxicity (the ability of a chemical agent to cause adverse effects on the cardiovascular system (i.e., heart and blood vessels));
- respiratory toxicity (the ability of a chemical agent to cause adverse effects on the respiratory system, which comprises the nasal passages, pharynx, trachea, bronchi, and lungs);
- reproductive toxicity (the ability of a chemical agent to cause adverse effects on the male or female reproductive systems such that normal reproduction is impaired);
- developmental toxicity (the ability of a chemical agent to interfere with the development of the embryo or fetus); and
- other diseases associated with use.

While not required for application acceptance or filing under § 1114.27, FDA recommends that an application contain a discussion of the toxicological potential for the tobacco product to cause additional chronic toxicities, other than those listed above, such as any end-organ toxicity or route of administration effects. These end-organ toxicities include, but are not limited to, the potential toxicity on the liver, kidneys, immune system, digestive system, and neurological system. An example of route of administration effects that FDA recommends be addressed is the toxic potential of a smokeless tobacco product to the oral cavity, including teeth.

FDA also recommends the application address acute toxicity, which concerns the ability of a chemical agent to cause adverse effects after either a single exposure or multiple exposures in a short period of time (usually less than 24 hours). If there are known acute toxicities for product constituents at the levels to which an individual may be exposed (e.g., carbon monoxide poisoning from waterpipe use, the ingestion of nicotine contained in e-liquids) including through accidental or unintended exposures, an applicant should justify how the product could contain such constituents and how permitting its marketing would be APPH. This could include a description of the design features, such as child-resistant packaging for e-liquids, that would prevent exposures to constituents that could result in acute toxicity as part of § 1114.7(i)(1)(vi)(B). See the discussion in section VII.B.9.a.vi. for more information about protective packaging.

FDA recommends that an applicant compare the toxicity of its product to the toxicity of other products in the same product category or subcategory. Additionally, FDA recommends that applicants consider use exposure in conjunction with the hazards posed by a particular product to determine the most appropriate group of comparator products.

While applicants are not required to conduct toxicological analyses under the rule, if an application does not contain substantive information regarding either the health risks of the new tobacco product or a comparison of the health risks compared to other tobacco product categories, FDA intends to refuse to file a PMTA as set forth in § 1114.27(b)(1)(ii) and described in section VIII.B of this document. Information about the product's toxicity and a comparison of its toxicity to other tobacco products could satisfy this substantive information requirement for filing; however, it should be noted that information from nonclinical studies alone, including a product's toxicological profile, is generally not sufficient to support a determination that

permitting the marketing of the product would be APPH. An applicant should also consider the existing valid scientific evidence regarding its new tobacco product to determine whether it would need to conduct and submit a full report of toxicological analyses to demonstrate the potential health risks of the new tobacco product as part of its PMTA. If an application does not contain sufficient information about the health risks of the new tobacco product to allow FDA to make a determination regarding the potential risks and benefits to the population as a whole under section 910(c)(4) of the FD&C Act, FDA will issue a marketing denial order for the new tobacco product.

Under § 1114.7(k)(1)(i)(C), a PMTA must contain all studies concerning the pharmacological profile of the new tobacco product that are published or known to, or which should reasonably be known to, the applicant, including investigations into the pharmacokinetics, pharmacodynamics, metabolism, and elimination profile, of each of the ingredients, additives, and HPHCs for the range of potential levels of exposure resulting from the use of or exposure to the product relative to other tobacco products. The applicant also must specify whether the studies were conducted in vitro, in vivo, ex vivo, or in silico. The pharmacological profile of the product and its constituents are important for FDA to consider when evaluating the relationship between the dose of the product and the body's response. As such, where published or known to, or which should reasonably be known to the applicant, the pharmacological profile of the tobacco product is part of the information required under section 910(b)(1)(A) of the FD&C Act because it provides important information regarding how the product constituents and human body interact with each other, which directly impacts whether and what health impacts the constituents can have on users and nonusers of the product.

The types of pharmacological information that the applicant must include in a PMTA if published or known to, or which should reasonably be known to, the applicant include pharmacokinetics and pharmacodynamics. Pharmacokinetics concern the movement of a constituent into, through, and out of the body. Types of pharmacokinetic information that an application must contain if published or known to, or which should reasonably be known to, the applicant include absorption (the rate and movement of a constituent into the bloodstream after administration), bioavailability (the extent to which the constituent reaches the site of action), distribution (the transfer of a constituent from one location in the body to another), metabolism (the breaking down of a constituent), and excretion (the elimination of a constituent). Pharmacodynamics refers to the effects of the constituent on the body including physiological (e.g., changes in blood pressure and heart rate) and subjective effects (e.g., whether the product is "liked" or produces other changes in affect). Types of pharmacodynamic information that an applicant must submit in a PMTA if published or known to, or which should reasonably be known to, the applicant include physiological and subjective effects data and information regarding drug-receptor interactions, chemical interactions, and dose-response relationships.

FDA received several comments regarding toxicological information, as discussed below.

(Comment 69) One comment stated that the pharmacological profile of many of the ingredients or constituents in a tobacco product might not be helpful to FDA's determination of health risks and that FDA should recommend inclusion of this information rather than require it. The comment noted that some constituents, such as nicotine, have already had their pharmacological profile established in literature and that other constituents are delivered at such low levels that they would not permit evaluation of their pharmacological profile.

(Response 69) FDA declines to revise the rule as a result of this comment. The pharmacological profile of the product and its constituents provide important information about the health risks of the product as well as its risk relative to other products. Specifically, this information is important for FDA to consider when evaluating the relationship between the dose of the product and the body's response. While the pharmacological profile of some ingredients and constituents, such as the nicotine pharmacokinetic (PK) profile, is well characterized for some general classes of tobacco products, slight changes in product features (e.g., cigarette ventilation (Ref. 128), tobacco pH and nicotine absorption site (Ref. 68), ENDS voltage (Refs. 129-133)) affect the nicotine PK profile. In general, the abuse potential of nicotine increases when absorption is rapid because the rewarding properties of the compound increase, and suppression of withdrawal symptoms occurs more quickly. Nicotine's pharmacological profile impacts use behavior that can then affect the overall exposure of the user to HPHCs and other constituents in the product. Changes in use behavior may result from the pharmacokinetic properties of the nicotine and can result in increased or decreased exposure to the constituents within a product (Refs. 4 and 132-134). Because this profile directly impacts use behaviors and abuse liability, it remains a critical piece to understanding a tobacco product's impact on public health.

(Comment 70) One comment stated that in addition to describing the health risks of the tobacco products contained within the new tobacco product, FDA should require applicants to present evidence that the product does not interfere with the pharmaceutical drugs that expected users of the new tobacco product may be taking.

(Response 70) As required under § 1114.7(k), a full report of each health risk investigation that is published or known to, or which should reasonably be known to, an

applicant concerning the potential for interaction between drugs and the new tobacco product must be included as part of a PMTA in order for it to be filed for review. FDA intends to consider the implications of such health risk information, or a lack thereof, during substantive review, as appropriate.

Under § 1114.7(k)(1)(i)(D), a PMTA must contain full reports of all investigations published or known to, or which should reasonably be known to the applicant concerning the health risks of the tobacco product compared to other tobacco products on the market, never using tobacco products, quitting tobacco product use, and using the tobacco product in conjunction with other tobacco products. Under section 910(b)(1)(A) of the FD&C Act, an applicant must submit investigations that have been made to show whether the tobacco product presents less risks than other tobacco products. Under section 910(b)(1)(G) of the FD&C Act, FDA requires applicants to submit investigations that have been made to show whether the tobacco product has the same or different potential health risks (not just less potential health risks) than other tobacco products to capture investigations that could potentially show a range of risks compared to other tobacco products. FDA requires applicants to include comparisons between the health risks of the tobacco product and never using tobacco product under the authority of section 910(b)(1)(A) and (G) of the FD&C Act because this information is relevant to determining the health risks faced by nonusers who initiate tobacco use with the tobacco product.

FDA also requires that an application contain, if published, known to, or which should be reasonably known to the applicant, comparisons between the health risks of the tobacco product and using the tobacco product in conjunction with other tobacco products because existing data indicates that a significant number (approximately 40 percent or more by some estimates) of both

adults and youth who currently use tobacco products use more than one type of tobacco product (Refs. 135 and 136). This information is important in determining the health risks faced by individuals that may use the new tobacco product in conjunction with other tobacco products because research indicates that individuals who use a tobacco product with lower health risks in conjunction with a tobacco product with potentially higher health risks may continue to face the potentially higher health risks of the more dangerous product above a certain threshold of usage (Refs. 137 and 138).

The types of investigations that a PMTA must contain if published or known to, or which should reasonably be known to the applicant, in this section include, for example:

- cross-sectional and longitudinal surveys (such as market analyses or publicly available national surveys such as NYTS);
- epidemiologic studies that are descriptive (which describe the occurrence of a prespecified or unknown outcome), such as case reports and case series; and
- analytic studies (which describe the association between exposure and outcome) such as randomized controlled clinical trials, cohort studies, and case control studies.

Additionally, clinical studies that employ surrogate endpoints (e.g., biomarker studies) may be used to draw conclusions regarding the effects of the product on a clinical benefit endpoint and patient reported outcome data (i.e., report of the status of health that comes directly from the subject without interpretation of the subject's response by a clinician) may be used as supportive evidence for health outcomes or effects.

For determining the health risks that are posed to a typical user of a tobacco product for the purposes of comparison, FDA recommends using an average of light, moderate, and heavy users. FDA also recommends including evidence and a description supporting the range of light,

moderate, and heavy use an applicant includes in its PMTA, including how they relate to the exposures in the submitted toxicology studies. Where an applicant does not have data regarding light, moderate, or heavy product use because the product has not been commercially marketed, including outside the United States, an applicant could, where applicable, bridge to data regarding a similar tobacco product or conduct clinical studies under ad libitum (i.e., unrestricted use) conditions.

As set forth in § 1114.27(b)(1)(ii) and described in section VIII.B, for an application to be filed it must contain substantive information comparing the new tobacco product's health risks to those generally presented by the same product category and at least one different product category that is used by the consumers an applicant expects to use their new tobacco product.

(Comment 71) One comment stated that § 1114.7(k)(1)(i) is unclear regarding the tobacco products to which an applicant must compare the new tobacco product that is the subject of an application. The comment stated requiring a comparison to just cigarettes could disincentivize the development of new, lower risk e-cigarettes.

(Response 71) FDA disagrees with the suggestion that the rule requires a comparison to cigarettes in each application. Section 1114.27(b)(1)(ii) requires a PMTA to contain substantive information regarding the health risks of the new tobacco product compared to the health risks generally presented by both products in the same product category and products in at least one different category that are used by the consumers an applicant expects will use its new tobacco product. While this could require a comparison to cigarettes for at least some applications, it would not be required in all applications. For the comparison to other products in the same category, this could include, for example, comparing an e-liquid to other e-liquids used in a similar manner. We also disagree with the suggestion that the comparative health risk

information requirements in the rule would disincentivize development of lower risk products because FDA also requires each PMTA to compare the health risk of its product to other tobacco products in the same product category. Because FDA's APPH determination considers changes in health risks to users of other products in the same category that switch to the new tobacco product, applicants have an incentive to ensure its product does not pose greater health risks than other products in the same category.

An applicant should consider the appropriate comparative health information a PMTA may need beyond the minimum requirement for substantive information to provide FDA with a full understanding of the potential risk and benefits to current tobacco users. If a PMTA lacks sufficient information to demonstrate the changes in risk to which current users of tobacco products would potentially be exposed if they switched to the new tobacco product or began using it in conjunction with their current product, FDA intends to issue a marketing denial order for the new tobacco product.

For demonstrating the health risks that are posed by the product in comparison to using other tobacco products, a PMTA must contain, under § 1114.27(b)(1)(ii), comparison to both products that are within the same category or subcategory of tobacco product and also to other categories of tobacco products currently on the market, as appropriate. As described in section VII.B.13.a, when determining an appropriate comparison product within the same category or subcategory of product, FDA recommends applicants consider products that consumers are most likely to consider interchangeable with the new tobacco product and other similar products. For example, for a PMTA for an e-liquid, FDA recommends the product be compared to other e-liquids likely to be used in the same manner. When determining appropriate comparator products that are not in the same tobacco product category, FDA recommends, in addition to the

requirements of § 1114.27(b)(1)(ii), comparing the health risks of the product to categories of products that users are likely to switch to. Applicants may compare to comparator products that have a substantial market share (e.g., cigarettes, smokeless tobacco, cigars); however, such comparisons may only be appropriate if users are likely to switch to the comparator products. Because it is expected that current consumers of products that are in the same category may switch products and consumers of different categories of tobacco product may also switch products or use a new product in conjunction with their current product, this comparative health risk data is an important part of the evaluation of whether switching could potentially result in a lower or higher population health risks.

iv. Impacts on tobacco use behavior of tobacco product users. FDA interprets the health risk investigations that must be provided under section 910(b)(1)(A) of the FD&C Act (where published or known to, or which should reasonably be known to the applicant) to include the effect of either the product or its label, labeling, or advertising, to the extent that advertising has been studied, on tobacco use behavior and tobacco use topography because use behavior and topography are directly related to levels of exposure to HPHCs, which, in turn, impacts health risks. For example, changes in tobacco product use behavior and topography that result in more frequent or intense use of the product will result in greater exposure to HPHCs and may result in increased health risks. Aspects of a product that could result in more frequent or intense use compared to currently marketed products can include differences in the appeal and design of the product, including ingredients; flavors; alteration in the amount or delivery of nicotine; physical differences such as changes in the velocity of the inhaled particles, the effort required to inhale, or the density of the smoke, vapor, or aerosol; or other changes which similarly affect user behavior (e.g., ventilation, filter density).

(1). Abuse liability. Section 1114.7(k)(1)(ii)(A) requires a PMTA to contain full reports of investigations into the abuse liability of the new tobacco product that are published or known to, or which should reasonably be known to the applicant. However, as set forth in § 1114.27(b)(1)(ii) and described in section VIII.B of this document, if a PMTA does not contain substantive information regarding the abuse liability of a new tobacco product, FDA may refuse to file the application. This means where there is no published information regarding the abuse liability or information that is otherwise known to the applicant or should reasonably be known to an applicant, including information from investigations using other products that an applicant could bridge to its product, an applicant would need to conduct its own investigation and include a full report of the results in its PMTA for filing.

Abuse liability refers to the potential of a substance to result in addiction and be used repeatedly or even sporadically resulting in undesirable effects. The abuse liability of a new tobacco product is important for FDA to evaluate because it indicates the degree to which users of the tobacco product are likely to use and develop an addiction to the product. Abuse liability may result in craving of the product and compulsive and continued use despite harm or risk of harm. FDA requires the submission of abuse liability information under its interpretation of section 910(b)(1)(A) and (G) of the FD&C Act because it indicates the likelihood of users to become addicted to the product and face the health risks posed by product use over the long term, and provides insight into the use and adoption of the product, which is an important part of FDA's assessment of the health risks of the new tobacco product as part of its determination of the risks and benefits to the population as a whole under section 910(c)(4) of the FD&C Act. If FDA lacks sufficient information regarding the potential abuse liability of the new tobacco product, it intends to issue a marketing denial order for the new tobacco product.

The types of investigations that inform an evaluation of a product's abuse liability can be wide ranging and are likely to overlap with data submitted elsewhere as part of the PMTA, including data regarding product chemistry, pharmacology, and pharmacokinetic characteristics. Where the data are included elsewhere in a PMTA, FDA recommends including content in this section by cross-reference to the full reports of relevant investigations in other sections. Applicants should analyze the results of all investigations included in the application that impact the abuse liability of the product and synthesize the findings in this section.

While applications need to contain some amount of substantive information concerning abuse liability under § 1114.27(b)(2)(ii) to be filed, the abuse liability of a tobacco product is an important part of FDA's finding of whether permitting the marketing of the new tobacco product would be APPH and applicants should consider conducting an abuse liability study if they do not believe there is sufficient existing data regarding their product. The "standard" abuse liability study is a double-blind, placebo-controlled, within-subject study comparing several doses of a new product to a comparator product with a known abuse liability. Generally, the primary outcome measure is peak "liking" (Emax) as reported via a visual analog scale. Applicants that wish to conduct abuse liability studies examining tobacco products may utilize a similar framework with additional assessments, although evaluating multiple doses may not be applicable to some tobacco products. These assessments may include use topography, and pharmacokinetics and pharmacodynamics assessments under both prescribed and ad libitum (i.e., unrestricted) use conditions. Real world, actual use data may also provide outcomes relevant to the products' abuse liability, including misuse. Abuse liability conclusions should be considered as an integral assessment of all outcome measures important to understanding the abuse liability of the new tobacco product both independently and relative to other tobacco products with a

known abuse liability. FDA generally expects abuse liability studies to contain a comparison to one or more tobacco products and applicants seeking to market a new tobacco product for which little abuse liability data has been established should ensure FDA has sufficient information to understand how the abuse liability of such a product compares to other relevant categories of tobacco products.

FDA received comments regarding abuse liability, as discussed below.

(Comment 72) One comment objected to the inclusion of a statement in numerous places throughout the preamble to the proposed rule indicating that an applicant would be required to conduct investigations in certain circumstances. The comment stated that the requirement should appear in the codified, rather than the preamble, and requested additional information regarding how a company that does not have a product on the market could meet such requirements.

(Response 72) FDA disagrees with the characterization that it is creating a requirement for the submission of information in the preamble rather than in the codified. The instances identified by the comment in which FDA references the potential need for applicants to conduct their own investigations for submission in a PMTA are each a part of a discussion regarding the substantive information required by § 1114.27(b)(1)(ii) for application filing. These portions of the preamble identified by the comment, make it clear that where there is no existing substantive information regarding these topics that an applicant could include in its PMTA, including published investigations or investigations it could bridge to its new tobacco product, the applicant would need to conduct its own investigation to generate such substantive information for inclusion in its application or have FDA refuse to file its application for failing to meet the requirement of § 1114.27(b)(1)(ii).

(Comment 73) One comment stated that the rule is overly broad in that it requires the submission of information regarding abuse liability and also contains recommendations concerning abuse liability studies that align with how FDA assesses abuse liability for drugs. The comment stated that because tobacco products are legal, there are no defined parameters regarding abuse or misuse. The comment also noted that there are a number of factors concerning individual users that affect whether they will develop dependence and that a number of social factors drive individual's decisions to start using and continue to regularly use tobacco products and these factors cannot be simulated in a premarket setting. The comment recommended that FDA use the term "dependence potential" and that FDA should limit the scope of required information only to the product that is the subject of the application and a comparator.

(Response 73) As described in the preceding paragraphs, the abuse liability of a new tobacco product is important for FDA to evaluate because it indicates the degree to which users of the tobacco product are likely to use or develop an addiction to the product. Despite tobacco products being marketed legally in the United States, nicotine is an addictive drug and there are diagnostic criteria for tobacco use disorder in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. There are a number of factors that contribute to the abuse liability of a substance and there are methodologies widely accepted to evaluate abuse liability in a research setting. These methodologies can be used to inform FDA about the abuse liability of product described in a PMTA. FDA requires the submission of abuse liability information because it indicates the likelihood of users to become addicted to the product and face the health risks posed by product use over the long term and may provide insight into the use and adoption of the product, which is an important part of FDA's assessment of the health risks of the new product.

Given the importance of this information in FDA's understanding of the abuse liability of the new product both independently and relative to other products with a known abuse liability, FDA declines to use the term "dependence potential" or limit the scope of required information to only the product that is subject of the application and a comparator product. FDA generally expects abuse liability studies to contain a comparison to one or more tobacco products to ensure that FDA has sufficient information to understand how the abuse liability of a product compares to other relevant categories of tobacco products.

(Comment 74) One comment stated that FDA should prioritize evidence about real-world actual use over clinical trials or laboratory studies and proposed revisions that appear to require the submission of actual use data that is relevant to the abuse liability of the new tobacco product.

(Response 74) We agree that information regarding actual use of a product and its abuse liability are important to FDA's review of an application, which is why, under § 1114.27(b)(1)(ii), FDA may refuse to file a PMTA that does not contain substantive information regarding those topics. We decline to require "real-world actual use data" concerning abuse liability as part of FDA's acceptance and filing requirements, because a determination of whether the data in an application adequately demonstrate the abuse liability of a product is more appropriately considered during substantive review on a case-by-case basis.

(2). Use Topography, Frequency, and Trends. Section 1114.7(k)(1)(ii)(B) of the rule requires a PMTA to contain investigations published or known to, or which should reasonably be known to the applicant into how consumers actually use the product, including use topography, the product use frequency, use trends over time, and how such use affects the health risks of the product to individual users. FDA requires this information because the ways in which

consumers actually use the product, instead of relying only on how manufacturers intend the product to be used, help to demonstrate the levels of constituents to which the users will be exposed.

An actual use study can include the use of actual product in either a simulated use setting or in a real use environment. Actual use studies are important to the evaluation of a PMTA because they provide information regarding whether consumers will use the product as intended. In addition, actual use studies help demonstrate whether consumers are likely to misuse the product, including in ways that may change the health risks that the product poses to users and nonusers. For example, ENDS users have applied e-liquid directly onto an exposed heater coil, a process known as dripping, which can lead to greater exposure to volatile aldehyde and a resulting change in the health risks of using the product (Ref. 83). Actual use studies may be conducted using outpatient protocols so that results are as close to actual use as possible. The format of the study should reflect the goals of the study and how the applicant believes the information will inform FDA's decision.

Use topography measures the way in which users consume a product. Use topography is an important measure to consider in assessing a product's health risk and abuse liability because the volume, frequency, and duration of product use determines the amount of, and manner in which, a user is exposed to HPHCs in a product and, consequently, affects the health risks of the product. For combusted or inhaled products, use topography could include measurements of the number of puffs taken, puff duration, puff volume, duration of use, and other relevant measures. For smokeless tobacco, use topography could include measures such as the number of smokeless tobacco tins used per week, the total dips per day, and the dip duration.

FDA received one comment regarding this issue, as described below.

(Comment 75) One comment requested that FDA clarify what information an applicant would be required to submit under § 1114.7(k)(1)(2)(ii)(B) to demonstrate how consumers actually use the product, including use topography, the product use frequency, use trends over time, and how such use affects the health risks of the product to individual users. The comment noted that the rule seemed to require actual use studies and requested that FDA clarify whether this needs to be real-world studies or they could be in a simulated setting.

(Response 75) Under § 1114.27(b)(1)(ii), FDA may refuse to file a PMTA that does not contain substantive information regarding how consumers actually use the product, including use topography, product use frequency, use trends over time, or how such use affects the health risks of the product to individual users. Thus, where there is no published information regarding actual use or information that is otherwise known to the applicant, including information from investigations using other products that an applicant could bridge to its product, an applicant would need to conduct its own investigation and include a full report of the results in its PMTA for filing. However, FDA does not require a particular type of actual use study. For example, applicants may conduct and submit results from an actual use study in a real or simulated setting. The types of studies that may provide this information on current tobacco use behavior can include, but are not limited to, actual use studies and national survey databases that could be used to bridge general data to the specific product. Ideally, the studies would look at the past, present, and likely future behaviors of tobacco product users. As described in the following paragraphs, FDA requires this information because the ways in which consumers actually use the product, instead of relying only on how manufacturers intend the product to be used, helps to demonstrate the levels of constituents to which the users will be exposed.

(3). Polyuse. Section 1114.7(k)(1)(ii)(C) of the rule also requires the PMTA to contain full reports of all investigations, published or known to, or which should reasonably be known to the applicant, regarding the likelihood that users will use the product in conjunction with other tobacco products (i.e., polyuse).

FDA received on comment regarding polyuse, as discussed below.

(Comment 76) One comment stated that to assess the health impacts of dual use, proposed rule § 1114.7(k)(1)(i)(D) should be strengthened to require submission of meaningful estimates of true levels of dual and polyuse based on research for the proposed product or comparable products.

(Response 76) FDA agrees that consideration of dual and polyuse are important to determining whether permitting the marketing of a new tobacco product would be APPH, which is why FDA is finalizing § 1114.7(k)(1)(ii)(C). Data indicate that a substantial number of tobacco product users are polyusers of tobacco products (Refs. 135 and 136). FDA requires information regarding the likelihood of dual or polyuse because such use may increase or decrease known health risks and may pose risks that are not currently known (Refs. 137 and 138). The likelihood of tobacco product users using the new tobacco product in conjunction with another tobacco product, when considered with the health effects resulting from such polyuse, will help FDA determine the health risks that polyusers may encounter. However, because the main purpose of the rule is to set requirements for application acceptance and filing that ensure that a PMTA contains sufficient information for FDA to conduct substantive review of the application, FDA declines to make the requested revisions. Questions about whether data regarding the potential for polyuse of other tobacco products along with the new tobacco product is meaningful, valid, or applicable are more appropriate to consider during substantive review,

rather than at filing review, because it requires an indepth, scientific evaluation to make such a determination.

(4). Start or continue use of product. Section 1114.7(k)(1)(ii)(D) through (F) of the rule also requires the PMTA to contain full reports of investigations published or known to, or which should reasonably be known to the applicant, regarding the likelihood that current tobacco product users:

- will start using the product;
- will starting using the product exclusively and then switch to other tobacco products that may present increased risks to individual health; and
- will start or continue to use the product when they otherwise would have quit using tobacco products.

While § 1114.7(k)(1)(ii)(a) through (f) requires a PMTA to contain only information published or known to, or which should reasonably be known to the applicant, as set forth in § 1114.27(b)(1)(ii), if a PMTA does not contain a substantive information regarding likelihood of changes to tobacco use behavior of current tobacco users, FDA intends to refuse to file the application. This means where there is no published information regarding the likelihood of changes in tobacco use behavior by current users of tobacco products or information that is otherwise known to the applicant, including information from investigations using other products that an applicant could bridge to its product, an applicant would need to conduct its own investigations and include a full report of the results in its PMTA to meet this requirement for application filing. Although the rule would not require an applicant address each potential change in tobacco product use behavior for the purposes of filing, FDA must be able to determine the potential risks and benefit to the population as a whole, including each of the

potential risks and benefits associated with changes in tobacco product use behavior by current tobacco product users in order to issue a marketing granted order. If a PMTA lacks sufficient information needed for FDA to make these determinations, FDA intends to issue a marketing denial order for the new tobacco product.

FDA requires information regarding the tobacco use behavior of current tobacco product users because these behavior patterns affect the health risks posed to those individuals. Current tobacco product users who start using the product may be switching from a product that may present greater, lower, or equal levels of individual health risk. Current tobacco product users that adopt the product may not continue use of the product in the future, so FDA seeks information regarding whether they are likely to switch back or switch to a product that may present higher levels of individual risk. Finally, current tobacco product users who would have otherwise quit using tobacco may use the new tobacco product instead, exposing them to health risks to which they might not have otherwise been exposed.

FDA received one comment regarding this issue, as discussed below.

(Comment 77) A comment stated that FDA should require applicants to submit all marketing research related to the development of any proposed new product, specifically including research considering the positioning of the proposed new product as a competitor to quitting. FDA also requires information regarding current tobacco product user behavior because to determine whether the product is appropriate for the protection of public health, FDA must take into account the increased or decreased likelihood that current tobacco product users will stop using tobacco products under section 910(c)(4)(A). The types of studies that will likely fall into this category can include actual use studies and national survey databases that could be

used to bridge general data to the specific product. Ideally, the studies would look at past, present, and likely future behaviors of the tobacco product users.

(Response 77) Each PMTA is required by § 1114.7(k)(1)(ii)(F) to contain full reports of all investigations that are published, known to, or which should reasonably be known to, an applicant concerning the likelihood that current tobacco product users who may have otherwise quit using tobacco products will instead start or continue to use the product. This could include information such as applicant-conducted or sponsored marketing research as part of the development of its marketing plans. The description of marketing plans required under § 1114.7(f)(2) could also provide relevant information concerning how an applicant would target the marketing of its new tobacco product to specific intended audiences.

v. Impacts on tobacco use initiation by nonusers, including youth, young adults, and other relevant vulnerable populations. The rule also requires a PMTA to contain full reports of investigations published or known to, or which should reasonably be known to the applicant, regarding the likelihood that consumers who have never used tobacco products, particularly youth, young adults, and other relevant vulnerable populations, will initiate use of the tobacco product and the likelihood that consumers who have never used tobacco products and adopt use of the tobacco product will switch to other tobacco products that may present higher levels of individual health risk; however, as set forth in § 1114.27(b)(1)(ii), if a PMTA does not contain substantive information regarding the likelihood of initiation of tobacco use by current nonusers of tobacco products, FDA intends to refuse to file the application. This means that where there is no published information or information that is otherwise known to the applicant regarding the likelihood of changes in tobacco use behavior by current nonusers of tobacco products, including information from investigations using other products that an applicant could bridge to its

product, an applicant would need to conduct its own investigations and include a full report of the results in its PMTA for filing. If FDA lacks sufficient information to determine the potential risks and benefits to the population as a whole, including the potential risks and benefits associated with changes in tobacco product use behavior by current tobacco product users, it may issue a marketing denial order for the new tobacco product.

The rule also requires a PMTA to contain full reports of investigations published or known to, or which should reasonably be known to the applicant, regarding the likelihood that former users of tobacco products will re-initiate use with the tobacco product. FDA include information regarding likelihood of re-initiation by former users as part of its interpretation of the requirements of section 910(b)(1)(A) and under its authority of section 910(b)(1)(G) of the FD&C Act because it will help FDA determine the health risks to which these former users may be exposed if they begin using the new tobacco product. Survey studies are one type of investigation that is likely to fall into this category.

FDA received several comments on initiation information, as discussed below.

(Comment 78) One comment requested clarity regarding a statement in the preamble regarding the assessment of current nonusers of tobacco products who initiate tobacco product use with the new tobacco product and that begin polyuse of tobacco products or switch completely to another tobacco product. The comment stated that predicting such potential future behaviors that would be made after the potential future initiation of tobacco product use would be challenging both in terms of reliability and precision.

(Response 78) FDA does not generally require applicants to conduct studies regarding the likelihood that nonusers would initiate tobacco product use with the new tobacco product and then transition to polyuse or switch to another tobacco product for the purposes of application

acceptance and filing under the rule. Applicants would only be required to submit full reports of such investigations where they are published or known to, or which should reasonably be known to an applicant. However, such information would be helpful to FDA's determination of whether the marketing of the new tobacco product would be APPH, specifically FDA's consideration of the likelihood that nonusers of the tobacco product will start using the product. Where there is no direct information about the new product and its impact on patterns of use among those who initiate, it's possible an applicant could use historical data on patterns of tobacco use (e.g., rates of switching between product categories), to discuss what they anticipate the impact of the new product might be. For example, this could be information about the proportion of new users of a tobacco product or tobacco product category that sustain use for a year and become polyusers of the new product or product category and another tobacco product or switch entirely to another tobacco product. This information may be available from sources such as existing longitudinal and repeated cross-sectional datasets available to the public.

FDA requires information regarding likelihood of tobacco use initiation and switching to potentially more harmful tobacco products, including among youth and young adults, as part of its interpretation of the requirements of section 910(b)(1)(A) of the FD&C Act because it will help FDA determine the number of current nonusers who will likely be exposed to the health risks presented by the tobacco product, as well as the risks posed by potentially more harmful products that individuals may go on to use. The information regarding initiation and switching by current nonusers of tobacco products is also being required under section 910(b)(1)(G) because FDA must take into account the increased or decreased likelihood that those who do not use tobacco products will start using tobacco products under section 910(c)(4)(A) of the FD&C Act. The types of studies that would likely fall into this category include survey studies and

focus groups. In order to assess whether permitting the marketing of a new tobacco product would be APPH, FDA will need to understand how individuals below the minimum age of sale may use or intend to use the new tobacco product because individuals below the minimum age of sale are a population of particular concern for initiating tobacco use.

(Comment 79) One comment supported the requirement to submit information regarding the potential health risks of the new product on youth and young adults, but it stated that tobacco companies should not be permitted to conduct research on youth because applicants could use such information to design their marketing campaigns to attract youth. In addition, multiple comments stated that FDA needs to be more explicit about whether it recommends conducting investigations using youth as test subjects. One comment requested explicit direction regarding what falls within the narrow scope of research using youth subjects that could be appropriate and how applicants should assess whether the benefits of the research outweigh its risks. Another comment requested more information regarding bridging methods and information on how it could be used to extrapolate the impact on youth from young adult data in the context of consumer and perception studies.

(Response 79) FDA does not require research to be conducted on individuals below the minimum age of sale and does not anticipate that will be necessary or an applicant to do so because inferences regarding individuals below the minimum age of sale may potentially be extrapolated from young adults, as well as derived from existing sources of data, reviews of published scientific literature, or bridging information obtained from other sources. Providing data from the published literature or marketing information in an application with appropriate bridging information may be one useful approach. If an applicant takes such an approach, FDA recommends a PMTA contain a clear explanation of how such data can be extrapolated to the

target population or populations of interest for the product that is the subject of the PMTA. Setting requirements with respect to different types of tobacco product research that an applicant may conduct is outside the scope of this rulemaking, which is why in the following paragraph we highlight some of the laws and ethical considerations applicable to research involving subjects below the minimum age of sale. If an applicant chooses to conduct a study in the United States using minors, it must use appropriate parental consent procedures, as well as follow the requirements of the Children's Online Privacy and Protection Act (15 U.S.C. 6501-6505), the Pupil Rights Amendment (20 U.S.C. 1232h), and their implementing regulations (See 16 CFR part 312 and 34 CFR part 98, respectively). FDA strongly recommends that any studies conducted outside of the United States are designed so that the rights, safety, and welfare of human subjects, including minors, are protected in accordance with ethical principles acceptable to the international community, such as those reflected in the ICH Good Clinical Practice standards.

Regardless of where a study is conducted, any studies using individuals under the minimum age of sale should have a narrow research scope and be as focused as possible given sensitivities around the conduct of research in these populations. Specifically, research priorities for individuals minimum age of sale should be focused on key questions relating to use (e.g., prevalence of use, characteristics of users, and patterns of use), risk perception, and intention to initiate/susceptibility among non-users. Studies conducted among individuals under the minimum age of sale focusing on issues beyond these key questions (e.g., exposing youth to advertisements or marketing material for tobacco products) would necessitate a very strong justification to demonstrate that the risks of conducting the research are minimal and do not outweigh the potential benefits of collecting such information.

vi. Perceptions and use intentions. The rule requires a PMTA to contain full reports of investigations published or known to, or which should reasonably be known to the applicant, regarding tobacco product perceptions and use intentions, including the effect of either the product or its label, labeling, or advertising, to the extent that advertising has been studied, on individuals' perception of the risks of the product, use intentions, and the ability of individuals to understand the labeling and instructions for use and use the product in accordance with those instructions.

FDA received one comment on this issue, as discussed below.

(Comment 80) One comment stated that FDA should require testing regarding product packaging, labeling, and advertising that shows they will not mislead consumers or otherwise encourage any harm-increasing uses of the product.

(Response 80) FDA agrees that information regarding consumer perception and use intentions is an important part of an APPH determination. Under § 1114.27(b)(1)(ii), FDA intends to refuse to file any PMTA that does not contain any substantive information regarding the potential impact of either the product or its label, labeling, or advertising on individuals' perception of the product, or their use intentions. This means where there is no published information or information that is otherwise known or should reasonably be known to the applicant regarding either the potential impact of the product or its label, labeling, or advertising on individuals' perception of the product, and their use intentions, including information from investigations using other products that an applicant could bridge to its product, an applicant would need to conduct its own investigation or testing regarding at least one of the topics and include a full report of the results in its PMTA for filing. If, based upon a fair evaluation of all material facts, FDA determines that the proposed labeling is false or misleading in any particular,

FDA must issue a marketing denial order as required by section 910(c)(2)(C) of the FD&C Act. Additionally, as described in section VII.B.6, because the advertising, marketing, and promotion of a tobacco product can have a significant impact on the potential for tobacco product initiation, especially by youth, where FDA is unable to determine the impact that the labeling, advertising, marketing, or promotion of the new tobacco product may have on consumer perceptions and use intentions, FDA intends to issue a marketing denial order for the new tobacco product.

(Comment 81) One comment stated that FDA should make it clear that investigations of perceptions and use intentions are required only for prospectively proposed labels, labeling, and advertising. The comment stated that because FDA is using section 910(b)(1)(G) of the FD&C Act as its authority and that section is limited to information that is relevant to the subject matter of the application, FDA should limit § 1114.7(k)(1)(iv) to investigations for prospectively proposed labels, labeling, and advertising, as this would be the relevant information. The comment added that this approach would avoid potential burdens on applicants and FDA from having to submit and review past materials, especially for products on the market for several years before the requirement took effect.

(Response 81) FDA disagrees with the comment because investigations regarding prior labels, labeling, and advertising can provide information that is relevant to FDA's review. FDA includes perception and use intention studies as part of its interpretation of the requirements of section 910(b)(1)(A), and under its authority of 910(b)(1)(G) of the FD&C Act because perception of the risk of the product may influence decisions to use the product and the resultant exposure to the health risks presented by the product (Ref. 139). If an applicant uses advertising as stimuli in a tobacco product perception and use intention study, the PMTA must indicate, as part of the full report of the study under § 1114.7(k)(3), whether it is representative of

advertising that the applicant intends to use in marketing the product that is required by § 1114.7(f)(2). If the advertising is not representative of the advertising an applicant intends to use in marketing the product, the applicant must indicate whether the study results are still relevant to the likely impact of product advertising on tobacco product perceptions and use intentions.

Additionally, information about individuals' understanding regarding the labeling is relevant to determining whether the labeling is misleading, which is a reason for which FDA must deny an application under section 910(c)(2)(C) of the FD&C Act, and also may provide information on the likelihood of individuals using the product. Further, whether consumers understand the instructions for use and use the product in accordance with those instructions can help show whether consumers will be exposed to potentially greater health risks by using the product improperly. Topics that should be examined in tobacco product perception and intention investigations overlap with the topics identified in the human factors section that follows.

vii. Human factors. The rule also requires a PMTA to contain full reports of investigations, published or known to, or which should reasonably be known to, the applicant regarding human factors that influence the health risks of the product, which includes use conditions, use environments, use related hazards, estimated use error risk, potential unintended uses, risk controls to ensure that harms and unintended consequences are minimized, and adverse experiences related to such uses.

FDA received comments regarding human factors, as discussed below.

(Comment 82) One comment stated that the human factors requirements in § 1114.7(k)(1)(v) and the corresponding description in the preamble did not address the complex nature of human factors or the numerous permutations and interactions among subcategories of

products. Given the complexity of "human factors" and unspecified "threshold amount of information" applicants are required to submit for FDA to file an application, the comment requested that FDA clarify how much information regarding human factors is required for filing.

(Response 82) Section 1114.27(b)(2)(ii) requires a PMTA to contain substantive information concerning the ways in which human factors can affect the health risks of the new tobacco product. This rule does not require an applicant to conduct an investigation regarding human factors for an application to be filed unless there is no information that is published or can otherwise be bridged to the new tobacco product that is the subject of the application. As described in section IX.B, FDA considers substantive information to be information that is relevant to the subject it claims to support and has evidentiary support. Any amount of substantive information regarding the ways in which human factors can affect the health risks of the new tobacco product is sufficient to meet the filing requirements of § 1114.27(b)(2)(ii).

Further, although the rule requires an application to contain some amount of substantive information for filing, FDA must be able to determine the potential risks and benefits of the new tobacco product to the population as a whole, which includes youth, young adults, and other vulnerable populations. If FDA lacks sufficient information to make this determination, it intends to issue a marketing denial order for the new tobacco product. FDA requires human factors information as part of its interpretation of the requirements of section 910(b)(1)(A) and (G) of the FD&C Act because it provides an assessment of use-related health hazards for the tobacco product.

In situations where it is critical for the end user to have instructions on how to properly use the product, it is important for applicants to demonstrate that the instructions for use are adequate. FDA recommends that human factors studies focus on the particular aspects of

labeling that provide instructions for use. For example, it may be appropriate for a human factors study to evaluate the tobacco product user's:

- ability to select the appropriate task from a set of instructions that include different options;
- understanding of how to identify a defective or expired product;
- awareness and understanding of the safety information provided in the instructions for use;
- recognition of any potential harms or dangers that would signify the need to seek medical attention, such as shortness of breath, allergic reaction, weakness, increased heart rate; and
- understanding of diagrams, if provided as part of the product labeling (which may overlap with investigations regarding consumer perception and understanding).

Analyzing use-related risks is a critical step in identifying use related hazards associated with the product and in characterizing high-risk hazards so that they can be mitigated or eliminated. FDA recommends that a PMTA contain a use-related risk analysis to help identify critical tasks that should be evaluated in human factors studies and inform the priority of testing the tasks in a human factors study, and determine if there are specific use scenarios to include in testing. If an applicant conducts human factors testing to determine tobacco product use-related risks, FDA recommends that the test considers potential users of the product, use environments, similar products used within the environments, and any associated medical factors or health conditions that may affect whether users may experience serious or unexpected adverse experiences. An applicant may also want to include information on known use related problems with similar products or previous versions of the product.

As part of the risk analysis, FDA recommends that an application first identify all users and use environments for the product, as well as unintended users who are likely to use the product and unintended environments, in which the product is likely to be used. For example, intended users may be characterized within the application according to their respective experience levels, skills, age ranges, and use responsibilities. Use environments are an important factor to consider because they can have diverse characteristics that affect the users' interactions with the product. In some cases, use of the product may be prohibited (e.g., laws prohibiting use of a product in the workplace, public spaces, airplanes).

(Comment 83) One comment stated that actual use studies concerning human factors are costly and time consuming, and in some cases, they are unnecessary. The comment recommended that FDA consider less costly alternatives to actual use studies, such as simulated use studies. The comment stated that data from the actual use of products that are already on the market should also be acceptable. The comment also noted that the preamble references a human factors validation study, which is referenced nowhere else in the rule, and requested this reference be better explained. The comment raised additional concerns with the human factor section's discussion of unintended users and unintended use environments, stating that there is no logical way for manufacturers to address all potential users and environments that fit into those categories.

(Response 83) FDA recommends that human factors investigations be conducted in the form of actual use studies, rather than simulated use studies. Because it may be difficult in some cases to simulate the conditions of use, physical characteristics of the product, or environment of use, actual use studies allow for better assessment of how users interface with the product. However, the rule does not require a specific type of human factors study. As described in this

section, the rule requires a PMTA to contain at least some amount of substantive information concerning the ways in which human factors can affect the health risks of the new tobacco product in order for the application to be filed for substantive review.

FDA recommends an applicant conduct human factors validation testing because it can demonstrate that the expected users can understand and follow the device instructions without serious use errors or problems under the expected use conditions. For ENDS, for example, the human factors validation study should demonstrate and provide evidence that an e-cigarette, as designed, can be used as intended by people who are representative of the expected users and under normal use conditions. If errors or failures or new findings are identified in a human factors validation study, then these problems should be evaluated to determine the root cause(s), potential for harm, and additional measures to eliminate or mitigate risk.

b. Literature search. Section 1114.7(k)(2) requires a PMTA to describe, and contain the results of, a literature search for each type of information described in § 1114.7(k)(1). FDA requires that an application contain the bibliography and literature search information because section 910(b)(1)(A) of the FD&C Act requires (in part) that a PMTA contain full reports of all published health risk investigations. FDA is also including these requirements in the rule under authority of sections 701(a) and 910(b)(1)(G) of the FD&C Act because they would help FDA to determine whether the application contains reports of all published investigations in an efficient manner rather than having to followup with the applicant about the inclusion or exclusion of specific studies.

FDA received multiple comments regarding the literature search requirement, as discussed below.

(Comment 84) One comment stated it was unclear how the literature search requirement would apply and what level of detail the Agency expects to see. The comment noted that in the case of a product not on the market, there would be no or limited scientific literature on the product.

(Response 84) Section 1114.7(k)(2) requires a PMTA to contain a description of the literature search performed, including the databases searched and the date searched, search terms, reasons for inclusion or exclusion of documents, and the strategy for study quality assessment. The PMTA must also contain a bibliography of all published studies and articles referenced in the application. If a literature search was performed and resulted in no information found, the application must contain a statement to that effect. FDA must determine whether the application contains all published investigations because the Agency needs to ensure it has all relevant health risk data to determine whether permitting the marketing of the product would be APPH. The description of the reasons for inclusion or exclusion of documents, in particular, will facilitate FDA's review of an application because it will explain, if applicable, why some investigations that initially appear relevant were excluded from the application and why some investigations that do not initially appear to be relevant were included in the application. For example, if an applicant limits the literature search to a certain time period, the applicant must include the reason for such limitations in their description of the literature search. For ease of review, FDA recommends that an applicant include internal hyperlinks to, or otherwise reference, the location of published studies that are included in an application. If applicable, it is also recommended that an application explain why an investigation that was conducted using a product other than the one that is the subject of the PMTA is relevant to the application to inform FDA's review of the PMTA.

It is possible that there may be less information captured by the literature search for novel products; however, there may be at least some applicable information, such as investigations on constituents delivered to users and nonusers under the range of conditions under which the product may be used, which may be bridged to the product that is the subject of the application.

c. Study reports. Section 1114.7(k)(3) sets requirements for the full report of each investigation that must be included as part of an application. An application must contain each type of documentation listed in § 1114.7(k)(3) to the extent that it is applicable to the type of investigation and to the extent that it is reasonably available to the applicant. FDA considers a document to be reasonably available unless it does not exist or it would be unduly burdensome to obtain the document due to the effort or expense involved. Where an applicant considers a document required by this section to not be reasonably available, the application must contain an explanation in the full report that describes the actions taken to obtain the document and specifies why the document is not reasonably available. It is important to note that failure to submit documents may affect the extent to which FDA is able to rely upon an investigation's findings during substantive application review. A full report of the investigation must contain:

i. Full copies of any published articles and other reference materials. FDA requires that an application contain full copies of published articles and other reference materials to facilitate the review process.

ii. Documentation of all actions taken to ensure the reliability of the study. The requirements for this item would differ based upon whether the investigation is a clinical investigation or a nonclinical laboratory investigation. For nonclinical laboratory investigations, an application must contain documentation demonstrating all actions taken to ensure the reliability of the study, including whether the investigation was conducted using good laboratory

practices (GLPs), such as those specified in part 58 (21 CFR part 58). FDA considers GLPs to be those that support the quality, reliability, and integrity of nonclinical laboratory investigations. This requirement helps FDA determine whether the study's findings are accurate and reliable. While this rule on its own does not require compliance with the GLP regulations found in part 58,[33] FDA would consider a nonclinical laboratory investigation that contains the documentation required by part 58 to be one way to satisfy the requirements of § 1114.7(k)(3)(ii).

FDA recommends that an application contain a final report of each nonclinical laboratory investigation that contains the following items, at minimum, to show that the study was accurate and reliable:

- name and address of the facility performing the study and the dates on which the study was initiated and completed;
- objectives and procedures stated in the approved protocol, including any changes in the original protocol;
- statistical methods employed for analyzing the data;
- the test and control articles identified by name, chemical abstracts number or code number, strength, purity, and composition or other appropriate characteristics;
- stability of the test and control articles under the conditions of administration;
- a description of the methods used;
- a description of the test system used. Where applicable, the final report should include the number of animals used, sex, body weight range, source of supply, species, strain and substrain, age, and procedure used for identification;

[33] It is important to note that in the *Federal Register* of August 24, 2016 (81 FR 58341), FDA issued a proposed rule that, when finalized, would require laboratory investigations regarding tobacco products to comply with the requirements of part 58.

- a description of the dosage, dosage regimen, route of administration, and duration;
- a description of all circumstances that may have affected the quality or integrity of the data;
- the name of the study director, the names of other scientists or professionals, and the names of all supervisory personnel, involved in the study;
- a description of the transformations, calculations, or operations performed on the data, a summary and analysis of the data, and a statement of the conclusions drawn from the analysis;
- the signed and dated reports of each of the individual scientists or other professionals involved in the study;
- the locations where all specimens, raw data, and the final report are stored;
- the statement prepared and signed by the quality assurance unit, if any, a description of the quality control review performed and its results;
- the study director's signature and date upon completion of the final report; and
- any corrections or additions to a final report, clearly identifying the part of the final report that is being added to or corrected and the reasons for the correction or addition, and bearing the dated signature of the person responsible.

The rule requires full reports of investigations (both clinical and nonclinical) to contain, to the extent reasonably available, a certification that the investigators do not have, or documentation fully disclosing, any potential financial conflicts of interest, such as the financial arrangements specified in the financial disclosure by clinical investigators regulation in part 54 (21 CFR part 54). While FDA does not currently require compliance with part 54 for tobacco product investigations, complying with those requirements for both clinical and nonclinical

investigators would be one way to satisfy the financial disclosure requirements of the rule. Financial conflicts information is important for FDA to consider because they address a potential source of bias in investigations. Applicants would be able to use these disclosures as well as appropriate procedures in the design and conduct of the study to demonstrate that a potential bias that may affect the results of the investigation has been minimized. FDA would use the information contained in these disclosures, in conjunction with information about the design and purpose of the study, as well as on-site inspections (if necessary) in its assessment of the reliability of the data.

The investigator financial arrangements that the applicant should disclose and describe, include:

- any financial arrangement entered into between the sponsor of the study and the investigator involved in the conduct of a clinical trial, whereby the value of the compensation to the investigator for conducting the study could be influenced by the outcome of the study;
- any significant payments of other sorts from the sponsor of the study, such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria;
- any proprietary interest in the tested product held by any investigator involved in a study;
- any significant equity interest in the sponsor of the study held by any investigator involved in any clinical study; and
- any steps taken to minimize the potential for bias resulting from any of the disclosed arrangements, interests, or payments.

iii. A copy of all protocols and amendments that were used in the study.

iv. Copies of all investigator instructions, if any were produced in addition to the protocol.

v. The statistical analysis plan. The rule requires that the applicant submit a statistical analysis plan, including a detailed description of the statistical analyses used (including all variables, confounders, and subgroup analyses), the scientific rationale for the choice of sample sizes, and any amendments to the plan. FDA requires the protocol, investigator instructions, and statistical analysis plan to be part of the full report of a study because they would enable FDA to understand a study's design, conduct, and analysis in its entirety and to evaluate the validity of a study.

FDA received one comment regarding statistical methods, as discussed below.

(Comment 85) One comment stated that FDA should require that all studies submitted in support of a PMTA be adequately powered, and § 1114.7(k)(3)(v) should be amended to require presentation of power data, including study power and minimum detectable effect size, as part of the statistical methods used.

(Response 85) FDA agrees that having adequately powered data is important to an applicant's prospects of receiving a marketing granted order, but the Agency disagrees with this comment insofar as it proposes to restrict the data companies would be required to submit in a PMTA. An applicant must submit full reports of health risk investigations as described in § 1114.7(k), regardless of whether an applicant considers them to be adequately powered. FDA will review the information and make its own determination as to whether the data are sufficient to support the issuance of a marketing granted order.

vi. Line data. To facilitate FDA's review, the application should contain line data in Statistical Analysis Software (SAS)-transport file in .xpt format, created by a procedure that

allows the files to be readily read by the JMP software. FDA also recommends that an application contain data definition files that include the names of the variables, codes, and formats used in each dataset, and copies of SAS programs and necessary macro programs used to create derived datasets and the results reported in the study reports. Such data are important for FDA to replicate applicant findings or conduct alternative statistical analyses. FDA intends to provide technical specifications on its website for submitting information, such as line data, in an electronic format that FDA can review, process, and archive (e.g., method of transmission, media, file formats, preparation, organization of files, accompanying metadata) (https://www.fda.gov/tobacco-products).

FDA received one comment regarding line data, as discussed below.

(Comment 86) One comment stated that where an applicant is using a published health risk investigation in its application, FDA should not require the applicant to obtain and submit underlying data from the study sponsor because, in most cases, the source data are unavailable and FDA lacks the resources to review, verify, and audit that data.

(Response 86) Under the rule, the full report of each health risk investigation in a PMTA must contain the items specified in § 1114.7(k)(3) to the extent those items are applicable to the type of investigation and to the extent they are reasonably available. For additional information on what constitutes a document that is reasonably available, please see section VIII.B.13.c. FDA declines to amend the rule such that the underlying data from published investigations would not need to be submitted where reasonably available. Reviewing data from a study can be an important part of FDA's assessment of the reliability of its results and where an application does not contain data, it may affect the extent to which FDA is able to rely upon an investigation's findings during substantive application review.

vii. Sites and clinical investigators. A list of sites and clinical investigators that conducted the study, including contact information and physical address(es).

viii. The location of all source data. If the site that conducted the study has not maintained all of the source data, indicate where the data are located.

ix. Format. The format of the records and data (e.g., electronic or hard copy).

x. Early termination sites. In the proposed rule, § 1114.7(k)(3)(x) would have required a PMTA to a list of all sites that had early termination, the reason for early termination, and audit certificates and inspection results for study sites with early terminations. We have revised this provision in response to this comment, as discussed below.

(Comment 87) One comment objected to the proposal to require audit certificates and inspection results for study sites that had an early termination, stating it contradicts long-standing FDA policy and should not be included in the final rule. The comment cited to FDA documents concerning the regulation of other products, which state that granting FDA access to quality assurance unit inspection reports would tend to weaken the inspection system and that confidentiality is necessary for inspections to be complete and candid. The comment states that FDA does not explain why it would fail to recognize this long-standing practice in the tobacco context and that it should not be changed as a part of this rule.

(Response 87) FDA agrees with the comment that the requirement to submit audit certificates and inspection results should be removed from the rule because of the policy concerns the comment describes and we have revised § 1114.7(k)(3)(x) accordingly to require only a list of all sites that had early termination and the reason for early termination. The rule also now clarifies that FDA may conduct inspections of sites that had early terminations. As part

of these inspections, FDA intends, as appropriate, to review a firm's written quality assurance program.

xi. Contractors. A list of contractors who participated in the study, the role of each contractor, and the initiation and termination dates of the participation of each contractor.

xii. Signed report. A signed full report of all findings.

xiii. Study materials and case report forms. For human subject studies, all versions of study materials and case report forms used, and all individual case report forms associated with participant deaths, other serious and unexpected adverse experiences, withdrawals, and discontinuations from the study. The rule requires the application to contain one blank copy of each version of the study materials (including, but not limited to, consent forms, questionnaires, and stimuli) and case report form, and only those completed individual case report forms regarding deaths, serious and unexpected adverse experiences, withdrawals, and discontinuations for individuals that were exposed to the tobacco product, or for individuals who were exposed to a similar or related product that the applicant is using to help demonstrate the health effects of its product. An example of where such case report forms from a study regarding a similar product are required is where a clinical biomarker study on a product that is similar to the new tobacco product in terms of design, ingredients, and HPHCs is used to provide information about the anticipated health risks of the new tobacco product. As described in § 1114.45, applicants must keep each questionnaire and case report form from the study as part of its own internal records, which FDA may inspect, as described in § 1114.27, or request that the applicant submit to facilitate its review of an application. If an applicant fails to keep such records, FDA may be unable to rely upon an investigation's findings during substantive application review.

Additionally, while clinical investigations for tobacco products are not currently required to be conducted in accordance with the requirements for the protocol and procedures implemented to protect human subjects in the Institutional Review Boards regulation in part 56 (21 CFR part 56) and the Protection of Human Subjects regulation in part 50 (21 CFR part 50), FDA plans to issue regulations requiring compliance with those parts for tobacco products. Until FDA takes such action, FDA strongly encourages applicants to follow the requirements of parts 50 and 56 or take sufficient actions to ensure that the investigation is conducted in a manner that comports with the ethical and moral considerations involved with conducting studies using human subjects. Each clinical investigation included in the PMTA should have been reviewed and approved by an institutional review board (IRB) operating to safeguard the rights, safety, and well-being of all trial subjects, with special attention being paid to potentially vulnerable study subjects including, but not limited to vulnerable populations, such as children, incarcerated persons, individuals with impaired decision-making capacity, or economically or educationally disadvantaged persons. For more information on some of the laws and ethical considerations applicable to research involving subjects below the minimum age of sale, please see section VIII.B.13.a.(5) of this document.

FDA recommends applicants retain documentation concerning efforts related to the protection of human subjects, including documents related to the IRB, such as:

- copies of all research proposals reviewed, scientific evaluations, if any, that accompany he proposals, approved sample consent documents, progress reports submitted by investigators, and reports of injuries to subjects;
- minutes of IRB meetings in sufficient detail to show attendance at the meetings; actions taken by the IRB; the vote on these actions including the number of members voting for,

against, and abstaining; the basis for requiring changes in or disapproving research; and a written summary of the discussion of controverted issues and their resolution;

- records of continuing review activities;
- copies of all correspondence between the IRB and the investigators;
- a list of IRB members identified by name; earned degrees; representative capacity; indications of experience such as board certifications, licenses, etc., sufficient to describe each member's chief anticipated contributions to IRB deliberations; and any employment or other relationship between each member and the institution (e.g., full-time employee, part-time employee, a member of governing panel or board, stockholder, paid or unpaid consultant);
- written procedures for the IRB; and
- statements of significant new findings provided to subjects, such as those discussed in § 50.25.

FDA also strongly recommends, but does not currently require, maintaining all documentation of the protocol and procedures implemented to protect human subjects, such as those set forth in the protection of human subjects regulation in part 50. Each clinical investigation included in the PMTA should have been conducted using only human subjects who gave their informed consent to participate in the study. As described in § 50.20, informed consent is consent that is obtained from the subject or the subject's authorized representative under circumstances that provide the prospective subject or representative with sufficient opportunity to consider whether to participate and that minimize the possibility of coercion or undue influence. The information that is given to the subject or the subject's representative should be in language understandable to the subject or the representative. The informed consent

should not include any exculpatory language through which the subject or representative is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution, or its agents from liability for negligence.

xiv. Perception and use intention studies. For perception and use intention studies that use a label, labeling, advertising, or other materials as stimuli, the rule requires the full report of the study to contain a statement regarding whether the label, labeling, or advertising used is representative of those the applicant intends to use in marketing the product. If the advertising used as stimuli is not representative of the advertising an applicant intends to use in marketing the product, the applicant must indicate whether and how the study findings are still relevant to the likely impact of product advertising on consumer tobacco product perceptions and use intentions. For more information about tobacco product perception and use intention studies, please see the description of § 1114.7(k)(1)(iv) in section VII.B.13.a.iv.

14. The Effect on the Population as a Whole

The rule requires a PMTA to contain an indepth analysis and discussion of how the data and information contained in the application establish that permitting the marketing of the new tobacco product would be appropriate for the protection of public health. This discussion must include the effect that the new tobacco product may have on the health of the population as a whole, including youth, young adult, and other relevant vulnerable populations with emphasis on the populations disproportionately affected by and most likely to use the new tobacco product by integrating all of the information (both qualitative and quantitative as available) regarding the product, its potential effects on health, as well as tobacco use behavior (including likelihood of both cessation and initiation), to provide an overall assessment of the potential effect that the marketing of the tobacco product may have on overall tobacco-related morbidity and mortality.

Relevant outcomes measures could include reductions in serious medical conditions and premature mortality and gains in life-years lived in the population. This requirement directly informs FDA's determination under section 910(c)(2)(A) of the FD&C Act as to whether permitting the marketing of the new tobacco product would be APPH.

FDA received one comment regarding population health analysis, as discussed below.

(Comment 88) One comment stated that FDA should require PMTAs to provide reasonable estimates of information regarding the future public health impacts from FDA issuing a marketing granted order for the new tobacco product, including comparisons to other products and the likelihood of changes in tobacco product use behavior. The comment suggested that this could include estimates regarding product harmfulness, possible harm-increasing consumer uses, mortality impacts or impacts on quality adjusted life years.

(Response 88) FDA agrees that information regarding the potential risks and benefits related to the tobacco product, including comparisons to other products and the likelihood of changes in tobacco product use behavior, is important to the evaluation of a PMTA. Accordingly, FDA requires a PMTA under § 1114.7(k) to contain full reports of investigations regarding the health risks of the tobacco product and to contain an analysis and discussion of all data and information under § 1114.7(*l*) that integrates the information regarding the likely effects of the new tobacco product on overall health and tobacco use behavior to provide an assessment of the likely effect that the marketing of the new tobacco product would have on overall tobacco-related morbidity and mortality.

15. Certification Statements

Section 1114.7(m) requires that the application contain a specific statement certifying that the applicant will maintain all records to substantiate the accuracy of the application

consistent with the record retention requirements in § 1114.45, that the information and accompanying submission are true and correct, that no material fact has been omitted, that the signer is authorized to submit the information on the applicant's behalf, and that the signer understands that anyone who knowingly and willfully makes a materially false, fictitious, or fraudulent statement to the Government of the United States is subject to criminal penalties under 18 U.S.C. 1001. This certification will help ensure that the applicant understands the responsibilities related to the application (including the potential consequences of submitting false information to the U.S. Government), the applicant intends to submit the PMTA, and the PMTA is ready for review.

C. Amendments (§ 1114.9)

FDA generally expects that when an applicant submits a PMTA, the submission will include all information required by section 910(b)(1) of the FD&C Act and part 1114 to enable FDA to determine whether it should authorize the marketing of a new tobacco product. However, FDA recognizes that additional information may be needed to complete the review of a PMTA and, therefore, allows the submission of amendments to a pending application.

Section 1114.9 provides that FDA may request, and an applicant may submit, an amendment to a pending PMTA together with the appropriate form (Ref. 140). Because FDA tracks PMTAs using the STN, an amendment must specify the STN that is assigned to the PMTA. An amendment must contain the certification statement set forth in § 1114.7(m), with the appropriate information inserted, and signed by an authorized representative of the applicant. FDA may, at any time after it receives and before it acts on an application, request that an applicant submit additional information that is necessary to complete the review of a PMTA. Similarly, an applicant may submit an amendment on its own initiative that is necessary for FDA

to complete its review of the pending PMTA. These amendments may include information such as newly completed or published studies that are relevant to the PMTA, clarifications, or a transfer in ownership of the PMTA as described in § 1114.13.

Section 1114.9(b)(2) describes the effect that minor amendments have on the 180-day review period. FDA considers minor amendments to be any amendments that are not major amendments. Minor amendments can be clarifications or other information that FDA needs to complete its review of a PMTA, but they will not require substantial review time. Examples of minor amendments that FDA has requested include a certificate of analysis and administrative information.

FDA received many comments regarding amendments, as discussed below.

(Comment 89) Multiple comments requested that FDA provide additional clarity regarding, and examples of, what constitutes a minor amendment or a major amendment.

(Response 89) Section 1114.9(b) describes how the submission of an amendment may affect the time required for the review (as described in § 1114.27(c)(1)) of the application. FDA intends to notify applicants regarding changes to the review period, including pausing, resuming, and resetting the review period for amendments as described in this section. If the applicant submits a major amendment to an application, either at FDA's request or on its own initiative, FDA will restart the 180-day review period. FDA considers major amendments to be those that will require substantial FDA review time. Examples of major amendments include: substantial new data from a previously unreported study, detailed new analyses of previously submitted data, or substantial new manufacturing information (e.g., addition of a new manufacturing site for primary and secondary processing, or a change in a manufacturing step or process to address a product quality or safety issue not initially provided in the application). When an applicant

submits a major amendment, FDA would consider the applicant to have submitted a new PMTA with the review period beginning on the date FDA receives the amendment. Therefore, under § 1114.9(b)(1), a new 180-day review period would begin on the date FDA receives a major amendment.

(Comment 90) One comment stated that FDA should allow applicants to submit amendments containing the results of studies that were ongoing when the PMTA was submitted and FDA should not automatically restart the 180-day review clock when an applicant does so. The comment suggested that FDA should instead only add the number of review days needed to complete review of the amendment.

(Response 90) FDA declines to take this suggestion because FDA does not expect that it will be able to reliably predict the number of days needed to review a major amendment, such as one containing the results from a new study, which could require FDA to conduct a potential inspection of the study site, at the time when it is received. While FDA will restart the 180-day review period after the receipt of a major amendment, the Agency intends to promptly act on an amended application, which might take fewer than 180 days.

(Comment 91) One comment stated that the rule implies that applicants would be unable to submit minor amendments on their own initiative. The comment requested that FDA amend the rule to allow for the submission of unsolicited minor amendments and give such amendments the same due consideration as solicited amendments.

(Response 91) As set forth in § 1114.9, FDA may request, or an applicant may submit on its own initiative, an amendment to a PMTA containing information that is necessary for FDA complete the review of a pending PMTA. This permits the submission of unsolicited minor amendments, which FDA will consider in the same manner as solicited minor amendments.

If FDA determines that a minor amendment is necessary to complete its review of a pending submission and requests that the applicant submit the amendment, FDA may pause the review period on the date that it issues the amendment request to the applicant. FDA will resume the review period on the date that it receives a written response from the applicant either submitting the requested information or declining to submit the amendment. For example, if FDA requests a minor amendment on day 80 of its review, the date FDA receives the amendment would be day 81, even though weeks or months may have passed from the date of request to receipt. An applicant may notify FDA that it is declining to submit an amendment; however, if an applicant declines to submit an amendment to FDA, and FDA is not be able to determine whether the PMTA meets the requirements to receive a marketing granted order without the amendment, it will issue a marketing denial order.

If FDA requests an amendment, either major or minor, and the applicant neither submits the amendment nor notifies FDA that it is declining to submit the amendment within the time period specified in FDA's request, FDA may, as described in § 1114.9(c), consider the applicant to have submitted a request to voluntarily withdraw its PMTA and issue an acknowledgement letter stating that the application has been withdrawn under § 1114.11. FDA will consider requests for more time to submit an amendment and may grant reasonable requests. Section 1114.9(c) is based on FDA's authority under section 701(a) of the FD&C Act to efficiently enforce section 910 of the FD&C Act because it would allow FDA to dedicate its resources to reviewing PMTAs that are more likely to receive a marketing granted order, rather than continuing to review a PMTA submitted by a nonresponsive applicant that is unlikely to provide FDA with the information it needs to complete its review.

If an application has been closed under § 1114.29 or withdrawn under § 1114.11, § 1114.9(d) does not allow the application to be amended. If an applicant wishes to make changes to an application after it is closed or withdrawn, it would have to do so through submission of a new application.

D. Withdrawal by Applicant (§ 1114.11)

Section 1114.11 discusses the ability of an applicant to withdraw a pending PMTA. At any time prior to FDA acting on the application (i.e., taking one of the actions described in § 1114.29), the applicant may request to withdraw its application by using the appropriate form (Ref. 140) to specify the name of the new tobacco product, the STN of the application, and state whether the withdrawal request is related to a health concern. If the request is related to a health concern, the applicant must describe the concern(s), including the extent, duration, and frequency of the health effects, and identify what gave rise to the concerns, such as adverse experience reports. FDA requires information about health concerns under authority of section 909 of the FD&C Act because the information would help FDA protect the public health (e.g., identifying a problem that could be present in similar currently marketed products) and section 701(a) of the FD&C Act because it allows FDA to efficiently enforce provisions of the FD&C Act (e.g., more quickly ensure an identified health concern was addressed if an application for the same product is submitted again). Once FDA receives and processes the withdrawal request, it will issue an acknowledgment letter to the applicant, at which time the application will be considered withdrawn. Withdrawing an application would not prejudice a future submission.

The application is an Agency record even if withdrawn. Thus, under § 1114.11(c), FDA will retain the withdrawn application consistent with Agency record retention schedules and

policies and will provide a copy to the applicant upon request, subject to the Agency's public information regulations in part 20 and under the fee schedule in § 20.45.

E. Change in Ownership of an Application (§ 1114.13)

Section 1114.13 describes the steps that an applicant must take when it transfers ownership of a PMTA. This section is intended to facilitate transfers of ownership and help ensure that FDA has current information regarding the ownership of a PMTA. An applicant may transfer ownership of its PMTA at any time prior to FDA taking one of the actions described in § 1114.29. Under § 1114.13, at the time of the transfer, the new and former applicants (or owners) of the PMTA must use the appropriate form (Ref. 140) and submit certain information to the Agency. First, the former applicant must submit a notice to FDA identifying the new applicant and stating that all rights to the PMTA have been transferred to the new applicant. Second, the new applicant must submit a signed notice to FDA containing the following information:

- to the extent applicable, the new applicant's commitment to agreements, promises, and conditions made by the former applicant and contained in the PMTA (e.g., certifications, proposed restrictions on the sales and distribution of the tobacco product);
- the date that the change in ownership is effective;
- either a statement that the new applicant has a complete copy of the PMTA (including any amendments, or any records required to be kept under § 1114.45); or a statement of intent to request a copy of the PMTA filed with FDA under the Freedom of Information Act (FOIA) (FDA's implementing regulations are in part 20); and
- a certification that no modifications have been made to the new tobacco product since the PMTA was submitted to FDA.

Although FDA expects that the new applicant will have a copy of the PMTA from the former applicant, if the new applicant requests a copy of the PMTA filed with FDA, FDA will provide a copy to the new applicant, subject to the public information regulations in part 20 and under the fee schedule in § 20.45.

The new applicant also would be required to make available all required records upon inspection by FDA (§ 1114.45 would impose a recordkeeping requirement).

F. Supplemental Application Submission (§ 1114.15)

Section 1114.15 discusses the availability of supplemental PMTAs. Supplemental PMTAs are an alternative format for a PMTA that meets the requirements of § 1114.7, which would reduce the burden associated with the submission and review of an application. Specifically, supplemental PMTAs are a standardized cross-referencing format that FDA is implementing under its authority of section 701(a) of the FD&C Act to efficiently enforce section 910 of the FD&C Act for submissions that are based on a PMTA that FDA has previously reviewed. Applicants that have received a marketing granted order would be able to submit a supplemental PMTA to seek marketing authorization for a new tobacco product that results from a modification or modifications to the original tobacco product that received the marketing granted order. An applicant can submit a supplemental PMTA only for modifications where the submission of limited info can demonstrate that permitting the marketing of the modified product would be APPH. FDA is restricting the use of supplemental PMTAs to ensure that FDA is able to efficiently review the application. An applicant could also submit a supplemental PMTA for modifications made to comply with a product standard issued under section 907 of the FD&C Act where FDA specifies in that product standard rule that the submission of supplemental PMTAs would be appropriate.

Applicants that have questions about whether it would be appropriate to submit a supplemental PMTA for the modifications they are seeking to implement should contact FDA for more information. To further illustrate when a supplemental PMTA could be submitted, FDA has prepared the following examples of modifications to ENDS products that are likely appropriate to be submitted using the supplemental PMTA format and likely not appropriate to be submitted using the supplemental PMTA format. After review and consideration of comments received in response to the proposed rule, we have added an additional example to provide clarity on the product modifications that are likely appropriate to be submitted using the supplemental PMTA format.

Potentially Appropriate for Supplemental PMTA Format

• Changes in connection type/thread size (e.g., 510);
• minor Software Changes not affecting device functionality; and
  o changes to user interface;
  o changes in recording/data capture properties; and
• certain changes to account for improvements in electronics technology or to improve use and convenience (e.g., use of haptics or simplification of device functions like cleaning cycle).
• Minor changes in e-liquid volume, viscosity or boiling temperature;
• minor changes in draw resistance;
• minor changes in air flow rate;
• changes to coil configuration if number of coils, coil gauge, material, and overall coil resistance remain unchanged; and
• changes to amount of wicking material

Likely Not Appropriate for Supplemental PMTA Format
• Any modification that might increase risk of harm to individual health from the product; • modifications that may alter tobacco product use behavior and initiation, such as modifications that have strong youth appeal; and • design modifications that change the category or subcategory of the product (e.g., modifying a closed e-cigarette to be an open e-cigarette)

Additionally, there are two other specific limitations on the submission of a supplemental PMTA. Under § 1114.15(a), a supplemental PMTA could not be submitted where the marketing granted order for the original tobacco product has been withdrawn or has been temporarily suspended or is the subject of temporary suspension or withdrawal proceedings by FDA, except where authorized by FDA in writing. FDA restricts the submission of supplemental PMTAs in these situations because, for example, withdrawal or suspension may involve consideration of whether the marketing of the original product is no longer appropriate for the protection of the public health, or the application was accompanied by an untrue statement of material fact. If the reason for the temporary suspension or withdrawal is unrelated to the sufficiency or reliability of information contained in a PMTA, an applicant may request, and FDA may grant, authorization to use a supplemental PMTA under these circumstances.

FDA received comments about the use of supplements generally, as discussed below.

(Comment 92) One comment stated that verifying compliance with a product standard under section 907 of the FD&C Act should require only a certification by the applicant and not a new PMTA, Supplemental or otherwise. The comment further stated that in adopting a product standard, FDA will have already determined that the standard "is appropriate for the protection

of the public health" for the products to which it applies, so product modifications made to comply with an applicable new standard thus will not require the same evaluation as a standard or supplemental PMTA. The comment asserted that any requirement beyond a certification of compliance would be needlessly burdensome and would unnecessarily delay consumer access to products that satisfy the new product standard.

(Response 92) The circumstances that would determine the actions a manufacturer would need to take to legally market a tobacco product after issuance of a product standard are fact-specific and are dependent upon the tobacco product, the modifications made (if any), and the product standard involved; however, FDA disagrees with the suggestion that modifications made to comply with a product standard would never need to be the subject of a PMTA or another premarket submission to seek marketing authorization. The rule for a future product standard would indicate whether an applicant may submit a supplemental PMTA, where applicable.

As discussed in § 1114.15(a), an applicant may not submit a supplemental PMTA where the modifications to the original tobacco product require the submission of new information or revisions to the extent that review of the PMTA for the new tobacco product in the supplemental PMTA format would be confusing, cumbersome, or otherwise inefficient and submitting a standard PMTA under § 1114.7(b) would better facilitate review.

(Comment 93) One comment requested that FDA make supplemental PMTAs available to be submitted for a broader range of modifications to reduce the burden on industry.

(Response 93) FDA declines to allow for broader use of the supplemental format because it would likely not result in a more efficient review process. Because supplemental PMTAs are based on a cross-referencing system that is supposed to reduce the burden of preparing and reviewing a PMTA, FDA has created this limitation to ensure PMTAs are submitted in the

format that is the easiest to review, process, and archive. Changes that require multiple, sweeping, or difficult-to-trace changes to the PMTA for the original tobacco product would be more efficient to review in the full text format of § 1114.7.

1. Required Format

Under § 1114.15(b) the supplemental PMTA format is the same as the format for standard PMTAs submitted under § 1114.7(b), except that applicants must include content in a supplemental PMTA by cross-referencing content in the PMTA and postmarket reports for the original tobacco product. FDA believes that including content in an application by cross-referencing to a PMTA for the original tobacco product is appropriate for supplemental applications because the referenced information will be presented in the proper context and format, and will facilitate application review.

2. Required Content

The required content for a supplemental PMTA is divided into two general categories: new content sections and content sections cross-referenced from the PMTA for the original tobacco product. The new content sections required under § 1114.15(c)(1) must contain the full text or a cross-reference to text in a tobacco product master file or postmarket reports for the original tobacco product. These sections may not include information by cross-reference to the PMTA for the original tobacco product. The new content sections that must be included under § 1114.15(c)(1) are:

- general information (as described in § 1114.7(c));
- new product information (as described in § 1114.15(d));
- statement of compliance with part 25 (as described in § 1114.7(g));

- labeling (as described in § 1114.7(f)) if the labeling is not identical to the labeling submitted in the PMTA or postmarket reports for the original tobacco product;
- postmarket information (as described in § 1114.15(e)); and
- certification statement (as described in § 1114.15(f));

A supplemental PMTA must also contain application sections that comprise information included by cross-reference to the PMTA for the original tobacco product and contain any additional information that is necessary to supplement or update the cross-referenced information. It is important to note that these cross-referenced sections must be accompanied by the full text of any updates or supplemental information that are necessary to tailor this information to the new tobacco product. These updates or supplemental information should consist of changes to application content that is not otherwise included as part of the new content sections required under § 1114.15(c)(1). For example, if a new health risk investigation on the product is published and it is not contained in the new content sections, the cross-referenced sections must contain a full report (as described in § 1114.7(k)(3)) of the investigation in full text with a cross-reference to the health risk investigations section in the PMTA for the original tobacco product. The cross-referenced sections that must be included under § 1114.15(c)(2) are:

- descriptive information (as described in § 1114.7(d));
- product samples (as described in § 1114.7(e)). Please note, however, that FDA may, request the submission of product samples after receipt of a supplemental PMTA;
- labeling (as described in § 1114.7(f)) if the labeling is identical to the labeling submitted in the PMTA or postmarket reports for the original tobacco product;
- summary of all research findings (as described in § 1114.7(h));
- product formulation (as described in § 1114.7(i));

- manufacturing (as described in § 1114.7(j)); and
- health risk investigations (as described in § 1114.7(k)).

3. New Product Information

Under § 1114.15(d), the new product information section required under § 1114.15(c)(1)(ii) must contain the following information concerning modifications to the original tobacco product, including:

- full descriptions of the modification(s) to the original tobacco product and comparisons of such modification(s) to the unmodified version(s) described in the PMTA for the original tobacco product;
- a statement as to whether the new tobacco product is intended to replace the original tobacco product if the new product receives a marketing granted order, is intended to be a line extension of the original tobacco product, or is intended to be introduced as an additional product by the same manufacturer;
- all data and information relating to the modification(s) that are required in an application under § 1114.7. This is data and information that can span across a number of application sections. A change in the connection type or thread size for an ENDS product, for example, may require a change in the design parameters and the manufacturing sections; and
- a concluding summary of how the new tobacco product meets the requirements to receive a marketing granted order. This summary must describe how the data and information concerning the product modification when viewed together with the information cross-referenced from the previously submitted PMTA demonstrate that the new tobacco

product meets the requirements of section 910(c) of the FD&C Act to receive a marketing granted order.

4. Postmarket Information

Under § 1114.15(c)(1)(v), a supplemental PMTA must contain postmarket information as specified in § 1114.15(e). Where an applicant has submitted postmarket reports for the original tobacco product, it must incorporate those reports by cross-reference. Where an applicant has yet to submit a postmarket report for the original tobacco product, it must submit a report as part of the supplemental application that contains all the information for the original tobacco product that would otherwise be required in a report under § 1114.41, covering the period in time from when it received its marketing granted order for the original tobacco product to when it submitted the supplemental PMTA. Because information that is contained in a postmarket report for the original tobacco product would likely be required content of a standard PMTA for the modified tobacco product, FDA is allowing applicants to cross-reference this content to avoid the burden of resubmitting information that FDA has previously reviewed.

5. Certification Statement

Under § 1114.15(f), the certification statement required under § 1114.15(c)(1)(vi) must be signed by an authorized representative and, in addition to the certification required under § 1114.7(m) for a standard PMTA, must certify that the modifications identified in the certification are the only modification(s) to the original tobacco product.

G. Resubmissions (§ 1114.17)

Section 1114.17 describes resubmissions, which are an alternative format for submitting an application that meets the requirements of § 1114.7(b) or § 1114.15 to seek a marketing granted order, by responding to the 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 a marketing denial order. This application format allows an applicant to address the deficiencies described in a marketing denial order without having to undertake the effort of submitting a standard PMTA. The resubmission format is available to resubmit an application that received a marketing denial order because FDA has completed its review of the PMTAs subject to the marketing denial order and can rely on the findings of these reviews to save time when reviewing a resubmission. The resubmission format is not available for PMTAs that FDA refused to accept, refused to file, cancelled, or administratively closed, or that the applicant withdrew, because FDA has not previously completed reviews of such applications upon which it can rely, and such applications may need significant changes to be successfully resubmitted. It is important to note that, as discussed in section VIII.E regarding § 1114.33, while FDA will identify deficiencies that resulted in the marketing denial order, the deficiencies specified in the order might not be an exhaustive listing of all deficiencies contained in the PMTA.

Similar to a supplemental PMTA, an applicant may not submit a resubmission to the extent that review would be confusing, cumbersome, or otherwise inefficient and submitting a standard PMTA under § 1114.7 would better facilitate review. Where responding to the deficiencies outlined in the marketing denial order requires broad or sweeping changes to the original PMTA, an applicant would need to submit a standard PMTA under § 1114.7 to better facilitate review. Where possible, FDA will specify in the marketing denial order if an applicant may not pursue a resubmission to address the identified flaws.

Applicants may request a meeting with FDA prior to submitting a resubmission to determine whether it may utilize the resubmission format and to discuss any issues related to the application, such as application organization and format. For example, applicants that have questions about whether it would be appropriate to pursue a resubmission for the modifications they are seeking to implement to respond to deficiencies identified in a marketing denial order may contact FDA for more information.

1. Format

Under § 1114.17(b) the resubmission format requirements are the same as the format in § 1114.7(b) for standard PMTAs, except that applicants must include content in a resubmission by cross-referencing content in the PMTA. FDA believes that including content in a PMTA by cross-referencing to a PMTA for the original tobacco product is appropriate for resubmissions because the referenced information will be presented in the proper context and format and will facilitate application review. In addition, an applicant may include content in a resubmission by cross-reference to a TPMF.

2. Content

The required content for resubmission is divided into two general categories: new content sections and cross-referenced content sections. The new content sections required under § 1114.17(c)(1) must contain the full text or cross-referenced text from a tobacco product master file. These sections may not include information by cross-reference to the PMTA or postmarket reports for the original tobacco product. The new content sections that must be included under § 1114.17(c)(1) are:

- general information (as described in paragraph § 1114.7(c));
- response to deficiencies (as described in § 1114.17(d)); and

- certification statement (as described in § 1114.17(e)).

A resubmission must also contain application sections that comprise information included by cross-reference to the PMTA for the original tobacco product and all additional information that is necessary to supplement or update the cross-referenced information. It is important to note that these cross-referenced sections must be accompanied by the full text of any updates or additional information that are necessary to tailor this information to the new tobacco product. These updates or additional information should consist of changes to application content that is not otherwise included as part of the response to deficiencies section. This information could include, for example, full reports of health risk investigations published after the applicant submitted the PMTA that received the marketing denial order. The cross-reference-based sections that must be included under § 1114.17(c)(2) are:

- descriptive information (as described in § 1114.7(d));
- product samples (as described in § 1114.7(e)). Please note that FDA may require the submission of product samples after it has received your application;
- labeling (as described in § 1114.7(f)), together with updates to the labeling made by the time of submission, if any;
- statement of compliance with 21 CFR part 25 (as described in § 1114.7(g));
- summary of all research findings (as described in § 1114.7(h));
- product formulation (as described in § 1114.7(i));
- manufacturing (as described in § 1114.7(j)); and
- health risk investigations (as described in § 1114.7(k)).

3. Response to Deficiencies

As described in § 1114.17(d), the response to deficiencies section required under § 1114.17(c)(1)(ii) must list and provide a separate response to each deficiency described by FDA in the marketing denial order, including all data and information necessary to complete each response, as well as any applicant-identified deficiencies. The deficiencies should be addressed in the order in which they are listed in the marketing denial order, followed by applicant-identified deficiencies. Where an applicant modifies the original tobacco product to address the deficiencies outlined in the marketing denial order, the applicant must also include: (1) a full description of each modification to the product and comparisons of that change to the original version described in the PMTA for the original tobacco product and (2) all data and information relating to each modification to the product that would be required in an application under § 1114.7.

4. Certification Statement

Under § 1114.17(e), the certification statement required under § 1114.17(c)(1)(iii) must be signed by an authorized representative and, in addition to the certification required under § 1114.7(*l*) for standard PMTA, must certify either: (1) that the application addresses all deficiencies specified in the marketing denial order and is being submitted for a tobacco product that is identical to the product for which FDA issued a marketing denial order or (2) the application addresses all deficiencies and the tobacco product is distinct from the original tobacco product, but the only modifications to the original tobacco product are those identified in the certification.

IX. FDA Review (Part 1114, Subpart C)

A. Communications Between FDA and Applicants (§ 1114.25)

Section 1114.25 sets forth general principles for the communications between FDA and applicants and is intended to provide more information to applicants about FDA communications. Section 1114.25 explains that, during the course of FDA's review of an application, FDA may seek to communicate with applicants about relevant matters including scientific, medical, and procedural issues that arise during the review process. Communications regarding human risk issues may arise if adverse experience reports exist for the tobacco product.

FDA received come comments regarding its communications with applicants, as discussed below.

(Comment 94) Some comments mentioned that while FDA states that it encourages applicants to meet with FDA, this is not what often happens. Instead of face-to-face meetings, the comment noted that FDA often provides written responses instead. The comment argued that there is no substitute for face-to-face meetings and encourages FDA to include provisions in the PMTA rule related to presubmission meetings that includes standards for face-to-face meetings.

(Response 94) FDA may use a variety of methods to communicate with applicants such as telephone conversation, letters, emails, or face-to-face meetings depending on the circumstances and issues. Furthermore, as discussed in the guidance entitled "Meetings with Industry and Investigators on Research and Development of Tobacco Products," while an applicant may request a face-to-face presubmission meeting, FDA may determine that this type of meeting is unnecessary and instead provide a written response to the questions raised in the meeting request. If an applicant feels that the written responses are insufficient, it may submit a subsequent request for a meeting.

FDA documents any communications regarding a PMTA in accordance with 21 CFR 10.65. While applicants may contact FDA with questions, as a general matter, FDA does not provide applicants with predecisional details about an ongoing application review, such as whether an initial submission is sufficient to receive a marketing granted order or the date and time at which FDA will act on an application. For additional information on requesting a face-to-face presubmission meeting, please consult the guidance for industry and investigators entitled "Meetings with Industry and Investigators on Research and Development of Tobacco Products."[34]

B. Review Procedure (§ 1114.27)

Section 1114.27 describes the procedures by which FDA would review a PMTA. When an applicant submits a PMTA, FDA performs an acceptance review of the submission. Currently, FDA performs its acceptance review of all premarket submissions based upon the criteria set forth in § 1105.10. The rule incorporates and builds upon these general criteria to set PMTA-specific acceptance criteria. Under the rule, FDA may refuse to accept an application for further review if, upon initial review, it:

- does not comply with the applicable format requirements for the type of PMTA (i.e., § 1114.7(b) for a standard PMTA, § 1114.15 for a supplemental PMTA § 1114.17 for a resubmission);
- is not administratively complete because it does not appear to contain the information required by the applicable application content requirements section. This means that the content required for the type of PMTA must be readily and easily identifiable as part of a cursory review of the application (i.e., a standard PMTA must appear to contain

[34] Available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/meetings-industry-and-investigators-research-and-development-tobacco-products.

information required by § 1114.7, a supplemental PMTA must appear to contain information required by § 1114.15, and a resubmission must appear to contain information required by § 1114.17). The acceptance review would assess the facial completeness of a submission only, and would not be an indepth, technical review. Examples of submissions that FDA would refuse to accept under this rule include, but are not limited to, applications that do not appear to contain:

- Labeling (as required by § 1114.7(f));
- Design parameter information (as required by § 1114.7(i)(2)(ii));
- An environmental assessment (as required by § 1114.7(g)); or
- A literature search (as required by § 1114.7(k)(2)).

- does not pertain to a tobacco product that is subject to chapter IX of the FD&C Act, as required by § 1105.10(a)(1). Under this provision FDA would refuse to accept the PMTA if it does not pertain to a product that is subject to the jurisdiction of CTP. CTP has premarket review jurisdiction over products that meet the definition of "tobacco product" in section 201(rr) of the FD&C Act and are subject to chapter IX of the FD&C Act either in section 901(b) of the FD&C Act or by regulation. Therefore, FDA will refuse to accept submissions for a product that is a drug under the definition in section 201(g)(1), a device under section 201(h), a combination product as described in section 503(g) of the FD&C Act, or otherwise does not meet the definition of a tobacco product; and
- may otherwise be refused under § 1105.10.

Once FDA has completed its acceptance review under § 1114.29(a)(1), FDA will issue a letter to the applicant informing it of FDA's decision. If FDA accepts the application for further

review, it will issue an acceptance letter to the applicant that specifies the STN for the PMTA. If FDA refuses to accept the application, it will issue a letter to the applicant that identifies the reasons, where practicable, that prevented FDA from accepting the application. The applicant may, after FDA has refused to accept a PMTA, correct the deficiencies and submit a new PMTA under § 1114.7. Because FDA is not issuing a marketing denial order under § 1114.33 when it refuses to accept a submission, an applicant may not utilize the resubmission format described in § 1114.17 to address the flaws outlined by FDA.

FDA implements the acceptance review procedures under authority of sections 701(a) and 910 of the FD&C Act. The content, format, and jurisdiction requirements that an application must meet to be accepted for review will ensure that FDA will be able to efficiently review applications and consider only applications that are more complete and better prepared for further review. By refusing to accept submissions that have clear deficiencies, FDA will be able to focus its resources on those submissions that are more likely to be filed for substantive review. After FDA accepts a PMTA for review, FDA may request product samples as described in § 1114.7(e).

FDA will also conduct a filing review to determine whether the application contains sufficient information to permit a full substantive review of the application. FDA may refuse to file a PMTA if:

- the PMTA does not include sufficient information required by section 910(b)(1) of the FD&C Act and by § 1114.7, 1114.15, or 1114.17, as applicable, to permit a substantive review of the application. These requirements include a sufficient EA for each type of PMTA, the absence of which is a reason for which FDA may refuse to file an application under § 25.15. The filing requirements also include product samples if required by FDA

after application acceptance. FDA's filing review is an examination of the submission to ensure it contains adequate technical information for FDA's substantive review of the application to proceed. Unlike the acceptance review, which considers whether a submission meets basic content, format, and jurisdiction requirements as described above, the filing review is a more indepth review to ensure the application contains sufficient information for initiating substantive review. For example, during acceptance review, FDA will check whether the PMTA appears to contain product design parameters, but during filing review, FDA will review to determine whether it contains the correct design parameters for the product category and has a value for each design parameter required by § 1114.7(i)(2)(ii). FDA implements the filing review requirements under authority of section 701 of the FD&C Act to improve the efficiency of the PMTA review process. By determining whether a PMTA contains sufficient information prior to conducting substantive review, FDA can commit the considerable resources necessary to conduct substantive review of a PMTA to only those submissions that are prepared for review;

- the application does not contain substantive information regarding certain specified broad categories of information that must be addressed in every PMTA for FDA to determine whether permitting the marketing of the new tobacco product would be APPH. FDA considers substantive information to be information that is relevant to the subject it claims to support and has evidentiary support. Bare statements that the marketing of the tobacco product is unlikely to result in tobacco product initiation or that it has no abuse liability without supporting information do not constitute the types of substantive information necessary for application filing. This information can come from a variety of

sources including investigations conducted by the applicant, investigations conducted using a different product that the applicant can bridge to its new tobacco product (as described in section VII.B.13.a.), or published reports of investigations that apply to, or are bridged to, the new tobacco product (such as those found in the literature search required by § 1114.7(k)(2)). Section 1114.27(b)(1)(ii) requires a PMTA to contain substantive information regarding certain categories of investigations described in § 1114.7(k)(1). While FDA retains discretion to file applications as set forth in § 1114.27(b)(1), we generally intend to refuse to file each application that does not meet the substantive information requirement in paragraph (ii). Where there is no substantive information that is published or known to an applicant regarding any of the categories of information outlined in this section, including information in scientific literature or an investigation that an applicant could bridge to its product, an applicant would be required to conduct its own investigations and include the resulting full report in its PMTA in order to meet the requirements for filing. In general, FDA expects that manufacturers seeking to market a new product in accordance with the requirements of the statute will have access to information to meet these requirements for filing.[35]

FDA is implementing the application filing requirement under its authority in sections 910(b) and 701(a) of the FD&C Act. As described in section VIII.D, FDA needs information regarding the potential health risks of the new tobacco product, the likelihood of changes in tobacco product use behavior, and the potential health consequences associated with those changes in behavior to determine the potential risks and benefits to the health of the population

[35] Information that is available to applicants includes, for example, the studies FDA has funded, published, and made available to the public, which are consolidated on our website. This database includes many ENDS related studies and can be searched by key terms (e.g., e-cigarettes): https://www.fda.gov/tobacco-products/research/ctp-supported-tobacco-regulatory-research-projects.

as a whole under section 910(c)(4) of the FD&C Act. Refusing to file PMTAs that contain no information regarding these broad categories of information allows FDA to efficiently enforce the premarket review requirements of section 910 of the FD&C Act by avoiding the significant expenditure of resources it would otherwise commit to the substantive review of applications that clearly lack sufficient information to receive a marketing granted order. FDA expects that this efficiency will significantly benefit those applicants seeking timely consideration of complete, high-quality applications.

Section 1114.27(b)(1)(ii) requires a PMTA to contain at least some amount of substantive information regarding each of the following topics:

- the health risks of the new tobacco product as described in either § 1114.7(k)(1)(i)(A), (B), or (C)). Information regarding the health risks of the new tobacco product is a basic piece of information that FDA needs to determine the potential risks and benefits to the population as a whole associated with changes in tobacco use behavior;
- the health risks of the new tobacco product compared to the health risks that are generally presented by both tobacco products in the same category as well as tobacco products in at least one different category that are used by the consumers an applicant expects to use their new tobacco product (as described in a portion of § 1114.7(k)(1)(i)(D)). To demonstrate the health risks that are generally presented by the same, or a different, product category, applicants may use the health risks generally presented by a product category as a whole, or the health risks that are presented by specific products that are generally representative of the risks of the product category as a whole (e.g., products that represent a significant share of the market for the product category). Comparative health risk information is a required part of FDA's review of an

application because, as described in section VII.B.13.a, it can demonstrate the potential risks and benefits that current tobacco users could face if they switched to the new tobacco product or used it in conjunction with their current tobacco product;

- the abuse liability of the new tobacco product (as set forth in § 1114.7(k)(1)(ii)(A)). Information regarding abuse liability indicates the likelihood of users to become addicted to the product and face the health risks posed by product use over the long term, and may provide insight into the use and adoption of the product, which FDA must consider as part of its determination of the risks and the benefits of permitting the marketing of the new tobacco product to the population as a whole under section 910(c)(4) of the FD&C Act;
- how consumers actually use the product, including use topography, product use frequency, use trends over time, and how such use affects the health risks of the product to individual users (as set forth in § 1114.7(k)(1)(ii)(B)). Information regarding how consumers will actually use the new tobacco product is necessary to FDA's review of a PMTA because it helps demonstrate the health risks of the new tobacco product by showing the levels, and frequency, of exposure to HPHCs and other toxic substances contained in and delivered from the new tobacco product;
- the potential impact that the marketing of the new tobacco product would have on the likelihood that current tobacco product users would start using the new tobacco product, use the product in conjunction with other tobacco products, and, after using the product, switch to other tobacco products that may present increased risks to individual health (i.e., any of the information described in either § 1114.7(k)(1)(ii)(C), (D), (E), or (F)).

Information regarding potential changes to tobacco product use of current tobacco product users is a required basis for FDA's findings under 910(c)(4)(A);

- the potential impact of the product and its label, labeling, or advertising, to the extent advertising has been studied, on tobacco product use behavior of current nonusers of tobacco products (i.e., any of the information described in § 1114.7(k)(1)(iii)). Information regarding potential impact that the marketing of the new tobacco product would have on tobacco product initiation by current nonusers of tobacco products is a required basis for FDA's findings under 910(c)(4)(B);
- the potential impact of the product and its label, labeling, or advertising (to the extent that advertising has been studied) on individuals' perception of the product, and individuals' use intentions (as described in § 1114.7(k)(1)(iv)). This information is important to FDA's review of a PMTA because perceptions of the health risk of the product can influence decisions to use the product and, as described in section VII.B.6, exposure to advertising can have a significant impact on the likelihood that nonusers of tobacco products, particularly youth, will initiate tobacco product use. Without information regarding perceptions and use intentions, FDA will be unable to complete its required determination under section 910(c)(4)(B) of the FD&C Act of the increased or decreased likelihood that nonusers of tobacco products will initiate tobacco product use. It is important to note that this substantive information requirement does not require an applicant to develop or study advertising for the purpose of filing;
- the ways in which human factors can affect the health risks of the new tobacco product (i.e., any of the information described in § 1114.7(k)(1)(v)). This information is

important to FDA's review of a PMTA because it provides an assessment of use-related health hazards for the tobacco product.

FDA may also refuse to file a PMTA if:

- the PMTA contains a false statement of material fact; or
- the PMTA is a supplemental PMTA that does not comply with § 1114.15 or the PMTA is a resubmission that does not comply with § 1114.17. FDA may refuse to file a supplemental PMTA or a resubmission that contains all of the required content but does not meet the criteria for when a supplemental PMTA or a resubmission may be submitted. For both supplemental PMTAs and resubmissions, this could occur when, as discussed in §§ 1114.15(a) and 1114.17(a), the modifications to the original tobacco product are not appropriate to review in these formats. As described in § 1114.15(a), FDA may also refuse to file a supplemental PMTA where the marketing granted order for the original tobacco product has been temporarily suspended (except where authorized in writing by FDA) or has been withdrawn. As described in § 1114.17(a), FDA will refuse to file a resubmission where the marketing denial order for the original tobacco product states that the applicant may not use the resubmission format. If FDA refuses to file an application, it will send a letter to the applicant identifying, where practicable, the deficiencies that prevented FDA from filing the application.

FDA received many comments regarding review procedures, as discussed below.

(Comment 95) One comment stated that FDA should include clear deadlines for the completion of acceptance and filing reviews. The comment stated that doing so would allow applicants to schedule the submission of PMTA in a way to ensure that the application is accepted and filed before the end of FDA's enforcement discretion policy. The comment stated

that in addition, it is inconsistent with FDA policies for other regulated product types such as the deadline of 60 days for the filing of new drug applications.

(Response 95) To the extent that this comment concerns the compliance policy for the submission of PMTAs as a result of the deeming final rule, it is outside the scope of this rule. As a general process matter, FDA declines to set a deadline for acceptance and filing reviews both because it would not affect the 180-day review period and because FDA wishes to retain some amount of flexibility in its review process as it gains more substantial experience in reviewing PMTAs. Unlike with new drug applications, FDA's decision to file an application does not affect the statutory 180-day review period.[36] As described later in this section of the document, regardless of when in the process FDA files a PMTA, the 180-day review period begins when the last piece of information necessary to complete a PMTA is received by FDA.

(Comment 96) Multiple comments expressed opinions regarding the standards for application acceptance and filing. One comment supported the filing requirements, urging FDA to apply a standard of review that will enable it to distinguish between applications that contain scientific information that is arguably sufficient to address the issues relevant to determining whether the marketing of a product is APPH, and those applications that do not. Another comment requested that FDA clarify what an application must contain to be filed for review under § 1114.27(b), stating that what constitutes "sufficient information" under the filing standard is not addressed in the rule. Another comment stated that FDA has failed to make any meaningful distinction between the information that satisfies FDA's ability to review a PMTA and the "sufficient information" necessary for industry to obtain a marketing order. In addition,

[36] Compare section 505(c)(1) of the FD&C Act "within one hundred and eighty days after filing of an application" to section 910(c) "as promptly as possible, but in no event later than 180 days after a receipt of an application under [910(b)(1)]."

several comments requested that FDA clarify the requirements related to acceptance, filing, and substantive review because it was unclear what threshold of information must be in a PMTA to meet the requirements of each.

(Response 96) As described in the rule, FDA may refuse to accept a PMTA under § 1114.27(a)(1) where it does not appear to have the information required by the rule. This is a cursory check for the presence or absence of information at a very high level (e.g., does the application contain labeling) and is intended to eliminate low-quality submissions. FDA may refuse to file an application where it does not contain sufficient information to permit a substantive review by FDA. Filing review is a limited examination to determine whether the technical elements of the application contain the information required by § 1114.7 (or other section as applicable), which FDA considers "sufficient information" at that time that would allow FDA to determine whether the application demonstrates the marketing of the product would be APPH. The "sufficient information" necessary to receive a marketing granted order is information that does, in fact, demonstrate the marketing of the product would be APPH and the PMTA meets the other requirements of section 910(c)(1)(A)(i) of the FD&C Act.

(Comment 97) Multiple comments stated that FDA should permit applicants to omit certain required information. One comment referenced the regulations for medical devices, in which FDA states that if an applicant believes that particular information is not applicable, an applicant can identify the omitted information and justify the omission. The comment stated that FDA cannot expect each applicant to provide information that will satisfy every requirement and that justified omissions should not result in marketing denial orders as currently stated in the PMTA proposed rule. Another comment requested flexibility regarding requirements to submit

information it does not consider to be dispositive of health risks, such as the pharmacological profile.

(Response 97) FDA declines to make any revisions in response to these comments. As discussed throughout the rule, section 910(b)(1) of the FD&C Act describes the required contents of a PMTA upon which FDA must base its determination under section 910(c)(1)(A) of whether to issue a marketing granted order. FDA has carefully described why the information required by this rule is important to FDA's determination of whether a marketing granted order should be issued and specifies where certain information would need to be submitted only if applicable to the new tobacco product that is the subject of the PMTA.

(Comment 98) One comment stated that FDA should file PMTAs for substantive review where they contain information about the various topics discussed in the rule, even where they do not include the final results of all referenced studies, so long as the applicant includes the study protocol and the expected date by which the applicant would submit the final study report to FDA. The comment also requested FDA identify application deficiencies before making its filing decision and request an amendment containing the specific information necessary for the application to be filed and do so under a reasonable timeline for the applicants' response before FDA issues a refuse to file decision.

(Response 98) FDA is establishing the filing requirements in order to encourage the submission of applications that contain the information FDA needs to determine whether a PMTA meets the requirements to receive a marketing granted order. FDA intends to refuse to file applications that do not contain the information required by § 1114.27(b), regardless of whether the applicant is conducting or sponsoring ongoing studies at the time of submission. FDA declines to, in every instance, identify application deficiencies before making its filing

decision. In some circumstances, where the PMTA meets the information requirements in § 1114.27(b), the fact that a study has not yet been completed might not affect FDA's filing decision; however, this is a fact specific determination based on the content of each PMTA.

FDA generally does not intend to submit requests for amendments before it makes its decision to file the application for substantive review and applicants cannot expect to rely on FDA feedback to complete a PMTA after submission. FDA has provided detailed information regarding what application content is necessary for filing in this rule.

(Comment 99) Another comment stated that the final rule should be amended to clarify that FDA's decisions to refuse to accept (RTA) and refuse to file (RTF) PMTAs are subject to judicial review. The comment requested that FDA amend the rule to state that RTA and RTF letters constitute a denial within the meeting of 910 and 912 of the FD&C Act.

(Response 99) FDA disagrees with the contention that its decision to RTA or RTF constitutes a denial of a PMTA as described in section 910(a)(2)(A) of the FD&C Act; rather, refusing to accept or refusing to file constitutes a determination that the submission is either incomplete or does not conform to basic administrative requirements and, therefore, is not ready for substantive review. FDA makes its determination of whether to grant or deny the applicant a marketing authorization order only after conducting substantive review. Refusing to accept or refusing to file an application is a decision that is made without prejudice to any future submission and, as described in section IX.B, FDA intends to provide information regarding how the applicant can address the specific issues that led FDA to RTA or RTF the submission. It is important to note that section 910(c)(1)(A) requires FDA to grant or deny an order within 180 days after receipt of an application under section 910(b) and where FDA chooses to RTA or RTF

an application, it is because it lacks required information and, therefore, does not constitute an application under section 910(b) of the FD&C Act.

After FDA files an application, it will begin its substantive review of the PMTA. Within 180 days after receipt of an application described in section 910(b)(1) of the FD&C Act, FDA intends to complete its review of a PMTA and, as described in § 1114.29, act on the application, except as described in §§ 1114.9 and 1114.27(c)(4) through (5).

(Comment 100) One comment stated that the final rule should be amended to clarify that acceptance and filing reviews do not extend the 180-day review clock.

(Response 100) FDA's acceptance and filing reviews do not extend the 180-day review period. To determine when the 180-day period begins, FDA generally relies on the date the last piece of information necessary to complete the submission is received by CTP's Document Control Center or the FDA laboratory (for product samples), not the date that the applicant sent it. It is important to note the event that starts the 180-day review clock is the receipt of an application that meets the requirements of section 910(b)(1) of the FD&C Act which also includes information required by the rule. Given that product samples are likely to be required after application acceptance, the review period would typically begin, at the earliest, when FDA receives product samples. Similarly, if an application is missing other pieces of required information, the review period would begin only upon receipt of that information. FDA intends to provide applicants with notice of the date on which the 180-day review period began, as well as notice of when it is paused, resumed, or reset.

(Comment 101) Multiple comments suggested that because FDA acknowledges the supplemental PMTA format will improve the efficiency of the review process, FDA should shorten the 180-day review period for supplemental PMTAs accordingly. Some comments

pointed to the application supplement framework used by FDA for other products, such as drugs, and urged FDA to adopt a tiered system with different notification requirements and timeframes for review corresponding to the nature of the modification and the evidence needed to support it. In addition, one comment stated that FDA should provide clarity about the product modifications for which an applicant would be able to submit a supplemental PMTA, stating that the list of examples provided is insufficient and the suggestion to request a meeting with FDA to discuss supplemental PMTA submission would lengthen what should be an abbreviated process.

(Response 101) FDA agrees that supplemental PMTAs will improve the efficiency of the PMTA review process; however, FDA declines to create a standard shortened review period because it does not yet have any experience in conducting such reviews. In addition, supplemental PMTAs could contain substantial information that was not included in the original PMTA, such as the addition of Bluetooth capability for ENDS which may affect device functionality and, that may affect the review time. The application supplement notification procedures and timelines for other product types regulated by FDA are not only based on different statutory authorities, they are also the result of decades of experience in conducting such reviews. In addition, while FDA will have a 180-day review period to review a supplemental PMTA application, FDA intends to promptly act on the application, which might take fewer than 180 days.

There are four instances in which the 180-day review period after receipt of a complete PMTA would not be 180 consecutive calendar days. First, as described in § 1114.9, the submission of or request for amendments may result in changes to the number of calendar days in the review period. Where FDA requests a minor amendment, the issuance of this request would result in a pause of the review period and receipt of the amendment would resume the

review period. As described in section VIII.C, the submission of a major amendment is considered to be the submission of a new PMTA, which resets the 180-day review period.

The second instance in which FDA's 180-day review period would not be 180 consecutive calendar days after receipt of a complete PMTA is where a new tobacco product, if introduced or delivered for introduction into interstate commerce, would be adulterated or misbranded due to the domestic manufacturer or importer being in violation of the user fee requirements of part 1150 (21 CFR part 1150).[37] Situations in which a new tobacco product would be adulterated or misbranded for failure to comply with user fee requirements are described in § 1150.17(a) and (b), which include failure to pay user fee assessments and failure to submit required reports. In this situation, FDA intends to pause the 180-day review period until any violation of the user fee requirement of part 1150 is resolved. FDA implements this provision under its section 701(a) authority to issue regulations for the efficient enforcement of the FD&C Act. It would be inefficient for FDA to expend the significant resources necessary to review an application for a product that could not be legally marketed. It would also not be reasonable for FDA to complete its review and issue a marketing granted order for a product that, if it is put into interstate commerce, would immediately be adulterated or misbranded and subject to FDA enforcement action. While FDA will not refuse to accept or refuse to file an application on the basis that the product would be adulterated for failure to pay user fees, FDA will not complete its review of a PMTA until the applicant is in compliance with part 1150. FDA will take this action, rather than refusing to accept or refusing to file an application, because noncompliance with the requirements of part 1150 can often be resolved quickly.

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[37] Currently, only the manufacturers of cigarettes, cigars, snuff, chewing tobacco, pipe tobacco, and RYO tobacco are subject to the requirements of part 1150. See the final rule, "Requirements for the Submission of Data Needed to Calculate User Fees for Domestic Manufacturers and Importers of Cigars and Pipe Tobacco" (81 FR 28707) (May 10, 2016), for more information.

The third instance in which FDA's 180-day review period would not be 180 consecutive calendar days after the receipt of a complete PMTA is where FDA is prevented from scheduling or conducting inspections of the manufacturing sites or the sites or entities involved with the clinical and nonclinical research (including third parties and contract research organizations) prevent FDA from completing its review of the PMTA in a timely manner. Where this occurs, FDA may pause the 180-day review period for the number of days necessary to complete the inspection after a delay occurs. FDA has experienced delays in both scheduling and conducting inspections, which results in FDA not having the information it needs to complete its required review in 180 consecutive calendar days.

The fourth instance in which FDA's 180-day review period may not be 180 consecutive calendar days after the receipt of a complete PMTA is where FDA determines after application filing that the applicant has not submitted an adequate EA. NEPA and regulations issued by the Council on Environmental Quality (42 U.S.C. 4332(2); 40 CFR parts 1500 to 1508) require FDA to assess, as an integral part of its decision-making process, the environmental impacts of any proposed Federal action to ascertain the environmental consequences of that action on the quality of the human environment and to ensure that the interested and affected public is appropriately informed. FDA has implemented the NEPA and CEQ requirements in part 25. Under § 25.15(a), failure to submit an adequate EA is grounds for refusing to authorize an application. Consistent with § 25.15(a), FDA may refuse to authorize the marketing of a new tobacco product where a PMTA contains an inadequate EA.

As described in § 1114.27(c)(4), FDA may conduct inspections of the applicant's manufacturing sites, and sites and entities involved with clinical and nonclinical research (including third parties and contract research organizations) to support FDA's review of the

PMTA. Inspecting the facilities and controls described in the application will allow FDA to ensure the applicant can manufacture the product in accordance with the manufacturing practices described in the application and would help FDA determine under section 910(c)(2) of the FD&C Act whether such practices conform to an applicable product standard issued under section 907 of the FD&C Act or tobacco product manufacturing practice requirement issued under section 906(e) of the FD&C Act, when in effect. Inspecting sites and entities involved with clinical and nonclinical research, including their records (such as those required to be kept under § 1114.45), will allow FDA the opportunity to verify the study findings and data that the applicant relies upon in the PMTA to demonstrate that the new tobacco product should receive a marketing granted order. Under § 1114.33, failure to grant FDA access at a reasonable time and in a reasonable manner, an opportunity to inspect these sites and have access to, copy, and verify all records pertinent to the application may result in the issuance of a marketing denial order because FDA would not be able to determine whether permitting the marketing of the new tobacco product would be APPH. During an inspection, an applicant should ensure that:

- all pertinent records can be viewed;
- documents written in a language other than English can be translated into English, if requested. Documents that have been translated from another language into English should be accompanied by a signed statement by an authorized representative of the manufacturer certifying that the English language translation is complete and accurate, and a brief statement of the qualifications of the person that made the translation; and
- if the tobacco product is in production (domestic or foreign) and is intended for U.S. commercial distribution, FDA can view the product being manufactured.

C. FDA Action on an Application (§ 1114.29)

Section 1114.29 lists six actions that FDA may take after receiving an application:

- first, FDA could refuse to accept the application, as described in § 1114.27(a);
- second, FDA could issue a letter administratively closing the application. This could occur where an applicant fails to respond to a request for an amendment within the time period specified in the amendment request under § 1114.9(b) or requests to withdraw an application under § 1114.11. In the proposed rule, FDA had previously stated that "this could occur where an applicant fails to response to a request for an amendment within 180 days." FDA changed this language in the final rule to be the time period to respond to the amendment request to reflect that fact that the time for response might vary according to the complexity of the amendment request and thus could be a period other than 180 days (e.g., an amendment request for relatively simple information might have a shorter response period).
- third, FDA could issue a letter canceling the application if FDA finds it mistakenly accepted the application (e.g., the application does not pertain to a new tobacco product, or the application was submitted in error);
- fourth, FDA could refuse to file the application as described in § 1114.27(b);
- fifth, FDA could issue a marketing granted order as described in § 1114.31; or
- sixth, FDA could issue a marketing denial order as described in § 1114.33.

D. Issuance of a Marketing Granted Order (§ 1114.31)

1. The Requirements to Receive a Marketing Granted Order

Under section 910(c)(1)(A)(i) of the FD&C Act, FDA will issue a marketing granted order for a new tobacco product after its review of a PMTA if it finds that none of the grounds for denial specified in section 910(c)(2) of the FD&C Act applies to the application. This means

that in order for FDA to issue a marketing granted order for a new tobacco product, FDA must be able to determine the following:

a. There is a showing that permitting the marketing of the new tobacco product would be APPH. Under section 910(c)(4) of the FD&C Act, FDA's finding that permitting the marketing of a new tobacco product would be APPH must be determined with respect to the risks and benefits to the population as a whole, including users and nonusers of tobacco products, and taking into account:

- the increased or decreased likelihood that existing users of tobacco products will stop using such products and
- the increased or decreased likelihood that those who do not use tobacco products (including youth and young adults) will start using such products.

Finding that there is a showing that permitting the marketing of a new tobacco product would be APPH is a complex determination that must be made with respect to risks and benefits to the population as a whole, considering the likelihood of changes in tobacco product use behavior (including initiation and cessation) caused by the marketing of the new tobacco product. When determining whether the marketing of a particular new tobacco product would be APPH, FDA will evaluate the factors in light of available information regarding the existing tobacco product market, tobacco use behaviors, and the associated health risks at the time of review. As described in section 910(c)(5) of the FD&C Act, the types of scientific data that FDA will consider in making its determination can include well-controlled investigations and, where appropriate, other valid scientific evidence that FDA determines to be sufficient to evaluate the tobacco product. FDA will consider the information supplied in the application

together with any other relevant sources of information, including a report or recommendation from TPSAC, when applicable, in making its determination.

Section 910(c) of the FD&C Act requires FDA to consider an array of potential risks and benefits of each new tobacco product with respect to the population as a whole when determining whether permitting the marketing of a new tobacco product would be APPH. As set forth in the criteria for withdrawing a marketing granted order in section 910(d)(1)(A) of the FD&C Act, FDA must continue to find the product meets the APPH standard over time.

FDA received many comments regarding the requirements to obtain a marketing granted order, as discussed below.

(Comment 102) Several comments stated that FDA has failed to explain or justify how it is interpreting and applying the APPH standard when evaluating PMTAs and must do so to allow a determination of whether its issuance of PMTA marketing orders is arbitrary and capricious. In addition, some comments expressed concern that the lack of articulated definitions and standards regarding the APPH standard would leave applicants guessing at what might satisfy the standard. In addition, another comment stated that failing to provide this essential direction could increase the likelihood of arbitrary and inconsistent decisions.

(Response 102) FDA disagrees with the assertion that is has failed to provide adequate information concerning the APPH standard in section 910(c)(2) of the FD&C Act. Similar to premarket standards for other products, such as medical devices or drugs, FDA does not provide a precise definition of the standard but instead provides information regarding the types of information that can be used to demonstrate the standard has been met. FDA intends to consider the marketing of a new tobacco product to be APPH where a PMTA contains sufficient valid scientific evidence to demonstrate that the potential risks and benefits of the marketing of the

new tobacco product would likely have a net positive effect on the health of the population as a whole, which includes youth, young adults, and other relevant vulnerable populations. This could include a variety of different types of evidence that may provide FDA with an overall assessment of the potential effect permitting the product to be marketed may have on tobacco-related morbidity and mortality. For example, FDA may consider scientific evidence such as whether levels of HPHCs and other constituents in the new tobacco product are similar or lower than levels of similar tobacco products currently on the market (see section VIII.B.9.a.v of this document), whether the use of the tobacco product has a lower risk of disease than the use of a similar product (see section VIII.B.13.a.ii), whether consumers are likely to use the product in a manner that will lead to possible lower risks (see section VIII.B.13.a.iv), and whether the marketing of the new tobacco product affects the likelihood of nonuser uptake, ways in which the product may be designed to limit or prevent youth access and use, cessation rates or other significant shifts in user demographics such that it decreases morbidity and mortality from tobacco product use, including youth, young adults, and other vulnerable populations (see section VIII.B.6.b). As described in this section, the APPH standard requires a balancing of product-specific potential risks and benefits. For example, an applicant maybe able to demonstrate that their product is APPH by providing sufficient valid scientific evidence to show, among several key considerations, that the tobacco product reduces morbidity and mortality. This could include showing the potential reductions in disease risk as compared to other tobacco products and weighing that against the potential for nontobacco users to use tobacco product and the accompanying potential changes in disease risk among new tobacco users. As a result, the factors that could help demonstrate that the marketing of a particular new tobacco product would be APPH might not support the marketing of a different new tobacco product. As a general

example, if an application demonstrates that using a new tobacco product would present significantly less toxicological risk to individual health than cigarettes in a marketplace where many addicted users currently smoke cigarettes, it could likely, depending on other factors, receive an order where the PMTA demonstrates that the vast majority of individuals who would use the product would be current users of cigarettes who otherwise would not have quit and would switch to using the new product exclusively. This can be seen in FDA's determination to authorize the marketing of a tobacco product that demonstrated, among several key considerations, that the product produced fewer or lower levels of some toxins than conventional cigarettes.[38] On the other hand, where a PMTA for a different tobacco product shows that individuals that would use the new tobacco product are predominately current users of tobacco products that have less toxicological risk to individual health, including products within the same product category, the application is likely, again depending on other factors, to result in the issuance of a marketing denial order because the product is not likely to have a net benefit to the population as a whole. As discussed in section VIII.B.14 of this document, understanding of the effect the new tobacco product may have on the health of the population as a whole, which includes youth, young adults, and other vulnerable populations, such as effects on tobacco use initiation, switching, and cessation, and reductions in premature mortality, or increases in life-years lived, directly informs FDA's determination as to whether permitting the marketing of the new tobacco product would be APPH. The discussion should include all of the information in the PMTA regarding the product and its potential effects on health, including, but not limited to adverse experiences, tobacco use behavior, and tobacco use initiation to provide an overall assessment of the potential effect that permitting the product to be marketed has or may have on

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

overall tobacco-related morbidity and mortality including on youth, young adults, and other vulnerable populations.

In addition to the information provided throughout this document, applicants may obtain information regarding how the APPH standard can be met from marketing granted orders and decision memoranda that FDA posts on its website.

(Comment 103) One comment stated that where an applicant proposes a restriction on the marketing of its product, such as a limitation on sales, FDA should apply that restriction in making its APPH determination.

(Response 103) FDA will consider proposed restrictions on the sales and distribution of a tobacco product as part of its review of a PMTA and may determine that it should impose such restrictions where FDA determines they are APPH. However, FDA's review is not constrained by such proposals and FDA intends to consider a variety of factors in determining whether it should include those restrictions, including, but not limited to, whether it would be feasible or realistic for the applicant to implement such restrictions, or the ease with which the implementation of the restrictions may be monitored or enforced as they pertain to all population groups, including among groups disproportionately affected by tobacco product use. FDA will also consider and may impose restrictions on sales and distribution different from, or in addition to, those proposed by the applicant.

(Comment 104) One comment stated that FDA should focus its evaluation on the population segments most likely to be affected by the marketing of the new tobacco product and require applicants to show a public health benefit for those specific groups.

(Response 104) FDA declines to make changes in response to this comment. FDA is required by section 910(c)(4) of the FD&C Act to determine its APPH finding based upon the

risks and the benefits to the population as a whole. This includes consideration of all parts of the population, including those more likely to be affected by the marketing of the new tobacco product, and it is not limited to only the effect on specific population segments.

(Comment 105) One comment requested a clear regulatory definition of the APPH standard, with product category-specific guidance about what is required to meet the target, noting that it is missing from the proposed rule and is crucial for applicants as they develop the data needed to substantiate that a new tobacco product meets the APPH standard and prepare their applications. The comment recommended that FDA provide further clarity in the final rule as to the factors to be considered in an APPH analysis and how the Agency will weigh those factors. The comment requested that FDA provide clarification as to whether a showing of reduced morbidity and mortality is required to receive a marketing order, asserting that the structure of the statute and congressional intent make clear that Congress intended a marketing order under section 910 of the FD&C Act to be a less burdensome standard than the standard for a marketing order for a modified risk product under section 911of the FD&C Act. The comment also requested additional information regarding how FDA will determine whether a product has had a net positive effect on the health of the population as a whole, including whether each factor has a threshold finding.

(Response 105) FDA declines to set static requirements that a new tobacco product could meet and be considered to meet the APPH standard because the tobacco product marketplace and trends in consumer behavior that inform FDA's APPH determination are not static. The factors that could demonstrate that permitting the marketing of a new tobacco product would be APPH at one point in time might not support the same determination with respect to a similar product in the future. For example, FDA may consider, in conjunction with other available data regarding

the new tobacco product, information showing that a product has reduced morbidity and mortality to help demonstrate that the potential risks and benefits of marketing the new tobacco product would have a net positive effect on the health of the population as a whole (which includes youth, young adults, and other vulnerable populations).

However, FDA does not make its APPH determination on one static set of requirements. FDA makes its APPH determination in consideration of the existing market (e.g., the products on the market, tobacco product use behaviors) at the time the determination is made. For example, FDA has authorized marketing of a product that would, among other things, potentially reduce nicotine dependence in adult smokers who may also benefit from decreasing nicotine exposure and cigarette consumption. In consideration of the existing market and based on the information provided by the applicant, FDA was able to determine that nonsmokers, including youth, would also be unlikely to start using the product, and those who experiment would be less likely to be become addicted than people who experiment with conventional cigarettes.[39] As the tobacco product market changes over time, the potential risks and benefits of marketing a new tobacco product to the population as a whole might also change. A new tobacco product that receives a marketing granted order under the current market conditions might not receive an order at a future time in which fewer individuals are using products that present higher levels of risk to individual health or such products are no longer on the market. Due to the nature of the Federal rulemaking process, if FDA were to codify what could satisfy the APPH standard under market conditions that are current at the time, FDA may not be able to update such standards in a timely manner.

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

(Comment 106) Several comments stated that FDA has failed to explain or justify how it is interpreting and applying the APPH standard when evaluating PMTAs and must do so to allow a determination of whether its issuance of PMTA marketing orders is arbitrary and capricious. In addition, some comments were concerned that the lack of articulated definitions and standards regarding the APPH standard would leave applicants guessing at what might satisfy the standard. In addition, another comment stated that failing to provide this essential direction could increase the likelihood of arbitrary and inconsistent decisions.

(Response 106) FDA disagrees with the assertion that is has failed to provide direction concerning the APPH standard in section 910(c)(2) of the FD&C Act. FDA describes its interpretation of the APPH standard in details in this section, including the statement that FDA intends to consider the marketing of a new tobacco product to be APPH where a PMTA contains sufficient valid scientific evidence to demonstrate that the potential risks and benefits of the marketing of the new tobacco product would have a net positive effect on the health of the population as a whole.

(Comment 107) Multiple comments stated that FDA should require that PMTAs contain information demonstrating that all available steps have been taken to make the product as minimally harmful as possible in order for the marketing of a tobacco product to be considered APPH.

(Response 107) As described in section IX.D, FDA interprets the APPH standard in section 910(c)(2)(A) to require a showing that permitting the marketing of a new tobacco product would likely have at least a net benefit to public health based upon the risks and benefits to the population as a whole. Where an applicant meets this standard along with the other criteria in section 910(c)(2) of the FD&C Act, FDA will issue a marketing granted order.

(Comment 108) Multiple comments stated that FDA should impose a number of conditions that products must meet to receive a marketing granted order. One comment stated FDA should apply a more rigorous standard than it did in previous PMTA reviews by requiring an applicant demonstrate, among other things that its product is significantly less harmful than other products current on the market and that any increase in health risks is significantly smaller than the likelihood and size of the benefits it presents. Another comment stated FDA should impose specific requirements that a flavored tobacco product must meet to receive a marketing granted order, including requirements such as having no appeal to youth, being substantially less harmful than smoking, and promoting complete cessation of tobacco products.

(Response 108) FDA declines to create a series of criteria that either all products or a specific subset of products must meet be in order for marketing of such products to be considered APPH as part of this rule. As described elsewhere in this section, FDA intends to consider marketing of a new tobacco product to be APPH where permitting its marketing would likely have at least a net benefit to public health based upon the risks and benefits to the population as a whole, which includes youth, young adults, and other vulnerable populations. While this determination would involve consideration of many factors, including some of the particular concerns cited by the comments, it will be made with respect to the risks and benefits to the health of the population as a whole, rather than whether a product meets each item in a series of specific criteria.

(Comment 109) Multiple comments made suggestions regarding how FDA should consider the risks and benefits that the marketing of the new tobacco product may have on specific groups of the population, with one comment emphasizing social justice concerns and highlighting the effects that the new tobacco product may have on disadvantaged or vulnerable

populations. Another comment stated that the FD&C Act does not permit FDA to weigh the risks and benefits a product may have on one group more strongly than another.

(Response 109) Section 910(c)(4) of the FD&C Act requires the finding of whether the marketing of a new tobacco product would be APPH to be determined with respect to the population as a whole. As noted elsewhere in this document, FDA has made edits to ensure the rule addresses the potential effects of permitting the marketing of a new tobacco product to vulnerable populations and FDA will consider the potential effects on such groups as part of its assessment of the effect on the population as a whole.

It is important to note that in order for FDA to issue a marketing granted order for a new tobacco product, section 910(c)(1)(A)(i) of the FD&C Act requires FDA to find there is "a showing" that the marketing of the new tobacco product would be APPH. FDA interprets this to mean that an applicant must submit sufficient information in its PMTA for FDA to be able to find whether the marketing of a product would be APPH. While FDA may consider outside sources of information during PMTA review, an applicant cannot rely on FDA to seek out or create additional data to fill information gaps that may exist in a PMTA. As discussed in section VIII.E., failure to submit sufficient information that FDA needs to make its required findings would result in the issuance of a marketing denial order.

This rule focuses primarily on PMTA review procedures and content requirements, particularly with respect to application acceptance and filing. An application may meet the acceptance and filing requirements, but still lack vital information that FDA needs to determine whether it should issue a marketing granted order. The rule creates a requirement to submit full reports of all existing health risk investigations; however, where there is not sufficient existing evidence that an applicant may utilize to demonstrate that the marketing of a new tobacco

product would be APPH, an applicant would need to conduct its own investigations to ensure that FDA has sufficient valid scientific evidence it needs to determine whether a marketing granted order should be issued for the new tobacco product.

Although an applicant may submit any type of evidence to FDA in an attempt to substantiate that the new tobacco product should receive a marketing granted order, FDA relies upon only valid scientific evidence to determine whether the marketing of the new tobacco product would be APPH.

(Comment 110) One comment stated that FDA should require the full report of each study to identify the source of funding and give less weight to the results of industry research than to independent scientific research and should explicitly consider bias in industry studies.

(Response 110) FDA declines to make changes as a result of this comment FDA's determination of whether there's a showing that permitting the marketing of a new tobacco product would be APPH must be determined on the basis of valid scientific evidence. FDA assesses all scientific evidence with the same rigor to determine whether it is valid, regardless of the source.

(Comment 111) One comment stated that FDA must require long-term clinical studies because it impossible to determine the risks and benefits of a tobacco product without them.

(Response 111) Long-term clinical studies can provide information that is important to FDA's review; however, the FD&C Act grants FDA the authority to consider other valid scientific evidence in making its APPH determination. Section 910(c)(5) of the FD&C Act explains that APPH "shall, when appropriate, be determined on the basis of well-controlled investigations." This section also explains that FDA may base its APPH determination on "valid scientific evidence (other than evidence derived from [well-controlled investigations]) which is

sufficient to evaluate the tobacco product." As discussed in this section, FDA does not expect that long-term clinical studies will need to be conducted for each PMTA; instead, it expects that it should be able to rely on other valid scientific evidence to evaluate some PMTAs.

FDA will determine whether the evidence submitted or otherwise available to FDA is valid scientific evidence for the purpose of determining the new tobacco product's impact on individual and population health, and whether the available evidence, when taken as a whole, is adequate to support a determination that permitting the new tobacco product to be marketed would be APPH.

Valid scientific evidence includes data from well-controlled investigations, as well as other sources upon which FDA may base its determinations under section 910(c)(5) of the FD&C Act. Other sources may include partially controlled studies, studies and objective trials without matched controls, and well-documented case histories conducted by qualified experts. The other sources of study data may be considered valid scientific evidence if they have been gathered using well-established or standardized methodologies from which it can fairly and responsibly be concluded by qualified experts that there is reasonable assurance of the reliability of their findings. The evidence required may vary according to the characteristics of the tobacco product, its conditions of use, the existence and adequacy of warnings and other restrictions, and the extent of consumer experience with its use. Isolated case reports, anecdotal experiences, reports lacking sufficient details to permit scientific evaluation, and unsubstantiated opinions are not considered valid scientific evidence.

As part of its determination of whether permitting the marketing of a new tobacco product would be APPH, FDA must be able to determine the likely health risks of the new tobacco product. While this rule does not necessarily require applicants to conduct new studies

for the purposes of application acceptance and filing (beyond the requirements of § 1114.27(b)(1)(ii)), FDA expects that it could not issue a marketing granted order unless an application contains data from a variety of sources, including both clinical and nonclinical investigations that give FDA comprehensive information about the product's likely health effects in the U.S. market. Where epidemiological evidence is available and comes from an investigation using a different product or one that was conducted outside the United States, FDA would examine whether the PMTA contains sufficient information, or the applicant has conducted bridging studies when needed, to demonstrate the data is applicable to the product and the U.S. population or provides adequate justification for how the information is relevant. FDA recognizes that this type of long-term epidemiological data is not available for all categories of products and does not expect that long-term clinical studies (i.e., those lasting approximately 6 months or longer) will need to be conducted for each PMTA; however, in the event long-term clinical study data should become available for the new product or similar product while the application is pending, this information should be submitted to FDA in an amendment.

Where a PMTA contains no long-term epidemiological evidence regarding the product or that could be bridged to the product, FDA would consider whether there are other sources of scientific evidence that sufficiently demonstrate the potential health risks of the product, such as actual use studies (e.g., clinical studies that assess real-world use conditions and health outcomes, or clinical studies that use scientifically valid endpoints as a predictor for potential long-term health effects). Where a PMTA lacks human subject study data regarding the product or that can be bridged to the product, FDA will examine how a PMTA attempts to estimate the health effects of the product on the U.S. population from the results of nonclinical investigations; however, it should be noted that information from nonclinical studies alone is generally not

sufficient to support a determination that permitting the marketing of the product would be APPH.

As part of FDA's consideration of the changes in tobacco product use behavior that are likely to be caused by the marketing of the new tobacco product, FDA will examine data regarding how the product, its label, labeling, and any available advertising, and description of the applicant's marketing plans will affect the tobacco use behavior of both users and nonusers of tobacco products, including the behaviors described in § 1114.7(k)(1)(ii) and (iii). FDA needs sufficient information to determine the potential changes in tobacco product use behavior and the health risks and benefits associated with the changes in user behavior will allow FDA to make a determination of whether permitting the marketing of the new tobacco product would be APPH. Where a PMTA does not contain sufficient information for FDA to make these determinations, FDA will issue a marketing denial order for the product because the PMTA lacks information necessary to determine the risks and benefits to the population as a whole as required by section 910(c)(4) of the FD&C Act.

(Comment 112) Multiple comments stated that a premarket assessment of a new tobacco product can neither fully nor precisely predict future tobacco use behavior patterns and recommended that FDA modify the rule to acknowledge such limitations on premarket research. Another comment expressed a similar opinion and noted that FDA has postmarket tools, including the ability to withdraw a marketing granted order to address unintended consequences.

(Response 112) FDA disagrees with the implication that it should discount the importance of information concerning the likelihood of changes in tobacco product use behavior during application review and, in essence, shift it to a postmarket determination. As discussed in the following paragraphs, the burden is on the applicant to make a showing that the marketing of

its new tobacco product would be APPH. Section 910(c)(4) of the FD&C Act requires FDA to consider the likelihood of changes in tobacco product use behavior in making its APPH determination and if an application lacks sufficient information to make this determination, FDA must issue a marketing denial order.

b. The methods used in and the facilities and controls used for, the manufacture, processing, or packing of such tobacco product conform to the requirements of section 906(e) of the FD&C Act. As discussed in section VII.B.12 regarding § 1114.7(j), FDA has not yet issued a regulation under section 906(e) of the FD&C Act, so demonstrating compliance with such regulations in a PMTA is not currently required; however, FDA plans to issue proposed rulemaking(s) under section 906(e), and once such regulations are effective, applicants must demonstrate that their methods, facilities, and controls are in conformance with applicable requirements to receive a marketing granted order under section 910(a)(1)(i)(A) of the FD&C Act. Until such a final rule issued under section 906(e) of the FD&C Act is effective, FDA will evaluate the manufacturing process and consider whether the product can be manufactured in a manner consistent with the information submitted within the application as part of its determination of whether the marketing of the new tobacco product is appropriate for the protection of public health. As part of this evaluation, FDA will consider whether the applicant would be able to consistently produce the new tobacco product as described in the PMTA. The potential for an applicant to produce nonconforming tobacco products that have higher levels of HPHCs than intended, have dangerous foreign material, or otherwise potentially presents a higher risk of harm than the product described in the PMTA may affect FDA's determination of whether the marketing of a product would be APPH.

(Comment 113) One comment stated that FDA should amend the rule to address how applicants will be able to address evolving requirements, such as product standard and manufacturing practice requirements, especially if changes become effective during application review.

(Response 113) The regulatory processes that FDA must follow to issue a product standard under section 907 of the FD&C Act or tobacco product manufacturing practices under section 906(e) of the FD&C Act are lengthy and would provide applicants with notice of proposed requirements well in advance of any change becoming effective. FDA generally intends to give applicants the opportunity to amend previously submitted applications to demonstrate conformance with new requirements under sections 906(e) or 907 of the FD&C Act; however, FDA may provide directions regarding how to demonstrate conformance in the text of any such rulemaking.

c. Based on a fair evaluation of all material facts, the proposed labeling is not false or misleading in any particular.

d. The tobacco product is shown to conform in all respects to a tobacco product standard in effect under section 907 of the FD&C Act or there is adequate information to justify a deviation from such standard. A PMTA submitted under the rule is required by § 1114.7(d)(2) to contain a statement identifying all tobacco product standards issued under section 907 of the FD&C Act that are applicable to the new tobacco product and a brief description of how the new tobacco product fully meets the identified tobacco product standard(s) or justifies a deviation from such standards, if applicable. FDA must be able to locate the data regarding the tobacco product's compliance with the product standard and determine that the tobacco product does, in fact, meet the requirements of the applicable product standard(s) or, if applicable, deviates from

such standards in a way that is justified. For example, if an applicant submitted a PMTA for a product that is subject to a product standard limiting the amount of an HPHC that may be delivered to product users, FDA must be able to verify though a review of the HPHC testing data contained in the product formulation section that the product complies with that product standard. Under section 910(c)(2)(D) of the FD&C Act, FDA will not issue a marketing granted order for a tobacco product unless a PMTA demonstrates that it meets any applicable product standard(s), or an applicant has justified the deviation from such standard, if applicable.

1. Restriction on The Sale and Distribution of a New Tobacco Product in a Marketing Granted Order

Section 1114.31(b) describes restrictions and additional requirements that FDA may include as part of a marketing granted order. Under section 910(c)(1)(B) of the FD&C Act, FDA may require the sale and distribution of the tobacco product be restricted to the extent that the sale and distribution of a tobacco product may be restricted under a regulation under section 906(d) of the FD&C Act. Section 1114.31(b)(1) reiterates this authority as part of the rule and § 1114.31(b)(2) allows FDA to include restrictions on sales and distribution proposed by the applicant in its PMTA as part of a marketing granted order.

A number of comments suggested that FDA impose a number of specific restrictions on the sales and distribution of tobacco products under the rule, as discussed below.

(Comment 114) One comment stated that the rule should be amended to require age verification for all websites and social media, and to prohibit the use of partners, sponsors, influencers, bloggers, or brand ambassadors to market or promote the product.

(Response 114) FDA declines to revise the rule in response to this comment because, at this time, FDA intends to consider which restrictions on sales and distribution should be included in a marketing granted order for a new tobacco product on a case-by-case basis.

(Comment 115) One comment stated that FDA should amend the rule to require preauthorization of all advertising and marketing materials during an initial 5-year period that a new tobacco product is permitted on the market.

(Response 115) FDA declines to make this revision because it is in conflict with section 903(b) of the FD&C Act.

(Comment 116) One comment stated that FDA should require each marketing granted order to include all available restrictions on the product packaging, labeling, marketing, sale, including the use of restrictions that require products to be sold with additional labeling and marketing requirements that would reduce the risk of youth exposure to the product or its advertising while also reducing the likelihood of increased tobacco-related harms and risks for current users. For example, FDA could require revisions to an ENDS product nicotine warning statement to include information such as the product is meant only as a complete substitute for traditional smoking and any other use will increase harms or risks to the user's health. The comment further stated that FDA must take advantage of readily accessible means in its issuing of marketing granted orders to avoid or reduce any unnecessary individual or public health harms or risks. The comment stated the belief that FDA's failure to implement or consider these types of restrictions to reduce the risk of harm of these products could lead to FDA being found arbitrary and capricious under the Administrative Procedure Act.

(Response 116) FDA agrees with the comment's general point that restricting the sales and distribution of a new tobacco product is an important way in which FDA can potentially

limit the health risks of a new tobacco product. FDA intends to consider whether and which restrictions are appropriate for the marketing of a new tobacco product under section 910(c)(1)(B) on a case-by-case basis during substantive review. FDA disagrees with the comment's broad assertion, which suggests that FDA is required to impose certain restrictions in every marketing order, when the FD&C Act does not so require.

(Comment 117) One comment requested that FDA, in issuing a marketed granted order, explicitly prohibit the marketing of a product in any way that targets vulnerable populations unless it only reaches users of more harmful tobacco products or users of more harmful products who have already switched.

(Response 117) FDA agrees with the general principle that a new tobacco product should be marketed in ways that will not increase the health risks to vulnerable populations. FDA declines to implement a blanket restriction on the scope of permissible advertising as part of this final rule and instead will consider restrictions on the sales and distribution of a new tobacco product under § 1114.31(b)(2) on a case-by-case basis for each new tobacco product that meets the requirements to receive a marketing granted order.

2. Requirements for Postmarket Records and Reports in a Marketing Granted Order

Section 1114.31(b)(3) allows FDA, using its authority in section 910(f) of the FD&C Act, to require an applicant to submit postmarket reports in addition to those described in § 1114.41, as appropriate. This can include, but is not limited to, requirements that an applicant provide information such as labeling, advertising, marketing, promotional materials, or marketing plans not previously submitted to FDA, and do so at least 30 days prior to the initial publication, dissemination to consumers, or use in engaging or communicating with consumers of such materials. Similar to what is described in section VII.B.6 of this document, these items provide

information that is important to FDA's determination of whether the continued marketing of the new tobacco product would be APPH or whether FDA must withdraw the marketing granted order under section 910(d)(1)(A) of the FD&C Act because the marketing of the new tobacco product is no longer APPH. Receiving this information in advance of its first use is not for pre-approval but will allow FDA to ensure it can appropriately track and monitor the impact that the use of such information has on tobacco use behavior. In addition, if needed, this information will allow FDA to provide applicants with advisory comments, including any concerns about possible impact on youth appeal and tobacco use initiation and with regard to the finding that the continued marketing of the product is appropriate for the protection of public health. FDA anticipates it will use this authority on a case-by-case basis, especially as it relates to novel tobacco products for which the body of knowledge is still growing.

E. Issuance of a Marketing Denial Order (§ 1114.33)

Section 1114.33 describes the circumstances under which FDA would issue a marketing denial order for a new tobacco product after PMTA review. Section 1114.33(a)(1) specifies that based on the information submitted as part of the application and any other information before FDA with respect to the new tobacco product, FDA will issue a marketing denial order if any of the grounds for denial listed in 910(c)(2) of the FD&C Act apply to the application. Any other information before FDA may include, for example, information received from a TPSAC report, toxicological information regarding a particular ingredient or combination of ingredients (e.g., diacetyl) from peer reviewed research results that were published after the PMTA was submitted, or preliminary results from a study that FDA is aware of (e.g., a Tobacco Centers of Regulatory Science study).

As discussed elsewhere in this document, meeting the requirements for application acceptance and filing does not mean that an application has sufficient information to receive a marketing granted order. For example, while FDA may accept and file an application that contains the information in § 1114.7(k), FDA will not issue a marketing granted order unless that information also makes a showing that permitting the marketing of a new tobacco product would be APPH. While the rule does not necessarily require the applicant to conduct studies on its product, applicants would need to do so for products for which insufficient information exists to demonstrate whether marketing of the product is APPH. Similarly, the information required in the manufacturing section of the application is required for acceptance and filing; however, unless the manufacturing process described ensures a product will be consistently produced as described in a PMTA (e.g., implementing sufficient controls), an applicant would receive a marketing denial order.

Examples of when FDA would be required to issue a marketing denial order for a lack of information necessary to make its required findings and determinations under sections 910(c)(2) and (c)(4) of the FD&C Act are contained throughout this document and include, but are not limited to, a lack of sufficient information regarding:

- the health risks of the new tobacco product;
- a comparison of the new tobacco product to the health risks of other tobacco products used by individuals that the applicant expects to use the new tobacco product, including products both within the same category as the new tobacco product and at least one different product category;
- the abuse liability of the new tobacco product;
- potential changes to tobacco product use behavior of current tobacco product users;

- the increased or decreased likelihood that those who do not use tobacco products will start using tobacco products;
- the impact of the product and its label, labeling, and advertising, to the extent that advertising has been developed and studied, on individuals' perception of the health risks of the product and their use intentions; and
- how human factors can influence the health risks of the new tobacco product.

Section 1114.33(a) also allows FDA to issue a marketing denial order where the applicant does not permit an authorized FDA employee, at a reasonable time and a reasonable manner, an opportunity to: (1) inspect the facilities and controls, and sites and entities involved with clinical and nonclinical research (including third parties and contract research organizations) described in the application or (2) have access to, copy, and verify all records pertinent to the application, where such refusal prevents FDA from making the required findings in 910(c) necessary to issue a marketing granted order. FDA would issue a marketing denial order where an applicant does not permit these inspections because the ability to access and inspect the facilities and controls and sites and entities involved with clinical and nonclinical research, as well as pertinent records, is important to FDA's ability to determine whether any of the denial criteria specified in section 910(c)(2) of the FD&C Act and § 1114.33(a)(1) apply to the application. Inspecting the facilities and controls described in the application will allow FDA to ensure the applicant can manufacture the product in accordance with the manufacturing practices described in the application. Inspecting records, including those required to be kept under § 1114.45, will allow FDA the opportunity to verify the study findings and data that the applicant relies upon in the PMTA to demonstrate that the new tobacco product should receive a marketing granted order. As stated in § 1114.45, the records would be required to be legible and written in English.

If FDA issues a marketing denial order, it will, where practicable, identify measures to address the reasons for which the application is being denied. While FDA will identify the deficiencies that resulted in the marketing denial order, the deficiencies specified in the order might not be an exhaustive listing of all deficiencies contained in the PMTA.

FDA received several comments regarding issuance of marketing denial order, as discussed below.

(Comment 118) One comment stated that § 1114.33(a) should be amended to provide that FDA will issue a marketing denial order if, after considering outside sources of information during PMTA review, FDA finds that the new tobacco product is not appropriate for the protection of the public health.

(Response 118) We have edited § 1114.33 to make it clear that FDA's issuance of a marketing denial order will be made, as required by section 910(c)(2) of the FD&C Act, on the basis of information submitted as part of an application and any other information before FDA with respect to the new tobacco product. If, during substantive review, FDA considers information outside of a PMTA that leads FDA to find that one or more of the grounds for denial in section 910(c)(2) of the FD&C Act apply, FDA intends to issue a marketing denial order for the new tobacco product.

(Comment 119) One comment stated that FDA should consider any public comments submitted in response to MRTP applications for the same new product that is the subject of the PMTA and FDA's assessment of these public comments should be explicitly addressed in any PMTA marketing order.

(Response 119) Under section 910(c)(2) of the FD&C Act, FDA will determine whether a PMTA should be denied on the basis of the information in a PMTA and any other information

before FDA with respect to such tobacco product. Where public comments on an MRTPA for the same product are before FDA during its consideration of a PMTA, FDA generally intends to consider those comments where relevant and clearly applicable to the marketing of the new tobacco product without modified risk information. FDA declines to explicitly address its assessment of public comments in a marketing granted order because it would further delay FDA's action on an application and a marketing granted order is not an appropriate venue to address comments to an MRTPA.

(Comment 120) One comment stated that § 1114.33 should be revised to include dual use and deterrence of complete quitting of all tobacco products as factors that FDA must explicitly consider when deciding whether to issue a marketing denial order.

(Response 120) Section 1114.33 incorporates the grounds for denial set forth in section 910(c)(2) of the FD&C Act, which FDA interprets to require consideration of these tobacco product use behaviors. In determining whether permitting the marketing of the new tobacco product would be APPH, FDA will consider dual use and potential changes to cessation as part of its determination of the risks and benefits to the health of the population as a whole.

(Comment 121) One comment suggested that FDA amend § 1114.33 to specifically state that FDA will issue a marketing denial order where FDA is unable to determine the impact that the labeling, advertising, marketing, and promotion of the new tobacco product may have on consumer perceptions and use intentions.

(Response 121) FDA considers information regarding consumer perceptions and use intentions to be an important part of PMTA review. If a PMTA does not contain sufficient information for FDA to determine that permitting the marketing of the product would be APPH, including impact on tobacco product and use intentions, it cannot authorize the marketing of the

new tobacco product. FDA recently issued a draft guidance for public comment regarding scientific issues for applicants to consider as they design and conduct tobacco product perception and use intention studies to support tobacco product applications. For more information, please see the guidance for industry entitled "Tobacco Products: Principles for Designing and Conducting Tobacco Product Perception and Intention Studies."[40]

(Comment 122) Several comments requested that FDA issue marketing denial orders for all products that meet certain criteria or in certain product categories, including flavored tobacco products, hookah, cigarillos, and little cigars. The comments asserted that FDA should deny all PMTAs for specific products because there is little or no evidence of health benefits and they are attractive to youth.

(Response 122) FDA declines to make revisions in response to these comments because the FD&C Act requires FDA to make an individualized determination of whether to deny an application based on the risks and benefits of a specific tobacco product to the health of the population as a whole (which includes youth, young adults, and other vulnerable populations).

F. Withdrawal of a Marketing Granted Order (§ 1114.35)

Section 1114.35 describes the grounds and procedures for withdrawing a marketing granted order for a new tobacco product. FDA will move to withdraw an order in the following situations:

1. Any of the Grounds for Withdrawal Under Section 910(d)(1) of the FD&C Act Apply

These grounds include situations in which FDA finds that the continued marketing of the tobacco product is no longer APPH. The marketing of a product may no longer be APPH in several situations, including, for example, where there are changes to tobacco product use

[40] Available at https://www.fda.gov/tobacco-products/rules-regulations-and-guidance/guidance.

behaviors that were not expected in FDA's assessment of the PMTA (e.g., more nonusers of tobacco products are initiating use with the product than expected and/or fewer users of potentially more harmful products are switching to the potentially less harmful new tobacco product). Another example is where studies conducted after the issuance of the marketing granted order show that the product presents greater risks to health than FDA understood during application review and, as a result, the product likely has or will have a net negative impact on the health of the population as a whole (which includes youth, young adults, and other vulnerable populations).

FDA also interprets section 910(d)(1)(A) of the FD&C Act to provide for the withdrawal of a marketing granted order where changes to the tobacco product marketplace result in FDA finding that the marketing of a product is no longer APPH:

- the application contained or was accompanied by an untrue statement of material fact;
- the applicant has failed to establish a system for maintaining records, or has repeatedly or deliberately failed to maintain records or make reports required by part 1114 or another applicable regulation under section 909 of the FD&C Act.
- the applicant has refused to permit access to, or copying or verification of, records as required by section 704 of the FD&C Act;
- the applicant has not complied with the requirements of section 905 of the FD&C Act;
- on the basis of new information before the Secretary with respect to such tobacco product, evaluated together with the evidence before the Secretary when the application was reviewed, that the methods used in, or the facilities and controls used for, the manufacture, processing, packing, or installation of such tobacco product do not conform with the requirements of section 906(e) of the FD&C Act and were not brought into

conformity with such requirements within a reasonable time after receipt of written notice from the Secretary of nonconformity;

- on the basis of new information before the Secretary, evaluated together with the evidence before the Secretary when the application was reviewed, that the labeling of such tobacco product, based on a fair evaluation of all material facts, is false or misleading in any particular and was not corrected within a reasonable time after receipt of written notice from the Secretary of such fact; or
- on the basis of new information before the Secretary, evaluated together with the evidence before the Secretary when such order was issued, that such tobacco product is not shown to conform in all respects to a tobacco product standard which is in effect under section 907 of the FD&C Act, compliance with which was a condition to the issuance of an order relating to the application, and that there is a lack of adequate information to justify the deviation from such standard.

FDA received comments regarding grounds for withdrawal, as discussed below.

(Comment 123) Multiple comments requested that FDA provide more clarity with regard to how the APPH standard may change over time with respect to determining whether a marketing granted order should be withdrawn. One comment noted concerns regarding the example FDA provided in section IX.F of the preamble to the proposed rule that appears to contemplate FDA withdrawing marketing orders under section 910(d)(1)(A) of the FD&C Act based on only the issuance of a product standard. The comment also stated that FDA should use the PMTA pathway to further the principles of tobacco product harm reduction and the potential for marketing orders to be withdrawn after an unduly short period of time or on an unpredictable

basis may discourage manufacturers from investing the significant resources necessary to bring harm-reducing products to market.

Another comment suggested that FDA develop a more systematized approach to determining whether the marketing of a product is no longer APPH. The comment suggested that because substantial shifts in consumer use of tobacco products are unlikely in the short term, FDA should determine whether marketing of a product is no longer APPH by comparing the product to a single comparator product in the same product class as the new tobacco product and that is used by the majority of likely users of the new tobacco product. The comment also requested that FDA reevaluate its APPH determination no sooner than 5 years after the issuance of a marketing granted order, noting that this approach is consistent with section 911 of the FD&C Act for the marketing of MRTPs and would allow FDA to use its authority to temporarily suspend a marketing order if significant health issues needed to be addressed before the end of the 5-year period.

(Response 123) FDA disagrees with the comment's characterization of the APPH standard as changing over time. As described in this document, FDA interprets the APPH standard in 910(c)(2) of the FD&C Act as requiring the marketing of a new tobacco product to likely present a net benefit to the health of the population as a whole to receive a marketing order. FDA interprets section 910(d)(1)(A) of the FD&C Act consistently to require that FDA withdraw a marketing granted order where FDA is no longer able to find that the marketing of the new tobacco product likely presents a net benefit to public health. Because market conditions will change over time, what might be APPH at one point in time may no longer be APPH in the future. Examples of changes that could affect FDA's determination that the marketing of the product is APPH could include the example from the proposed rule mentioned

by the comment: FDA's implementation of a tobacco product standard pursuant to section 907 of the FD&C Act that alters the relative health risks presented by other tobacco products. For instance, if FDA issued a marketing granted order for a new (non-cigarette) tobacco product, in part, because it presented significantly lower risks to individual health than cigarettes, and FDA later implemented a product standard that significantly lowered the health risks of cigarettes, FDA may determine that the continued marketing of the new (non-cigarette) tobacco product is no longer APPH. If FDA were to be unable to consider changing market conditions when evaluating whether the marketing of a new tobacco product continues to be APPH after it is granted a marketing granted order, FDA would potentially be unable to address the continued marketing of products that have higher levels of relative health risks, thus undermining its core statutory mandate to reduce the harm caused by tobacco product use. Accordingly, FDA declines to limit its consideration of whether a product continues to be APPH to just one comparator product in the same product category, as suggested by the comment.

The example regarding the issuance of a product standard that changes the health risks to current tobacco product users is a general example of a circumstance that could affect whether the marketing of a new tobacco product continues to be APPH. This example does not dictate that marketing orders for a different category of tobacco products must be withdrawn should such a product standard be implemented; rather, the determination of whether a marketing order should be withdrawn under section 910(d)(1)(A) of the FD&C Act would be made on a fact-specific basis for each new tobacco product based on whether its marketing continues to be APPH and a change to the health risks presented by a tobacco product category an applicant relied on to demonstrate a likely net benefit to public health may affect this APPH determination.

FDA also notes that marketing granted orders do not come with a guaranteed time duration. Applicants concerned about the effect of tobacco product standards on the PMTA pathway should consider the process required under section 907 of the FD&C Act to issue and implement product standards and make business decisions accordingly. FDA also declines to establish a minimum 5-year period in which applicants may market a new tobacco product without having its APPH determination reassessed. FDA intends to review new information regarding the health risks of tobacco products and changes in tobacco product use behavior, including information submitted as part of periodic and adverse experience reports, on an ongoing basis and consider whether it affects FDA's APPH determination for any new tobacco products that have received marketing granted orders. FDA also notes that, contrary to the assertion in the comment, waiting 5 years before reevaluating the issuance of a marketing granted order is not consistent with section 911 of the FD&C Act because 911(j)(1), like 910(d)(1)(A), provides for withdrawal prior to expiration of the order if standard for authorization is no longer met.

2. Any Postmarket Requirement Imposed by the Marketing Granted Order or by this Part That Has Not Been Met and Results in FDA Finding That One or More of the Grounds for Withdrawal Specified in Section 910(d)(1) of the FD&C Act Apply

This requirement will allow the withdrawal of a marketing granted order where an applicant fails to meet requirements imposed by a marketing granted order or part 1114, including postmarket restrictions on the sales and distribution of the tobacco product as described in section VIII.D and results in FDA finding one or more of the grounds for withdrawal specified in section 910(d)(1) of the FD&C Act apply.

FDA received multiple comments on this issue, as discussed below.

(Comment 124) Multiple comments stated that FDA should include bright lines or triggers in all marketing orders that would result in the automatic withdrawal of marketing authorization. One comment stated that FDA should withdraw or temporarily suspend a marketing order if it learns from any source that the tobacco product is impacting the health of youth and young adults, including increases in the percentages of youth and young adults who report use of the product. Another comment stated that FDA should set a threshold for problems with nonconforming products in the manufacturing process and require an order to be withdrawn if these thresholds are exceeded.

(Response 124) As set forth in § 1114.35(a)(1), FDA will move to withdraw a marketing granted order if FDA finds, after due notice and opportunity for an informal hearing, that the continued marketing of such tobacco product is no longer APPH. As described throughout the preamble to the final rule, FDA must make its APPH determination with respect to the risks and benefits of the population as a whole. FDA agrees that the potential for nonconforming tobacco products and underage use of tobacco products are an important consideration in making this determination and FDA will give them due consideration as part of its ongoing evaluation of whether the marketing of the tobacco product is APPH.

FDA may seek advice on scientific matters from any appropriate FDA advisory committee in deciding whether to withdraw a marketing granted order and may use information other than that submitted by the applicant in deciding whether to withdraw a marketing granted order. Prior to withdrawing a marketing granted order, FDA will notify the holder of the marketing granted order of the opportunity for an informal hearing under 21 CFR part 16. If the holder of the marketing granted order does not request an informal hearing or if FDA decides to withdraw the marketing granted order after the informal hearing is held, FDA will issue an order

withdrawing the marketing granted order. FDA will notify the public that the marketing granted order for the product has been withdrawn and state the basis for the withdrawal.

G. Temporary Suspension of a Marketing Granted Order (§ 1114.37)

Section 1114.37 describes the grounds and procedures by which FDA will temporarily suspend a marketing granted order under section 910(d)(3) of the FD&C Act. FDA is required by section 910(d)(3) to initiate a temporary suspension of a marketing granted order when it determines that there is a reasonable probability that the continued distribution of the product will cause serious, adverse health consequences or death, that is greater than what is ordinarily caused by tobacco products on the market. FDA interprets this language to mean serious, adverse health consequences at a rate or of a severity, or death at a rate, that is greater than what is ordinarily caused by tobacco product currently on the market. Under the rule, FDA will notify the holder of the marketing granted order of the opportunity to hold an informal hearing. If FDA determines after the opportunity for the informal hearing that the marketing granted order for the tobacco product should be temporarily suspended, the Agency will issue an order temporarily suspending the marketing granted order. FDA recommends that the applicant submit a plan demonstrating how it intends to comply with the temporary suspension, including a description of how the applicant will ensure that the tobacco product will not cause or continue to cause the serious, adverse health consequences or death (or reasonable probability of such events) that resulted in the temporary suspension, and the steps the applicant plans to take to ensure that the product is not further distributed, imported, sold, marketed, or promoted in the United States. Once FDA temporarily suspends a marketing granted order, it will proceed expeditiously to withdrawal. Where appropriate, FDA may combine the notices and hearings for temporary suspension of a marketing granted order and withdrawal of a marketing granted order into one

notice and hearing. Whether the determinations occur separately or in one combined proceeding, the determination regarding temporary suspension and the determination regarding withdrawal will be made separately by the Agency as the findings are separate and distinct.

X. Postmarket Requirements (Part 1114, Subpart D)

A. Postmarket Changes (§ 1114.39)

Section 1114.39 describes the scope of a marketing granted order. FDA issues marketing granted orders for the specific new tobacco product described in the PMTA.

FDA received several comments regarding this section, as discussed below.

(Comment 125) One comment stated that FDA should issue marketing orders for e-cigarettes that allow for the independent sale of components and parts that are identical to the ones contained in the authorized e-cigarette for use as replacements. The comment stated that because the components and parts would have already been reviewed as part of the complete e-cigarette, it would be redundant and unduly costly to require a company to submit a separate PMTA for an individual component or part.

(Response 125) FDA declines to make the revisions suggested by this comment. Unless an applicant otherwise satisfies the requirements of premarket review in section 910(a)(2) of the FD&C Act, it must submit a PMTA and receive a marketing granted order prior to introducing a new tobacco product, or delivering it for introduction, into interstate commerce. This requirement applies to both an entire e-cigarette and its components and parts where sold separately. Applicants seeking to market an e-cigarette and its components and parts in such a manner should consider whether a bundled submission containing the information required to support multiple PMTAs would be appropriate.

An applicant may not make any modification to the specific product that is the subject of the order, as any modification to the tobacco product results in a new tobacco product under the definition in section 910(a)(1) of the FD&C Act. Changes that do not result in a new tobacco product, such as manufacturing process changes that do not modify the finished tobacco product, must be reported under § 1114.41.

(Comment 126) One comment stated that the proposed requirement in § 1114.39 is redundant and unnecessary because it is no different from the plain meaning of section 910(a)(1)(B) of the FD&C Act and, therefore, should not be included in the final rule.

(Response 126) FDA declines to remove § 1114.39 because it serves to emphasize that the requirements of premarket review apply to modifications to new tobacco products that have already received a marketing granted order.

(Comment 127) One comment stated that FDA should clarify the circumstances in which "changes" are considered "modifications," and the pathways available when modifications are made. The manufacturer stated that based on its interpretation of the rule, FDA would not require reporting of any changes that do not rise to the level of modifications resulting in a new tobacco product, other than the specific types of manufacturing-related and labeling changes described in proposed § 1114.41.

(Response 127) FDA has provided numerous examples throughout this document, and guidance documents,[41] regarding modifications that result in a new tobacco product. Under section 910(a)(1)(B) of the FD&C Act, new tobacco products include those that are new because they have been rendered new through any modification (including a change in design, any

[41] Please see ENDS PMTA Guidance and the guidance for industry entitled "Demonstrating the Substantial Equivalence of a New Tobacco Product: Responses to Frequently Asked Questions," both of which are available at https://www.fda.gov/tobacco-products/rules-regulations-and-guidance/guidance.

component, any part, or any constituent, including a smoke constituent, or in the content, delivery or form of nicotine, or any other additive or ingredient) of a tobacco product where the modified product was commercially marketed in the United States after February 15, 2007. The discussion of the definition of the term "new tobacco product" in section VII.B. contains information about what constitutes a new tobacco product, including the description of modifications to cigarette paper, container closure systems (e.g., change from glass to plastic e-liquid vials or from plastic to tin container closures), product quantity, or tobacco cut size as some examples of changes that result in a new tobacco product.

Where an applicant seeks to modify a new tobacco product that has received a PMTA marketing order, it may choose to seek premarket authorization through any of the three premarket pathways described in section VII.B; however, we note that the requirements of the PMTA pathway are distinct from those of the SE pathway. Under the SE pathway, an applicant must rely on a tobacco product that was commercially marketed (other than for test marketing) in the United States as of February 15, 2007, or a tobacco product that FDA has previously found substantially equivalent under section 910(a)(2)(A)(i) of the FD&C Act; the issuance of a PMTA marketing order would not independently create a valid predicate product for use in the SE pathway. Therefore, an applicant seeking to modify a new tobacco product that has received a PMTA marketing order (and does not have a corresponding SE order), has three options to receive premarket authorization: (1) it could submit a new PMTA for the product with the modifications; (2) depending on the type of modification, it could seek authorization through the SE exemption pathway; or (3) it could seek authorization through the SE pathway relying on a valid predicate, i.e., a product FDA has previously found SE or a product that was commercially marketed in the United States (other than for test marketing) as of February 15, 2007. The

modifications for which an SE exemption request may be submitted are set forth in § 1107.1. The circumstances under which an applicant may submit a supplemental PMTA for a new tobacco product that results from a modification or modifications to the original tobacco product that received a marketing granted order are described in section VIII.F.

Marketing a new tobacco product without required premarket authorization would render the product adulterated under section 902(6)(A) of the FD&C Act and misbranded under section 903(a)(6) of the FD&C Act and subject to an FDA enforcement action.

B. Reporting Requirements (§ 1114.41)

Section 1114.41 requires applicants that receive a marketing granted order to submit postmarket reports. FDA is requiring postmarket reports under the authority of section 910(f) of the FD&C Act, which requires applicants to establish and maintain records and make reports that FDA requires as necessary to determine or facilitate a determination of whether there may be grounds to withdraw or temporarily suspend a marketing granted order. In addition, under section 909 of the FD&C Act, FDA is permitted to require the reporting of information to assure that a tobacco product is not adulterated or misbranded and to otherwise protect public health. Section § 1114.41 describes the reports that FDA requires through this regulation; however, FDA may require additional reporting in an individual applicant's marketing granted order.

Applicants are required under § 1114.41 to submit two types of reports after receiving a marketing granted order: periodic reports and adverse experience reports. Applicants must submit periodic reports within 60 calendar days of the reporting date specified in the marketing granted order (or potentially sooner if they choose to use the application as the basis for a supplemental PMTA under § 1114.15). FDA anticipates that the reports will be required on an

annual basis, but FDA may require, by a specific order, that reports be made more or less frequently depending upon a number of factors (e.g., the novelty of the type of product).

C. Requirements for Periodic Reports

Applicants must submit the following information electronically together with the appropriate form (Ref. 140) as part of each periodic report under § 1114.41(a)(1). The materials provided in these reports can provide important information regarding whether the marketing of the product is no longer APPH under section 910(d)(1)(A) of the FD&C Act or whether the marketing granted order should be temporarily suspended under section 910(d)(3) of the FD&C Act:

- a cover letter that includes basic identifying information, such as the product name(s) (including the original product name, if different) and application STN;
- a full description of the changes made to the methods used in, and the facilities and controls used for, the manufacture, processing, and, when relevant, packing and installation of, such tobacco product, if any, during the reporting period. This description, which we are requiring under section 909 of the FD&C Act, must include sufficient information for FDA to determine whether a change to methods used in, and the facilities and controls used for, the manufacture, processing, and, when relevant, packing and installation of, such tobacco product results in a new tobacco product or do not conform to the requirements of section 906(e) and potentially be a basis to withdraw or temporarily suspend the marketing granted order. This information includes a comparison to the methods used in, and the facilities and controls used for, the manufacture, processing, and, when relevant, packing and installation of, such tobacco product, described in the PMTA, the rationale for making the change, and an explanation

of why the change does not result in a new tobacco product and why there are no grounds for FDA to withdraw or temporarily suspend the marketing granted order on the basis of the change (i.e., the marketing of product continues to be APPH, the manufacturing process complies with the requirements of section 906(e) of the FD&C Act, and the product still conforms to any product standards under section 907 of the FD&C Act);

- An inventory of all ongoing and completed studies about the tobacco product conducted by, or on behalf of, the applicant that are within the scope of § 1114.7(k) and were not already submitted as part of the PMTA or previous postmarket reports. These reports can provide important information regarding health risks or changes in tobacco product use behavior, including initiation, which helps FDA determine whether the marketing of the product is no longer APPH under section 910(d)(1)(A) of the FD&C Act;
- full reports of information (as described in § 1114.7(k)(3)) published or known to, or which should reasonably be known to, the applicant concerning scientific investigations and literature about the tobacco product that would be required in a PMTA under § 1114.7(k)(1) not previously submitted as part of the PMTA or previous postmarket reports, including significant findings from publications not previously reported;
- a summary and analysis of all serious and unexpected adverse experiences associated with the tobacco product that have been reported to the applicant or that the applicant is aware of, accompanied by a statement of any changes to the overall risk associated with the tobacco product, including the nature and frequency of the adverse experience, and potential risk factors;
- a summary of sales and distribution of the tobacco product, to the extent that the applicant collects or receives such data, for the reporting period, including:

- total U.S. sales reported in dollars, units, and volume with breakdowns by U.S. census region, major retail markets, and channels in which the product is sold. Sales and distribution information may constitute confidential commercial information under § 20.61 that is exempt from public disclosure. See § 1114.47 and part 20 for more information about the confidentiality of information submitted to FDA;
- the Universal Product Code that corresponds to the product(s) identified in the PMTA; and
- Demographic characteristics of product purchasers, such as age, gender, race or ethnicity, geographic region, and tobacco use status. After reviewing and considering comments received in response to the proposed rule, FDA has updated this language here and throughout the rule as the consideration of vulnerable populations is an important part of determining whether permitting the continued marketing of a new tobacco product is APPH;

- a summary of the implementation and effectiveness of policies and procedures regarding verification of the age and identity of purchasers of the product;
- a summary of all formative consumer research studies conducted (if any), among any audiences, in the formation of new labeling, advertising, marketing, or promotional materials, not previously submitted, including qualitative and quantitative research studies used to determine message effectiveness, consumer knowledge, attitudes, beliefs, intentions and behaviors toward using the products, and including the findings or these studies and copies of the stimuli used in testing;
- a summary of all consumer evaluation research studies conducted (if any), among any audiences, not previously submitted, to determine the effectiveness of labeling,

advertising, marketing, or promotional materials and shifts in consumer knowledge, attitudes, beliefs, intentions, and behaviors toward using the products, and including the findings of these studies and copies of the stimuli used in testing;

- a summary of the creation and dissemination of the products' labeling, advertising, marketing, and promotional materials (if any), including a list of all entities involved and a description of their involvement, including a description of contractual agreements with such entities. For example, a list of entities involved in the creation and dissemination of marketing materials might include the names of advertising agencies, media companies, public relations firms, market research companies, partners, sponsors, bloggers and social media influencers;
- specimens of all labeling that has not been previously submitted in the PMTA, prior postmarket reports, or under section 905(i) of the FD&C Act and descriptions of all labeling changes including the date the labeling was first disseminated and the date when dissemination was completely terminated. This labeling information can help FDA determine whether the withdrawal grounds under section 910(d)(1)(E) of the FD&C Act apply;
- full color copies of all advertising, marketing, and promotional materials for the tobacco product that have not been previously submitted, the original date the materials were first disseminated, and the date when their dissemination was completely terminated. FDA is requiring the submission of this information under authority of section 910(f) because as discussed in section VIII.B.6.b., the way in which a tobacco product is advertised, marketed, and promoted can play an important role in FDA's determination of whether the marketing of a tobacco product is APPH. A substantial body of evidence illuminates

the powerful impact of tobacco product labeling, advertising, marketing, and promotion on youth perceptions of tobacco products, youth appeal of tobacco products, the likelihood of youth initiation and use of tobacco products, even when said marketing is purportedly targeted or designed to appeal to adults. Youth are a significant population of concern as their current stage of brain development makes them especially susceptible to nicotine addiction. Thus, for FDA to help ensure that the continued marketing of a new tobacco product is appropriate for the protection of public health, it is critical for FDA to conduct ongoing review and evaluation of the product's labeling, advertising, marketing, and promotional materials and activities to assess any possible effects on perceptions, appeal, intentions, and behaviors among intended and unintended audiences, especially youth. The information, together with other postmarket information concerning the marketing of the tobacco product, will facilitate determination of whether there are or may be grounds to withdraw a marketing granted order under section 910(d)(1)(A) of the FD&C Act;

- a description of the implementation of all advertising and marketing plans, not previously submitted to FDA (whether conducted by the applicant, on its behalf, or at its discretion), including strategic creative briefs and paid media plans by channel and by product, and the dollar amount(s) and flighting of such plans, by channel and by product, including a description of any of the following activities that an applicant may have engaged in:
  - use of competent and reliable data sources, methodologies, and technologies to establish, maintain, and monitor highly targeted advertising and marketing plans and media buys, including a list of all data sources used to target advertising and marketing plans and media buys;

- Targeting of specific group(s) by age-range(s), including young adults, ages 21-24, and other demographic or psychographic characteristics that reflect the intended audience including the source of such data;
- with respect to individuals below the minimum age of sale, actions taken to restrict access to the product and limit exposure to the product labeling, advertising, marketing, promotion, or other consumer-directed activities;
- use of owned, earned, shared, or paid media to create labeling for, advertise, market, or promote the product;
- use of partners, influencers, bloggers, or brand ambassadors to create labeling for, advertise, market, or promote the product;
- consumer engagements--whether conducted by an applicant, on its behalf, or at its direction--including events at which the product was demonstrated and how access was restricted to individuals at or above minimum age of sale; or
- use of public relations or other communications outreach to create labeling for, advertise, market, or promote the products;

- a summary of media tracking and optimization (e.g., assessment of marketing campaigns in market, and adjustments to a media buy to improve or correct delivery of advertising to the intended audience) by channel, by product, and by audience demographics (e.g., age, gender, race/ethnicity, geographic region), including a summary of any real-time digital media monitoring (e.g., tracking the use of a specific hashtag, reviewing audience engagement metrics such as “likes”, “comments”, and “shares”) and including a summary of implementation of any corrective and preventive measures to identify,

correct, and prevent delivery of advertising to individuals below the minimum age of sale, not previously submitted;

- a report or summary of the actual delivery of advertising impressions (e.g., instances where the intended audience had the opportunity to view or consume the product's advertising and marketing), by channel, by product, and by audience demographics (e.g., age, gender, race/ethnicity, geographic region), not previously submitted. This report or summary must be based on post-launch delivery-verification reports submitted to the tobacco product company from an accredited source, where applicable;
- additional information required to be reported under the terms of a marketing granted order (if applicable); and
- an overall assessment of how the marketing of the tobacco product continues to be APPH.

Postmarket information concerning the marketing of a tobacco product is critical to FDA's evaluation of whether the continued marketing of the product is APPH under section 910(d)(1)(A) of the FD&C Act. Determining whether the continued marketing of the tobacco product is APPH requires FDA to consider the likelihood that those who do not use tobacco products, including youth, will start using the product. As discussed in section VIII.B.6.b., youth exposure to tobacco product advertising, marketing, and promotion has a direct and powerful impact on youth trial and uptake of tobacco product use, making it directly relevant to FDA's determination of the likelihood that nonusers and users of other products switching to the new product, including youth will use the product. Accordingly, section § 1114.41(a)(1) seeks information that directly informs FDA's evaluation of youth exposure to marketing materials for the product and youth access to the product. Information regarding paid media plans for the

product, such as the channels used and the dollar amount(s) and flighting of the plans, as well as information regarding the use (or nonuse) of competent and reliable data sources, methodologies, and technologies to establish, maintain, and monitor highly targeted advertising and marketing plans and media buys, allows FDA to estimate the scale and potential reach of advertising, marketing, and promotion for the product and thereby directly informs its determination of the likelihood that youth will be exposed to such marketing materials. For example, the use of social media platforms known to reach youth, such as Twitter, Instagram, and YouTube, without use of methods to restrict and monitor youth access to marketing on those platforms may indicate a higher likelihood of youth exposure to marketing for the tobacco product and youth use of the tobacco product (see, e.g., Refs. 12-14 and 16). Additionally, use of partners, influencers, bloggers, or brand ambassadors to create labeling for, advertise, market, or promote a tobacco product may also indicate a higher likelihood of youth exposure to marketing materials for the product and youth use of the product, given studies demonstrating that such methods, including the use of "organic" depictions of tobacco use and endorsements of tobacco products by cultural icons and other influencers, are especially effective among youth who are particularly susceptible to social influences (Ref. 9). Moreover, information regarding actions taken to restrict access to the product and limit exposure to the product labeling, advertising, marketing, promotion, or other consumer-directed activities for individuals below the minimum age of sale directly informs FDA's evaluation of youth access to the product.

D. Serious and Unexpected Adverse Experience Reporting

Applicants must report all serious and unexpected adverse experiences associated with the tobacco product that have been reported to the applicant or of which the applicant is aware under § 1114.41(a)(2). The serious and unexpected adverse experience reports must be

submitted to CTP's Office of Science through the Health and Human Services (HHS) Safety Reporting Portal or in another manner designated by FDA (if applicable) within 15 calendar days after receiving or becoming aware of a serious or unexpected adverse experience. FDA notes that the submission of a report under this section (and any release by FDA of that report) will not constitute an admission that the tobacco product caused or contributed to an adverse experience.

FDA received several comments regarding the requirements for periodic reports, as discussed below.

(Comment 128) One comment stated that section 910 of the FD&C Act does not authorize FDA to require postmarket reporting for manufacturing changes. The comment stated that if a manufacturing change of the nature described by the proposed rule results in a new product, then there can be no "postmarket" information for FDA to evaluate because such a product cannot be placed on the market until a new marketing order has been obtained. The comment further stated that, if the manufacturing change does not result in a new tobacco product, then this change cannot alter FDA's prior determination that the marketing of the product is appropriate for the protection of public health nor would it enable FDA to determine, or facilitate a determination, that there are any other statutory grounds for withdrawing or suspending a marketing order. The comment concluded that in the future, manufacturing changes may result in a withdrawal or suspension but as no manufacturing regulations exist under section 906(e) of the FD&C Act, this does not seem applicable.

(Response 128) FDA declines to make any changes as a result of this comment. As discussed in the rule, whether the applicant can consistently manufacture the new tobacco product described in the PMTA is important to FDA's determination of whether a tobacco product is APPH, and given the dangers associated with nonconforming tobacco products,

reviewing manufacturing changes on a postmarket basis is necessary for FDA to determine whether the continued marketing of the product is APPH. Additionally, reviewing manufacturing changes would allow FDA to determine whether they would result in a modification (intended or unintended) to the product and is therefore a different new tobacco product without premarket authorization, which would render that tobacco product adulterated under section 902(6)(A) of the FD&C Act and misbranded under section 903 of the FD&C Act. FDA is requiring such information, in part, under its section 909 of the FD&C Act authority, which allows FDA to require the reporting of information to assure that a tobacco product is not adulterated or misbranded and to otherwise protect public health.

(Comment 129) One comment stated that section 910 of the FD&C Act does not authorize FDA to require postmarket reporting of sales and marketing information. The comment noted that while FDA states that this information will inform a determination of whether the marketing of the new tobacco product continues to be APPH, it claimed that this statement does not establish that all of the information required in the proposed rule is necessary for FDA to make its determination and, as such, many of the postmarket reporting requirements should be deleted in the final rule.

(Response 129) FDA disagrees with the statement that this reporting is not authorized by the FD&C Act. As discussed throughout this document, this postmarket information is necessary to help inform FDA's determination of whether the continued marketing of the tobacco product is APPH. FDA requires applicants to submit sales data under its authority in section 910(f) of the FD&C Act to help inform its determination of whether the continued marketing of the product is APPH. Sales data in conjunction with other data such as demographics of purchasers and information on retail channels can provide information that can

help indicate trends in tobacco use behavior across the United States and potential changes in tobacco use behaviors among certain subsets of the population. For example, if tobacco use of a specific product was previously low among a certain demographic and, through the postmarket reporting, is now being reported at higher levels of tobacco use that also correlates with sales of the new product among the same demographic group, this type of information would be important to FDA's determination of whether the continued marketing of the tobacco product is APPH. In addition, sales of tobacco products by retail channel, combined with other required data, can help FDA understand where products are being sold as well as help FDA better understand the potential for youth access to the products. In particular, the data help FDA to assess whether the information regarding likely tobacco product use behavior described in the PMTA was consistent with actual use after authorization. For example, data that indicate significantly higher rates of youth initiation with the tobacco product than among other nonusers than anticipated in the PMTA could result in FDA finding that continued marketing of the tobacco product is no longer APPH and the marketing granted order should be withdrawn under section 910(d)(1)(A) of the FD&C Act. Furthermore, because youth exposure to tobacco product labeling, advertising, marketing, and promotion has a direct and powerful impact on youth trial and uptake of tobacco product use, information regarding the marketing of the tobacco product and potential youth exposure to marketing directly informs FDA's consideration of the likelihood that youth will use the product, which is relevant to determining whether continued marketing of a product is APPH and consistent with its statutory mandate to protect youth from the dangers of tobacco use. In addition, as discussed below, information regarding the marketing of the product can help FDA determine whether the withdrawal grounds under section 910(d)(1)(E) of the FD&C Act apply.

(Comment 130) One comment requested that the rule require the submission of postmarket information to demonstrate that all labeling, instructions for use, and other communications related to the product have been carefully designed and tested to ensure they will provide accurate, not misleading, information and guidance to all consumers, including those with less education, or weaker or non-existent English literacy, and will not encourage harm-increasing uses of the product among any subpopulations.

(Response 130) FDA intends to consider the labeling, advertising, and marketing, and promotion for a new tobacco product, including labels, instructions for use and other advertising and marketing materials, that an applicant uses after receiving a marketing granted order as part of FDA's evaluation of whether the continued marketing of a new tobacco product is APPH. FDA is not requiring formal testing of advertising and marketing materials. However, when determining whether the continued marketing of a new tobacco product is APPH, under section 910(d)(1)(E) of the FD&C Act, FDA is required to consider whether the labeling of the tobacco product is false or misleading. In addition, FDA will review advertising and marketing materials with consideration of the potential for use among nonusers, including youth, as well as product misuse and dual use among current tobacco product users (see section VII.B.6 regarding § 1114.7(f) for a discussion of the impact of advertising).

(Comment 131) One comment stated that FDA should, similar to language FDA uses for other regulated product categories, make it clear that submission of required postmarket reports, including adverse experience reports, does not reflect a conclusion or admission by the applicant or FDA that the product at issue caused or contributed to the adverse experience.

(Response 131) In section X.B., FDA has amended this document to clarify that reporting an adverse experience will not constitute an admission that the tobacco product caused or contributed to the adverse experience.

E. Submission of Additional Information

As part of its review of a postmarket report, FDA could require the applicant to submit additional information to enable it to determine whether a change results in a new tobacco product, or to facilitate a determination of whether there are or may be grounds to withdraw or temporarily suspend the marketing granted order. FDA may notify an applicant that FDA has determined that a change described in a periodic report made under this section results in a new tobacco product outside the scope of the marketing granted order, requiring the submission of a new PMTA under § 1114.7 or a supplemental PMTA under § 1114.15 and issuance of a marketing granted order if the applicant seeks to market the new tobacco product, unless the new tobacco product can be legally marketed through a different premarket pathway. Failure to obtain marketing authorization for a new tobacco product would render it adulterated under section 902(6) of the FD&C Act and misbranded under section 903(a)(6) of the FD&C Act and could be subject to enforcement action.

FDA received one comment on this issue, as discussed below.

(Comment 132) One comment stated that they expected some e-liquid manufacturers to join controlled distribution networks to show youth access to tobacco products would be limited. The comment recommended that the rule be amended to allow third party entities (e.g., controlled distribution networks or their auditing agents) to submit reports directly to the Agency that reference and link to participants' approved PMTAs. This would allow applicants or their designated distribution networks and auditors to submit to FDA all information required.

(Response 132) We decline to make this change. The rule concerns the postmarket reports that applicants are required to make, rather than the information that third parties or other entities may submit to FDA about a tobacco product; however, note that where an applicant obtains sales data about its product from a third party, the applicant would need to report it to FDA as required by § 1114.41. As noted in section VIII.B.2, applicants have the ability to cross-reference third-party owned information through TPMFs, including in the submission of postmarket reporting requirements.

XI. Miscellaneous (Part 1114, Subpart E)

Subpart E describes other procedures and requirements related to PMTAs, including record retention, electronic submission requirements, and confidentiality considerations.

A. Record Retention (§ 1114.45)

Consistent with the authority to require recordkeeping under sections 909 and 910(f) of the FD&C Act, § 1114.45 requires applicants receiving a marketing granted order to maintain all records necessary to facilitate a determination of whether there are or may be grounds to withdraw or temporarily suspend the marketing granted order and ensure that such records remain readily available to the Agency upon request. The records must be legible, written in English, and available for inspection and copying by officers or employees designated by the Secretary.

1. Record Retention by the Applicant

Under § 1114.45(a)(1), an applicant must retain all documents submitted to FDA as part of an application and postmarket reports. An applicant must also retain any additional documentation supporting the application and postmarket reports that was not submitted to FDA. This additional documentation includes information that demonstrates:

- nonclinical laboratory studies were conducted using laboratory practices that ensure the reliability and validity of the study. This information includes documents that were generated during the performance of nonclinical studies, but were not required to be submitted as part of a full study report under § 1114.7(k)(3). One way that an applicant may satisfy this requirement is to retain all of the documentation described in part 58 and
- whether any investigators had financial conflicts of interest. One approach to satisfying this requirement is to retain all of the documentation described in part 54 for both clinical and nonclinical investigations.

Applicants must also retain all other documents generated during the course of a study that are necessary to substantiate the study results (e.g., certain communications, case reports) including:

- communications related to the investigation between the investigator and the sponsor, the monitor, or FDA and
- all source data and related summaries, including records regarding each study subject's case history and exposure to tobacco products used in the investigation, which can include, but is not limited to case report forms, progress notes, hospital records, clinical charts, x-rays, lab reports, and subject diaries.

The applicant must also maintain a record of each complaint associated with the tobacco product that has been reported to the applicant as well as a summary and an analysis of all complaints associated with the tobacco product reported to the applicant. The records and analysis of complaints should reflect all reports made about the product, including those made during clinical investigations. FDA is requiring that records and analysis of such complaints be

kept to demonstrate whether there are any potential issues with the product that could present health or safety issues.

FDA received comments regarding record retention by applicants, as discussed below.

(Comment 133) One comment suggested that the language of the proposed rule be amended to allow for either applicants or their third-party representatives to retain the records required by § 1114.45. The applicant stated that this could be more efficient and save costs.

(Response 133) FDA has amended the language of the preamble to clarify that an applicant may utilize a third-party entity to store records on their behalf. If an applicant uses a third-party entity to store records, it is important to note that the applicant is still solely responsible for ensuring that all records necessary to facilitate a determination of whether there are or may be grounds to withdraw or temporarily suspend the marketing granted order are readily available to the Agency upon request. This requirement will ensure that records are available to FDA during an inspection.

Applicants that have stopped marketing a tobacco product may want to retain the records for a longer period if the product might be reintroduced in order to avoid the time and expense of having to generate the information again. FDA may, under the terms of section 910(f) of the FD&C Act, impose additional recordkeeping and reporting requirements as part of a marketing granted order in addition to the requirements in the rule.

(Comment 134) One comment expressed support for the requirement for applicants to retain records but suggested the proposed rule should be amended to include retention requirements for specific information that would enable FDA to track and trace a product from the manufacturing source to the shelf.

(Response 134) FDA declines to make such a change because it is outside the scope of this rulemaking. Consistent with sections 909 and 910(f) of the FD&C Act, the rule (as described in § 1114.45) requires applicants to retain all records necessary to facilitate a determination of whether there are or may be grounds to withdraw or temporarily suspend the marketing order as well as ensure that the tobacco product that is the subject of the marketing order is not adulterated or misbranded.

2. Record Format and Availability

The rule requires the applicant to maintain records that are legible and in the English language, and make them available for inspection and copying by officers or employees duly designated by the Secretary.

3. Retention Period

Applicants must retain the records as described in § 1114.45(a)(3). Records relating to the PMTA must be retained for a period of no less than 4 years from the date the marketing granted order is issued. Records relating to the postmarket reports, including both periodic reporting and adverse experience reporting must be retained for a period of at least 4 years from the date the postmarket report was submitted or the date FDA inspects the records, whichever occurs sooner. FDA has selected 4 years as a means to help ensure that the records would be available for at least one biennial FDA inspection under sections 704 and 905(g) of the FD&C Act.

B. Confidentiality (§ 1114.47)

Section 1114.47 states that FDA will determine the public availability of any part of any PMTA and other content related to a PMTA, including all data and information submitted with or incorporated by reference in the application, as provided under this section and part 20 (Public

Information). FOIA (5 U.S.C. 552), as well as certain provisions of the FD&C Act, (e.g., section 301(j) (21 U.S.C. 331(j)) and section 906(c)), govern the disclosure of the existence of a pending PMTA and the information contained in such a PMTA. Under FOIA, the public has broad access to government documents. However, FOIA provides certain exemptions from mandatory public disclosure. One such provision, 5 U.S.C. 552(b)(4), exempts records that are "trade secrets and commercial or financial information obtained from a person and privileged or confidential" from the requirement of mandatory disclosure. Part 20 of FDA's regulations sets forth FDA's general regulations concerning public availability of FDA records.

FDA received several comments regarding confidentiality, as discussed below.

(Comment 135) One comment suggested that a public database be established that lists the products for which a PMTA has been filed, accepted, or is pending substantive review. The comment stated that this is important because it would allow other state and federal agencies to know whether a product has the ability to remain on the shelves of stores. Similarly, another comment stated that by not making the application process more public, FDA is not permitting adequate participation by stakeholders other than the applicant and is contrary to established FDA practice.

(Response 135) As discussed in the preamble of the proposed rule, like with drugs and devices, the intent to market a tobacco product that is not currently marketed is often considered confidential commercial information. This is consistent with the recent Supreme Court decision that addressed the legal standard for determining whether information is confidential. See *Food Mktg. Inst.* v. *Argus Leader Media*, 139 S. Ct. 2356, 2366 (2019). Therefore, § 1114.47(b) addresses the confidentiality of a PMTA prior to the issuance of a marketing granted order. Under the rule, FDA will not publicly disclose the existence of a PMTA unless the applicant has

publicly disclosed or acknowledged that it has submitted the application to FDA (as such disclosure is defined in § 20.81), the applicant has authorized FDA in writing to publicly disclose or acknowledge the submission of the PMTA, or FDA has referred the application to TPSAC. Section 1114.47(b)(2) provides that FDA will not disclose the fact or contents of an FDA communication with an applicant or regarding an application or information contained in the application unless the applicant has publicly disclosed, acknowledged, or authorized FDA in writing to publicly disclose or acknowledge the existence of the FDA communication or information contained in the application. However, if the applicant has disclosed information contained in the application or that it received a communication from FDA regarding the application, FDA may disclose the record of the communication after redacting confidential commercial or trade secret information. Section 1114.47(b)(3) provides that if FDA refers the application to TPSAC, the PMTA will be available for public disclosure under part 20 as described in § 14.75 (21 CFR 14.75) (which concerns the public disclosure of advisory committee records), except information that that is exempt from public disclosure under part 20, including trade secrets, confidential commercial information, and personal privacy information. This is consistent with FDA's practice for tobacco product premarket applications, as well as for premarket applications generally.

(Comment 136) One comment stated that section 910 of the FD&C Act does not authorize FDA to make PMTAs publicly available as part of FDA or TPSAC review. The comment argued that if Congress intended FDA to have the authority to divulge the content of a PMTA, it would have stated so in the Tobacco Control Act. Another comment argued that the only information that should be referred to TPSAC is a limited summary of the relevant portions of the application.

(Response 136) As stated above, prior to the issuance of a marketing granted order, FDA will not publicly disclose the existence of a PMTA unless the applicant has publicly disclosed or acknowledged that it has submitted the application to FDA, the applicant has authorized FDA in writing to publicly disclose or acknowledge the submission of the PMTA, or FDA has referred the application to TPSAC. Except as described in § 1114.47(b)(4) regarding referral to TPSAC, FDA will not disclose information contained in an application unless the applicant has publicly disclosed or acknowledged, or authorized FDA in writing to publicly disclose or acknowledge, the existence of that particular information.

FDA disagrees with the assertion that it cannot make a PMTA publicly available as part of TPSAC review because it is required to do so under section 10(b) of the Federal Advisory Committee Act (Pub. L. 92-463, 5 U.S.C. App) and its implementing regulations. If FDA refers the application to TPSAC, the PMTA will be available for public disclosure under part 20 as described in § 14.75 (which concerns the public disclosure of advisory committee records), except information that is exempt from disclosure under part 20, including trade secrets, confidential commercial information, and personal privacy information

Section 1114.47(c) describes the information that FDA will make available after issuing a marketing granted order. Under § 1114.47(c), FDA can make available data previously disclosed to the public, protocols for a test or study, information and data in the application that demonstrate the new tobacco product is appropriate for the protection of the public health, any correspondence between FDA and the applicant, the environmental assessment or request for categorical exclusion, and information and data contained in postmarket reports, so long as the information listed above is not exempted from disclosure under part 20.

Even after receipt of a marketing denial order for an application for a product that is not currently marketed, the intent to market may still constitute confidential commercial information, as the applicant may still have the intent to market the new tobacco product that is the subject of the PMTA and it is the type of information that is customarily and actually treated as private by its owner. Under § 1114.47(d), FDA may also make certain information available after it issues a marketing denial order unless the information is otherwise exempt from disclosure under part 20. The information that FDA may disclose includes product category, subcategory, package size, and the basis for the marketing denial order. FDA notes that where an applicant receives a marketing denial order for, or FDA refuses to accept or file, a PMTA for a new tobacco product that is currently on the market as a result of FDA's compliance policy for deemed tobacco products on the market as of August 8, 2016, FDA may disclose additional identifying information about the product to help ensure that it is taken off of the market. Where a product is marketed, basic identifying information regarding the product is not a trade secret or confidential commercial information.

(Comment 137) One comment states that the final rule should be amended to state that all aspects of the PMTA, including all data and information submitted with or incorporated by reference into the application, are confidential information under § 1114.47.

(Response 137) As explained elsewhere in this section, FDA will determine the public availability of any information contained in a PMTA under § 1114.47 and part 20. This includes the data and information in the application submitted in both full text and incorporated by cross-reference. FDA has amended the language in this section, to clarify what information would be confidential under the rule and part 20.

(Comment 138) One comment stated that the final rule should be amended to state that all data and information received in an ITP submission prior to a PMTA being filed with the Agency is also confidential. Furthermore, the comment stated that FDA should update part 20 to describe the legal standard for FOIA exemption 4 established by the Supreme Court in *Food Mktg. Inst.* v. *Argus Leader Media*.

(Response 138) This rulemaking addresses the general process by which PMTAs are submitted and reviewed. Any comments concerning the investigational tobacco product submission process or FDA's public information regulations under part 20 are outside the scope of this rule.

(Comment 139) One comment stated that FDA should publicly disclose the existence of PMTAs for which the applicant has previously submitted a MRTPA or submits an MRTPA concurrently with the PMTA.

(Response 139) FDA has amended § 1114.47 to state that it will disclose the existence of a PMTA for a new tobacco product for which an MRTPA has been made available for public comment under section 911(e) of the FD&C Act. Once FDA makes an MRTPA for the new tobacco product publicly available, the intent to market the new tobacco product would no longer be confidential commercial information. Further, as stated previously, the contents of a PMTA that is referred to TPSAC (either as a standalone application or concurrently with an MRTPA) will be available for public disclosure under part 20 as described in § 14.75 (which concerns the public disclosure of advisory committee records), including withholding information that is trade secrets, confidential commercial information, or personal privacy information.

(Comment 140) One comment stated that it is important for FDA to publicly disclose all data and information submitted to demonstrate the marketing of a product would be APPH,

marketing plans, and postmarket reporting for each new tobacco product that is authorized by FDA. The comment stated that marketing plans concern the sale and distribution of tobacco products, which under section 916 of the FD&C Act (21 U.S.C. 387p) may also be subject to state and local regulation, even if such regulations are different or stricter than Federal regulations. The comment further stated that the public health interest in disclosure outweighs other interests and should result in marketing plans and postmarket reporting being disclosed to the public.

(Response 140) As described in this section, FDA may make information publicly available after the issuance of a marketing granted order consistent with § 1114.47(c) and part 20. FDA is unable to make any information in an application, including descriptions of marketing plans, publicly available to the extent that it constitutes trade secrets or confidential commercial information unless it is disclosed publicly or authorized to be disclosed publicly by the applicant.

C. Electronic Submission (§ 1114.49)

Consistent with FDA's authority to issue regulations for the efficient enforcement of the FD&C Act, § 1114.49 requires an applicant to submit a PMTA and all supporting and related documents to FDA in electronic format that FDA can process, review, and archive unless an applicant requests, and FDA grants, a waiver from this requirement. Reasons that an applicant might request a waiver would include that the applicant has no access to email or a computer. Under § 1114.49(c), an applicant that has a waiver would submit a paper submission to the address that FDA provides in the letter granting the waiver.

FDA received one comment regarding the proposed electronic submission provision, as discussed below.

(Comment 141) One comment stated that while the submission of electronic documents may be a preferred delivery mechanism, it should not be a requirement that an applicant submit a PMTA and all supporting and related documents in electronic format.

(Response 141) FDA declines to take this recommendation. FDA is implementing § 1114.49 based on FDA's general experience with electronic submissions, which FDA has found help facilitate premarket reviews because electronic submissions typically enable FDA to receive, access, search, and review a submission more efficiently than a paper submission. FDA has provided technical specifications on its website for submitting information in an electronic format that FDA can review, process, and archive (e.g., method of transmission, media, file formats, preparation, organization of files, accompanying metadata) (https://www.fda.gov/tobacco-products/manufacturing/electronic-submissions-tobacco-products) and update this information as needed to accommodate changes in technology. As previously discussed, applicants who have limited access to email or a computer may apply for a waiver from the electronic submission requirement, which if granted by FDA, would allow an applicant to submit a paper submission to the address that FDA provides.

XII. Paperwork Reduction Act of 1995

This final rule contains information collection provisions that are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501-3521). The title, description, and respondent description of the information collection provisions are shown in the following paragraphs with an estimate of the annual reporting and recordkeeping burden. Included in the estimate is the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing each collection of information.

Title: Premarket Tobacco Product Applications and Recordkeeping Requirements, OMB Control Number 0910-0879

Description: This rule interprets and codifies requirements related to the content and format of PMTAs, the procedure by which FDA reviews PMTAs, and the maintenance of records regarding the legal marketing of certain tobacco products without PMTAs. The rule also addresses issues such as the procedures of retention of records related to the PMTA, confidentiality of application information, electronic submission of the PMTA and amendments, and postmarket reporting requirements.

Description of Respondents: This rule applies to tobacco product manufacturers. Manufacturer is defined here as any person, including any repacker or relabeler, who: (1) manufactures, fabricates, assembles, processes, or labels a tobacco product or (2) imports a finished tobacco product for sale or distribution in the United States.

As required by section 3506(c)(2)(B) of the Paperwork Reduction Act of 1995 (PRA), FDA provided an opportunity for public comment on the information collection requirements of the proposed rule that published in the *Federal Register* of September 25, 2019 (84 FR 50566). In response to this rule FDA received two PRA-related comments:

(Comment 142) One comment made specific comments requesting changes to elements in Form 4057.

(Response 142) FDA has considered these comments and agrees that many updates are necessary. The list below details the updates we have made to the form in response to the comments.

- FDA has harmonized, as appropriate, terms used within the PMTA and other FDA forms.

- FDA has revised the form by adding fields for address and contact information for manufacturer information to provide for the situation where the manufacturer is different from the Applicant.
- FDA agrees that the form does not collect organization information for certain parties. FDA has revised the form by providing fields to enter organization information for certain parties, e.g., the authorized representative. Additionally, FDA has revised the form by providing additional fields to describe the alternate point of contact.
- FDA has revised section III which now contains additional fields to identify cross-referenced submissions (ITP, SE, and MRTPA) and formal meetings held with FDA that pertain to the PMTA. For example, the applicant can now input in the revised form document keywords, document filenames, and submission dates for cross-referenced content. For formal meetings with FDA, the applicant can now input in the revised form the new tobacco product name. These fields would also help ensure FDA identify the cross-referenced content or related submission.
- Section III of the revised form also contains new fields (e.g., "document keyword" and "document filename") that allow the submitter to adequately describe the content they are cross-referencing. Section III now allows the applicant to indicate if the cross-referenced content is relevant to a specific product or to all bundled products in the application. Across all product categories, the subcategory of "co-package" has been removed. However, co-packaged items can be grouped within the same submission and the unique identification of this co-packaged product would include the specific items needed to identify each product within the co-package.

- In section IV, FDA has added a "Submission Table of Contents" with fields for "filename," "title," "table of contents category," and "keyword" in order that FDA can easily identify the application contents listed in section IV.

(Comment 143) One comment made specific comments requesting changes to elements in Form FDA 4057a.

(Response 143) FDA has considered these comments and agrees that many updates are necessary. The list below details the updates we have made to the form in response to the comments.

- FDA has combined sections I and IV to only ask for current owner's information once. The current owner's information is now only required in section I of the revised form.
- FDA now allows the manufacturer's address and contact information to be provided (if a different entity from the applicant) contact information is to be provided.
- FDA has revised the form to allow the organization's name to be provided (where an organization is an alternate point of contact). Additionally, FDA added a field so that organizational affiliation of the authorized representative information can be provided.
- For a change in authorized representative FDA agrees that "Replace" is the appropriate step and has added this as an option in section I, subsection C of the form.
- The form has been edited to allow the submitter to indicate the purpose of the amendment (i.e., whether it was for a single new tobacco product or for a bundled/grouped submission).
- Section III of the form has been revised to allow the submitter to indicate the addition, updating or removal of cross-referenced content, related submissions, and meetings with FDA. Section III now allows the submitter to describe the cross-referenced content,

related submissions, and meetings, and to indicate the purpose of the cross-referenced content, related submissions, and meetings. Additionally, section III allows the submitter to indicate whether the submitter intends to "add," "update" or "remove" referenced content, related submissions, and meetings.

- Section III of the revised form now contains a "submission summary" field which allows the applicant to be used to describe the subject of the amendment.
- Section II of the revised form now allows information for "bundled" or grouped PMTAs to be submitted. Section II now allows submitters to submit updated tobacco product information for all new tobacco products including co-packaged products. Additionally, section II of the revised form enables submitters to describe the subject of their correspondence and provide a submission summary describing the intended use of the submitted contents.

Where appropriate, FDA has harmonized the terminology in the form with other FDA forms and has harmonized the layout of the Amendment and General Correspondence submission form with the layout of the PMTA submission form. For example, section I of the revised PMTA form is used to describe the applicant, the authorized representative, the alternate point of contact and other applicant information. Correspondingly, section I of the revised Amendment and General Correspondence submission form is used to update applicant information. Similarly, section II of the revised PMTA form is used to set out tobacco product information. Correspondingly, section II of the revised Amendment and General Correspondence submission form is used to update tobacco product information.

FDA received generally supportive comments regarding proposed Form FDA 4057b. Comments agreed the form was a positive step towards streamlining the current PMTA submission process, as well as promoting efficient processing and review of bundled PMTAs.

(Comment 144) One comment noted that Form FDA 4057b failed to include an "oral tobacco-derived nicotine (OTDN)" category or subcategory designation. The comment argued that OTDN products are both distinct, being tobacco-free and non-dissolvable, and one of the fastest growing tobacco product segments in the U.S. market. Including an OTDN product subcategory would provide clarity for applicants and streamline FDA review of these products. The comment also noted that Form FDA 4057b requires applicants to include characterizing flavor information but does not define this term in Form FDA 4057b or within the proposed rule.

(Response 144) Providing unique identifying information, such as product category or subcategory, ensures FDA can identify the new tobacco product and distinguish it from other tobacco products, including additional new tobacco products in a bundled submission submitted using Form FDA 4057b, and assists FDA in performing its acceptance and filing reviews. At this time, FDA does not yet have the experience necessary to create requirements for OTDN as a standalone product category or subcategory. Review of OTDN products will be handled on a case-by-case basis and any future decision to update or change the requirements of the rule and form to include OTDN products will follow appropriate notice and comment procedures. While the rule does not specifically include OTDN as a category or subcategory, where an applicant believes its new tobacco product, such as OTDN, does not fit within a product category set forth in the rule, it should identify the product category as "other". Applicants are encouraged to include any properties in addition to those required by the "other" category or subcategory to fully identify the tobacco product, if applicable.

In addition, the requirement for applicants to include product-specific information, such as characterizing flavor(s), corresponds to the general information requirements of § 1114.7.(c)(3)(iii) that will allow FDA to quickly check whether the product is within CTP's purview and identify the specific product that is the subject of the submission. For the characterizing flavor item, FDA is looking to see how the applicant identifies the tobacco product as having no characterizing flavor or having a particular characterizing flavor. If applicants do not consider the product to have a characterizing flavor, applicants must state "none". As discussed in the proposed rule, applicants that have questions regarding how to describe their product's characterizing flavor are encouraged to contact FDA prior to submission.

(Comment 145) Another comment noted that while the use of Form FDA 4057b would be a positive step, the current PMTA process is prohibitively expensive for most individual manufacturers of nicotine e-liquids.

(Response 145) As discussed in the proposed regulatory impact analysis, FDA has considered the costs and benefits associated with the rule, if finalized. While there are costs associated with the rule, the analysis also noted that the rule, would create cost savings for firms and for FDA by reducing the number of follow-on submission for PMTAs (i.e., additional PMTAs submitted for the same product(s) after FDA refuses to accept or file, or issues a marketing denial order in response to, an initial PMTA). The analysis also noted small manufacturers who submit ENDS PMTA bundles would benefit from the proposed rule, if finalized. Submitted bundles, such as those submitted via Form FDA 4057b, would receive marketing orders through the PMTA pathway earlier with rulemaking than without rulemaking, increasing lifetime profits for the ENDS products included in the submitted ENDS bundles.

FDA is finalizing requirements for the content, format, submission, and review of PMTAs, as well as other requirements related to PMTAs, including recordkeeping requirements, and postmarket reporting. FDA is also finalizing recordkeeping requirements regarding the legal marketing of Pre-Existing Tobacco Products and products that are exempt from the requirements of demonstrating substantial equivalence.

Section 910(a)(2) of the FD&C Act generally requires that a new tobacco product be the subject of a PMTA marketing order unless FDA has issued an order finding it to be substantially equivalent to a predicate product or it is exempt from the requirements of demonstrating substantial equivalence. A manufacturer may choose to submit a PMTA under section 910(b) of the FD&C Act in an attempt to satisfy the requirements of premarket review. Section 910(b)(1) describes the required contents of a PMTA, which in addition to specific items, allows FDA to require applicants to submit other information relevant to the subject matter of the application.

Under § 1114.5 an applicant may submit a PMTA to demonstrate that a new tobacco product meets the requirements to receive a marketing order. A new tobacco product may not be introduced or delivered for introduction into interstate commerce under this part until FDA has issued a marketing order for the product. Section § 1114.7 describes the required content and format of the PMTA. The PMTA must contain sufficient information for FDA to determine whether any of the grounds for denial specified in section 910(c)(2) of the FD&C Act apply. The application must contain the following sections: general information, descriptive information, product samples as required by FDA, a statement of compliance with part 25, a summary, product formulation, manufacturing, health risk investigations, and a certification statement.

Section § 1114.9 provides that FDA may request, and an applicant may submit, an amendment to a pending PMTA. FDA generally expects that when an applicant submits a PMTA, the submission will include all information required by section 910(b)(1) of the FD&C Act and part 1114 to enable FDA to determine whether it should authorize the marketing of a new tobacco product. However, FDA recognizes that additional information may be needed to complete the review of a PMTA and, therefore, section § 1114.9 allows the submission of amendments to a pending application.

Section § 1114.13 describes the steps that requires an applicant to take when it changes ownership of a PMTA. This section is intended to facilitate transfers of ownership and help ensure that FDA has current information regarding the ownership of a PMTA. An applicant may transfer ownership of its PMTA at any time, including when FDA has yet to act on it.

Section § 1114.15 discusses supplemental PMTAs, which are an alternative format for submitting a PMTA. Specifically, supplemental PMTAs are a standardized cross-referencing format that FDA would implement under its authority of section 701(a) of the FD&C Act to efficiently enforce section 910 for submissions that are based on a PMTA that FDA has previously reviewed. Applicants that have received a marketing order are able to submit a supplemental PMTA to seek marketing authorization for a new tobacco product that results from a modification or modifications to the original tobacco product that received the marketing order. FDA is restricting the use of supplemental PMTAs to only changes that require the submission of limited information or revisions to ensure that FDA is able to efficiently review the application. An applicant is also be able to submit a supplemental PMTA for modifications made to comply with a product standard issued under section 907 of the FD&C Act where FDA specifies that the submission of supplemental PMTAs would be appropriate.

Section § 1114.17 describes resubmissions, which are an alternative format for submitting an application that meets the requirements of § 1114.7(b) or § 1114.15 to seek a marketing order for a tobacco product by responding to the 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 a marketing denial order. This application format allows an applicant to address the deficiencies described in a marketing denial order without having to submit a standard PMTA. The resubmission format is not available for PMTAs that FDA refused to accept, refused to file, cancelled, or administratively closed, or that the applicant withdrew because FDA has not previously completed reviews of such applications upon which it can rely, and such applications may need significant changes to be successfully resubmitted.

Section § 1114.41 requires applicants that receive a marketing order to submit postmarket reports. FDA requires such reports as necessary to determine or facilitate a determination of whether there may be grounds to withdraw or temporarily suspend a marketing order. Section § 1114.41 describes the reports that FDA would require through this regulation; however, FDA may require additional reporting in an individual applicant's marketing order. Applicants would be required under § 1114.41 to submit two types of reports after receiving a marketing order: periodic reports and adverse experience reports.

Applicants need to submit periodic reports within 60 calendar days of the reporting date specified in the marketing order. FDA requires the submission of these reports on an annual basis, but FDA may require in a specific order that reports be made more or less frequently depending upon a number of factors. Applicants are also required to report all serious and

unexpected adverse experiences associated with the tobacco product that have been reported to the applicant or of which the applicant is aware under section § 1114.41(a)(2). The serious and unexpected adverse experience reports must be submitted to CTP's Office of Science through the HHS Safety Reporting Portal within 15 calendar days after receiving or becoming aware of a serious and unexpected adverse experience.

Section § 1114.45 requires applicants receiving a marketing order to maintain all records necessary to facilitate a determination of whether there are or may be grounds to withdraw or temporarily suspend the marketing order, including records related to both the application and postmarket reports, and ensure that such records remain readily available to the Agency upon request. Under section § 1114.45(a)(1), an applicant must retain all documents submitted to FDA as part of an application and postmarket reports. An applicant must also retain any additional documentation supporting the application and postmarket reports that was not submitted to FDA.

Section § 1100.200 states that subpart C of part 1100 establishes requirements for the maintenance of records by tobacco product manufacturers who introduce a Pre-Existing Tobacco Product, or deliver it for introduction, into interstate commerce

Section § 1107.3 describes that each applicant who submits an abbreviated report under section 905(j)(1)(A)(ii) of the FD&C Act and receives a letter acknowledging the receipt of an abbreviated report from FDA must maintain all records to support a determination that their exemption request meets the requirements of section 905(j)(3)(A)(i) of the FD&C Act that the modification to a product additive described in the exemption request was a minor modification made to a tobacco product that can be sold under the FD&C Act.

Section § 1114.49 requires an applicant to submit a PMTA and all supporting and related documents to FDA in electronic format. Under section § 1114.49(c), an applicant that has a waiver would submit a paper submission to the address that FDA provides in the letter granting the waiver. FDA's section § 1114.49 is based on FDA's general experience with electronic submissions, which FDA has found help facilitate premarket reviews because electronic submissions typically enable FDA to receive, access, search, and review a submission more quickly than a submission submitted on paper through postal mail.

FDA estimates the burden of this collection of information as follows:

Table 1.--Estimated Annual Reporting Burden[1]

Activity	No. of Respondents	No. of Responses per Respondent	Total Annual Responses	Average Burden per Response	Total Hours
PMTA Submission (ENDS)	200	3.75	750	1,713	1,284,750[2]

[1] There are no capital costs or operating and maintenance costs associated with this collection of information.
[2] This total will not be added to the total burden for this rule as its currently approved under a separate OMB control number 0910-0768.

Table 2.--Estimated Annual Reporting Burden[1]

21 CFR Part; Activity	No. of Respondents	No. of Responses per Respondent	Total Annual Responses	Average Burden per Response	Total Hours
1114.5--Submission of Standard Bundled PMTAs[2]	1	1	1	1,713	1,713
1114.7--Premarket Tobacco Product Application (PMTA) Submission (Form FDA 4057)	24	1	24	0.75 (45 minutes)	18
Premarket FDA Tobacco Product Application Amendment and General Correspondence Submission (Form FDA 4057a)	24	14	336	0.16 (10 minutes)	54
Premarket Tobacco Product Unique Identifying Information for New Tobacco Products Submission (Form FDA 4057b)	24	1	24	0.75 (45 minutes)	18
1114.41--Reporting Requirements (periodic reports)	3	1	3	50	150
1114.9--Amendments	24	2	48	188	9,024
1114.13--Change in Ownership	1	1	1	1	1

1114.15--Supplemental applications	2	1	2	428	856
1114.17--Resubmissions	3	1	3	565	1,695
1114.41(a)(2)--Adverse Experience Reports	3	6	18	0.6 (36 minutes)	11
1114.49(b) and (c)--Waiver from Electronic Submission	1	1	1	0.25 (15 minutes)	0.25
Total					13,540

[1] There are no capital costs or operating and maintenance costs associated with this collection of information.
[2] FDA anticipates that applicants will submit bundled PMTAs, which are single submissions containing PMTAs for a number of similar or related products. We estimate that a bundle will contain on average (between 6 and 11) with most submitting 9 distinct products.

FDA has based these estimates on the full analysis of economic impacts and experience with current PMTA submissions. Table 1 describes the current estimates for OMB control number 0910-0768 which covers the burden for ENDS products PMTA submissions. These estimates were originally published in the deeming final rule and recently in the *Federal Register* of April 22, 2019 (84 FR 16673). FDA estimates that it will take each respondent approximately 1,500 hours to prepare a PMTA seeking an order from FDA allowing the marketing of a new tobacco product. FDA also estimates that it would on average take an additional 213 hours to prepare an environmental assessment in accordance with the requirements of § 25.40, for a total of 1,713 hours per PMTA application.

Table 1 describes the estimated annual reporting burden per the requirements that the rule would create beyond what is covered in the existing information collection. For this analysis, FDA assumes that firms will submit all applications as PMTA bundles. We also considered updated data on market consolidation that has occurred since the deeming final rule was published. For originally regulated products we expect to receive one full PMTA submission for a total of 1,713 hours.

FDA conducted a thorough analysis of the current paperwork burden associated with the PMTA program and other similar forms and applied the most accurate burden to the forms; however, upon further review and certain updates made to the form based on comments received

and product categorization changes, FDA has revised the burden associated with entering the data into the form (which includes searching existing data sources and gathering and maintaining the data needed) to be 45 minutes per individual product (rather than 30 minutes per product) on Form FDA 4057. For Form FDA 4057a, FDA has revised the burden for this form to 10 minutes (from 5 minutes). This form serves several purposes from changing a point of contact (minimal burden) to providing additional substantive information for the purpose of the review of the PMTA application (more burdensome).

FDA developed Form FDA 4057 for use when submitting PMTA single and bundled submissions. FDA estimates that 24 respondents will submit PMTA bundles using this form at 0.75 (45 minutes) per response. The number 24 is accounting for the bundles of ENDS products and the 1 bundle we expect to receive yearly for originally regulated products. (200 +1 = 201/8.5 products on average in a bundle) for a total of 12 hours.

FDA developed Form FDA 4057a for use when firms are submitting amendments and other general correspondence. Our estimate is 0.16 (10 minutes) per response to fill out this form. We estimate there will be at least one amendment per application for a total of 28 hours. With most applications being submitted toward the end of our 3-year range, we expect fewer amendments during this period. However, FDA expects correspondence from earlier applications to be submitted during this period.

FDA developed an additional form (Form FDA 4057b) that will assist industry and FDA in identifying the products that are the subject of a submission where an applicant groups multiple PMTAs into a single submission (referred to as a bundled submission or a grouped submission). FDA has previously stated that one approach to submitting PMTAs could be to group applications for products that are both from the same manufacturer or domestic importer

and in the same product category and subcategory into a single submission. FDA discussed bundled submissions in the proposed rule (84 FR 50566 at 50578) and noted that FDA intends to consider information on each tobacco product as a separate, individual PMTA. The form will assist applicants in providing the unique identifying information for each product in a grouped submission of PMTAs that are required § 1114.7(c)(3)(iii). By having the identifying information for products contained in a submission be more clearly organized, FDA will be able to more efficiently process and review the applications contained in a grouped submission.

Based on the Form FDA 4057 for use when submitting PMTA single and bundled submissions, a respondent would utilize Form FDA 4057b once for each submission containing more than one PMTA. We assume the submitter could include from 2 to 2,000 products in each Form FDA 4057b. Entering data for up to 2,000 rows can take approximately 4 hours on average per Form FDA 4057b for manual data entry. However, FDA's original estimate that Form 4057b would estimate 4 hours per response was a high-end estimate and not an average. We now reflect the average time of 45 minutes per response based on the assumption that we expect to receive an average of nine bundled products per submission. Assuming 45 minutes per Form FDA 4057b for 24 applications, we estimate a total burden of 18 hours for this activity.

FDA estimates under § 1114.41 that three respondents will submit a periodic report. This number is based on the average number of periodic report submissions expected between 2020-2022. The regulatory impact analysis (RIA) estimates that periodic reports will take between 20 and 80 hours per submission. For this estimate, we use the average of 50 per response for a total of 150 hours.

Under § 1114.9 firms will prepare amendments to PMTA bundles in response to deficiency letters. These amendments contain additional information that we need to complete

substantive review. In the RIA we state in our limited history reviewing PMTAs, we on average issue two deficiency letters. Based on this, we would anticipate two responses back per bundle. Therefore, we estimate that 24 respondents will submit 48 amendments (24 × 2). Assuming 1,500 hours as the time to prepare and submit a full PMTA and amendments may on average take 10 percent to 15 percent of that time (150-225). We averaged this time out (12.5 percent of a full submission preparation time) and arrived at 188 hours per response. FDA estimates the total burden hours for preparing amendments is 9,024 hours.

Section § 1114.13 would allow an applicant to transfer ownership of a PMTA to a new owner. FDA believes this will be infrequent, so we have assigned 1 token hour acknowledging the requirement.

Section § 1114.15 is an alternative format of submitting a PMTA that meets the requirements of § 1114.7 that would reduce the burden associated with the submission and review of an application. Our estimated number of 2 respondents is based on the number estimated for postmarket reports, which is 3 bundles (which is approximately 26 products). Not all applicants will resubmit modifications to previously authorized products, so we estimate 2 bundles (which is approximately 17 products). FDA estimates further that a supplemental PMTA will take 25 percent of the time it takes to do an original submission (including EA hours) for 428 hours per response. We estimate a total of 856 burden hours for this activity.

Under § 1114.17 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 a marketing denial order. Based on the preliminary regulatory impact analysis, we are estimating that out of all bundles received in 2020, 2021, and 2022, that an average of three bundles are authorized. If we receive 24 bundles

yearly, and based on historical data, 58 percent fail at acceptance (down to 8 bundles remaining), 17 percent fail at filing (down to 7 bundles remaining), and 25 percent receive marketing orders (5 left). We estimate that 50 percent will try to resubmit in a year. Thus, this number of respondents is three (rounded up). FDA estimates that a resubmission will take 33 percent of the time it takes to complete an original submission (including EA hours) at 565 hours per response for a total of 1,695 hours.

Under § 1114.41(a)(2), firms would also submit adverse experience reports for tobacco products with marketing orders. We assume the same number of firms submitting periodic reports will submit adverse experience reports. Currently, firms may voluntarily submit adverse experience reports using Form FDA 3800 under OMB control number 0910-0645. We have based our estimates on this information collection which estimates that it takes 1 hour (for mandatory reporting) to complete this form for tobacco products for a total of 18 hours.

Section § 1114.49 would require an applicant to submit a PMTA and all supporting and related documents to FDA in electronic format that FDA can process, review, and archive unless an applicant requests, and FDA grants, a waiver from this requirement. FDA does not believe we will receive many waivers, so we have assigned one respondent to acknowledge the option to submit a waiver. Consistent with our other application estimates for waivers, we believe it would take .25 hours (15 minutes) per waiver for a total of .25 hours.

Table 3.--Estimated Annual Recordkeeping Burden[1]

21 CFR Part; Activity	No. of Recordkeepers	No. of Records per Recordkeeper	Total Annual Records	Average Burden per Recordkeeping	Total Hours
1114.45--PMTA Records	24	1	24	2	48
1100.204--Pre-Existing Tobacco Product Records	1	1	1	2	2
1107.3--Exemptions from Substantial Equivalence Records	1	1	1	2	2
Total					52

[1] There are no capital costs or operating and maintenance costs associated with this collection of information.

Table 3 describes the annual recordkeeping burden per the requirements in this rule. FDA estimates that 26 recordkeepers will maintain records at 2 hours per record. Additionally, the rule requires that firms establish and maintain records related to SE Exemption Requests and Pre-Existing Tobacco Products. We expect the burden hours of this rule to be negligible for SE Exemption Requests. Firms would have already established the required records when submitting the SE Exemption Request. Similarly, we expect the hours of this rule to be negligible for any Pre-Existing Tobacco Products that have already submitted Standalone Pre-Existing Tobacco Product Submissions, because firms would have established the required records when submitting the Standalone Pre-Existing Tobacco Product Submissions. We believe this time is usual and customary for these firms. We estimate that it would take 2 hours per record to establish the required records for a total of 4 hours. Therefore, the total recordkeeping burden hours is estimated to be 52 hours.

The total burden for these new collections of information in this rulemaking is 13,540 reporting hours and 52 recordkeeping hours for a total of 13,592 hours.

The information collection provisions in this final rule have been submitted to OMB for review as required by section 3507(d) of the Paperwork Reduction Act of 1995.

Before the effective date of this final rule, FDA will publish a notice in the *Federal Register* announcing OMB's decision to approve, modify, or disapprove the information collection provisions in this final rule. An Agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

XIII. Federalism: Executive Order 13132

We have analyzed this rule in accordance with the principles set forth in Executive Order 13132. Section 4(a) of the Executive Order requires Agencies to "construe ... a Federal statute to preempt State law only where the statute contains an express preemption provision or there is some other clear evidence that the Congress intended preemption of State law, or where the exercise of State authority conflicts with the exercise of Federal authority under the Federal statute."

Section 916(a)(2) of the FD&C Act is an express preemption provision. Section 916(a)(2) provides that "no State or political subdivision of a State may establish or continue in effect with respect to a tobacco product any requirement which is different from, or in addition to, any requirement under the provisions of this chapter relating to…premarket review." Thus, the final rule creates requirements that fall within the scope of section 916(a)(2) of the FD&C Act.

XIV. Congressional Review Act

Pursuant to the Congressional Review Act (5 U.S.C. § 801 et seq.), the Office of Information and Regulatory Affairs designated this rule as not a "major rule," as defined by 5 U.S.C. § 804(2).

XV. Consultation and Coordination with Indian Tribal Governments

We have analyzed this rule in accordance with the principles set forth in Executive Order 13175. We have determined that the rule does not contain policies that have substantial direct effects on one or more Indian Tribes, on the relationship between the Federal Government and Indian Tribes, or on the distribution of power and responsibilities between the Federal Government and Indian Tribes. Accordingly, we conclude that the rule does not contain policies

that have tribal implications as defined in the Executive Order and, consequently, a tribal summary impact statement is not required.

XVI. Analysis of Environmental Impact

The Agency has determined under § 25.30(h) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. No extraordinary circumstances exist to indicate that the specific proposed action may significantly affect the quality of the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

XVII. Economic Analysis of Impacts

A. Introduction

We have examined the impacts of the final rule under Executive Order 12866, Executive Order 13563, Executive Order 13771, 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). Executive Order 13771 requires that the costs associated with significant new regulations "shall, to the extent permitted by law, be offset by the elimination of existing costs associated with at least two prior regulations." 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 $156 million, using the most current (2019) 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 and manufacturers of products that are exempt from the requirements of demonstrating SE to maintain records to demonstrate that they can legally market their products. For products that receive a 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 4, 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 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 final 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 4, 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 4.--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							

In line with Executive Order 13771, in table 5 we estimate present and annualized values of costs and cost savings over an infinite time horizon. Based on these costs, the final rule is considered a regulatory action under EO 13771.

Table 5.--Executive Order 13771 Summary Table (in $ Millions 2016 Dollars, Over an Infinite Time Horizon)

	Primary Estimate (7%)	Lower Bound (7%)	Upper Bound (7%)	Primary Estimate (3%)	Lower Bound (3%)	Upper Bound (3%)
Present Value of Costs	$56.68	$28.30	$95.40	$162.91	$68.02	$300.80
Present Value of Cost Savings	$21.03	$13.94	$29.51	$53.23	$35.86	$75.09
Present Value of Net Costs	$35.65	$7.78	$73.51	$109.68	$16.47	$245.49
Annualized Costs	$3.71	$1.85	$6.24	$4.75	$1.98	$8.76
Annualized Cost Savings	$1.38	$0.91	$1.93	$1.55	$1.04	$2.19
Annualized Net Costs	$2.33	$0.51	$4.81	$3.19	$0.48	$7.15

XVIII. Effective Date

This rule will become effective 30 days after it publishes in the *Federal Register*.

(Comment 146) One comment stated that FDA must not apply any requirements from the final rule retroactively to applications that have already been submitted because doing so would be fundamentally unfair. The comment further stated, for instance, that FDA should not discount

the results of a study on the basis that it does not contain the newly required statements or documentation regarding financial conflicts of interest.

(Response 146) FDA agrees with this comment insofar as it applies to the acceptance and filing criteria. FDA does not intend to retroactively apply any new acceptance and filing criteria added by § 1114.27 to applications that have been submitted before the final rule is effective. If an applicant has submitted an application before this rule is effective, FDA will not refuse to accept or refuse to file the PMTA unless the FD&C Act or other existing regulations require information that the application is missing. It is important to note that while FDA will not apply acceptance and filing criteria required by this rule retroactively, the information required for acceptance and filing under this rule remains important to FDA's substantive review of an application. The comment's example of information regarding financial conflicts of interest is particularly relevant because determining the reliability of a study's results is an important part of FDA's substantive review of an application, regardless of whether it's applied as a filing criteria. Other provisions in this rule, such as those regarding application amendments, temporary suspension and withdrawal, postmarket changes, postmarket reporting, and recordkeeping, will take effect for all PMTAs, as applicable, once the rule is effective. In addition, all the requirements in section 910 of FD&C Act are in effect.

XIX. References

The following references marked with an asterisk (*) are on display at the Dockets Management Staff and are available for viewing by interested persons between 9 a.m. and 4 p.m., Monday through Friday; they also are available electronically at https://www.regulations.gov. References without asterisks are not on public display at https://www.regulations.gov because they have copyright restriction. Some may be available at

the website address, if listed. References without asterisks are available for viewing only at the Dockets Management Staff, Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852, 240-402-7500. FDA has verified the website addresses, as of the date this document publishes in the *Federal Register*, but websites are subject to change over time.

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List of Subjects

21 CFR Part 1100

Administrative practice and procedure, Smoke, Smoking, Tobacco, Tobacco products.

21 CFR Part 1107

Administrative practice and procedure, Smoke, Smoking, Tobacco, Tobacco products.

21 CFR Part 1114

Administrative practice and procedure, Smoke, Smoking, Tobacco, Tobacco products.

Therefore, under the Federal Food, Drug, and Cosmetic Act, and under authority delegated to the Commissioner of Food and Drugs, chapter I of title 21 of the Code of Federal Regulations is amended as follows:

PART 1100--GENERAL

1. The authority citation for part 1100 is revised to read as follows:

Authority: 21 U.S.C. 371, 374, 387a(b), 387e, and 387i; Pub. L. 111-31.

2. Revise the part heading to read as set forth above.

Subpart A—Tobacco Products Subject to FDA Authority

3. Add subpart A consisting of §§ 1100.1, 1100.2, 1100.3, and 1100.5 to read as set forth above:

Subpart B [Reserved]

4. Add and reserve subpart B.

5. Add subpart C, consisting of §§ 1100.200, 1100.202, and 1100.204, to read as follows:

Subpart C--Maintenance of Records Demonstrating That a Tobacco Product Was Commercially Marketed in the United States as of February 15, 2007

Sec.

1100.200 Purpose and scope.
1100.202 Definitions.
1100.204 Recordkeeping requirements.

Subpart C-- Maintenance of Records Demonstrating That a Tobacco Product Was Commercially Marketed in the United States as of February 15, 2007.

§ 1100.200 Purpose and scope.

This subpart sets out requirements under the Federal Food, Drug, and Cosmetic Act for the maintenance of records by tobacco product manufacturers that introduce a Pre-Existing Tobacco Product, or deliver it for introduction, into interstate commerce.

§ 1100.202 Definitions.

For the purposes of this part:

Commercially marketed means selling or offering for sale a tobacco product in the United States to consumers or to any person for the eventual purchase by consumers in the United States.

Pre-Existing Tobacco Product means a tobacco product (including those products in test markets) that was commercially marketed in the United States as of February 15, 2007. A Pre-Existing Tobacco Product is not subject to the premarket requirements of section 910 of the Federal Food, Drug, and Cosmetic Act.

Tobacco product means any product made or derived from tobacco that is intended for human consumption, including any component, part, or accessory of a tobacco product (except for raw materials other than tobacco used in manufacturing a component, part, or accessory of a tobacco product). The term "tobacco product" does not mean an article that under the Federal

Food, Drug, and Cosmetic Act is a drug (section 201(g)(1)), a device (section 201(h)), or a combination product (section 503(g)).

Tobacco product manufacturer means any person, including any repacker or relabeler, who--

(1) Manufactures, fabricates, assembles, processes, or labels a tobacco product; or

(2) Imports a finished tobacco product for sale or distribution in the United States.

§ 1100.204 Recordkeeping requirements.

(i) Any tobacco product manufacturer that introduces a Pre-Existing Tobacco Product, or delivers it for introduction, into interstate commerce must maintain records that demonstrate that the tobacco product was commercially marketed in the United States as of February 15, 2007, as described in this subpart. These records may include items such as:

(A) Dated copies of advertisements;

(B) Dated catalog pages;

(C) Dated promotional material;

(D) Dated trade publications;

(E) Dated bills of lading;

(F) Dated freight bills;

(G) Dated waybills;

(H) Dated invoices;

(I) Dated purchase orders;

(J) Dated customer receipts;

(K) Dated manufacturing documents;

(L) Dated distributor or retailer inventory lists; or

(M) Any other dated document that demonstrates that the tobacco product was commercially marketed in the United States as of February 15, 2007.

(ii) All records must be legible, in the English language, and available for inspection and copying by officers or employees duly designated by the Secretary. Documents that have been translated from another language into English (e.g., advertisements written in a language other than English) must be accompanied by the original language version of the document, a signed statement by an authorized representative of the manufacturer certifying that the English language translation is complete and accurate, and a brief statement of the qualifications of the person that made the translation.

(iii) All records required by this subpart must be retained for a period of not less than 4 years after the date either FDA makes a determination that the product is a Pre-Existing Tobacco Product, or the tobacco product manufacturer permanently ceases the introduction or delivery for introduction into interstate commerce of the tobacco product, whichever occurs sooner.

PART 1107--EXEMPTION REQUESTS AND SUBSTANTIAL EQUIVALENCE REPORTS

6. The authority citation for part 1107 is revised to read as follows:

Authority: 21 U.S.C. 371, 374, 387e(j), 387i, 387j.

7. Revise the part heading as set forth above.

8. Add § 1107.3 to subpart A to read as follows:

§ 1107.3 Recordkeeping.

(a) *Definition*. The term "Pre-Existing Tobacco Product" means a tobacco product (including those products in test markets) that was commercially marketed in the United States as of February 15, 2007. A Pre-Existing Tobacco Product is not subject to the premarket requirements of section 910 of the Federal Food, Drug, and Cosmetic Act.

(b) *Record maintenance*. (1) Each applicant who submits an abbreviated report under section 905(j)(1)(A)(ii) of the Federal Food, Drug, and Cosmetic Act and receives a letter acknowledging the receipt of an abbreviated report from FDA must maintain all records (including those created by third parties on the applicant's behalf) that support the submission. Such records may include, but are not limited to:

(i) A copy of the abbreviated report and, if applicable, the exemption request and all amendments thereto.

(ii) A copy of the acknowledgement letter issued in response to an abbreviated report and, if applicable, the exemption order issued by FDA.

(iii) Documents related to formulation of product, design specifications, packaging, and related items.

(iv) Documents showing design specifications are consistently met.

(v) Documents related to product packing and storage conditions.

(vi) Analytical test method records, including:

(A) Performance criteria.

(B) Validation or verification documentation; and

(C) Reports/results from these test methods.

(vii) Source data and related summaries.

(2) An applicant that submits an abbreviated report for a modification to a Pre-Existing Tobacco Product must also maintain records demonstrating that the Pre-Existing Tobacco Product was commercially marketed in the United States as of February 15, 2007, such as the records described in § 1100.204 of this chapter.

(3) An applicant that submits an abbreviated report for a modification to a tobacco product that previously received premarket authorization (i.e., an exemption (and for which the

applicant has submitted an abbreviated report under section 905(j)(1)(A)(ii) of the Federal Food, Drug, and Cosmetic Act, a substantially equivalent order under section 910(a), or a marketing granted order under section 910(c)) must maintain a copy of the exemption order, substantially equivalent order, or marketing granted order.

(4) An applicant that submits an abbreviated report for a modification to a tobacco product that is the subject of a pending SE report and is marketed pursuant to section 910(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act must maintain all communications to and from FDA relating to the pending SE Report (e.g., acknowledgement letter, deficiency letters), including the SE Report.

(c) *Record quality*. All records must be legible, in the English language, and available for inspection and copying by officers or employees duly designated by the Secretary. Documents that have been translated from another language into English (e.g., advertisements written in a language other than English) must be accompanied by the original language version of the document, a signed statement by an authorized representative of the manufacturer certifying that the English language translation is complete and accurate, and a brief statement of the qualifications of the person that made the translation.

(d) *Record retention*. All records required by this subpart must be retained for a period of 4 years from the date that an acknowledgement letter is issued by FDA.

9. Add part 1114 to subchapter K to read as follows:

PART 1114--PREMARKET TOBACCO PRODUCT APPLICATIONS

Subpart A--General Provisions

Sec.

1114.1 Scope.
1114.3 Definitions.

Subpart B--Premarket Tobacco Product Applications

1114.5 Application submission.
1114.7 Required content and format.
1114.9 Amendments.
1114.11 Withdrawal by applicant.
1114.13 Change in ownership of an application.
1114.15 Supplemental applications.
1114.17 Resubmissions.

Subpart C--FDA Review

1114.25 Communication between FDA and applicants.
1114.27 Review procedure.
1114.29 FDA action on an application.
1114.31 Issuance of a marketing granted order.
1114.33 Issuance of a marketing denial order.
1114.35 Withdrawal of a marketing granted order.
1114.37 Temporary suspension of a marketing granted order.

Subpart D--Postmarket Requirements

1114.39 Postmarket changes.
1114.41 Reporting requirements.

Subpart E--Miscellaneous

1114.45 Record retention.
1114.47 Confidentiality.
1114.49 Electronic submission.

Authority: 21 U.S.C. 371, 374, 387a, 387i, and 387j.

Subpart A--General Provisions

§ 1114.1 Scope.

(a) This part sets forth the procedures and requirements for submitting a premarket tobacco product application (PMTA), the general procedures FDA will follow when evaluating a PMTA, and postmarket reporting requirements.

(b) This part does not apply to modified risk tobacco product applications, except that single applications seeking both a marketing granted order under section 910(c) of the Federal

Food, Drug, and Cosmetic Act and an order under section 911(g) of the Federal Food, Drug, and Cosmetic Act must satisfy the requirements of this part in addition to the requirements of section 911 of the Federal Food, Drug, and Cosmetic Act.

(c) References in this part to regulatory sections of the Code of Federal Regulations are to chapter I of title 21, unless otherwise noted.

(d) This part does not apply to "premium" cigars as defined in § 1114.3.

§ 1114.3 Definitions.

For purposes of this part:

Accessory means any product that is intended or reasonably expected to be used with or for the human consumption of a tobacco product; does not contain tobacco and is not made or derived from tobacco; and meets either of the following:

(1) Is not intended or reasonably expected to affect or alter the performance, composition, constituents, or characteristics of a tobacco product; or

(2) Is intended or reasonably expected to affect or maintain the performance, composition, constituents, or characteristics of a tobacco product, but:

(i) Solely controls moisture and/or temperature of a stored tobacco product; or

(ii) Solely provides an external heat source to initiate but not maintain combustion of a tobacco product.

Additive means any substance the intended use of which results or may reasonably be expected to result, directly or indirectly, in its becoming a component or otherwise affecting the characteristic of any tobacco product (including any substances intended for use as a flavoring or coloring or in producing, manufacturing, packing, processing, preparing, treating, packaging,

transporting, or holding), except that such term does not include tobacco, or a pesticide chemical residue in or on raw tobacco or a pesticide chemical.

Adverse experience means any unfavorable physical or psychological effect in a person that is temporally associated with the use of or exposure to a tobacco product, whether or not the person uses the tobacco product, and whether or not the effect is considered to be related to the use of or exposure to the tobacco product.

Applicant means any person that submits a premarket tobacco product application to receive a marketing granted order for a new tobacco product.

Brand means a variety of tobacco product distinguished by the tobacco used, tar content, nicotine content, flavoring used, size, filtration, packaging, logo, registered trademark, brand name(s), identifiable pattern of colors, or any combination of such attributes.

Characteristics means the materials, ingredients, design, composition, heating source, or other features of a tobacco product.

Commercially marketed means selling or offering for sale a tobacco product in the United States to consumers or to any person for the eventual purchase by consumers in the United States.

Component or *part* means any software or assembly of materials intended or reasonably expected:

(1) To alter or affect the tobacco product's performance, composition, constituents, or characteristics; or

(2) To be used with or for the human consumption of a tobacco product. Component or part excludes anything that is an accessory of a tobacco product.

Composition means the materials in a tobacco product, including ingredients, additives, and biological organisms. The term includes the manner in which the materials, for example, ingredients, additives, and biological organisms, are arranged and integrated to produce a tobacco product.

Constituent means any chemical or chemical compound in a tobacco product that is or potentially is inhaled, ingested, or absorbed into the body, any chemical or chemical compound in an emission (e.g., smoke, aerosol, droplets) from a tobacco product, that either transfers from any component or part of the tobacco product to the emission or that is formed by the product, including through combustion or heating of tobacco, additives, or other components of the tobacco product.

Container closure system means any packaging materials that are a component or part of a tobacco product.

Design means the form and structure concerning, and the manner in which components or parts, ingredients, software, and materials are integrated to produce a tobacco product.

Finished tobacco product means a tobacco product, including all components and parts, sealed in final packaging (e.g., filters or filter tubes sold to consumers separately or as part of kits, or e-liquids sealed in final packaging sold to consumers either separately or as part of kits) or in the final form in which it is intended to be sold to consumers.

Harmful or potentially harmful constituent or *HPHC* means any chemical or chemical compound in a tobacco product or tobacco smoke or emission that:

(1) Is or potentially is inhaled, ingested, or absorbed into the body, including as an aerosol or any other emission; and

(2) Causes or has the potential to cause direct or indirect harm to users or nonusers of tobacco products.

Heating source means the source of energy used to burn or heat the tobacco product.

Ingredient means tobacco, substances, compounds, or additives contained within or added to the tobacco, paper, filter, or any other component or part of a tobacco product, including substances and compounds reasonably expected to be formed through a chemical reaction during tobacco product manufacturing.

Label means a display of written, printed, or graphic matter upon the immediate container of any article.

Labeling means all labels and other written, printed, or graphic matter upon any article or any of its containers or wrappers, or accompanying such article.

Line data means an analyzable dataset of observations for each individual study participant, laboratory animal, or test replicate.

Marketing denial order means the order described in section 910(c)(1)(A)(ii) of the Federal Food, Drug, and Cosmetic Act stating that the product may not be introduced or delivered for introduction into interstate commerce.

Marketing granted order means the order described in section 910(c)(1)(A)(i) of the Federal Food, Drug, and Cosmetic Act stating that the new tobacco product may be introduced or delivered for introduction into interstate commerce.

Material means an assembly of ingredients. Materials are assembled to form a tobacco product or components or parts of a tobacco product.

New tobacco product means:

(1) Any tobacco product (including those products in test markets) that was not commercially marketed in the United States as of February 15, 2007; or

(2) Any modification (including a change in design, any component, any part, or any constituent, including a smoke constituent, or in the content, delivery or form of nicotine, or any other additive or ingredient) of a tobacco product where the modified product was commercially marketed in the United States after February 15, 2007.

Other features means any distinguishing qualities of a tobacco product similar to those specifically enumerated in section 910(a)(3)(B) of the Federal Food, Drug, and Cosmetic Act. Such other features include harmful and potentially harmful constituents and any other product characteristics that relate to the chemical, biological, and physical properties of the tobacco product.

Package or *packaging* means a pack, box, carton, or container of any kind or, if no other container, any wrapping (including cellophane), in which a tobacco product is offered for sale, sold, or otherwise distributed to consumers.

Premarket tobacco product application or *PMTA* means the application described in section 910(b) of the Federal Food, Drug, and Cosmetic Act. This term includes the initial premarket tobacco product application and all subsequent amendments.

"Premium" cigar means a type of cigar that:

(1) Is wrapped in whole tobacco leaf;

(2) Contains a 100 percent leaf tobacco binder;

(3) Contains at least 50 percent (of the filler by weight) long filler tobacco (i.e., whole tobacco leaves that run the length of the cigar);

(4) Is handmade or hand rolled (i.e., no machinery was used apart from simple tools, such as scissors to cut the tobacco prior to rolling);

(5) Has no filter, nontobacco tip, or nontobacco mouthpiece;

(6) Does not have a characterizing flavor other than tobacco;

(7) Contains only tobacco, water, and vegetable gum with no other ingredients or additives; and

(8) Weighs more than 6 pounds per 1,000 units.

Serious adverse experience means an adverse experience that results in any of the following outcomes:

(1) Death;

(2) A life-threatening condition or illness;

(3) Inpatient hospitalization or prolongation of existing hospitalization;

(4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;

(5) A congenital anomaly/birth defect; or

(6) Any other adverse experience that, based upon appropriate medical judgment, may jeopardize the health of a person and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

Submission tracking number or *STN* means the number that FDA assigns to submissions that are received from an applicant, such as a PMTA and a supplemental PMTA.

Tobacco product means any product made or derived from tobacco that is intended for human consumption, including any component, part, or accessory of a tobacco product (except for raw materials other than tobacco used in manufacturing a component, part, or accessory of a

tobacco product). The term "tobacco product" does not mean an article that under the Federal Food, Drug, and Cosmetic Act is a drug (section 201(g)(1)), a device (section 201(h)), or a combination product (section 503(g)).

Tobacco product manufacturer means any person, including a repacker or relabeler, who:

(1) Manufactures, fabricates, assembles, processes, or labels a tobacco product, or

(2) Imports a finished tobacco product for sale or distribution in the United States.

Unexpected adverse experience means an adverse experience occurring in one or more persons in which the nature, severity, or frequency of the experience is not consistent with:

(1) The known or foreseeable risks of adverse experiences associated with the use or exposure to the tobacco product as described in the PMTA and other relevant sources of information, such as the product labeling and postmarket reports;

(2) The expected natural progression of any underlying disease, disorder, or condition of the persons(s) experiencing the adverse experience and the person's predisposing risk factor profile for the adverse experience; or

(3) The results of nonclinical investigations.

Vulnerable populations means groups that are susceptible to tobacco product risk and harm due to disproportionate rates of tobacco product initiation, use, burden of tobacco-related diseases, or decreased cessation. Vulnerable populations can include, but are not limited to, youth and young adults, those with lower socioeconomic status, certain races or ethnicities, sexual or gender minorities, underserved rural populations, those pregnant or trying to become pregnant, those in the military or veterans, those with mental health conditions or substance use disorders.

Subpart B--Premarket Tobacco Product Applications

§ 1114.5 Application submission.

An applicant may submit a PMTA to demonstrate that a new tobacco product meets the requirements to receive a marketing granted order. A new tobacco product may not be introduced or delivered for introduction into interstate commerce under this part until FDA has issued a marketing granted order for the product.

§ 1114.7 Required content and format.

(a) *General*. The PMTA must contain sufficient information for FDA to determine whether any of the grounds for marketing denial order specified in section 910(c)(2) of the Federal Food, Drug, and Cosmetic Act apply. The application must contain the following sections:

(1) General information (as described in paragraph (c) of this section);

(2) Descriptive information (as described in paragraph (d) of this section);

(3) Product samples (as described in paragraph (e) of this section);

(4) Labeling and description of marketing plans (as described in paragraph (f) of this section);

(5) Statement of compliance with 21 CFR part 25 (as described in paragraph (g) of this section);

(6) Summary (as described in paragraph (h) of this section);

(7) Product formulation (as described in paragraph (i) of this section);

(8) Manufacturing (as described in paragraph (j) of this section);

(9) Health risk investigations (as described in paragraph (k) of this section); and

(10) The effect on the population as a whole (as described in paragraph (l) of this section);

(11) Certification statement (as described in paragraph (m) of this section).

(b) *Format.* (1) The application must be submitted using the form(s) that FDA provides, contain a comprehensive index (i.e., a listing of files and data associated with those files) and table of contents, be well-organized and legible, and be written in English. Documents that have been translated from another language into English (e.g., original study documents written in a language other than English) must be accompanied by: the original language version of the document, signed a statement by an authorized representative of the manufacturer certifying that the English language translation is complete and accurate, and a brief statement of the qualifications of the person that made the translation. As described in § 1114.49, the applicant must submit the application and all information supporting the application in an electronic format that FDA can process, read, review, and archive, unless FDA has granted a waiver.

(2) An applicant may include content in a submission by cross-reference to a tobacco product master file or a pending modified risk tobacco product application for the same tobacco product. Applicants using a master file must provide documentation of their right of reference for the master file and clearly identify the specific content being incorporated into the PMTA submission. Except as provided for in §§ 1114.15 and 1114.17, FDA will not consider content included by cross-reference to other sources of information outside of the submission.

(c) *General information*. The applicant must, by using the form(s) FDA provides, specify the following general information:

(1) Applicant name, address, and contact information;

(2) Authorized representative or U.S. agent (for a foreign applicant), including the name, address, and contact information;

(3) The following information to uniquely identify the product:

(i) Manufacturer;

(ii) Product name(s), including brand and subbrand (or other commercial name(s) used in commercial distribution); and

(iii) The product category, product subcategory, and product properties as provided in the following table. If the product does not have a listed product property, such as ventilation or characterizing flavor, the application must state "none" for that property.

Table 1 to paragraph (c)(3)(iii)

Tobacco product category:	Tobacco product subcategory:	Product properties:
(A) Cigarettes	*(1)* Filtered	--Package type (e.g., hard pack, soft pack, clam shell) --Product quantity (e.g., 20 cigarettes, 25 cigarettes) --Length (e.g., 89.1 millimeters (mm), 100.0 mm) --Diameter (e.g., 6.0 mm, 8.1 mm) --Ventilation (e.g., none, 10.0%, 25.0%) --Characterizing flavor(s) (e.g., none, menthol) --Additional properties needed to uniquely identify the tobacco product (if applicable)
	(2) Non-filtered	--Package type (e.g., hard pack, soft pack, clam shell) --Product quantity (e.g., 20 cigarettes, 25 cigarettes) --Length (e.g., 89.1 mm, 100.0 mm) --Diameter (e.g., 6.0 mm, 8.1 mm) --Characterizing flavor(s) (e.g., none, menthol) -- Additional properties needed to uniquely identify the tobacco product (if applicable)
	(3) Other	--Package type (e.g., hard pack, soft pack, clam shell) --Product quantity (e.g., 20 cigarettes, 25 cigarettes) --Length (e.g., 89.1 mm, 100.0 mm) --Diameter (e.g., 6.0 mm, 8.1 mm) --Ventilation (e.g., none, 10.0%, 25.0%) --Characterizing flavor(s) (e.g., none, menthol) --Additional properties needed to uniquely identify the tobacco product (if applicable)
(B) Roll-Your-Own Tobacco Products	*(1)* Roll-Your-Own Tobacco Filler	--Package type (e.g., bag, pouch) --Product quantity (e.g., 20.1 grams [g], 16.0 ounces [oz.]) --Characterizing flavor(s) (e.g., none, menthol)

		--Additional properties needed to uniquely identify the tobacco product (if applicable)
	(2) Rolling Paper	--Package type (e.g., box, booklet) --Product quantity (e.g., 50 sheets, 200 papers) --Length (e.g., 79.1 mm, 100.0 mm, 110.2 mm) --Width (e.g., 28.1 mm, 33.0 mm, 45.2 mm) --Characterizing flavor(s) (e.g., none, menthol) --Additional properties needed to uniquely identify the tobacco product (if applicable)
	(3) Cigarette Tube, Filtered	--Package type (e.g., bag, box) --Product quantity (e.g., 100 tubes, 200 tubes) --Length (e.g., 89.1 mm, 100.0 mm) --Diameter (e.g., 6.0 mm, 8.1 mm) --Ventilation (e.g., none, 10.0%, 25.0%) --Characterizing flavor(s) (e.g., none, menthol, tobacco) --Additional properties needed to uniquely identify the tobacco product (if applicable)
	(4) Cigarette Tube, Non-filtered	--Package type (e.g., bag, box) --Product quantity (e.g., 100 tubes, 200 tubes) --Length (e.g., 89.1 mm, 100.0 mm) --Diameter (e.g., 6.0 mm, 8.1 mm) --Characterizing flavor(s) (e.g., none, menthol, tobacco) --Additional properties needed to uniquely identify the tobacco product (if applicable)
	(5) Filter	--Package type (e.g., bag, box) --Product quantity (e.g., 100 filters, 200 filters) --Length (e.g., 8.0 mm, 12.1 mm) --Diameter (e.g., 6.0 mm, 8.1 mm) --Characterizing flavor(s) (e.g., none, menthol, tobacco) --Additional properties needed to uniquely identify the tobacco product (if applicable)
	(6) Paper Tip	--Package type (e.g., bag, box) --Product quantity (e.g., 200 tips, 275 tips) --Length (e.g., 12.0 mm, 15.1 mm) --Width (e.g., 27.1 mm) --Characterizing flavor(s) (e.g., none, menthol, tobacco) --Additional properties needed to uniquely identify the tobacco product (if applicable)
	(7) Other	--Package type (e.g., bag, box) --Product quantity (e.g., 200 tips, 100 filters, 200 tubes

		--Characterizing flavor(s) (e.g., none, menthol, tobacco) --Additional properties needed to uniquely identify the tobacco product
(C) Smokeless Tobacco Products	*(1)* Moist Snuff, Loose	--Package type (e.g., plastic can with metal lid, plastic can with plastic lid) --Product quantity (e.g., 20.0 g, 2.1 oz.) --Characterizing flavor(s) (e.g., none, menthol, cherry, wintergreen) --Additional properties needed to uniquely identify the tobacco product (if applicable, e.g., fine cut, long cut, straight cut)
	(2) Moist Snuff, Portioned	--Package type (e.g., plastic can with metal lid, plastic can with plastic lid) --Product quantity (e.g., 22.5 g, 20.0 g) --Portion count (e.g., 15 pouches, 20 pieces) --Portion mass (e.g., 1.5 g/pouch, 1.0 g/piece) --Portion length (e.g., 15.0 mm, 20.1 mm) --Portion width (e.g., 10.0 mm, 15.1 mm) --Portion thickness (e.g., 5.0 mm, 7.1 mm) --Characterizing flavor(s) (e.g., none, menthol, cherry, wintergreen) --Additional properties needed to uniquely identify the tobacco product (if applicable)
	(3) Snus, Loose	--Package type (e.g., plastic can with metal lid, plastic can with plastic lid) --Product quantity (e.g., 20.0 g, 2.1 oz.) --Characterizing flavor(s) (e.g., none, menthol, cherry, wintergreen) --Additional properties needed to uniquely identify the tobacco product (if applicable)
	(4) Snus, Portioned	--Package type (e.g., plastic can with metal lid, plastic can with plastic lid) --Product quantity (e.g., 22.5 g, 20.0 g) --Portion count (e.g., 15 pouches, 20 pieces) --Portion mass (e.g., 1.5 g/pouch, 1.0 g/piece) --Portion length (e.g., 15.0 mm, 20.1 mm) --Portion width (e.g., 10.0 mm, 15.1 mm) --Portion thickness (e.g., 5.0 mm, 7.1 mm) --Characterizing flavor(s) (e.g., none, menthol, cherry, wintergreen) --Additional properties needed to uniquely identify the tobacco product (if applicable)
	(5) Dry Snuff, Loose	--Package type (e.g., plastic can with metal lid, plastic can with plastic lid) --Product quantity (e.g., 20.0 g, 2.1 oz.)

		--Characterizing flavor(s) (e.g., none, menthol, cherry, wintergreen) --Additional properties needed to uniquely identify the tobacco product (if applicable)
	(6) Dissolvable	--Package type (e.g., plastic can with metal lid, plastic can with plastic lid) --Product quantity (e.g., 22.5 g, 20.0 g) --Portion count (e.g., 15 sticks, 20 pieces) --Portion mass (e.g., 1.5 g/strip, 1.0 g/piece) --Portion length (e.g., 10.0 mm, 15.1 mm) --Portion width (e.g., 5.0 mm, 8.1 mm) --Portion thickness (e.g., 3.0 mm, 4.1 mm) --Characterizing flavor(s) (e.g., none, menthol, cherry, wintergreen) --Additional properties needed to uniquely identify the tobacco product (if applicable)
	(7) Chewing Tobacco, Loose	--Package type (e.g., bag, pouch, wrapped) --Product quantity (e.g., 20.0 g, 3.1 oz) --Characterizing flavor(s) (e.g., none, menthol, cherry, wintergreen) --Additional properties needed to uniquely identify the tobacco product (if applicable)
	(8) Chewing Tobacco, Portioned	--Package type (e.g., plastic can with metal lid, plastic can with plastic lid) --Product quantity (e.g., 22.5 g, 20.0 g) --Portion count (e.g., 10 bits) --Portion mass (e.g., 2.1 g/bit) --Portion length (e.g., 8.0 mm, 10.1 mm) --Portion width (e.g., 6.0 mm, 8.1 mm) --Portion thickness (e.g., 5.1 mm, 7.0 mm) --Characterizing flavor(s) (e.g., none, menthol, cherry, wintergreen) --Additional properties needed to uniquely identify the tobacco product (if applicable)
	(9) Other	--Package type (e.g., bag, box, can) --Product quantity (e.g., 20.1 g, 22.5 g, 3.0 oz.) --Characterizing flavor(s) (e.g., none, menthol, cherry, wintergreen, tobacco) --Additional properties needed to uniquely identify the tobacco product
(D) Electronic Nicotine Delivery System (ENDS) (Also referred to as vapes)	*(1)* E-Liquid, Open	--Package type (e.g., bottle, box, pod) --Product quantity (e.g., 1 bottle, 5 bottles) -- E-liquid volume (e.g., 0.5 milliliters [ml]), 2.0 ml, 5.1 ml) --Nicotine concentration (e.g., 0 milligrams/milliliter [mg/ml], 0.2 mg/ml, 0.4 mg/ml, 1%, 0.2 mg/bottle)

		--Propylene glycol (PG)/ vegetable glycerin (VG) ratio (e.g., not applicable [N/A], 0/100, 50/50, 100/0) --Characterizing flavor(s) (e.g., none, tobacco, menthol, cherry, wintergreen) --Additional properties needed to uniquely identify the tobacco product (if applicable)
	(2) E-Liquid, Closed	--Package type (e.g., cartridge, pod) --Product quantity (e.g., 1 cartridge, 5 cartridges) --E-liquid volume (e.g., 0.5 ml, 2.0 ml, 5.1 ml) -- Nicotine concentration (e.g., 0 mg/ml, 0.2 mg/ml, 0.4 mg/ml, 1%, 2.0 mg/bottle) --PG/VG ratio (e.g., N/A, 0/100, 50/50, 100/0) --Characterizing flavor(s) (e.g., none, tobacco, menthol, cherry, wintergreen) --Additional properties needed to uniquely identify the tobacco product (if applicable)
	(3) E-Cigarette, Closed	--Package type (e.g., box, none, plastic clamshell) --Product quantity (e.g., 1 e-cigarette, 5 e-cigarettes) --Length (e.g., 100.0 mm, 120.0 mm) --Diameter (e.g., 6.0 mm, 8.0 mm) --Wattage (e.g., 100 watts [W], 200 W) --Battery capacity (e.g., 100 milliampere hours [mAh], 200 mAh) --E-liquid volume (e.g., 0.5 ml, 2.0 ml, 5.1 ml) -- Nicotine concentration (e.g., 0 mg/ml, 0.2 mg/ml, 0.4 mg/ml, 1%, 0.2 mg/e-cigarette) --PG/VG ratio (e.g., N/A, 0/100, 50/50, 100/0) --Characterizing flavor(s) (e.g., none, tobacco, menthol, cherry, wintergreen) --Additional properties needed to uniquely identify the tobacco product
	(4) E-Cigarette, Open	--Package type (e.g., box, none, plastic clamshell) --Product quantity (e.g., 1 e-cigarette, 5 e-cigarettes) --Length (e.g., 100.0 mm, 120.0 mm) --Diameter (e.g., 6.0 mm, 8.0 mm) --E-liquid volume (e.g., 0.5 ml, 2.0 ml, 5.1 ml) --Wattage (e.g., 100 W, 200 W) --Battery capacity (e.g., 100 mAh, 200 mAh) --Characterizing flavor(s) (e.g., none, tobacco, menthol, cherry, wintergreen) --Additional properties needed to uniquely identify the tobacco product (if applicable)
	(5) ENDS Component	--Package type (e.g., box, none, plastic clamshell) --Product quantity (e.g.,1 coil)

		--Characterizing flavor(s) (e.g., none, tobacco, menthol, cherry, wintergreen) --Additional properties needed to uniquely identify the tobacco product (if applicable)
	(6) ENDS Other	--Package type (e.g., box, none, plastic clamshell) --Product quantity (e.g., 1 e-cigarette, 5 bottles) --Characterizing flavor(s) (e.g., none, cherry, wintergreen, tobacco, menthol) --Additional properties needed to uniquely identify the tobacco product
(E) Cigars	*(1)* Cigar, Filtered Sheet-Wrapped	--Package type (e.g., hard pack, soft pack, clam shell) --Product quantity (e.g., 20 filtered cigars, 25 filtered cigars) --Length (e.g., 89.1 mm, 100.0 mm) --Diameter (e.g., 6.0 mm, 8.1 mm) --Ventilation (e.g., none, 0%, 10.0%, 25.0%) --Characterizing flavor (e.g., none, menthol) --Additional properties needed to uniquely identify the tobacco product (if applicable)
	(2) Cigar, Unfiltered Sheet-Wrapped	--Package type (e.g., box, film sleeve) --Product quantity (e.g., 1 cigar, 5 cigarillos) --Length (e.g., 100.1 mm, 140.0 mm) --Diameter (e.g., 8.0 mm, 10.1 mm) --Tip (e.g., none, wood tips, plastic tips) --Characterizing flavor (e.g., none, menthol) --Additional properties needed to uniquely identify the tobacco product (if applicable)
	(3) Cigar, Unfiltered Leaf-Wrapped	--Package type (e.g., box, film, sleeve, none) --Product quantity (e.g., 1 cigar, 5 cigars) --Length (e.g., 150.1 mm, 200.0 mm) --Diameter (e.g., 8.0 mm, 10.1 mm) -Wrapper material (e.g., burley tobacco leaf, Connecticut shade grown tobacco leaf) --Characterizing flavor (e.g., none, whiskey) --Additional properties needed to uniquely identify the tobacco product (if applicable)
	(4) Cigar Component	--Package type (e.g., box, booklet) --Product quantity (e.g., 10 wrappers, 20 leaves) --Characterizing flavor (e.g., none, menthol, cherry) --Additional properties needed to uniquely identify the tobacco product (if applicable)
	(5) Cigar Tobacco Filler	--Package type (e.g., bag, pouch) --Product quantity (e.g., 20.0 g, 16.1 oz.) --Characterizing flavor (e.g., none, menthol, cherry)

		--Additional properties needed to uniquely identify the tobacco product (if applicable)
	(6) Other	--Package type (e.g., box, booklet) --Product quantity (e.g., 1 cigar, 5 cigars, 20 leaves, 16 g) --Characterizing flavor(s) (e.g., none, menthol, cherry) --Additional properties needed to uniquely identify the tobacco product
(F) Pipe Tobacco Products	*(1)* Pipe	--Package type (e.g., box, none) --Product quantity (e.g., 1 pipe) --Length (e.g., 200.0 mm, 300.1 mm) --Diameter (e.g., 25.1 mm) --Characterizing flavor(s) (e.g., none, menthol, cavendish, cherry) --Additional properties needed to uniquely identify the tobacco product (if applicable)
	(2) Pipe Tobacco Filler	--Package type (e.g., bag, none) --Product quantity (e.g., 20.0 g, 16.1 oz) --Tobacco cut style(e.g., standard cut, such as shag cut, bugler cut, loose cut, etc., or a pressed cut, such as flake, cube cut, roll cake, etc., or a mixture) --Characterizing flavor(s) (e.g., none, menthol, cavendish, cherry) --Additional properties needed to uniquely identify the tobacco product (if applicable)
	(3) Pipe Component	--Package type (e.g., box, bag, none) --Product quantity (e.g., 1 bowl, 1 stem, 100 filters) --Characterizing flavor(s) (e.g., none, cherry) --Additional properties needed to uniquely identify the tobacco product (if applicable)
	(4) Other	--Package type (e.g., bag, box, none) --Product quantity (e.g., 1 pipe, 1 bowl, 1 stem, 100 filters) --Characterizing flavor(s) (e.g., none, cherry) --Additional properties needed to uniquely identify the tobacco product
(G) Waterpipe Tobacco Products	*(1)* Waterpipe	--Package type (e.g., box, none) --Product quantity (e.g., 1 waterpipe) --Height (e.g., 200.0 mm, 500.1 mm) --Width (e.g., 100.1 mm, 300.0 mm) --Diameter (e.g., 100.1 mm, 300.0 mm)--Number of hoses (e.g., 1, 2, 4) --Characterizing flavor(s) (e.g., none) --Additional properties needed to uniquely identify the tobacco product (if applicable)

	(2) Waterpipe Tobacco Filler	--Package type (e.g., bag, pouch) --Product quantity (e.g., 20.0 g, 16.1 oz.) --Characterizing flavor(s) (e.g., none, tobacco, menthol, apple) --Additional properties needed to uniquely identify the tobacco product (if applicable)
	(3) Waterpipe Heat Source	--Package type (e.g., box, film sleeve, bag, none) --Product quantity (e.g., 150.0 g, 680.0 g) --Portion count (e.g., 20 fingers, 10 discs, 1 base) --Portion mass (e.g., 15.0 g/finger, 10.0g/brick) --Portion length (e.g., 40.0 mm, 100.0 mm) --Portion width (e.g., 10.0 mm, 40.0 mm) --Portion thickness (e.g., 10.0 mm, 40.0 mm) --Source of energy (e.g., charcoal, battery, electrical) --Characterizing flavor(s) (e.g., none, menthol, apple) --Additional properties needed to uniquely identify the tobacco product (if applicable)
	(4) Waterpipe Component	--Package type (e.g., bag, box, none) --Product quantity (e.g., 1 base, 1 bowl, 1 hose, 10 mouthpieces) --Characterizing flavor(s) (e.g., none, menthol, cherry) --Additional properties needed to uniquely identify the tobacco product (if applicable)
	(5) Waterpipe Other	--Package type (e.g., bag, box, none) --Product quantity (e.g., 1 base, 1 bowl, 1 hose, 10 mouthpieces) --Characterizing flavor(s) (e.g., none, cherry) --Additional properties needed to uniquely identify the tobacco product (if applicable)
Heated Tobacco Products (HTP)	Closed HTP	--Package type (e.g., box, none, plastic clamshell) --Product quantity (e.g., 1 device, 1 HTP) --Length (e.g., 100.0 mm, 120.0 mm) --Diameter (e.g., 6.0 mm, 8.1 mm) --Wattage (e.g., 100 W, 200 W) --Battery capacity (e.g., 100 mAh, 200 mAh) --Characterizing flavor(s) (e.g., none) --Additional properties needed to uniquely identify the tobacco product (if applicable)
	Open HTP	--Package type (e.g., box, none, plastic clamshell) --Product quantity (e.g., 1 device, 1 HTP) --Length (e.g., 100.0 mm, 120.0 mm) --Diameter (e.g., 6.0 mm, 8.1 mm) --Wattage (e.g., 100 W, 200 W)

		--Battery capacity (e.g., 100 mAh, 200 mAh) --Characterizing flavor(s) (e.g., none) --Additional properties needed to uniquely identify the tobacco product (if applicable)
	HTP Consumable	--Package type (e.g., hard pack, soft pack, plastic clamshell) --Product quantity (e.g., 20 sticks, 25 cartridges) --Length (e.g., 60.0 mm, 82.0 mm) --Diameter (e.g., 6.0 mm, 8.1 mm) --Ventilation (e.g., none, 10.0%, 25.0%) --Characterizing flavor(s) (e.g., none, menthol) --Additional properties needed to uniquely identify the tobacco product (if applicable)
	HTP Component	--Package type (e.g., box, none, plastic clamshell) --Product quantity (e.g., 1 mouthpiece, 1 spacer) --Characterizing flavor(s) (e.g., none, tobacco, menthol) --Additional properties needed to uniquely identify the tobacco product (if applicable)
	Other	--Package type (e.g., box, bag, plastic clamshell, none) --Product quantity (e.g., 1 base, 5 capsules) --Characterizing flavor(s) (e.g., none, tobacco, menthol, cherry) --Additional properties needed to uniquely identify the tobacco product (if applicable)
Other	Other	--Package type (e.g., box, bag, plastic clamshell, none) --Product quantity (e.g., 1 base, 5 capsules) --Characterizing flavor(s) (e.g., none, tobacco, menthol, cherry) --Additional properties needed to uniquely identify the tobacco product (if applicable)

(4) The type of PMTA (i.e., PMTA, supplemental PMTA, or resubmission);

(5) Whether the applicant requests that FDA refer the PMTA to the Tobacco Products Scientific Advisory Committee (TPSAC);

(6) Identifying information regarding any prior submissions regarding the tobacco product (e.g., submissions related to investigational tobacco products, substantial equivalence reports, PMTAs), including submission tracking numbers (STNs) where applicable;

(7) Dates and purpose of any prior meetings with FDA regarding the new tobacco product;

(8) If applicable, the dates when the tobacco product was commercially marketed in the United States;

(9) Address and the Facility Establishment Identifier (FEI) number(s), if available, of the establishment(s) involved in the manufacture of the new tobacco product;

(10) A brief statement regarding how the PMTA satisfies the content requirements of section 910(b)(1) of the Federal Food, Drug, and Cosmetic Act;

(11) A brief description of how marketing of the new tobacco product would be appropriate for the protection of the public health; and

(12) A list identifying all enclosures, labels, and labeling being submitted with the application.

(d) *Descriptive information.* The application must contain descriptive information in this section that outlines the major aspects of the new tobacco product, including the following items:

(1) A concise description of the new tobacco product;

(2) A statement identifying all tobacco product standards issued under section 907 of the Federal Food, Drug, and Cosmetic Act that are applicable to the new tobacco product and a brief description of how the new tobacco product fully meets any identified tobacco product standard, or if the new tobacco product deviates from a product standard, if applicable, the application must include adequate information to identify and justify those deviations;

(3) The name(s) of the product as designated on the product's label;

(4) A description of problems that were identified in prototypes that are the subject of studies in the application and previous or similar versions of the new tobacco product that were

marketed, if any. If there are previous or similar versions that are the subject of studies in the application or were marketed, the application must contain a bibliography of all reports regarding the previous or similar version of the product, whether adverse or supportive; and

(5) Any restrictions on the sale, distribution, advertising, or promotion of the new tobacco product that the applicant proposes to be included as part of a marketing granted order under section 910(c)(1)(B) of the Federal Food, Drug, and Cosmetic Act to help support a showing that the marketing of the product is appropriate for the protection of the public health. If there are no proposed restrictions, the application must contain a statement to that effect.

(e) *Samples of new tobacco products*. After FDA accepts a PMTA for review, it may require the submission of samples of the new tobacco product, including its components and parts. If required, the applicant must submit samples of the finished tobacco product or its components or parts in accordance with instructions provided by FDA. FDA may also require the submission of additional samples to further aid in its review.

(f) *Labeling and description of marketing plans*--(1) *Labeling*. The application must contain specimens of all proposed labeling for the new tobacco product, including labels, inserts, onserts, instructions, and other accompanying information. The specimens of labeling must include all panels, reflect the actual size and color proposed to be used for the tobacco product, and include any warning label statements and other information required by regulation or statute, as applicable.

(2) *Description of Marketing Plans*. A PMTA must contain a description of the applicant's plans to market the new tobacco product, for at least the first year the product would be marketed after receiving a marketing granted order, in way that is both consistent with the applicant's discussion of the increased or decreased likelihood of changes in tobacco product use

behavior, including switching, initiation, cessation, and polyuse, under § 1114.7(l), and permits FDA to determine permitting the new tobacco product to be marketed would be appropriate for the protection of public health. The description must include actions to market the product that would be taken by the applicant, on behalf of the applicant, or at the applicant's direction, and also discuss any restrictions on the sales and distribution the applicant proposes to be included in a marketing order under section 910(c)(1)(B) of the Federal Food Drug and Cosmetic Act. The description of marketing plans must contain, at minimum:

(i) A description of the specific group(s) to which the labeling, advertising, marketing, promotion, and other consumer-directed activities for the new tobacco product would be targeted (i.e., the intended audience(s));

(ii) A discussion of how the labeling, advertising, marketing, promotion, and other consumer-directed activities for the new tobacco product would be targeted to reach the intended audience(s) identified in paragraph (i) and what other group(s) would foreseeably be exposed to those materials and activities as a result;

(iii) A discussion of, for individuals below the minimum age of sale, how access to the new tobacco product would be restricted and exposure to the labeling, advertising, marketing, promotion, and other consumer-directed activities would be limited; and

(iv) A concluding summary describing how the applicant's plans for marketing the new tobacco product are consistent with the applicant's discussion of the increased or decreased likelihood of changes in tobacco product use behavior, including switching, initiation, cessation, and polyuse, under § 1114.7(l) and permits FDA to determine permitting the new tobacco product to be marketed would be appropriate for the protection of public health

(g) *Statement of compliance with 21 CFR part 25*. (1) The application must contain an environmental assessment prepared in accordance with § 25.40 of this chapter, or a valid claim of categorical exclusion, if applicable. If the applicant believes that the action qualifies for an available categorical exclusion, the applicant must state under § 25.15(a) and (d) of this chapter that the action requested qualifies for a categorical exclusion, citing the particular exclusion that is claimed, and that to the applicant's knowledge, no extraordinary circumstances exist under § 25.21 of this chapter.

(h) *Summary*. The application must include a summary of all information contained in the application. The summary must include the following items, highlighting the effects on youth, young adults, and other relevant vulnerable populations:

(1) A summary of the product formulation section of the application;

(2) A summary of the manufacturing section of the application;

(3) A summary of the health risk investigations section of the application, including all information regarding the following items, and identify areas in which there is a lack of information, where applicable:

(i) The health risks of the tobacco product to both users and nonusers of the product and whether the tobacco product may present less health risk than other tobacco products;

(ii) The impact the product and its marketing will have on the likelihood of changes in tobacco use behavior, including cessation, switching, and polyuse, of tobacco product users;

(iii) The impact the product and its marketing will have on the likelihood of tobacco use initiation by tobacco product nonusers;

(iv) How users and nonusers perceive the risk of the tobacco product based upon its label, labeling, and advertising, to the extent that advertising has been studied;

(v) Whether users are able to understand the labeling and instructions for use, and use the product in accordance with those instructions; and

(vi) The impact of human factors on the health risks to product users and nonusers (as described in paragraph (k)(1)(v) of this section);

(4) A concluding discussion describing how the data and information contained in the PMTA both constitute valid scientific evidence and establish that permitting marketing of the new tobacco product is appropriate for the protection of the public health, as determined with respect to the risks and benefits to the population as a whole, including users and nonusers of the tobacco product. This discussion must specifically describe the effects on youth, young adults, and other relevant vulnerable populations with an emphasis on populations that are most likely to use the new tobacco product. The summary must also identify any key or pivotal studies on which an applicant is relying to establish that permitting the marketing of the new tobacco product would be APPH.

(i) *Product formulation*. The application must contain a full statement of the components or parts, materials, ingredients, additives, constituents, properties, and the principle or principles of operation, of the tobacco product, including the following information:

(1) *Components or parts, materials, ingredients, additives, and constituents*. The applicant must provide a full statement of:

(i) *Components or parts*. The quantity, function, and purpose of, and, where applicable, target specification(s) of, each component or part in the product. Where the tobacco product contains software components, the applicant must provide:

(A) A description of the software or technology (e.g., Bluetooth);

(B) The purpose of the software or technology, such as monitoring where tobacco products are located, activated, or used;

(C) A description of the data collected by the software and how it will be used.

(ii) *Materials*. For each material in the product, include:

(A) The material name and common name(s), if applicable;

(B) The component or part of the tobacco product where the material is located;

(C) The subcomponent or subpart where the material is located, if applicable;

(D) The function of the material;

(E) The quantities (including ranges or means and acceptance limits) of the material(s) in the new tobacco product (with any specification variation, if applicable);

(F) The specification(s) (including quality/grades and suppliers) used for the new tobacco product (including any specification variations, if applicable); and

(G) Any other material properties to fully characterize the new tobacco product.

(iii) *Ingredients other than tobacco*. For ingredients other than tobacco in each component or part of the product, include:

(A) The International Union of Pure and Applied Chemistry (IUPAC) chemical name and common name, if applicable;

(B) The Chemical Abstracts Service (CAS) number or FDA Unique Ingredient Identifier (UNII), if applicable;

(C) The function of the ingredient;

(D) The quantity of the ingredient in the tobacco product, with the unit of measure (including ranges or means and acceptance limits) reported as mass per gram of tobacco for

nonportioned tobacco products and as mass per portion for portioned tobacco products (with any specification variation, if applicable);

(E) The specification(s) (including purity or grade and supplier); and

(F) For complex purchased ingredients, each single chemical substance reported separately.

(iv) *Tobacco ingredients*. For tobacco ingredients in each component or part, include the following information or, if applicable, a statement that the product does not contain tobacco ingredients:

(A) The type(s) (e.g., Bright, Burley, reconstituted);

(B) The quantity with the unit of measure (including ranges or means, acceptance limits) of each tobacco ingredient in the tobacco product reported as mass per gram of tobacco for nonportioned tobacco products and as mass per portion for portioned tobacco products (with any specification variation, if applicable);

(C) The specification of tobacco used for the new tobacco product (with any specification variation, if applicable); and

(D) A description of any genetic engineering of the tobacco that impacts product characteristics.

(v) *Constituents*. Constituents, including HPHCs and other constituents, contained within, or emitted from (including its smoke or aerosol), the product, including any reaction product from leaching or aging, by providing:

(A) The constituent names in alphabetical order;

(B) The common name(s);

(C) The Chemical Abstract Services number;

(D) The mean quantity and variance with unit of measure;

(E) The number of samples and measurement replicates for each sample;

(F) A description of method procedure, method validation information and rationale for selecting each test method;

(G) The name and location of the testing laboratory or laboratories and documentation showing that the laboratory or laboratories is (or are) accredited by a nationally or internationally recognized external accreditation organization;

(H) Length of time between dates of manufacture and date(s) of testing;

(I) Storage conditions of the tobacco product before it was tested;

(J) Test data including test protocols, any deviation(s) from the test protocols, quantitative acceptance (pass/fail) criteria, and line data for all testing performed. Test data for combusted or inhaled products must reflect testing conducted using both intense and nonintense smoking or aerosol-generating regimens, where established; and

(K) Complete descriptions of any smoking or aerosol-generating regimens used for analytical testing that are not standardized or widely accepted by the scientific community, if applicable

(vi) *Container closure system*. A description of the container closure system, including:

(A) Information describing how the container closure system protects and preserves the product from damage during transport, environmental contaminants, and potential leaching and migration of packaging constituents into the new tobacco product; and

(B) Information describing design features developed to prevent the risk of accidental exposure, if any.

(vii) *Statement of tobacco blending, reconstitution, or manipulation*. Information regarding tobacco blending, reconstitution, or manipulation, where applicable.

(2) *Other properties*. The applicant must provide a full description of the additional properties of the tobacco product that includes:

(i) *Product dimensions and construction*. The product dimensions and the overall construction of the product using a diagram or schematic drawing that clearly depicts the finished tobacco product and its components with dimensions, operating parameters, and materials.

(ii) *Design parameters and test data*. (A) All final design parameters of the product, specifying nominal values or the explicit range of values as well as the design tolerance (where appropriate), including, but not limited to, the parameters specified in tables 1 to 22 of this paragraph as applicable. If a design parameter specified in tables 1 to 22 does not apply to the tobacco product, applicants must explain why the required design parameter does not apply or how an alternative design parameter would satisfy the required design parameter. If the product has additional design parameters that are not specified in tables 1 to 22, the application must contain a description of the design specifications as well as test data and processes to demonstrate that the design parameters and their associated processes are adequately controlled; and

(B) A quantitative description of the performance criteria, including test protocols, line data, and a summary of the results, for each applicable intermediate and final design parameter and manufacturing step, that includes, but is not limited to the test data specified in tables 1 to 22 of this paragraph for the product category as applicable. If the test data specified in the applicable table does not apply to the tobacco product, applicants must explain why the test data

does not apply or how alternative test data would satisfy this requirement. Where tobacco cut size or particle size is a required design parameter for a product category or subcategory and the target specifications and range limits are not available, the following alternative information may be submitted in place of this information: a description of the tobacco cutting process (including a complete description of the milling, cutting, and sifting process; the control parameters of the miller or cutter; and any sift specifications), or the measured particle size distribution;

Table 2 to paragraph (i)(2)(ii)--Required Design Parameter Information for Cigarettes

Provide target specification with upper and lower range limits for:	Provide test data (include test protocols, quantitative acceptance criteria, data sets, and a summary of the results) for:
• Cigarette length (mm) • Cigarette circumference or diameter (mm) • Tobacco filler mass (mg) • Tobacco rod density (g/cm^3) • Tobacco cut size (mm or CPI) • Tobacco moisture or oven volatiles (%) • Cigarette paper length (mm) • Cigarette paper base paper porosity (permeability) (CU) • Cigarette paper band porosity (permeability) (CU) [alternatively, band diffusivity (cm^2/s)] (if applicable) • Cigarette paper band width (mm) • Cigarette paper band space (mm) • Filter length (mm) • Filter pressure drop (mm H_2O) • Filter efficiency (%) (If no filter efficiency data is available for the products, include information sufficient to show that the cigarette filter is unchanged (e.g., denier per filament, total denier, and filter density)) • Tipping paper length (mm) • Filter ventilation (%)	• Tobacco filler mass (mg) • Tobacco rod density (g/cm^3) • Tobacco cut size (mm or CPI) • Tobacco moisture or oven volatiles (%) • Cigarette paper base paper porosity (permeability) (CU) • Cigarette paper band porosity or permeability (CU) or Cigarette paper band diffusivity (cm^2/s) • Filter pressure drop (mm H_2O) • Filter efficiency (%)(If no filter efficiency data is available for the products, include information sufficient to show that the cigarette filter is unchanged (e.g., denier per filament, total denier, and filter density)) • Filter ventilation (%)

Table 3 to paragraph (i)(2)(ii)--Required Design Parameter Information for Portioned and Nonportioned Smokeless Tobacco Products

Provide target specification with upper and lower range limits for:	Provide test data (include test protocols, quantitative acceptance criteria, data sets, and a summary of the results) for:
Portioned Smokeless Tobacco Products	
• Tobacco cut size (mm or CPI) or tobacco particle size (mm or micron) • Tobacco moisture (%) • Portion length (mm) • Portion width (mm) • Portion mass (mg) • Portion material thickness (mm) (if applicable) • Pouch material basis weight (g/m^2) (if applicable) • Pouch material porosity (permeability) (CU or L/m^2/s) (if applicable) • Nicotine dissolution rate (%/min)	• Tobacco cut size (mm or CPI) or tobacco particle size (mm or micron) • Tobacco moisture (%) • Portion mass (mg) • Pouch material basis weight (g/m^2) • Pouch material porosity (CU) (permeability) (L/m^2/s) • Nicotine dissolution rate (%/min)
Nonportioned Smokeless Tobacco Products	
• Tobacco cut size (mm or CPI) or tobacco particle size (mm or micron) • Tobacco moisture (%)	• Tobacco cut size (mm or CPI) or tobacco particle size (mm or micron) • Tobacco moisture (%)

Table 4 to paragraph (i)(2)(ii)--Required Design Parameter Information for RYO Tobacco Rolling Papers

Provide target specification with upper and lower range limits for:	Provide test data (include test protocols, quantitative acceptance criteria, data sets, and a summary of the results) for:
• Roll-your-own (RYO) paper length (mm) • RYO paper width (mm) • RYO mass per paper (mg) • RYO paper base paper basis weight (g/m^2) • RYO paper base paper porosity (permeability) (CU) • RYO paper band porosity (permeability) (CU) or [alternatively, RYO paper band diffusivity (cm^2/s)] (if applicable) • RYO paper band width (mm) (if applicable) • RYO paper band space (mm) (if applicable)	• RYO mass per paper (mg) • RYO paper base paper basis weight (g/m^2) • RYO paper base paper porosity (permeability) (CU) • RYO paper band porosity (permeability) (CU) or [alternatively, RYO paper band diffusivity (cm^2/s)] (if applicable)

Table 5 to paragraph (i)(2)(ii)--Required Design Parameter Information for RYO Tobacco Tubes

Provide target specification with upper and lower range limits for:	Provide test data (include test protocols, quantitative acceptance criteria, data sets, and a summary of the results) for:
• Tube mass (mg) • Tube length (mm) • Tube circumference or diameter (mm) • Tube paper width (mm)• Tube paper base paper basis weight (g/m^2) • Tube paper base paper porosity (permeability) (CU) • Tube paper band porosity (permeability) (CU) (if applicable) or Tube paper band diffusivity (cm^2/s) (if applicable) • Tube paper band width (mm) (if applicable) • Tube paper band space (mm) (if applicable)	• Tube mass (mg) • Tube paper base paper basis weight (g/m^2) • Tube paper base paper porosity (permeability) (CU) • Tube paper band porosity (permeability) (CU) (if applicable) or Tube paper band diffusivity (cm^2/s) (if applicable)

Table 6 to paragraph (i)(2)(ii)--Required Design Parameter Information for RYO Tobacco Filtered Tubes

Provide target specification with upper and lower range limits for:	Provide test data (include test protocols, quantitative acceptance criteria, data sets, and a summary of the results) for:
• Tube mass (mg) • Tube length (mm) • Tube circumference or diameter (mm) • Tube paper length (mm) • Nonfilter tube length (mm) • Tube paper width (mm) • Tube paper base paper basis weight (g/m^2) • Tube paper base paper porosity (permeability) (CU) • Tube paper band porosity (permeability) (CU) (if applicable) or Tube paper band diffusivity (cm^2/s) (if applicable) • Tube paper band width (mm) (if applicable) • Tube paper band space (mm) (if applicable) • Filter length (mm) • Filter pressure drop (mm H_2O) • Filter efficiency (%) (If no filter efficiency data is available for the	• Tube paper base paper basis weight (g/m^2) • Tube paper base paper porosity (permeability) (CU) • Tube mass (mg) • Tube paper band porosity (permeability) (CU) (if applicable) or Tube paper band diffusivity (cm^2/s) (if applicable) • Filter pressure drop (mm H_2O) • Filter efficiency (%) (If no filter efficiency data is available for the products, include information sufficient to show that the cigarette filter is unchanged (e.g., denier per filament (DPF), total denier (g/9000m), and filter density (g/cm^3))) • Filter ventilation (%)

Provide target specification with upper and lower range limits for:	Provide test data (include test protocols, quantitative acceptance criteria, data sets, and a summary of the results) for:
products, include information sufficient to show that the cigarette filter is unchanged (e.g., denier per filament (DPF), total denier (g/9000m), and filter density (g/cm^3))) • Tipping paper length (mm) • Filter ventilation (%)	

Table 7 to paragraph (i)(2)(ii)--Required Design Parameter Information for RYO Tobacco

Provide target specification with upper and lower range limits for:	Provide test data (include test protocols, quantitative acceptance criteria, data sets, and a summary of the results) for:
• Tobacco cut size (mm or CPI) • Tobacco moisture or oven volatiles (%)	• Tobacco cut size (mm or CPI) • Tobacco moisture or oven volatiles (%)

Table 8 to paragraph (i)(2)(ii)--Required Design Parameter Information for RYO Tobacco Paper Tips

Provide target specification with upper and lower range limits for:	Provide test data (include test protocols, quantitative acceptance criteria, data sets, and a summary of the results) for:
• RYO paper tip length (mm) • RYO paper tip width (mm) • RYO paper tip mass (mg) • RYO paper base paper basis weight (g/m^2) • RYO paper porosity (permeability) (CU) • RYO paper tip ventilation (%)	• RYO paper base paper basis weight (g/m^2) • RYO paper porosity (permeability) (CU) • RYO paper tip ventilation (%)

Table 9 to paragraph (i)(2)(ii)--Required Design Parameter Information for Filtered Sheet-Wrapped Cigars

Provide target specification with upper and lower range limits for:	Provide test data (include test protocols, quantitative acceptance criteria, data sets, and a summary of the results) for:
• Cigar mass (mg) • Cigar wrapper basis weight (g/m^2) • Cigar binder length (mm) • Cigar binder width (mm)	• Cigar mass (mg) • Puff count • Cigar wrapper basis weight (g/m^2)

Provide target specification with upper and lower range limits for:	Provide test data (include test protocols, quantitative acceptance criteria, data sets, and a summary of the results) for:
• Cigar binder basis weight (g/m^2) • Cigar length (mm) • Cigar overall diameter (mm) • Cigar minimum diameter (mm) if applicable • Cigar maximum diameter (mm) if applicable • Tobacco filler mass (mg) • Tobacco rod density (g/cm^3) • Tobacco cut size (CPI or mm) • Tobacco moisture or oven volatiles (%) • Cigar wrapper porosity (permeability) (CU) • Cigar wrapper length (mm) • Cigar wrapper width (mm) • Cigar wrapper band porosity (permeability) (CU) (if applicable) • Cigar wrapper band width (mm) (if applicable) • Cigar wrapper band space (mm) (if applicable) • Cigar binder porosity (permeability) (CU) • Cigar binder band porosity (permeability) (CU) (if applicable) • Cigar binder band width (mm) (if applicable) • Cigar binder band space (mm) (if applicable) • Filter length (mm) • Filter diameter (mm) • Filter pressure drop (mm H_2O) • Filter efficiency (%) {If no filter efficiency data is available for the products, include information sufficient to show that the cigar filter is unchanged [e.g., denier per filament (DPF), total denier (g/9000m), and filter density(g/cm^3)]} • Tipping paper length (mm) • Filter ventilation (%)	• Cigar wrapper porosity (permeability) (CU) • Cigar binder porosity (permeability) (CU) • Cigar binder basis weight (g/m^2) • Tobacco filler mass (mg) • Tobacco rod density (g/cm^3) • Tobacco cut size (CPI or mm) • Tobacco moisture or oven volatiles (%) • Cigar wrapper band porosity (permeability) (CU) [alternatively, band diffusivity (cm^2/s)](if applicable) • Cigar binder band porosity (permeability) (CU) [alternatively, band diffusivity (cm^2/s)] (if applicable) • Cigar minimum diameter (mm) (if applicable) • Cigar maximum diameter (mm) (if applicable) • Filter pressure drop (mm H_2O) • Filter efficiency (%) (if no filter efficiency data is available for the products, include information sufficient to show that the cigar filter is unchanged [e.g., denier per filament (DPF), total denier (g/9000m), and filter density (g/cm^3)]} • Filter ventilation (%)

Table 10 to paragraph (i)(2)(ii)--Required Design Parameter Information for Unfiltered Sheet-Wrapped Cigars

Provide target specification with upper and lower range limits for:	Provide test data (include test protocols, quantitative acceptance criteria, data sets, and a summary of the results) for:
• Cigar mass (mg) • Cigar length (mm) • Cigar overall diameter (mm) • Cigar minimum diameter (mm) (if applicable) • Cigar maximum diameter (mm) (if applicable) • Tobacco rod density (g/cm^3) • Tobacco moisture or oven volatiles (%) • Tobacco cut size (CPI or mm) • Tobacco filler mass (mg) • Cigar wrapper porosity (permeability) (CU) • Cigar wrapper length (mm) • Cigar wrapper width (mm) • Cigar wrapper basis weight (g/m^2) • Cigar binder porosity (permeability) (CU) • Cigar binder width (mm) • Cigar binder basis weight (g/m^2) • Cigar tip length (mm) (if applicable) • Cigar tip inner diameter (mm) (if applicable) • Cigar tip mass (mg) (if applicable) • Cigar wrapper band space (mm) (if applicable) • Cigar wrapper band width (mm) (if applicable) • Cigar binder band width (mm) (if applicable) • Cigar binder band space (mm) (if applicable) • Cigar wrapper band porosity or permeability (CU) [alternately, band diffusivity (cm2/s)] (if applicable) • Cigar binder band porosity (permeability) (CU) [alternately, band diffusivity (cm2/s)] (if applicable)	• Puff count • Cigar mass (mg) • Tobacco rod density (g/cm^3) • Tobacco cut size (CPI or mm) • Tobacco moisture or oven volatiles (%) • Tobacco filler mass (mg) • Cigar minimum diameter (mm) (if applicable) • Cigar maximum diameter (mm) (if applicable) • Cigar wrapper porosity (permeability) (CU) • Cigar wrapper basis weight (g/m^2) • Cigar binder basis weight (g/m^2) • Cigar binder porosity (permeability) (CU) • Cigar tip mass (mg) (if applicable) • Cigar wrapper band porosity (permeability) (CU) [alternately, band diffusivity (cm2/s)] (if applicable) • Cigar binder band porosity (permeability) (CU) [alternately, band diffusivity (cm2/s)] (if applicable)

Table 11 to paragraph (i)(2)(ii)--Required Design Parameter Information for Leaf-Wrapped Cigars

Provide target specification with upper and lower range limits for:	Provide test data (include test protocols, quantitative acceptance criteria, data sets, and a summary of the results) for:
• Cigar mass (mg) • Cigar length (mm) • Overall diameter (mm) • Cigar minimum diameter (mm) • Cigar maximum diameter (mm) • Tobacco moisture or oven volatiles (%) • Tobacco filler mass (mg) • Tobacco rod density (g/cm^3) • Tobacco cut size (CPI or mm) • Cigar wrapper length (mm) • Cigar wrapper width (mm) • Cigar wrapper basis weight (g/m^2) • Cigar binder width (mm) • Cigar binder basis weight (g/m^2)	• Puff count • Cigar mass (mg) • Cigar minimum diameter (mm) • Cigar maximum diameter (mm) • Cigar wrapper basis weight (g/m^2) • Cigar binder basis weight (g/m^2) • Tobacco filler mass (mg) • Tobacco rod density (g/cm^3) • Tobacco cut size (CPI or mm) • Tobacco moisture or oven volatiles (%)

Table 12 to paragraph (i)(2)(ii)--Required Design Parameter Information for Cigar Tobacco

Provide Target Specification With Upper and Lower Range Limits for:	Provide test data (include test protocols, quantitative acceptance criteria, data sets, and a summary of the results) for:
• Tobacco cut size (CPI or mm) • Tobacco moisture or oven volatiles (%)	• Tobacco cut size (CPI or mm) • Tobacco moisture or oven volatiles (%)

Table 13 to paragraph (i)(2)(ii)--Required Design Parameter Information for Cigar Wrappers

Provide Target Specification With Upper and Lower Range Limits for:	Provide test data (include test protocols, quantitative acceptance criteria, data sets, and a summary of the results) for:
• Cigar wrapper length (mm) • Cigar wrapper width (mm) • Cigar wrapper basis weight (g/cm^2)	• Cigar wrapper length (mm) • Cigar wrapper width (mm) • Cigar wrapper basis weight (g/cm^2)

Table 14 to paragraph (i)(2)(ii)--Required Design Parameter Information for Waterpipes

Provide Target Specification With Upper and Lower Range Limits for:	Provide test data (include test protocols, quantitative acceptance criteria, data sets, and a summary of the results) for:
• Hose length (mm) • Hose materials • Hose internal diameter (mm) • Stem length (mm) • Stem internal diameter (mm)	• Hose length (mm) • Hose internal diameter (mm) • Stem length (mm) • Stem internal diameter (mm) • Base diameter (mm)

Provide Target Specification With Upper and Lower Range Limits for:	Provide test data (include test protocols, quantitative acceptance criteria, data sets, and a summary of the results) for:
• Base diameter (mm) • Base volume (cm^3) • Base shape • Pressure drop (mm H_2O) • Water filter efficiency (%) • Hose air permeability (CU) • Head height (mm) • Head top diameter (mm) • Head bottom diameter (mm) • Number of holes • Head volume (mm^3) • Heating source type • Head materials	• Base volume (cm^3) • Pressure drop (mm H_2O) • Water filter efficiency (%) • Head height (mm) • Head top diameter (mm) • Head bottom diameter (mm) • Head volume (mm^3)

Table 15 to paragraph (i)(2)(ii)--Required Design Parameter Information for Waterpipe Tobacco

Provide Target Specification With Upper and Lower Range Limits for:	Provide test data (include test protocols, quantitative acceptance criteria, data sets, and a summary of the results) for:
• Tobacco cut size (CPI or mm) • Tobacco moisture or oven volatiles (%)	• Tobacco cut size (CPI or mm) • Tobacco moisture or oven volatiles (%)

Table 16 to paragraph (i)(2)(ii)--Required Design Parameter Information for Waterpipe Heating Sources

Provide Target Specification With Upper and Lower Range Limits for:	Provide test data (include test protocols, quantitative acceptance criteria, data sets, and a summary of the results) for:
• Heating element temperature range (°C) • Heating element mass (mg) • Heating element density (g/cm^3) • Heating element resistance (ohms) (if applicable) • Number of heating elements • Heating element configuration • Heating element diameter (gauge) (if applicable) • Battery current rating (mA) (if applicable) • Battery capacity (mAh) (if applicable) • Battery voltage operating range (volts) (if applicable) • Battery current operating range (amps) (if applicable)	• Heating element temperature range (°C) • Heating element mass (mg) • Heating element density (g/cm^3) • Heating element resistance (ohms) (if applicable) • Heating element diameter (gauge) • Battery current rating (mA) (if applicable) • Battery capacity (mAh) (if applicable) • Battery voltage operating range (volts) (if applicable) • Battery current operating range (amps) (if applicable) • Power delivery unit (PDU) temperature cut-off (°C) (if applicable)

Provide Target Specification With Upper and Lower Range Limits for:	Provide test data (include test protocols, quantitative acceptance criteria, data sets, and a summary of the results) for:
• Power delivery unit (PDU) temperature cut-off (°C) (if applicable) • Power delivery unit (PDU) voltage operating range (volts) (if applicable) • PDU current operating range (amps) (if applicable) • PDU wattage operating range (watts) (if applicable)	• Power delivery unit (PDU) voltage operating range (volts) (if applicable) • PDU current operating range (amps) (if applicable) • PDU wattage operating range (watts) (if applicable) •

Table 17 to paragraph (i)(2)(ii)--Required Design Parameter Information for Waterpipe Foil

Provide Target Specification With Upper and Lower Range Limits for:	Provide test data (include test protocols, quantitative acceptance criteria, data sets, and a summary of the results) for:
• Foil length (mm) (for square or rectangular shape foil) • Foil width (mm) (for square or rectangular shape foil) • Diameter (mm) (for circular shape foil) • Foil thickness (mm) • Number of holes • Diameter of the holes (mm)	• Foil length (mm) (for square or rectangular shape foil) • Foil width (mm) (for square or rectangular shape foil) • Diameter (mm) (for circular shape foil) • Foil thickness (mm) • Diameter of the holes (mm)

Table 18 to paragraph (i)(2)(ii)--Required Design Parameter Information for Waterpipe Head

Provide Target Specification With Upper and Lower Range Limits for:	Provide test data (include test protocols, quantitative acceptance criteria, data sets, and a summary of the results) for:
• Head height (mm) • Head top diameter (mm) • Head bottom diameter (mm) • Number of holes • Head volume (mm^3) • Head materials	• Head height (mm) • Head top diameter (mm) • Head bottom diameter (mm) • Head volume (mm^3)

Table 19 to paragraph (i)(2)(ii)--Required Design Parameter Information for Pipes

Provide Target Specification With Upper and Lower Range Limits for:	Provide test data (include test protocols, quantitative acceptance criteria, data sets, and a summary of the results) for:
• Bowl chamber cover outer diameter (mm)	• Bowl chamber volume (cm^3)

Provide Target Specification With Upper and Lower Range Limits for:	Provide test data (include test protocols, quantitative acceptance criteria, data sets, and a summary of the results) for:
• Bowl chamber cover inner diameter (mm) • Draught hole diameter (mm) • Screen (if applicable) • Draught hole shape • Draught hole location • Bowl chamber hole shape • Bowl chamber volume (cm^3) • Airway volume (cm^3) • Stem length (mm) • Stem diameter (mm) • Shank length (mm) • Shank diameter (mm) • Draught hole dimension • Pressure drop through air valve (mm H_2O) • Air flow through air valve (cc/min) • Filter efficiency (%) {If no filter efficiency data is available for the products, include information sufficient to show that the cigar filter is unchanged [e.g., denier per filament (DPF), total denier (g/9000m), and filter density(g/cm^3)]} • Filter pressure drop (mm H_2O) • Filter length (mm)	• Pipe pressure drop (mm H_2O) • Air flow through air valve (cc/min) • Airway volume (cm^3) • Filter pressure drop (mm H_2O) • Filter efficiency (%) {If no filter efficiency data is available for the products, include information sufficient to show that the cigar filter is unchanged [e.g., denier per filament (DPF), total denier (g/9000m), and filter density(g/cm^3)]}

Table 20 to paragraph (i)(2)(ii)--Required Design Parameter Information for Pipe Tobacco

Provide Target Specification With Upper and Lower Range Limits for:	Provide test data (include test protocols, quantitative acceptance criteria, data sets, and a summary of the results) for:
• Tobacco cut size (CPI or mm) • Tobacco moisture or oven volatiles (%)	• Tobacco cut size (CPI or mm) • Tobacco moisture or oven volatiles (%)

Table 21 to paragraph (i)(2)(ii)--Required Design Parameter Information for ENDS

Provide Target Specification With Upper and Lower Range Limits for:	Provide test data (include test protocols, quantitative acceptance criteria, data sets, and a summary of the results) for:
• Draw resistance (mm H_2O) • Puff count (for full tank/cartridge) • Atomizer tank/cartridge volume (mL) • Number of heating elements (e.g., coil)	• Draw resistance (mm H_2O) • Puff count (for full tank/cartridge) • Atomizer tank/cartridge volume (mL)

Provide Target Specification With Upper and Lower Range Limits for:	Provide test data (include test protocols, quantitative acceptance criteria, data sets, and a summary of the results) for:
• Heating Element diameter (gauge) • Heating Element length (mm) • Heating Element resistance (Ohms) • Heating Element temperature range (°C) • Heating Element configuration (target only) • Battery voltage operating range (V) • Battery current operating range (mA) • Battery Capacity (mAh) • Battery Nominal Voltage (V) • Battery Current rating (mA) • Battery charging temperature limits (°C) • Battery discharge temperature limits (°C) • Battery end of discharge voltage (V) • Battery maximum charging current (mA) • Battery maximum discharging current (mA) • Battery upper limits charging voltage (V) • Power Delivery Unit (PDU) voltage operating range (V) • PDU current operating range (mA) • PDU wattage operating range (watts) • PDU temperature cut-off (°C) (if applicable) • Airflow rate (L/min) (if applicable) • PDU Current cut-off (mA) (if applicable) • PDU Temperature cut-off (°C) (if applicable) • Inhaled aerosol temperature (°C) • Ventilation (%)	• Heating Element diameter (gauge) • Heating Element resistance (Ohms) • Heating Element temperature range (°C) • Battery voltage operating range (V) • Battery current operating range (mA) • PDU voltage operating range (V) • PDU current operating range (mA) • PDU wattage operating range (watts) • PDU Current cut-off (mA) (if applicable) • PDU temperature cut-off (°C) (if applicable) • Battery Capacity (mAh) • Battery Nominal Voltage (V) • Battery Current rating (mA) • Battery charging temperature limits (°C) • Battery discharge temperature limits (°C) • Battery maximum charging current (mA) • Battery maximum discharging current (mA) • Battery upper limits charging voltage (V) • Inhaled aerosol temperature (°C) • Airflow rate (L/min) (if applicable) • Ventilation (%)

Table 22 to paragraph (i)(2)(ii)--Required Design Parameter Information for E-liquids

Provide Target Specification With Upper and Lower Range Limits for:	Provide test data (include test protocols, quantitative acceptance criteria, data sets, and a summary of the results) for:
• E-liquid viscosity (at 20°C) • E-liquid volume (ml) • Particle number concentration (#/cm^3) • Count median diameter (nm) • PM2.5 (µg/m^3)	• E-liquid viscosity (at 20°C) • E-liquid volume (ml) • Particle number concentration (#/cm^3) • Count median diameter (nm) • PM2.5 (µg/m^3)

Table 23 to paragraph (i)(2)(ii)--Required Design Parameter Information for Heated Tobacco Products (HTP)

Provide Target Specification With Upper and Lower Range Limits for:	Provide test data (include test protocols, quantitative acceptance criteria, data sets, and a summary of the results) for:

• Overall Product
  ○ Mass (mg)
  ○ Length (mm)
  ○ Width (mm)
  ○ Height (mm)
  ○ Diameter (mm)
  ○ Draw resistance (mm H_20)
  ○ Puff Count (for full tank/cartridge)
  ○ Puff volume (mL)
  ○ Product volume (mL)
  ○ Airflow rate (L/min) (if applicable)
  ○ Ventilation (%)
  ○ Operational Temperature (°C)
  ○ Temperature sensor (if applicable)
  ○ Material wrapper length (mm) (if applicable)
  ○ Material wrapper width (mm) (if applicable)
  ○ Material wrapper basis weight (g/m^2)(if applicable)
  ○ Material porosity (permeability) (CU) (if applicable)
• Heating element
  ○ Heating element source/ type/approach (electrical, carbon, aerosol, etc.)
  ○ Heating element temperature range (°C)
  ○ Heating element operational temperature (°C)
  ○ Heating element maximum temperature (boost temperature) (°C)
  ○ Heating element material
	• Overall Product
	  ○ Draw resistance (mm H_2O)
	  ○ Puff count (for full tank/cartridge)
	  ○ Product volume (mL)
	  ○ Airflow rate (L/min) (if applicable)
	  ○ Ventilation (%)
	  ○ Operational Temperature (°C)
	  ○ Temperature sensor (if applicable)
	  ○ Material wrapper length (mm) (if applicable)
	  ○ Material wrapper width (mm) (if applicable)
	  ○ Material wrapper basis weight (g/m^2) (if applicable)
	  ○ Material porosity (permeability) (CU) (if applicable)
	• Heating element
	  ○ Heating Element diameter (gauge)
	  ○ Heating Element resistance (Ohms)
	  ○ Heating Element temperature range (°C)
	• E-liquid
	  ○ E-liquid viscosity (at 20°C)
	  ○ E-liquid volume (ml)
	• Tobacco (if applicable)
	  ○ Tobacco moisture (%)
	  ○ Tobacco cut size (CPI or mm)
	  ○ Tobacco density (g/cm^3)
	• Battery
	  ○ Battery voltage operating range (V)
	  ○ Battery current operating range (mA)
	  ○ PDU voltage operating range (V)
	  ○ PDU current operating range (mA)PCU wattage operating range (W)

Provide Target Specification With Upper and Lower Range Limits for:	Provide test data (include test protocols, quantitative acceptance criteria, data sets, and a summary of the results) for:
○ Heating element Configuration (i.e., the shape and design of the heating element. If the heating element is a coil, it is the shape and arrangement of the coil. If the heating element is a novel design, provide the configuration and its design targets.) ○ Heating element length (mm) ○ Heating element mass (mg) ○ Heating element location ○ Number of heating elements (e.g., coil) (dimensionless) ○ Heating Element diameter (gauge) (if applicable) ○ Heating Element resistance (Ohms) (if applicable) • Tobacco / E-liquid ○ Tobacco mass (mg) (if applicable) ○ Tobacco density (g/cm^3) (if applicable) ○ Tobacco moisture or oven volatiles (%) (if applicable) ○ Tobacco cut size (CPI or mm) (if applicable) ○ E-liquid volume (mL) (if applicable) ○ E-liquid viscosity (at 20°C) (if applicable) • Battery (if applicable) ○ Battery capacity (mA) ○ Battery Voltage Operating Range (V) or Wattage (W) ○ Battery Current Charging range (amps) ○ Battery Nominal Voltage (V) ○ Battery Current rating (mA) ○ Batter charging temperature limits (°C)	○ PDU Current cut-off (mA) (if applicable) ○ ○ PDU temperature cut-off (°C) ○ Battery Capacity (mAh) ○ Battery Nominal Voltage (V) ○ Battery Current rating (mA) ○ Battery charging temperature limits (°C) ○ Battery discharge temperature limits (°C) ○ Battery maximum charging current (mA) ○ Battery maximum discharging current (mA) ○ Battery upper limits charging voltage (V) • Aerosol ○ Inhaled aerosol temperature (°C) ○ Aerosol Particle number concentration (#/cm^3) ○ Count median diameter (nm) ○ PM2.5 (µg/m^3) • Filter (if applicable) ○ Filter efficiency (%) {If no filter efficiency data is available for the products, include information sufficient to show that the cigar filter is unchanged [e.g., denier per filament (DPF), total denier (g/9000m), and filter density(g/cm^3)]} ○ Filter ventilation (%) ○ Filter pressure drop (mm H_2O)

Provide Target Specification With Upper and Lower Range Limits for:	Provide test data (include test protocols, quantitative acceptance criteria, data sets, and a summary of the results) for:
○ Battery discharge temperature limits (°C) ○ Battery end of discharge voltage (V) ○ Battery maximum charging current (mA) ○ Battery maximum discharging current (mA) ○ Battery upper limits charging voltage (V) ○ Power Delivery Unit (PDU) voltage operating range (V) ○ PDU current operating range (mA) ○ PDU wattage operating range (watts) ○ PDU temperature cut-off (°C) (if applicable) ○ PDU Current cut-off (mA) (if applicable) • Aerosol ○ Inhaled aerosol temperature (°C) ○ Aerosol Particle number concentration (#/cm^3) ○ Count median diameter (nm) ○ PM2.5 (µg/m^3) • Filter (if applicable) ○ Filter efficiency (%) {If no filter efficiency data is available for the products, include information sufficient to show that the cigar filter is unchanged [e.g., denier per filament (DPF), total denier (g/9000m), and filter density(g/cm^3)]} ○ Filter pressure drop (mm H_2O) ○ Filter length (mm) ○ Filter diameter (mm) ○ Filter ventilation (%)	

(iii) *Function*. How the product is intended to function.

(iv) *Product pH and nicotine formulation*. The pH of the product and the formulation of nicotine in the product, if applicable, including the form (e.g., unprotonated nicotine, nicotine salts) and quantity.

(v) *Fermentation process*. For smokeless tobacco products and tobacco products that contain fermented tobacco (including naturally fermented tobacco), information on the fermentation process, including the following:

(A) Description of the fermentation process;

(B) Composition of the inoculum (starter culture) with genus and species name(s) and concentration(s) (if applicable);

(C) Any step(s) taken to reduce endogenous microbes (e.g., cleaning of product contact surfaces);

(D) Specifications and test data for pH, temperature, moisture content, and water activity;

(E) Frequency of aeration or turning (if applicable);

(F) Duration of fermentation;

(G) Added ingredients;

(H) Method used to stabilize or stop fermentation (e.g., heat treatment) (if applicable), including parameters of the method (e.g., length of treatment, temperature) and method validation data; and

(I) Storage conditions of the fermented tobacco prior to further processing or packaging and duration of storage (if applicable).

(vi) *Heat treatment process*. For tobacco products that are heat treated, the application must contain the following information regarding the heat treatment process:

(A) Description of the heat treatment process;

(B) Type of heat treatment;

(C) Conditions of heat treatment, including time, temperature, and moisture; and

(D) Method validation data, including microbial loads (including bacteria, spores, yeast, and fungi) and TSNAs before and after heat treatment.

(vii) *Shelf life and stability information*. With the exception of applications for roll-your-own tobacco products and cigarettes that are not HTPs, the application must contain information on the stability of the tobacco product over the shelf life and including the following:

(A) The length of the shelf life, a description of how the shelf life is determined, and a description of how shelf life is indicated on the tobacco product, if applicable;

(B) Stability data assessed at the beginning (zero time), middle, and end of the expected shelf life. If a tobacco product does not have a defined shelf life, provide stability data over a specified amount of time and a justification for why that time period is appropriate. Stability testing must be performed for the microbial and chemical endpoints as follows: microbial content data, including total aerobic microbial count and total yeast and mold count; water activity; tobacco-specific nitrosamines (TSNAs) yields (total TSNAs, N′-nitrosonor-nicotine (NNN), 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone) (NNK)); and preservatives content.

(C) Stability testing details for each microbial and chemical endpoint, including: the mean quantity and variance with unit of measures; the number of samples and measurement replicates for each sample; the methods used, associated reference(s) including any deviation(s) from the methods and full validations reports for each method; the testing laboratory or laboratories and documentation showing that the laboratory or laboratories is (or are) accredited by a nationally or internationally recognized external accreditation organization; length of time

between date of tobacco product manufacture and date(s) of testing; storage conditions of the tobacco product before it was tested; a statement that the testing was performed on a tobacco product in the same container closure system in which the tobacco product is intended to be marketed; and full test data (including quantitative acceptance (pass/fail) criteria, complete data sets, and a summary for the results) for all stability testing performed.

(viii) *Product and packaging design risks and misuse hazards*. A review and assessment of reasonably foreseeable risks associated with the design of the tobacco product and its package that may occur during normal use of the tobacco product or during any foreseeable misuse of the product, including user error, which may cause illness, injury, or death not normally associated with the use of the tobacco product. The review and assessment must identify the measures taken to reduce or eliminate each risk associated with the design of the tobacco product and package.

(3) *Principles of operation*. The applicant must provide a full statement of the principle or principles of operation of the tobacco product, including full narrative descriptions of:

(i) The way in which a typical consumer will use the new tobacco product, including a description of how a consumer operates the product, how long a single unit of product is expected to last (e.g., total length of time of use to consume a unit, number of use sessions expected per unit), and, where applicable, how a consumer can change the product design and add or subtract ingredients;

(ii) A justification for an applicant's determination of what constitutes a single unit of product as described in the PMTA; and

(iii) Whether the product incorporates a heating source, and if so, a description of the heating source.

(4) *Product testing and analysis information*. Each analysis required in this paragraph must be performed on test samples that reflect the finished tobacco product composition and design, and must be conducted using a sufficient sample size and number of replicates to substantiate the results of the type of testing conducted. Additionally, the applicant must provide the following information:

(i) The name and location of the testing laboratory or laboratories and documentation showing that the laboratory or laboratories is (or are) accredited by a nationally or internationally recognized external accreditation organization;

(ii) The length of time between dates of manufacture and date(s) of testing;

(iii) The storage conditions of the tobacco product before it was tested;

(iv) The number of samples and measurement replicates for each sample;

(v) A description of method procedure, method validation information and rationale for selecting each test method, including relevant voluntary testing standards, test protocols, quantitative acceptance criteria, line data, and a summary of the results;

(vi) Reports of product formulation testing that include test protocols, quantitative acceptance criteria, line data, and a summary of the results, for each applicable design parameter; and

(vii) Complete descriptions of any smoking or aerosol-generating regimens used for analytical testing that are not standardized or widely accepted by the scientific community, if applicable.

(j) *Manufacturing*. The application must contain a full description of the methods used in, and the facilities and controls used for, the design (including design validation and design verification, to assess whether the tobacco product, as manufactured, performs in accordance

with design specifications), manufacture, packing, and storage of the tobacco product in sufficient detail to demonstrate whether the product meets manufacturing specifications, can be manufactured in a manner consistent with the information submitted in the application, and conforms to the requirements of any regulations issued under section 906(e) of the Federal Food, Drug, and Cosmetic Act, including:

(1) A list of all manufacturing, packaging, storage, and control facilities for the product, including the facility name, address, and FEI number, if applicable, and a contact name and telephone number for a representative from each facility;

(2) A narrative description, accompanied by a list and summary, of all standard operating procedures (SOPs) and examples of relevant forms and records for the following categories of information for all manufacturing, design controls, packing, and storage for the tobacco product:

(i) Manufacturing and production process activities at each establishment, including a description of each establishment, all production steps, and process controls, process specifications with relevant acceptance criteria, and monitoring and acceptance activities;

(ii) Managerial oversight and employee training related to the manufacture, processing, packing, and installation of the tobacco product, as applicable;

(iii) Monitoring procedures and manufacturing controls for product design, product characteristics, and changes in products, specifications, methods, processes, or procedures, including a hazard analysis that details the correlation of the product design attributes with public health risk, as well as any mitigation strategies implemented;

(iv) Activities related to identifying and monitoring suppliers and the products supplied (including, for example, purchase controls and product acceptance activities);

(v) Handling of complaints, nonconforming products and processes, and corrective and preventative actions;

(vi) Testing procedures carried out before the product is released to market, including:

(A) A list and summary of any standards used for all testing methods;

(B) Validation and verification activities for all test methods used to ensure that the tobacco product meets specifications;

(C) Documentation of accreditation information for all testing laboratories;

(D) Complete description of smoking or aerosol-generating regimes used for analytical testing, if any; and

(E) Tobacco product specifications (including any physical, chemical, and biological specifications) and acceptance criteria for those specifications;

(F) Reports of release testing performed on finished products to demonstrate conformity with established specifications, including test protocols, line data, and a summary of the results for each applicable testing.

(k) *Health risk investigations*--(1) *Study types*. The application must contain full reports of all information, both favorable and unfavorable, published or known to, or which should reasonably be known to, the applicant concerning investigations, including nonclinical and human subject studies regarding the following topics. If no substantive information exists regarding the topics specified in § 1114.27(b)(1)(ii), including information from published literature or that may be bridged from an investigation of another tobacco product, an applicant may need to conduct its own investigation(s) to ensure substantive information is included in the PMTA to meet the application filing requirements.

(i) *Health risks of the product*. The potential health risks of the tobacco product to users and nonusers, including potential exposures and information regarding risks to youth, young adults, and other relevant vulnerable populations, and whether the product may present different risks than other tobacco products, including:

(A) The health effects of the constituents, including HPHCs, at the quantitative levels delivered to both users and nonusers under the range of conditions under which the product might be used;

(B) The toxicological profile of the new tobacco product related to the route of administration, including the genotoxicity, carcinogenicity, reproductive toxicity, immunotoxicity, acute toxicity, and repeat dose (chronic) toxicity of the new tobacco product relative to other tobacco products. The toxicological profile also includes information on the toxicity of the ingredients, additives, and HPHCs, relative to the route of administration and the range of potential levels of exposure resulting from the use of, or exposure to, the new tobacco product, including studies which discuss the toxicological effects of any leachables and extractables that can appear from the container closure system and the ingredient mixture, such as additive or synergistic effects;

(C) The pharmacological profile of the new tobacco product, including the pharmacokinetics, pharamacodynamics, metabolism, and elimination profile, of any of the ingredients, additives, and HPHCs for the range of potential levels of exposure resulting from the use of, or exposure to, the new tobacco product relative to other tobacco products. The applicant must specify whether the studies were conducted in vitro, in vivo, ex vivo, or in silico; and

(D) The health risks of the tobacco product compared to other tobacco products on the market, never using tobacco products, quitting tobacco product use, and using the tobacco product in conjunction with other tobacco products.

(ii) *Impacts on tobacco use behavior of tobacco product users.* How the product and its label, labeling, and advertising, to the extent that advertising has been studied, will affect the tobacco use behavior of tobacco product users, specifically considering youth, young adults, and other relevant vulnerable populations, including:

(A) The abuse liability of the tobacco product;

(B) How users actually use the product, including use topography, product use frequency, use trends over time, and how such use affects the health risks of the product to individual users;

(C) The likelihood that users will use the product in conjunction with other tobacco products;

(D) The likelihood that current tobacco product users will start using the product;

(E) The likelihood that current tobacco users who adopt the product will switch to or switch back to other tobacco products that may present increased risks to individual health; and

(F) The likelihood that current tobacco users who may have otherwise quit using tobacco products will instead start or continue to use the product.

(iii) *Impacts on tobacco use initiation by nonusers, including youth, young adults, and other relevant vulnerable populations*. The impact of the tobacco product and its label, labeling, or advertising, to the extent that advertising has been studied, on tobacco use initiation by nonusers, including:

(A) The likelihood that consumers who have never used tobacco products, particularly youth, young adults, and other relevant vulnerable populations, will initiate use of the tobacco product;

(B) The likelihood that nonusers of tobacco products who adopt the tobacco product will switch to other tobacco products that may present higher levels of individual health risk; and

(C) The likelihood that former users of tobacco products will re-initiate use with the tobacco product.

(iv) *Perceptions and use intentions*. The impact of the product and its label, labeling, and advertising, to the extent that advertising has been studied, on individuals:

(A) Perception of the product;

(B) Use intentions; and

(C) Ability to understand the labeling and instructions for use and use the product in accordance with those instructions.

(v) *Human factors*. The impact of human factors on product risk, including discussion of use conditions, use environments, use related hazards, estimated use error risk, potential unintended uses, risk controls to ensure that harms and unintended consequences are minimized, and adverse experiences related to such uses.

(2) *Literature search*. The applicant must conduct a literature search for each type of information described in paragraph (k)(1) of this section, and the application must contain a description of the literature search performed, including the databases searched and the date searched, search terms, reasons for inclusion or exclusion of documents, and the strategy for study quality assessment. The application must also contain a bibliography of all published

studies and articles referenced in the application. If a literature search was performed and resulted in no information found, the application must contain a statement to that effect.

(3) *Study reports*. The full report of each study included in the application must describe the specific product studied and include the following items, where applicable and to the extent reasonably available. For applicable items not contained in the full report of an investigation, the applicant must contain a description of the actions taken to obtain the information and why the document is not reasonably available.

(i) Full copies of any published articles and other reference materials;

(ii) Documentation of all actions taken to ensure the reliability of the study. For all studies, to the extent reasonably available or obtainable, the application must contain a certification that investigators do not have, or documentation fully disclosing, any financial conflicts of interest, such as the financial arrangements specified in the Financial Disclosure by Clinical Investigators regulation in part 54 of this chapter. Additionally, for nonclinical laboratory studies, the application must contain, for each study, documentation of all actions taken to ensure the reliability of the study, e.g., documentation of whether the study was conducted in accordance with good laboratory practices, such as those specified in part 58 of this chapter;

(iii) Copies of all versions of protocols and amendments that were used in the study;

(iv) Copies of all versions of investigator instructions, if any were produced in addition to the protocol;

(v) The statistical analysis plan, including a detailed description of the statistical analyses used (including all variables, confounders, and subgroup analyses), the scientific rationale for the choice of sample sizes, and any amendments to the plan;

(vi) Line data, including data definition files that include the names of the variables, codes, and formats in each dataset, and copies of programs and any necessary macro-programs used to create derived datasets, and the results included in the study reports;

(vii) A list of sites and clinical investigators that conducted the study, including contact information and physical address(es);

(viii) The location of all source data. If the site where the study was conducted has not maintained all of the source data, indicate where the data are located;

(ix) The format of the records and data (e.g., electronic or hard copy);

(x) A list of all sites that had early termination and the reason for early termination, if applicable;

(xi) A list of contractors who participated in the study, the role of each contractor, and the initiation and termination dates of the participation of each contractor;

(xii) A signed full report of all findings;

(xiii) For human subject studies:

(A) All versions of study materials (e.g., consent forms, questionnaires, stimuli) used;

(B) All versions of case report forms used; and

(C) Individual case report forms related to participant deaths, other serious and unexpected adverse experiences, withdrawals, and participant discontinuation where the study participant was exposed to the tobacco product that is the subject of the PMTA or similar products; and

(xiv) For tobacco product perception and use intention studies that use advertising as stimuli, a statement describing whether the advertising used is representative of advertising that the applicant intends to use in marketing the product. If the advertising is not representative of

the advertising an applicant intends to use in marketing the product, the applicant must describe whether the study results are still relevant to the likely impact of the advertising on tobacco product perceptions and use intentions.

(l) *The effect on the population as a whole*. The application must contain an analysis and discussion of how the data and information contained in the application establish that permitting the tobacco product to be marketed would be appropriate for the protection of public health determined with respect to the population as a whole, including users and nonusers of the tobacco product. The analysis and discussion must integrate all of the information in the application regarding the product and its likely effects on health, and tobacco use behavior, including tobacco use cessation and initiation, to provide an overall assessment of the likely effect that the marketing of the tobacco product may have on overall tobacco-related morbidity and mortality.

(m) *Certification statement*. The application must contain the following certification, with the appropriate information inserted (as indicated by parenthetical italicized text), signed by an authorized representative of the applicant:

"I (*name of responsible official*) on behalf of the applicant, (*applicant name*), hereby certify that the applicant will maintain all records to substantiate the accuracy of this application for the period of time required in 21 CFR 1114.45 and ensure that such records remain readily available to FDA upon request. I certify that this information and the accompanying submission are true and correct, that no material fact has been omitted, and that I am authorized to submit this on the applicant's behalf. I understand that under section 1001 of title 18 of the United States Code anyone who knowingly and willfully makes a materially false, fictitious, or fraudulent statement or representation in any matter within the jurisdiction of the executive, legislative, or judicial branch of the Government of the United States is subject to criminal penalties."

§ 1114.9 Amendments.

(a) *General*. FDA may request, or an applicant may submit on its own initiative, an amendment to a PMTA containing information that is necessary for FDA complete the review of a pending PMTA. An amendment must include the appropriate form and specify the STN assigned to the original submission and, if submitted other than at FDA's request, the reason for submitting the amendment. An amendment must also include the certification statement set forth in § 1114.7(m), with the appropriate information inserted, and signed by an authorized representative of the applicant.

(b) *Review of an amendment*. Submission of an amendment may affect the timing of review of an amended submission as follows:

(1) If the amendment is a major amendment (e.g., an amendment that contains significant new data from a previously unreported study, detailed new analyses of previously submitted data, or substantial new manufacturing information), FDA will restart the 180-day review period after receipt of the amendment.

(2) If FDA requests a minor amendment (i.e., an amendment that is not a major amendment) and receives a written response submitting the requested amendment, FDA may pause the review period for the number of days elapsed between the date of the request and the date that FDA receives the written response.

(c) *Failure to respond to amendment request*. If FDA requests an amendment and the applicant does not respond within the time period specified in FDA's request, FDA may consider the applicant to have submitted a request to voluntarily withdraw the pending PMTA under § 1114.11 and issue an acknowledgment letter notifying the applicant of the withdrawal.

(d) *No amendment to closed or withdrawn application*. An applicant may not amend an application after FDA has closed the application through an action under § 1114.29 or it has been withdrawn under § 1114.11.

§ 1114.11 Withdrawal by applicant.

(a) An applicant may at any time make a written request using the appropriate form to withdraw a PMTA that FDA has not acted on as described in § 1114.29. The withdrawal request must state:

(1) Whether the withdrawal is due to a health concern related to the tobacco product and, if so, a description of those concerns, including the extent, duration, and frequency of the health effects, and what gave rise to the concerns, such as reports of adverse experiences;

(2) The application STN; and

(3) The name(s) of the new tobacco product that is the subject of the application.

(b) An application will be considered withdrawn when FDA issues an acknowledgement letter stating that the application has been withdrawn.

(c) The application is an Agency record, even if withdrawn. FDA will retain the withdrawn application under Federal Agency records schedules. The availability of the withdrawn application will be subject to FDA's public information regulation in Part 20 of this chapter.

§ 1114.13 Change in ownership of an application.

An applicant may transfer ownership of a PMTA. At or before the time of transfer, the new owner and the former owner must submit information to FDA using the appropriate form as follows:

(a) The new and former owner must sign and submit a notice to FDA stating that all of the former applicant's rights and responsibilities relating to the PMTA have been transferred to the new owner. This notice must identify the name and address of the new owner and the PMTA transferred by tobacco product name(s) and STN.

(b) The new owner must sign and submit a notice to FDA containing the following:

(1) The new owner's commitment to agreements, promises, and conditions made by the former owner and contained in the application and marketing granted order, if applicable;

(2) The date that the change in ownership is effective;

(3) Either a statement that the new owner has a complete copy of the application, including all amendments, the marketing granted order (if applicable), and any records that are required to be kept under § 1114.45, or a request for a copy of the application, including all amendments, and the modified risk order (if applicable) from FDA's files in accordance with part 20 of this chapter. In accordance with the Freedom of Information Act, FDA will provide a copy of the application to the new owner under the fee schedule in FDA's public information regulations in § 20.45 of this chapter; and

(4) A certification that no modifications have been made to the tobacco product since the application, including amendments (if any), was submitted to FDA.

§ 1114.15 Supplemental applications.

(a) *Supplemental PMTA submission*. Applicants that have received a marketing granted order for a tobacco product may, as an alternative format of submitting an application that meets the content requirements of § 1114.7, submit a supplemental PMTA to seek marketing authorization for modifications to such product, which result in a new tobacco product under section 910(a)(1) of the Federal Food, Drug, and Cosmetic Act. Supplemental PMTAs must

include new information concerning modifications that create the new tobacco product but allow the applicant to satisfy the remaining application requirements by cross-referencing applicable content from the previously submitted PMTA for the original tobacco product. Applicants may submit supplemental PMTAs only for modifications that require the submission of limited new information or where specified in a rule under section 907 of the FD&C Act. Except as permitted in a rule under section 907 of the Federal Food, Drug, and Cosmetic Act, an applicant may not submit a supplemental PMTA where:

(1) Modifications to the product that result in the new tobacco product require the submission of new information or revisions to the PMTA for the original product to the extent that reviewing a supplemental application for the new tobacco product would be confusing, cumbersome, or otherwise inefficient and submitting a standard PMTA under § 1114.7 would better facilitate review.

(2) The marketing granted order for the original tobacco product has been withdrawn; or

(3) The marketing granted order for the original tobacco product has been temporarily suspended or is subject to temporary suspension or withdrawal proceedings by FDA, except where authorized in writing by FDA.

(b) *Required format.* The supplemental PMTA must comply with format requirements of § 1114.7(b), except that an applicant must include certain content in a supplemental PMTA by cross-referencing a PMTA, or, where applicable, a supplemental PMTA, for an original tobacco product that is owned by that applicant, and may include other content by cross-referencing a tobacco product master file and postmarket reports for the original tobacco product. FDA will not consider content included by cross-reference to other sources of information outside of the submission.

(c) *Required content*. The supplemental PMTA must provide sufficient information for FDA to determine whether any of the grounds for denial listed in section 910(c)(2) of the Federal Food, Drug, and Cosmetic Act apply to the application.

(1) The application must contain the full text of all the information described in the following sections:

(i) General information that identifies the submission as a supplemental PMTA (as described in § 1114.7(c));

(ii) New product information (as described in paragraph (d) of this section);

(iii) Statement of compliance with 21 CFR part 25 (as described in § 1114.7(g));

(iv) Labeling (as described in § 1114.7(f)) if the labeling is not identical to the labeling submitted in the PMTA or postmarket reports for the original product;

(v) Postmarket information (as described in paragraph (e) of this section); and

(vi) Certification statement (as described in paragraph (f) of this section);

(2) The application must include the following sections by cross-reference to the PMTA for the original tobacco product and contain any additional information that is necessary to supplement or update the cross-referenced information:

(i) Descriptive information (as described in § 1114.7(d));

(ii) Product samples (as described in § 1114.7(e));

(iii) Labeling (as described in § 1114.7(f)) if the labeling is identical to the labeling that was submitted in the PMTA or postmarket reports for the original tobacco product;

(iv) Summary of all research findings (as described in § 1114.7(h));

(v) Product formulation (as described in § 1114.7(i));

(vi) Manufacturing (as described in § 1114.7(j)); and

(vii) Health risk investigations (as described in § 1114.7(k)).

(d) *New product information*. The application must contain a section that includes:

(1) Full descriptions of each modification to the product and comparisons to the original product version described in the previously authorized PMTA;

(2) A statement as to whether the new tobacco product, if it receives a marketing granted order, will replace the original tobacco product, will be a line extension of the original tobacco product, or will be introduced as an additional product by the same manufacturer;

(3) All data and information relating to each modification to the product that would be required in an application under § 1114.7; and

(4) A concluding summary of how the new tobacco product meets the requirements to receive a marketing granted order, including how the data and information contained in both the supplemental PMTA and cross-referenced from the previously authorized PMTA constitute valid scientific evidence and establishes that the PMTA meets the requirements of section 910(c) of the Federal Food, Drug, and Cosmetic Act to receive a marketing granted order, including that permitting the new tobacco product to be marketed would be appropriate for the protection of the public health determined with respect to the risks and benefits to the population as a whole, including users and nonusers of the tobacco product.

(e) *Postmarket reports*. (1) If an applicant has submitted postmarket reports for the original tobacco product, the applicant must include all such reports in the application by cross-reference.

(2) If an applicant is required to, but has not yet submitted a postmarket report, the applicant must submit a report as part of its application that contains all of the information for the original tobacco product that would otherwise be required in a report under § 1114.41

covering the period of time from when it received a marketing granted order for the original tobacco product to when it submits the supplemental PMTA.

(f) *Certification statement*. The application must contain the following certification, with the appropriate information inserted as indicated by parenthetical italicized text, signed by an authorized representative of the applicant:

"I, (*name of responsible official*), on behalf of (*name of applicant*), certify that (*new tobacco product name*) has a different (*describe each modification to the product*) than (*name of original tobacco product*) described in (*STN of the PMTA for the original product*) but is otherwise identical to (*name(s) of original tobacco product*). I certify that (*name of applicant*) understands this means there is no other modification to the materials, ingredients, design, composition, heating source, or any other feature of the original tobacco product. I also certify that (*name of applicant*) will maintain all records that substantiate the accuracy of this application and ensure that such records remain readily available to FDA upon request for the period of time required in 21 CFR 1114.45. I certify that this information and the accompanying submission are true and correct, and that I am authorized to submit this on the applicant's behalf. I understand that under section 1001 of title 18 of the United States Code, anyone who knowingly and willfully makes a materially false, fictitious, or fraudulent statement or representation in any matter within the jurisdiction of the executive, legislative, or judicial branch of the Government of the United States is subject to criminal penalties."

§ 1114.17 Resubmissions.

(a) *General*. An applicant may, as an alternative format of submitting an application that meets the content requirements of § 1114.7 or 1114.15 (if applicable), submit a resubmission to address deficiencies set forth in a marketing denial order. The resubmission must contain new information necessary to address application deficiencies and cross-reference applicable content from the PMTA that received the marketing denial order. An applicant may utilize the resubmission format for the same tobacco product for which FDA issued a marketing denial order or a new tobacco product that results from modifications to the product necessary to

address the deficiencies described in a marketing denial order. An applicant may not submit a resubmission when:

(1) It incorporates new information or revisions to the PMTA for the original product to the extent that reviewing a resubmission for the new tobacco product would be confusing, cumbersome, or otherwise inefficient and submitting a standard PMTA under § 1114.7 would better facilitate review; or

(2) The marketing denial order states that the applicant may not submit a resubmission.

(b) *Required format.* The resubmission must comply with format requirements of § 1114.7(b), except that an applicant must include content in the resubmission by cross-referencing the PMTA, or, where applicable, supplemental PMTA, that received the marketing denial order. An applicant may also include content in a resubmission by cross-reference to a TPMF. FDA will not consider content included by cross-reference to other sources of information outside of the submission.

(c) *Required content*. The resubmission must provide sufficient information for FDA to determine whether any of the grounds for denial listed in section 910(c)(2) of the Federal Food, Drug, and Cosmetic Act apply to the application.

(1) The application must include the full text of the information described in the following paragraphs:

(i) General information that identifies the submission as a resubmission (as described in paragraph § 1114.7(c));

(ii) Response to deficiencies (as described in paragraph (d) of this section); and

(iii) Certification statement (as described in paragraph (e) of this section).

(2) The application must include the following sections from the PMTA that received a marketing denial order by cross-reference to the PMTA and contain all additional information, in full text or by reference to a tobacco product master file, that is necessary to supplement or update the cross-referenced information:

(i) Descriptive information (as described in § 1114.7(d));

(ii) Product samples (as described in § 1114.7(e));

(iii) Labeling (as described in § 1114.7(f));

(iv) Statement of compliance with 21 CFR part 25 (as described in § 1114.7(g));

(v) Summary of all research findings (as described in § 1114.7(h));

(vi) Product formulation (as described in § 1114.7(i));

(vii) Manufacturing (as described in § 1114.7(j)); and

(viii) Health risk investigations (as described in § 1114.7(k)).

(d) *Response to deficiencies*. (1) The application must include a section that lists and provides a separate response to each deficiency described by FDA in the original marketing denial order, including all data and information necessary to complete each response, and that also addresses any applicant-identified deficiencies.

(2) Where an applicant modifies the product in a way that would result in a new tobacco product under section 910(a)(1) of the Federal Food, Drug, and Cosmetic Act in order to address the deficiencies, the application must also include:

(i) A full description of each modification to the product and comparisons of that change to the original version of the product described in the previously submitted PMTA; and

(ii) All data and information relating to each modification to the product that would be required in an application under § 1114.7.

(e) *Certification statement*. The application must contain one of the two following certifications that corresponds to the application, with the appropriate information inserted as indicated by parenthetical italicized text, signed by an authorized representative of the applicant.

(1) *Same tobacco product certification*. An application for the same tobacco product must contain the following certification:

"I, (*name of responsible official*), on behalf of (*name of applicant*), certify that this submission for (*new tobacco product name(s)*) responds to all deficiencies outlined in the marketing denial order issued in response to (*STN of the previously submitted PMTA*) and the new tobacco product described herein is identical to the product described in the previously submitted PMTA. I certify that (*name of applicant*) understands this means there is no modification to the materials, ingredients, design, composition, heating source, or any other feature. I also certify that (*name of applicant*) will maintain all records that substantiate the accuracy of this statement, and ensure that such records remain readily available to FDA upon request for the period of time required in 21 CFR 1114.45. I certify that this information and the accompanying submission are true and correct, and that I am authorized to submit this on the company's behalf. I understand that under section 1001 of title 18 of the United States Code, anyone who knowingly and willfully makes a materially false, fictitious, or fraudulent statement or representation in any matter within the jurisdiction of the executive, legislative, or judicial branch of the Government of the United States is subject to criminal penalties."

(2) *Different tobacco product certification*. An application for a different tobacco product than the original tobacco product that results from changes necessary to address the deficiencies must contain the following certification:

"I, (*name of responsible official*), on behalf of (*name of applicant*), certify that this submission for (*new tobacco product name(s)*) responds to all deficiencies outlined in the marketing denial order issued in response to (*STN of the previously submitted PMTA*) and the new tobacco product described herein has a different (*describe each modification to the product*) than (*name(s) of original tobacco product*) described in (*STN of the previously submitted PMTA*) but is otherwise identical to (*name(s) of original tobacco product*) described in (*STN of the previously submitted PMTA*). I certify that (*name of applicant*) understands this means there is no modification to the materials, ingredients, design features, heating source, or any other feature of the original tobacco product,

except for the (*describe each modification to the tobacco product*). I also certify that (*name of applicant*) will maintain all records that substantiate the accuracy of this statement, and ensure that such records remain readily available to FDA upon request for the period of time required in 21 CFR 1114.45. I certify that this information and the accompanying submission are true and correct, and that I am authorized to submit this on the company's behalf. I understand that under section 1001 of title 18 of the United States Code, anyone who knowingly and willfully makes a materially false, fictitious, or fraudulent statement or representation in any matter within the jurisdiction of the executive, legislative, or judicial branch of the Government of the United States is subject to criminal penalties."

Subpart C--FDA Review

§ 1114.25 Communication between FDA and applicants.

During the course of reviewing an application, FDA may communicate with an applicant about relevant matters, including scientific, medical, and procedural issues that arise during the review process and inspections. These communications may take the form of telephone conversations, letters, electronic communications, or meetings, and will be documented in the administrative file in accordance with § 10.65 of this chapter.

§ 1114.27 Review procedure.

(a) *Acceptance review*. (1) After an applicant submits a PMTA, FDA will perform an initial review of the PMTA to determine whether it may be accepted for further review. FDA may refuse to accept an application that:

(i) Does not comply with the applicable format requirements in § 1114.7(b), 1114.15, or 1114.17 (as applicable);

(ii) Is not administratively complete because it does not appear to contain the information required by § 1114.7 (excluding product samples), § 1114.15 or 1114.17, as applicable;

(iii) Does not pertain to a tobacco product subject to chapter IX of the Federal Food, Drug, and Cosmetic Act (as required by § 1105.10 of this chapter); or

(iv) FDA can otherwise refuse to accept under § 1105.10.

(2) If FDA accepts an application for further review, FDA will issue an acknowledgement letter to the applicant that specifies the PMTA STN. If FDA determines that it will require product samples as part of the PMTA, it will send instructions on how and where to submit product samples, as described in § 1114.7(e) of this chapter.

(3) If FDA refuses to accept an application, FDA will issue a letter to the applicant identifying the deficiencies, where practicable, that prevented FDA from accepting the application.

(b) *Filing review*. (1) After accepting a PMTA, FDA will make a threshold determination of whether the application contains sufficient information to permit a substantive review. FDA may refuse to file a PMTA if any of the following applies:

(i) The PMTA does not contain sufficient information required by section 910(b)(1) of the Federal Food, Drug, and Cosmetic Act and by § 1114.7, 1114.15, or 1114.17, as applicable, to permit a substantive review of the application;

(ii) The application does not contain any substantive information, including information from published literature or bridged from an investigation of another tobacco product, regarding each of the following topics.

(A) The health risks of the new tobacco product as described in either § 1114.7(k)(1)(i)(A), (B), or (C));

(B) The health risks of the new tobacco product compared to the health risks generally presented by products in the same product category as well as products in at least one different category that are used by the consumers an applicant expects will use its new tobacco product (as described in a portion of § 1114.7(k)(1)(i)(D)).

(C) The abuse liability of the new tobacco product (as set forth in § 1114.7(k)(1)(ii)(A));

(D) How consumers would be expected to actually use the product, such as use frequency, use trends over time, and how such use affects the health risks of the product to individual users (as described in § 1114.7(k)(1)(ii)(B));

(E) The potential impact that the marketing of the new tobacco product would have on the likelihood that current tobacco product users would change their tobacco product use behavior, such as starting to using the new tobacco product, using the product in conjunction with other tobacco products, or, after using the product, switching to or switch back to other tobacco products that may present increased risks to individual health (i.e., any of the information set forth in either § 1114.7(k)(1)(ii)(C), (D), (E), or (F));

(F) The impact of the tobacco product and its label, labeling, or advertising, to the extent that advertising has been studied, on tobacco product use behavior of current nonusers of tobacco products (i.e., any of the information described in § 1114.7(k)(1)(iii));

(G) The impact of the product and its label, labeling, or advertising, to the extent that advertising has been studied, on individuals' perception of the product and their use intentions (i.e., any of the information described in § 1114.7(k)(1)(iv)); and

(H) The ways in which human factors can affect the health risks of the new tobacco product (i.e., any of the information described in § 1114.7(k)(1)(v));

(iii) The PMTA contains a false statement of material fact;

(iv) The PMTA is a supplemental PMTA that does not comply with § 1114.15; or

(v) The PMTA is a resubmission that does not comply with § 1114.17.

(2) If FDA refuses to file an application, FDA will issue a letter to the applicant identifying the deficiencies, where practicable, that prevented FDA from filing the application.

(3) If FDA files an application, FDA will issue a filing letter to the applicant.

(c) *Application review*. (1) Except as described in this paragraph and § 1114.9(b), within 180 days of receipt of an application described in section 910(b)(1) of the Federal Food, Drug, and Cosmetic Act meeting the filing requirements set out in 1114.27(b), FDA will complete its review of the PMTA and act on the application.

(2) FDA will begin substantive review of the application after it is filed under paragraph (b) of this section. FDA may communicate with the applicant as set forth under § 1114.25 to seek additional or clarifying information.

(3) FDA may refer the PMTA or portions of the PMTA, upon its own initiative or applicant request, to TPSAC for reference and for the submission of a report and recommendation respecting the application, together with all underlying data and the reasons or basis for the recommendation.

(4) FDA may conduct inspections of the applicant's manufacturing sites, and sites and entities involved with clinical and nonclinical research (including third parties and contract research organizations) to support FDA's review of the PMTA. Where an applicant prevents FDA from scheduling and conducting inspections that are necessary for FDA to complete its review of the PMTA in a timely manner, FDA may pause the 180-day review period for the number of days necessary to complete the inspection.

(5) FDA may defer review of a PMTA for a new product that, if introduced or delivered for introduction into interstate commerce, would be adulterated or misbranded due to the manufacturer or importer's failure to comply with user fee payment and reporting requirements under part 1150.

§ 1114.29 FDA action on an application.

After receipt of an application, FDA will:

(a) Refuse to accept the application as described in § 1114.27(a);

(b) Issue a letter administratively closing the application;

(c) Issue a letter canceling the application if FDA finds that it mistakenly accepted the application or that the application was submitted in error;

(d) Refuse to file the application as described in § 1114.27(b);

(e) Issue a marketing granted order as described in § 1114.31; or

(f) Issue a marketing denial order as described in § 1114.33.

§ 1114.31 Issuance of a marketing granted order.

(a) FDA will issue a marketing granted order if it finds that none of the grounds for denial listed in section 910(c)(2) of the Federal Food, Drug, and Cosmetic Act apply. A marketing granted order becomes effective on the date it is issued.

(b) FDA may include, as part of the marketing granted order:

(1) Restrictions on the sale and distribution of the product, including restrictions on the access to, and the advertising and promotion of, the tobacco product, to the extent that it would be authorized to impose such restrictions under a regulation issued under section 906(d) of the Federal Food, Drug, and Cosmetic Act;

(2) Any restrictions on the sales, distribution, advertising, and promotion of the new tobacco product that the applicant proposed to be included as part of a marketing granted order under section 910(c)(1)(B) of the Federal Food, Drug, and Cosmetic Act to support a finding by FDA that permitting the product to be marketed would be appropriate for the protection of the public health; and

(3) Requirements to establish and maintain records, and submit postmarket reports under section 910(f) of the Federal Food, Drug and Cosmetic Act in addition to those described in §

1114.41, including but not limited to information such as labeling, advertising, marketing, promotional materials, or marketing plans not previously submitted to FDA.

§ 1114.33 Issuance of a marketing denial order.

(a) *Issuance*. FDA will issue a marketing denial order if:

(1) Upon the basis of the information submitted as part of the application and any other information before FDA with respect to the new tobacco product, FDA finds that any of the grounds for denial listed in section 910(c)(2) of the Federal Food, Drug, and Cosmetic Act apply;

(2) The applicant does not permit an authorized FDA employee, at a reasonable time and in a reasonable manner, an opportunity to:

(i) Inspect the facilities and controls described in the application; or

(ii) Have access to, copy, and verify all records pertinent to the application,

which results in FDA finding that one or more of the grounds for denial specified in section 910(c)(2) of the Federal Food, Drug and Cosmetic Act apply.

(b) *Description of deficiencies*. The marketing denial order will, where practicable, identify measures to remove the application from deniable form.

§ 1114.35 Withdrawal of a marketing granted order.

(a) *Grounds for withdrawal*. FDA will withdraw a marketing granted order for a new tobacco product issued under this part if FDA determines that:

(1) Any of the grounds for withdrawal under section 910(d)(1) of the Federal Food, Drug, and Cosmetic Act apply; or

(2) Any postmarket requirement imposed by the marketing granted order or by this part has not been met, which results in FDA finding that one or more of the grounds for withdrawal specified in section 910(d)(1) of the Federal Food, Drug and Cosmetic Act apply.

(b) *Advice and other information*. (1) FDA may seek advice on scientific matters from any appropriate FDA advisory committee in deciding whether to withdraw a marketing granted order.

(2) FDA may use information other than that submitted by the applicant in deciding whether to withdraw a marketing granted order.

(c) *Informal hearing*. Prior to withdrawing a marketing granted order, FDA will offer the holder of the marketing granted order an opportunity for an informal hearing under part 16 of this chapter.

(d) *Order issuance*. If the applicant does not request a hearing or, if after the part 16 hearing is held, the Agency decides to proceed with the withdrawal, FDA will issue to the holder of the marketing granted order an order withdrawing the marketing granted order for the new tobacco product.

(e) *Public notice*. FDA will give the public notice of an order withdrawing a marketing granted order for a tobacco product and will announce the basis of the withdrawal.

§ 1114.37 Temporary suspension of a marketing granted order.

(a) FDA will temporarily suspend a marketing granted order if FDA determines that there is a reasonable probability that the continued distribution of such tobacco product would cause serious, adverse health consequences or death, that is greater than ordinarily caused by tobacco products on the market.

(b) Before temporarily suspending a marketing granted order of a tobacco product, FDA will offer the holder of the marketing granted order an opportunity for an informal hearing under part 16 of this chapter.

(c) If, after offering the holder of the marketing granted order an opportunity for a part 16 hearing, the Agency decides to proceed with the temporary suspension, FDA will issue an order temporarily suspending the marketing granted order for a tobacco product.

(d) After issuing an order temporarily suspending the marketing granted order, FDA will proceed expeditiously to withdraw the marketing granted order for the tobacco product.

Subpart D--Postmarket Requirements

§ 1114.39 Postmarket changes.

A marketing granted order authorizes the marketing of a new tobacco product in accordance with the terms of the order. Prior to the introduction or delivery for introduction into interstate commerce of a new tobacco product that results from modification(s) to the product, an applicant must submit a new PMTA under § 1114.7 or a supplemental PMTA under § 1114.15 and obtain a marketing granted order for the new tobacco product, unless the new tobacco product can be legally marketed through another premarket pathway.

§ 1114.41 Reporting requirements.

(a) *Required reports*. Each applicant that receives a marketing granted order must submit to FDA all information required by the terms of the marketing granted order and by this section as described below. Each postmarket report must be well-organized, legible, and written in English. Documents that have been translated from another language into English (e.g., original study documents written in a language other than English) must be accompanied by the original language version of the document, a signed statement by an authorized representative of the manufacturer certifying that the English language translation is complete and accurate, and a brief statement of the qualifications of the person that made the translation.

(1) *Periodic reports*. Each applicant must submit a periodic report to the Center for Tobacco Products (CTP) within 60 calendar days of the reporting dates specified in the applicant's marketing granted order for the life of the order and as may be required for the submission of a supplemental PMTA under § 1114.15. The report must include the following:

(i) A cover letter that contains the PMTA STN, tobacco product name(s) (including the original name described in the PMTA if different), company name, date of report, and reporting period;

(ii) A description of all changes made to the manufacturing, facilities, or controls during the reporting period, including:

(A) A comparison of each change to what was described in the PMTA;

(B) The rationale for making each change and, if any, a listing of any associated changes; and

(C) The basis for concluding that each change does not result in a new tobacco product that is outside the scope of the marketing granted order and will not result in a finding that the marketing granted order must be withdrawn or temporarily suspended under section 910(d) of the Federal Food, Drug, and Cosmetic Act;

(iii) An inventory of ongoing and completed studies about the tobacco product conducted by, or on behalf of, the applicant that are within the scope of § 1114.7(k) and that have not been previously reported;

(iv) Full reports of information published or known to, or which should be reasonably known to, the applicant concerning scientific investigations and literature about the tobacco product that have not been previously reported, including significant findings from publications not previously reported;

(v) A summary and analysis of all serious and unexpected adverse experiences associated with the tobacco product that have been reported to the applicant or that the applicant is aware of, accompanied by a statement of any changes to the overall risk associated with the tobacco product, and a summary of any changes in the health risks, including the nature and frequency of the adverse experience, and potential risk factors;

(vi) A summary of sales and distribution of the tobacco product for the reporting period, to the extent that the applicant collects or receives such data, including:

(A) Total U.S. sales reported in dollars, units, and volume with breakdowns by U.S. census region, major retail markets, and channels in which the product is sold;

(B) The Universal Product Code that corresponds to the product(s) identified in the PMTA; and

(C) Demographic characteristics of product(s) purchasers, such as age, gender, race or ethnicity, geographic region, and tobacco use status;

(vii) A summary of the implementation and effectiveness of policies and procedures regarding verification of the age and identity of purchasers of the product; and

(viii) A summary of all formative consumer research studies conducted (if any), among any audiences, in the formation of new labeling, advertising, marketing, or promotional materials, not previously submitted, including qualitative and quantitative research studies used to determine message effectiveness, consumer knowledge, attitudes, beliefs, intentions and behaviors toward using the products, and including the findings or these studies and copies of the stimuli used in testing;

(xi) A summary of all consumer evaluation research studies conducted (if any), among any audiences, not previously submitted, to determine the effectiveness of labeling, advertising,

marketing, or promotional materials and shifts in consumer knowledge, attitudes, beliefs, intentions, and behaviors toward using the products, and including the findings of these studies and copies of the stimuli used in testing;

(xii) A summary of the creation and dissemination of the products' labeling, advertising, marketing, and promotional materials (if any), including a list of all entities involved and a description of their involvement, including a description of contractual agreements with such entities;

(xiii) Specimens of all labeling and descriptions of all labeling changes that have not been previously submitted under section 905(i) of the Federal Food, Drug, and Cosmetic Act, including the date the labeling was first disseminated and the date when dissemination was completely terminated;

(xiv) Full color copies of all advertising for the tobacco product that has not been previously submitted, and the original date the materials were first disseminated and the date when their dissemination was completely terminated;

(xv) A description of the implementation of all advertising and marketing plans, not previously submitted to FDA, by channel and by product, including strategic creative briefs and paid media plans, and the dollar amount(s) and flighting of such plans, by channel and by product, including a description of any of the following activities that an applicant may have engaged in:

(A) Use of competent and reliable data sources, methodologies, and technologies to establish, maintain, and monitor highly targeted advertising and marketing plans and media buys, including a list of all data sources used to target advertising and marketing plans and media buys;

(B) Targeting of specific group(s) by age-range(s), including young adults, ages 21 to 24, and other demographic or psychographic characteristics that reflect the intended target audience, including the source of such data;

(C) With respect to individuals below the minimum age of sale, actions taken to restrict access to the products and exposure to the products' labeling, advertising, marketing, or promotion, or other consumer-directed activities;

(D) Use of owned, earned, shared, or paid media to create labeling for, advertise, market, or promote the product;

(E) Use of partners, influencers, bloggers, or brand ambassadors to create labeling for, advertise, market, or promote the product;

(F) Consumer engagements conducted by the applicant, on its behalf, or at its direction, including events at which the products were demonstrated and how access was restricted to individuals at or above the minimum age of sale;

(G) Use of public-relations or other communications outreach to create labeling for, advertise, market, or promote the products;

(xvi) A summary of media tracking and optimization, by channel, by product, and by audience demographics (e.g., age, gender, race/ethnicity, geographic region), including a summary of any real-time digital media monitoring and including a summary of implementation of any corrective and preventive measures to identify, correct, and prevent delivery of advertising to individuals below the minimum age of sale, not previously submitted;

(xvii) An analysis of the actual delivery of advertising impressions, by channel, by product, and by audience demographics, that have not been previously submitted, and verified

against post-launch delivery-verification reports submitted to the applicant from an accredited source, where applicable;

(xviii) Additional information required to be reported under the terms of a marketing granted order (if applicable); and

(xix) An overall assessment of how the tobacco product continues to be appropriate for the protection of the public health.

(2) *Serious and unexpected adverse experience reporting*. The applicant must report all serious and unexpected adverse experiences associated with the tobacco product that have been reported to the applicant or that the applicant is aware of to CTP's Office of Science through the Health and Human Services' Safety Reporting Portal or in another manner designated by FDA (if applicable) within 15 calendar days after the report is received by the applicant.

(b) *FDA review of postmarket reports*. (1) As part of its review of a postmarket report, FDA may require the applicant to submit additional information to enable it to determine whether a change results in a new tobacco product, or to facilitate a determination of whether there are or may be grounds to withdraw or temporarily suspend the marketing granted order.

(2) FDA may notify an applicant that FDA has determined that a change described in a periodic report made under this section results in a new tobacco product outside the scope of the marketing granted order, requiring the submission of a new PMTA under § 1114.7 or a supplemental PMTA under § 1114.15 and issuance of a marketing granted order if the applicant seeks to market the new tobacco product, unless the new tobacco product can be legally marketed through a different premarket pathway.

Subpart E--Miscellaneous

§ 1114.45 Record retention.

(a) *Record retention by the applicant*. (1) Each applicant that receives a marketing granted order must maintain all records necessary to facilitate a determination of whether there are or may be grounds to withdraw or temporarily suspend the marketing granted order, including records related to both the application and postmarket reports, and ensure that such records remain readily available to the Agency upon request (including where records are maintained by a third party on an applicant's behalf). These records include, but are not limited to:

(i) All documents submitted to FDA as part of an application, periodic postmarket reports, and adverse experience reports;

(ii) All documentation demonstrating whether each:

(A) Nonclinical laboratory study was conducted in accordance with good laboratory practices that support the reliability of the results, such as the records described in part 58 of this chapter; and

(B) Clinical investigator has any financial conflicts of interest that may be a source of bias, such as the documentation described in part 54 of this chapter;

(iii) All other documents generated during the course of a study necessary to substantiate the study results, including:

(A) Communications related to the investigation between the investigator and the sponsor, the monitor, or FDA; and

(B) All source data for human subject and nonclinical investigations included in the application and postmarket reports, including records of each study subject's case history and exposure to tobacco products used in the investigation, including case report forms, progress notes, hospital records, clinical charts, X-rays, lab reports, and subject diaries; and

(iv) A list of each complaint, and a summary and analysis of all complaints, associated with the tobacco product reported to the applicant;

(2) These records must be legible, in the English language, and available for inspection and copying by officers or employees duly designated by the Secretary. Documents that have been translated from another language into English (e.g., original study documents written in a language other than English) must be accompanied by the original language version of the document, a signed statement by an authorized representative of the manufacturer certifying that the English language translation is complete and accurate, and a brief statement of the qualifications of the person that made the translation.

(3) All records must be retained as follows:

(i) Records related to and including the PMTA must be retained for a period of at least 4 years from the date that the marketing granted order is issued.

(ii) Records related to postmarket reports, including both periodic and adverse experience reports, must be retained for a period of at least 4 years from the date the report was submitted to FDA or until FDA inspects the records, whichever occurs sooner.

(b) *Record retention by FDA*. FDA will retain information submitted to it in accordance with Federal Agency Records schedules and will provide a copy to persons to whom such information may legally be disclosed on request under the fee schedule in FDA's public information regulations in § 20.45 of this chapter.

§ 1114.47 Confidentiality.

(a) *General*. FDA will determine the public availability of any part of an application and other content related to such an application, including all data and information submitted with or incorporated by reference in the application, under this section and part 20 of this chapter.

(b) *Confidentiality of data and information prior to an order*. Prior to issuing an order under this part:

(1) FDA will not publicly disclose the existence of an application unless:

(i) The applicant has publicly disclosed or acknowledged (as such disclosure is defined in § 20.81 of this chapter), or has authorized FDA in writing to publicly disclose or acknowledge, that the applicant has submitted an application to FDA; or

(ii) FDA refers the application to TPSAC.

(2) Except as described in paragraph (b)(4) of this section, FDA will not disclose the existence or contents of an FDA communication with an applicant regarding its application except to the extent that the applicant has publicly disclosed or acknowledged, or authorized FDA in writing to publicly disclose or acknowledge, the existence or contents of that particular FDA communication.

(3) Except as described in paragraph (b)(4) of this section, FDA will not disclose the existence or contents of information contained in an application unless the applicant has publicly disclosed or acknowledged, or authorized FDA in writing to publicly disclose or acknowledge, the existence or contents of that particular information. If the applicant has publicly disclosed or acknowledged, or authorized FDA in writing to publicly disclose or acknowledge, the existence or contents of that particular information contained in an application, FDA may disclose the existence or contents of that particular information.

(4) If FDA refers an application to TPSAC, the contents of the application will be available for public disclosure, except information that is exempt from disclosure under part 20 of this chapter.

(c) *Disclosure of data and information after issuance of a marketing granted order*. After FDA issues a marketing granted order, it may make the following information related to the application and order available for public disclosure upon request or at FDA's own initiative, including information from amendments to the application and FDA's reviews of the application:

(1) All data previously disclosed to the public, as such disclosure is defined in § 20.81 of this chapter;

(2) Any protocol for a test or study, unless it is shown to fall within the exemption established for trade secrets and confidential commercial information in § 20.61 of this chapter;

(3) Information and data submitted to demonstrate that the new tobacco product is appropriate for the protection of public health, unless the information is shown to fall within the exemptions established in § 20.61 of this chapter for trade secrets and confidential commercial information, or in § 20.63 of this chapter for personal privacy;

(4) Correspondence between FDA and the applicant, including any requests FDA made for additional information and responses to such requests, and all written summaries of oral discussions between FDA and the applicant, unless it is shown to fall within the exemptions in § 20.61 of this chapter for trade secrets and confidential commercial information, or in § 20.63 of this chapter for personal privacy;

(5) In accordance with § 25.51(b) of this chapter, the environmental assessment or, if applicable, the claim for categorical exclusion from the requirement to submit an environmental assessment under part 25 of this chapter; and

(6) Information and data contained in postmarket reports submitted to FDA, unless the information is shown to fall within the exemptions established in § 20.61 of this chapter for trade

secrets and confidential commercial information, or in § 20.63 of this chapter for personal privacy

(d) *Disclosure of data and information after the issuance of a marketing denial order*. After FDA issues a marketing denial order, FDA may make certain information related to the application and the order available for public disclosure upon request or at FDA's own initiative unless the information is otherwise exempt from disclosure under part 20 of this chapter. Information FDA may disclose includes, but is not limited to the tobacco product category (e.g., cigarette), tobacco product subcategory (e.g., filtered, combusted cigarette), package size, product quantity, characterizing flavor, and the basis for the marketing denial order.

§ 1114.49 Electronic submission.

(a) *Electronic format requirement*. Applicants submitting any documents to the Agency under this part must provide all required information to FDA using the Agency's electronic system, except as provided in paragraph (b) of this section. The application and all supporting information must be submitted in an electronic format that FDA can process, review, and archive.

(b) *Waivers from electronic format requirement*. An applicant may submit a written request, that is legible and in English, to the Center for Tobacco Products asking that FDA waive the requirement for electronic format and content. Waivers will be granted if use of electronic means is not reasonable for the applicant. To request a waiver, applicants can send the written request to the address included on our website (www.fda.gov/tobacco-products). The request must include the following information:

(1) The name and address of the applicant, a list of individuals authorized by the applicant to serve as the contact person and contact information. If the applicant has submitted a

PMTA previously, the regulatory correspondence should also include any identifying information about the previous submission.

(2) A statement that creation and/or submission of information in electronic format is not reasonable for the applicant, and an explanation of why creation and/or submission in electronic format is not reasonable. This statement must be signed by the applicant or by a representative who is authorized to make the declaration on behalf of the applicant.

(c) *Paper submission*. An applicant who has obtained a waiver from filing electronically must send a written application through the Document Control Center to the address provided in the FDA documentation granting the waiver.

Dated: January 13, 2021.

Alex M. Azar II,
Secretary,
Department of Health and Human Services.

Dated: January 11, 2021.

Stephen M. Hahn,
Commissioner of Food and Drugs.

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