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: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is issuing a proposed rule that would set forth requirements for premarket tobacco product applications (PMTAs) and would require manufacturers to maintain records establishing that their tobacco products are legally marketed. The proposed rule would help to ensure that PMTAs contain sufficient information for FDA to determine whether a marketing order should be issued for a new tobacco product, including detailed information regarding the physical aspects of a tobacco product, as well as full reports of information to demonstrate the scope of, and details regarding, investigations that may show the potential health risks of the product. The proposed rule would codify the general procedures FDA would follow when evaluating PMTAs, including application acceptance, application filing, and inspections, and would also create postmarket reporting requirements for applicants that receive marketing orders. The proposed rule would allow for the submission of PMTAs in alternative formats in certain instances to reduce the burden of submitting a PMTA for modifications to a product that previously received a PMTA marketing order or resubmitting a PMTA to address deficiencies specified in a no marketing order. The proposed rule would also require tobacco product manufacturers to keep records regarding the legal marketing of certain tobacco products without a PMTA, such as documents showing that a tobacco product is not required to undergo premarket review or has received premarket authorization.

DATES: Submit either electronic or written comments on the proposed rule by November 25, 2019.

ADDRESSES: You may submit comments as follows:

Electronic Submissions

Submit electronic comments in the following way:

- *Federal eRulemaking Portal: https://www.regulations.gov.* Follow the instructions for submitting comments. Comments submitted electronically, including attachments, to *https://www.regulations.gov* will be posted to the docket unchanged. Because your comment will be made public, you are solely responsible for ensuring that your comment does not include any confidential information that you or a third party may not wish to be posted, such as medical information, your or anyone else's Social Security number, or confidential business information, such as a manufacturing process. Please note that if you include your name, contact information, or other information that identifies you in the body of your comments, that information will be posted on *https://www.regulations.gov.*
- If you want to submit a comment with confidential information that you do not wish to be made available to the public, submit the comment as a written/paper submission and in the manner detailed (see ''Written/Paper Submissions'' and ''Instructions'').

Written/Paper Submissions

Submit written/paper submissions as follows:

- *Mail/Hand Delivery/Courier (for written/paper submissions):* Dockets Management Staff (HFA–305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.
- For written/paper comments submitted to the Dockets Management Staff, FDA will post your comment, as well as any attachments, except for information submitted, marked and identified, as confidential, if submitted as detailed in ''Instructions.''

Instructions: All submissions received must include the Docket No. FDA–2019–N–2854 for ''Premarket Tobacco Product Applications and Recordkeeping Requirements.'' Received comments will be placed in the docket and, except for those submitted as ''Confidential Submissions,'' publicly viewable at *https://www.regulations.gov* or at the Dockets Management Staff between 9 a.m. and 4 p.m., Monday through Friday.

- Confidential Submissions—To submit a comment with confidential information that you do not wish to be made publicly available, submit your comments only as a written/paper submission. You should submit two copies total. One copy will include the information you claim to be confidential with a heading or cover note that states ''THIS DOCUMENT CONTAINS CONFIDENTIAL INFORMATION.'' The Agency will review this copy, including the claimed confidential information, in its consideration of comments. The second copy, which will have the claimed confidential information redacted/blacked out, will be available for public viewing and posted on *https://www.regulations.gov.* Submit both copies to the Dockets Management Staff. If you do not wish your name and contact information to be made publicly available, you can provide this information on the cover sheet and not in the body of your comments and you must identify this information as ''confidential.'' Any information marked as ''confidential'' will not be disclosed except in accordance with 21 CFR 10.20 and other applicable disclosure law. For more information about FDA's posting of comments to public dockets, see 80 FR 56469, September 18, 2015, or access the information at: *https://www.fda.gov/regulatory-information/dockets-management.*

Docket: For access to the docket to read background documents or the electronic and written/paper comments received, go to *https://www.regulations.gov* and insert the docket number, found in brackets in the heading of this document, into the ''Search'' box and follow the prompts and/or go to the Dockets Management Staff, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.

Submit comments on information collection issues to the Office of Management and Budget in the following ways: Fax to the Office of Information and Regulatory Affairs, OMB, Attn: FDA Desk Officer, Fax: 202–395–7285, or email to *oira_submission@omb.eop.gov.* All comments should be identified with the title, ''Premarket Tobacco Product Applications and Recordkeeping Requirements.''

FOR FURTHER INFORMATION CONTACT: Paul Hart or Samantha Loh Collado at the Office of Regulations, Center for Tobacco Products (CTP), Food and Drug Administration, Document Control Center, 10903 New Hampshire Ave., Bldg. 71, Rm. G335, Silver Spring, MD 20993, 877–287–1373, *AskCTP@fda.hhs.gov.*

SUPPLEMENTARY INFORMATION:

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Executive Summary

A. Purpose of the Regulatory Action

This proposed rule would interpret and set forth requirements related to the content and format of PMTAs, the procedure by which FDA would review PMTAs, and the maintenance of records regarding the legal marketing of certain tobacco products without PMTAs. The proposed content and format requirements for PMTAs would assist FDA in completing initial, procedural reviews of applications, which include a determination of whether an application has sufficient information for FDA to initiate a substantive review of the PMTA. These content requirements would require 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 proposing to require 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.

FDA is basing this proposed rule on the experience the Agency has gained 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. FDA has received thousands of premarket applications that range widely in the level of detail they contain. For example, some have very little of the information that is necessary for FDA to complete its statutorily required review, while other applications are more detailed and provide the necessary sufficient supporting information. This experience has been helpful in developing the proposed rule, which describes the information FDA is proposing that an applicant must include in a PMTA for FDA to be able to complete a substantive review of an application.

Although FDA has conducted acceptance and filing reviews of hundreds of PMTAs, it is still gaining experience in applying the statutory authorization standard to PMTAs because few have contained sufficient information to reach substantive review. The main focus of the proposed rule's content requirements is the threshold amount of information necessary for application filing, rather than every piece of information necessary to receive a marketing order both because FDA is still gaining experience in applying the authorization standard to PMTAs and because at this time, FDA believes applicants have some flexibility in the types of scientific information they can submit in order to provide sufficient health risk information to meet the standard.

The proposed rule also addresses issues such as the procedures by which FDA will review a PMTA, the retention of records related to the PMTA, confidentiality of application information, electronic submission of the PMTA and amendments, and postmarket reporting requirements. The proposed rule would also create requirements for the maintenance of records demonstrating the legal marketing status of grandfathered tobacco products and products that are exempt from the requirements of demonstrating substantial equivalence.

B. Legal Authority

This proposed 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

The proposed rule would create requirements for tobacco product manufacturers to maintain records regarding the legal marketing of grandfathered tobacco products and products that are exempt from the requirements of demonstrating substantial equivalence. This proposed rule would also set forth content and format requirements for PMTAs. Under the proposed rule, a PMTA must contain information necessary for FDA to determine whether it should issue a marketing 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: There is a showing that marketing of the new tobacco product would be appropriate for the protection of the public health; 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)); the product labeling is not false or misleading in any particular; and 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 proposed rule would also allow applicants to submit a supplemental PMTA or a resubmission, which would reduce the burden of submitting and reviewing an application. A supplemental PMTA could 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 PMTA marketing order. A resubmission could be submitted to address application deficiencies following the issuance of a no marketing order. The proposed rule would also require the submission of postmarket reports by applicants that receive a PMTA marketing order.

In addition, the proposed rule would explain how an applicant could amend or withdraw a PMTA and how an applicant may transfer ownership of a PMTA to a new owner. The proposed rule also addresses FDA communications with applicants and identifies the actions that FDA may take after receipt of a PMTA. The proposed rule addresses when FDA may withdraw a PMTA marketing order and explains how long an applicant would be required to maintain the records related to the PMTA and postmarket reports. The proposed rule would also set forth FDA's disclosure procedures regarding PMTAs and require the electronic submission of PMTAs, unless the applicant requests and obtains a waiver.

D. Costs and Benefits

If finalized, the proposed rule would create cost savings for firms and for FDA by reducing the number of follow-on submissions for PMTAs (*i.e.,* additional PMTAs submitted for the same product(s) after FDA refuses to accept or file, or issues a no marketing order in response to, an initial PMTA). The proposed rule would also create cost savings for FDA by reducing the cost of review, reducing the number of deficiency letters we would issue during substantive scientific review, and eliminating the need to process unnecessary data. We estimate that average annualized benefits over 20 years would equal $5.54 million at a 7 percent discount rate and $5.44 million at a 3 percent discount rate.

If finalized, the proposed rule would create costs for firms and for FDA by increasing the number of complete PMTA submissions for deemed and originally regulated tobacco products. Moreover, because this is the first regulation to account for the costs of the PMTA requirements for originally regulated products, we also include the costs to submit and review PMTAs for these tobacco products; we already included the costs to submit and review PMTAs for deemed tobacco products in the final regulatory impact analysis for the final rule entitled ''Deeming Tobacco Products To Be Subject to the Food, Drug, and Cosmetic Act, as Amended by the Family Smoking Prevention and Tobacco Control Act; Regulations Restricting the Sale and Distribution of Tobacco Products and Required Warning Statements for Tobacco Product Packages and Advertisements'' (Deeming Rule), which was published in the **Federal Register** of May 10, 2016 (81 FR 28973). Firms would incur costs to maintain and submit postmarket reports, and we would incur costs to review postmarket reports. Finally, firms would incur costs to read and understand the rule and costs to maintain records for some grandfathered products. We estimate that average annualized costs over 20 years would equal $7.05 million at a 7 percent discount rate and $6.76 million at a 3 percent discount rate.

Table of Abbreviations/Commonly Used Acronyms

Abbreviation/ acronym	What it means
FDA	Food and Drug Administration.
CTP	Center for Tobacco Products.
FD&C Act	Federal Food, Drug, and Cosmetic Act.
EA	Environmental assessment.
ENDS	Electronic nicotine delivery systems.
FEI	Facility Establishment Identifier.
APPH	Appropriate for the protection of public health.
CAS	Chemical Abstracts Service.
FOIA	Freedom of Information Act.
GLP	Good laboratory practice.
HPHC	Harmful and potentially harmful constituent.
IUPAC	International Union of Pure and Applied Chemistry.
ICH	International Council for Harmonization.
IRB	Institutional Review Board.
ISO	International Organization for Standardization.
MRTPA	Modified risk tobacco product application.
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.
PDU	Power delivery unit.
PG/VG	Propylene glycol/vegetable glycerin.
PMTA	Premarket tobacco product application.
PRIA	Preliminary regulatory impact analysis.
RYO	Roll-your-own.
SE	Substantial equivalence.
The Secretary	The Secretary of Health and Human Services.
STN	Submission tracking number.
TPMF	Tobacco product master file.
TSNA	Tobacco specific nitrosamine.
TPSAC	Tobacco products scientific advisory committee.
UNII	Unique Ingredients Identifier.

I. Background

The Family Smoking Prevention and Tobacco Control Act (Tobacco Control Act) 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 before a new tobacco product may be introduced or delivered for introduction into interstate commerce, it must undergo premarket review by FDA. 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 [1] for a new tobacco product:

- Submission of a PMTA under section 910(b);

[1] As described in the Preliminary Economic Analysis of Impacts (Ref. 118), we expect that manufacturers will submit PMTAs primarily for ENDS and will generally submit SE Reports or exemption requests for cigars and other deemed products. We also expect that a number of cigars and pipe tobacco products are grandfathered tobacco products (see section III of this document) not subject to premarket review. This is consistent with FDA's experience so far in issuing SE marketing orders for cigars and determining cigars to be grandfathered tobacco products, and is also consistent with the regulatory impact analysis for the Deeming Rule (''Deeming Tobacco Products To Be Subject to the Food, Drug, and Cosmetic Act, as Amended by the Family Smoking Prevention and Tobacco Control Act; Regulations Restricting the Sale and Distribution of Tobacco Products and Required Warning Statements for Tobacco Product Packages and Advertisements,'' (81 FR 28973) (May 10, 2016)).

- Submission of an application 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); [2] 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 PMTA or SE marketing order or a finding of exemption from substantial equivalence, 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.

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 on two sets of bundled PMTAs, which are single submissions containing PMTAs for a number of similar or related tobacco products (totaling 12 applications), all of which received marketing orders. To assist manufacturers in preparing PMTAs, FDA has issued guidance, conducted webinars, met with manufacturers, hosted a public meeting regarding premarket submissions, and posted the technical project lead reviews (which describe the reviews completed on specific PMTAs) and marketing orders issued to date. If finalized, the proposed rule would interpret and set forth requirements related to the PMTA premarket pathway and outline the information needed for FDA to determine whether it will issue a marketing order under the pathway.

FDA has also processed hundreds of exemption requests and thousands of voluntarily-submitted grandfathered status reviews. The proposed rule would state the records that a company would be required to keep regarding the legal marketing of its tobacco product.

II. Legal Authority

As described in the following paragraphs, FDA is proposing 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 proposing recordkeeping requirements regarding the legal marketing of grandfathered 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 would be established by this proposed rule be severable and that the invalidation of any provision of this proposed 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 PMTA marketing 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.[3] 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)–(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 marketing the 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.

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 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 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.

[2] 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 an applicant 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.

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

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. In addition, section 701(a) of the FD&C Act 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. Proposed Regulations for the Maintenance of Records Demonstrating That a Tobacco Product Was Commercially Marketed in the United States as of February 15, 2007 (Part 1100, Proposed Subpart C)

The proposed rule would add subpart C regarding records to Part 1100 of subchapter K of title 21.

A. Purpose and Scope (Proposed § 1100.200)

Proposed § 1100.200 states that subpart C of part 1100 would establish requirements for the maintenance of records by tobacco product manufacturers who introduce a grandfathered tobacco product, or deliver it for introduction, into interstate commerce. FDA is proposing requirements for tobacco product manufacturers to maintain records regarding the legal marketing of their tobacco products under the authority of section 909 of the FD&C Act. 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). The records that would be required under this subpart would demonstrate that a tobacco product is grandfathered and therefore not required by section 910(a) to have premarket review and are not adulterated if marketed without an FDA order. FDA is basing these requirements on its experience gained by performing thousands of grandfathered status reviews conducted during its review of substantial equivalence reports and at manufacturers' voluntary requests. In the absence of these required records, manufacturers do not always maintain sufficient documentation to demonstrate whether their tobacco product is grandfathered. The records that would be required under this rule would allow FDA to more quickly and efficiently determine whether a tobacco product is grandfathered.

B. Definitions (Proposed § 1100.202)

Proposed § 1100.202 sets forth the meaning of terms as they apply to proposed part 1100 and includes the following definitions from the FD&C Act:

1. Tobacco Product

As defined in section 201(rr)(1) of the FD&C Act (21 U.S.C. 321(rr)(1)), the term ''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 the 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 FD&C Act is a drug (section 201(g)(1)), a device (section 201(h)), or a combination product (section 503(g) (21 U.S.C. 353(g))).

2. Tobacco Product Manufacturer

As defined in section 900(20) of the FD&C Act (21 U.S.C. 387(20)), the term ''tobacco product manufacturer'' means any person, including a repacker or relabeler, who: (1) Manufacturers, 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. Manufacturing activities typically do not include the activities of de-stemming, drying, or packaging tobacco leaves; mechanically removing foreign material from tobacco leaves; and humidifying tobacco leaves with nothing other than potable water in the form of steam or mist. For the purposes of this definition ''finished tobacco product'' would mean a tobacco product, including all components and parts, sealed in final packaging (*e.g.,* filters or filter tubes sold separately to consumers or as part of kits).

In addition, FDA proposes the following definitions:

3. Commercially Marketed

FDA proposes to define ''commercially marketed'' to mean the offering of a tobacco product for sale to consumers in all or parts of the United States. Factors FDA may consider include advertising or other means used to communicate that the tobacco product is available for purchase. Tobacco products that are exclusively in a test market are not commercially marketed.

4. Grandfathered Tobacco Product

FDA proposes to define a ''grandfathered tobacco product'' to mean a tobacco product that was commercially marketed in the United States on February 15, 2007. This term does not include tobacco products exclusively marketed in a test market as of that date. FDA interprets the statutory phrase ''as of February 15, 2007,'' as meaning that the tobacco product was commercially marketed in the United States ''on February 15, 2007,'' and this interpretation is based on a plain language reading of the term ''as of.'' The proposed definition reflects this interpretation, which has been included as part of previously issued regulations and guidance.[4] This definition is also in the proposed rule, ''Content and Format of Substantial Equivalence Reports; Food and Drug Administration Actions on Substantial Equivalence Reports'' (SE Proposed Rule), which was published in the **Federal Register** of April 2, 2019 (84 FR 12740).[5] A grandfathered tobacco product is not subject to the premarket requirements of section 910 of the FD&C Act.

A tobacco product that the applicant test marketed after February 15, 2007, is not a grandfathered tobacco product because it was not commercially marketed in the United States as of February 15, 2007 and, therefore, it is a new tobacco product subject to premarket review under section 910(a) of the FD&C Act.

As described in the SE Proposed Rule and in the definition of ''new tobacco product'' proposed in 21 CFR part 1114 below, FDA is considering whether to add the following definition of test marketing: ''test marketing'' means distributing or offering for sale (which

[4] See the final rule ''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 ''Establishing That a Tobacco Product Was Commercially Marketed in the United States as of February 15, 2007'' (Grandfathered Tobacco Product Guidance) (79 FR 58358, September 29, 2014), available at *https://www.fda.gov/tobacco-products/rules-regulations-and-guidance/guidance.*

[5] FDA intends the PMTA provisions in this proposed rule to be consistent with the SE Proposed Rule wherever it is appropriate. FDA intends to harmonize any differences between definitions in these proposed rules when issuing final rules.

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:

- Offered in a limited number of regions;
- Offered for a limited time; or
- Offered to a chosen set of the population or specific demographic group.

C. Recordkeeping Requirements (Proposed § 1100.204)

1. Required Records

Consistent with the authority to require recordkeeping under section 909 of the FD&C Act, proposed § 1100.204(a) would require any tobacco product manufacturer that introduces a grandfathered 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 proposed requirement would ensure that records are available to FDA during an inspection. The proposed rule would 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. These records may include items such as:

(1) Dated copies of advertisements;
(2) Dated catalog pages;
(3) Dated promotional material;
(4) Dated trade publications;
(5) Dated bills of lading;
(6) Dated freight bills;
(7) Dated waybills;
(8) Dated invoices;
(9) Dated purchase orders;
(10) Dated customer receipts;
(11) Dated manufacturing documents;
(12) Dated distributor or retailer inventory lists; or
(13) Any other dated document that demonstrates that the tobacco product was commercially marketed (not exclusively in test markets) in the United States as of February 15, 2007. For additional information on records related to grandfathered tobacco products, see the Grandfathered Tobacco Product Guidance.

2. Record Maintenance

Proposed § 1100.204(b) would require that all records required to be 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. FDA is also proposing 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.

3. Record Retention

Proposed § 1100.204(c) would require that the records and documents demonstrating that the tobacco product was commercially marketed be retained for a period of 4 years from the date that either FDA makes a grandfather 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 as a means to help ensure that the records would be available for at least one biennial FDA inspection under section 704 and 905(g) of the FD&C Act. FDA's biennial inspections under section 905(g) 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 would allow FDA to verify the grandfathered 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 would still need to retain the records to allow FDA to verify the grandfathered status of the product when they resume marketing the product. Additionally, manufacturers might also want to retain records for longer than 4 years to help establish their product is grandfathered for use as a predicate product in an SE Report.

IV. Proposed Regulations for the Maintenance of Records Relating to Exemptions From the Requirements of Demonstrating Substantial Equivalence (Proposed § 1107.3)

The proposed rule would add § 1107.3 to part 1107 of subchapter K of title 21. Proposed § 1107.3 would establish recordkeeping requirements related to tobacco products that are exempt from the requirements of demonstrating substantial equivalence 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, proposed § 1107.3 would require 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 proposed rule would require 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

Proposed § 1107.3(a) would define ''grandfathered tobacco product'' as a tobacco product that was commercially marketed in the United States on February 15, 2007. The term would not include a tobacco product exclusively in test markets as of that date. 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,'' this interpretation is based on a plain language reading of the term ''as of.'' [6]

B. Record Maintenance

The proposed rule would require applicants to maintain all documents that support their abbreviated report, which includes the documents listed in proposed § 1107.3(b)(1). The proposed rule would not require an applicant to create new or additional records; rather, it would require 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

[6] *Id.*

documents an applicant would be required to create by other regulatory or statutory sections such as the submission of exemption requests under § 1107.1, PMTAs under section 910(b) of the FD&C Act (or proposed part 1114 when finalized), SE Reports under section 905(j) FD&C Act, and tobacco product manufacturing requirements issued under section 906(e) of the FD&C Act. The records an applicant would be 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 would include, for example, items such as the types of information described in proposed § 1114.7(i) as described in section VII.B.;
- 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 proposed § 1114.7(j) as described in section VII.B.;
- Product labeling. As defined in section 201(m) of the FD&C Act, ''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. This would include, for example, specimens of all labeling for the new tobacco product, including labels, inserts, onserts, instructions, and other accompanying information. The specimens of labeling would 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;
- 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 proposed § 1107.3(b)(1), proposed § 1107.3(b)(2) through (b)(4) would 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 would need to maintain records demonstrating that the modification is being made to either a grandfathered 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 grandfathered tobacco product, proposed § 1107.3(b)(2) would require 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 marketing order from FDA (*i.e.,* an order from FDA authorizing the marketing of the new tobacco product after review of an SE Report or PMTA), proposed § 1107.3(b)(3) would require applicants to maintain a copy of the exemption or marketing 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 consistent with section 910(a)(2)(B) of the FD&C Act for which FDA has not issued an SE marketing order, an applicant would be required to 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

Proposed § 1107.3(c) would require 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 is also proposing that documents that have been translated from another language into English must 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 would help FDA ensure that the English language translations of documents are complete and accurately reflect the content of the original documents.

D. Record Retention

Proposed § 1107.3(d) would require the records described in § 1107.3 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 would be available for at least one biennial FDA inspection under section 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.

V. Proposed Regulations for Premarket Tobacco Product Applications (Proposed Part 1114)

The proposed rule would add part 1114 to subchapter K of Title 21. The requirements set forth in this proposed part would apply to PMTAs for new tobacco products. Proposed subpart A sets out the scope and definitions that apply to this proposed part. Proposed subpart B sets out the proposed 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. Proposed subpart C describes how FDA proposes to review and act on applications, including provisions for withdrawal and temporary suspension of orders. Proposed subpart D describes proposed postmarket restrictions, reporting requirements, and inactivation and reactivation of a marketing order. Proposed subpart E sets out proposed miscellaneous requirements such as record retention, confidentiality, and electronic submissions.

VI. General (Proposed Part 1114, Subpart A)

A. Scope (Proposed § 1114.1)

Proposed § 1114.1 describes the scope of proposed part 1114 and its application to the submission, review, and postmarket requirements related to PMTAs. Proposed § 1114.1 provides that proposed part 1114 would not apply to MRTPAs, except instances where a single application is submitted under section 911(l)(4) of the FD&C Act instead of a separate PMTA and MRTPA

for the product. Under the proposed rule, an applicant that submits a single application seeking both a PMTA marketing order and a modified risk order under section 911(g) would need to meet the requirements of both part 1114 and section 911 of the FD&C Act. This section also notes that references in the proposed rule to regulatory sections of the Code of Federal Regulations (CFR) are to chapter I of title 21, unless otherwise noted. This means that any CFR reference that begins with ''part'' 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).

B. Definitions (Proposed § 1114.3)

Proposed § 1114.3 sets forth the meaning of terms as they apply to proposed part 1114. Proposed § 1114.3 includes the following definitions from the FD&C Act:

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, 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 proposed § 1114.3.

4. Label

As defined in section 201(k) of the FD&C Act (21 U.S.C. 321(k)), ''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.

Under the FD&C Act, and as reflected in the proposed 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, specifications that change characteristics (*e.g.,* a modification to a different tobacco cut size) would render a tobacco product new.

Manufacturers sometimes co-package tobacco products. 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. Examples include a carton of cigarette packs and a variety pack of three smokeless tins shrink-wrapped together where the cigarette packs and smokeless tins, respectively, could be legally marketed separately. However, if a manufacturer wishes to co-package two or more tobacco products (including their respective container closure systems), premarket review is required for any new tobacco product that the manufacturer intends to include in the co-package. An example includes shrink-wrapping grandfathered tobacco filler (in its unmodified container closure system) with new rolling papers; here premarket authorization would be required for the rolling papers. In addition, co-packaging two or more tobacco products within the same container closure system results in a new tobacco product, unless such co-packaged product is grandfathered. Examples include an RYO kit where rolling papers are placed inside the tin of tobacco filler, and shrink-wrapping together two soft-packs of cigarettes, neither of which had been individually shrink-wrapped prior to being co-packaged. FDA invites comment on approaches to its review of these types of PMTAs, including, where relevant, how co-packaging products impacts consumer use and behavior.

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'' can be considered to encompass 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) (finding that a change in product quantity results in a new tobacco product under the Tobacco Control Act). Consequently, a change in product quantity (*e.g.,* decreasing the weight of a smokeless package from 24 grams to 15 grams) results in a new tobacco product subject to premarket review since such a modification ''necessarily entails a change in the amount of the constituent ingredients and additives within the tobacco product, including nicotine'' (id. at 56).

FDA also interprets section 910(a)(1)(A) of the FD&C Act to mean

that a tobacco product marketed exclusively in test markets on February 15, 2007, is a new tobacco product that is subject to premarket review by FDA. A tobacco product that the applicant test marketed after February 15, 2007, is also a new tobacco product subject to premarket review under section 910(a) of the FD&C Act because it was not commercially marketed in the United States as of February 15, 2007.

Because the terms ''test marketing'' and ''commercially marketed'' are not interchangeable, FDA is considering whether it would be useful to applicants for the rule to expand on or further define the terms ''test marketing'' and ''commercially marketed.'' Specifically, as set forth in the description of proposed part 1100 and described in the SE Proposed Rule, FDA is 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:

- Offered in a limited number of regions;
- Offered for a limited time; or
- Offered to a chosen set of the population or specific demographic group.

As set forth in the description of proposed part 1100, FDA is considering whether to define ''commercially marketed'' to mean offering a tobacco product for sale to consumers in all or in parts of the United States. Factors FDA may consider include advertising or other means used to communicate that the tobacco product was available for purchase, including dated advertisements, dated catalog pages, dated promotional material, dated trade publications, dated bills of lading, dated freight bills, dated waybills, dated invoices, dated purchase orders, dated manufacturing documents, inventory lists, or any other document that demonstrates that the product was commercially marketed (other than exclusively in test markets) in the United States as of February 15, 2007. FDA invites comment on what evidence would be sufficient to demonstrate that a product was commercially marketed (other than in test markets) as of February 15, 2007.

FDA is inviting comments on: (1) Whether the rule should further expand on the interpretation or include definitions of these terms, (2) the substance of the definitions, if included, and (3) whether or not the approach described is adequate to protect the public health.

7. Package or Packaging

As defined in section 900(13) of the FD&C Act, the term ''package,'' also referred to in the proposed 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 proposed 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 characteristics of the 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.

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. Manufacturing activities typically do not include the activities of de-stemming, drying, or packaging tobacco leaves; mechanically removing foreign material from tobacco leaves; and humidifying tobacco leaves with nothing other than potable water in the form of steam or mist. A proposed definition for the term ''finished tobacco product'' is also included in the proposed rule.

In addition, FDA proposes the following definitions:

10. Accessory

FDA proposes to define ''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:

(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 product or

(ii) 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 and contained in the SE Proposed Rule. 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 proposes to define ''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.

12. Applicant

FDA proposes to define ''applicant'' as any person that submits a premarket tobacco product application to receive a marketing order for a new tobacco product.

13. Component or Part

FDA proposes to define ''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 proposed 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 proposed 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 proposed definition matches the definition in § 1100.3 and that was published in the SE Proposed Rule and FDA invites comments on this approach in the PMTA context.

14. Composition

FDA proposes to define ''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. This proposed definition matches the definition published in the SE Proposed Rule.

15. Constituent

FDA proposes to define ''constituent'' as any chemical or chemical compound in a tobacco product or in tobacco smoke or emission that is or potentially is inhaled, ingested, or absorbed into the body. Examples of constituents include harmful or potentially harmful constituents, total particulate matter, nicotine-free dry particulate matter, and water. A constituent also could include any other chemical or chemical compound contained in or produced by a tobacco product under conditions of use. This proposed definition matches the definition that was published in the SE Proposed Rule.

16. Container Closure System

FDA proposes to define ''container closure system'' as any packaging materials that are a component or part of the tobacco product. This proposed definition matches the definition published in the SE Proposed Rule.

Examples of what is typically a container closure system include the blister pack around a dissolvable tablet (in this example, if there is a box around a blister pack, the box is not considered a container closure system if it is not intended or reasonably expected to alter or affect the dissolvable tablet), the can that contains and protects a moist snuff product, and the plastic-wrapped hard pack or soft pack used to contain and protect cigarettes. A container closure system is a component or part of a tobacco product because of its potential to alter or affect the performance, composition, constituents, or other physical characteristics of the product.

In addition, considering a distinct subset of packaging (*i.e.,* container closure system) to be a component or part is consistent with the FD&C Act. For example, section 903(a)(2) of the FD&C Act describes when, under certain conditions, a tobacco product ''in package form'' is misbranded, thereby recognizing that at least some portion of the package is subsumed within the ''tobacco product'' (and the components and parts thereof). Similarly, the definition of ''additive'' in section 900(1) of the FD&C Act 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, further evinces Congress's understanding that packaging is not entirely separable from the tobacco product. Finally, 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.

According to the proposed definition above, packaging constitutes the container closure system if it is intended or reasonably expected to affect or alter the performance, composition, constituents, or characteristics of a tobacco product, even if it is also used to protect or contain the tobacco product. For example, packaging materials constitute the 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 (Ref. 1). Another example of this is when menthol or other ingredients are applied to the inner foil to become incorporated into the consumed product (Ref. 2). 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 also diffuse into snuff and affect its characteristics (Ref. 3). 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 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) (Refs. 4 and 5).

Treating a distinct subset of packaging as a component or part thus furthers the fundamental purpose of the Tobacco Control Act to protect the public health. This interpretation is also consistent with the broad definition of ''tobacco product,'' as well the definition of ''additive,'' which includes substances that may be reasonably expected to result, directly or indirectly, in it becoming a component or otherwise affecting the characteristics of any tobacco product—and not just substances that do *in fact* have such effects. This shows that Congress did not intend for FDA to be required to show that the container closure system did in fact alter or affect the tobacco product's performance, composition, constituents, or other characteristics. Indeed, if FDA were to adopt a narrow

construction of ''tobacco product'' to exclude these materials, it would impede the Agency's ability to evaluate whether authorizing the marketing of the tobacco product would be appropriate for the protection of the public health, thereby leaving the Agency unable to fully execute its mission to protect the public health.

17. Design

FDA proposes to define ''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 and matches the definition published in the SE Proposed Rule. Examples of design parameters include ventilation, paper porosity, filter efficiency, battery voltage and current operating range, and electrical heater coil resistance.

18. Finished Tobacco Product

FDA proposes to define ''finished tobacco product'' to mean a tobacco product, including all components and parts, sealed in final packaging (*e.g.,* filters or filter tubes sold separately to consumers or as part of kits, e-liquids sold separately or packaged with an e-cigarette). This proposed definition matches the definition published in the SE Proposed Rule.

19. Harmful or Potentially Harmful Constituent (HPHC)

FDA proposes to define ''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 proposed definition matches the definition published in the SE Proposed Rule.

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

20. Heating Source

FDA proposes to define ''heating source'' as the source of energy used to burn or heat the tobacco product. This proposed definition matches the definition published in the SE Proposed Rule. Examples of a heating source include a flame or a rechargeable battery.

21. Ingredient

FDA proposes to define ''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. This proposed definition matches the definition published in the SE Proposed Rule. 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.
- Products of acid-base reactions, such as removal of a proton from protonated nicotine to generate the basic form of nicotine (''free'' nicotine).

22. Line Data

FDA proposes to define ''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 proposing to require that an applicant submit line data rather than source data to allow for a more efficient review process. As described in proposed § 1114.45, applicants would be required to retain all source data in the event that FDA needs to inspect the data as part of its application review.

23. Material

FDA proposes to define ''material'' to mean an assembly of ingredients. Materials are assembled to form the tobacco product, or components or parts of tobacco product. This proposed definition matches the definition published in the SE Proposed Rule. For example, material would include 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.

24. Marketing Order

FDA proposes to define ''marketing 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.

25. No Marketing Order

FDA proposes to define ''no marketing 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.

26. Other Features

FDA proposes to define ''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. This proposed definition matches the definition published in the SE Proposed Rule. The definition would include: (a) 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 (b) any other product characteristics that relate to the chemical, biological, or physical properties of the tobacco product. Other features also would encompass 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.

27. Premarket Tobacco Product Application or PMTA

FDA proposes to define ''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.

28. Serious Adverse Experience

FDA proposes to define ''serious adverse experience'' to mean an adverse experience that results in any of the following outcomes:

(a) Death;

(b) a life-threatening condition or illness;

(c) inpatient hospitalization or prolongation of existing hospitalization;

(d) a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions (*e.g.,* seizures not that do not result in hospitalization, burns that result in damage to a limb or nerve damage);

(e) a congenital anomaly/birth defect; or

(f) 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.

29. Unexpected Adverse Experience

FDA proposes to define ''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:

(a) 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;

(b) 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

(c) the results of nonclinical investigations.

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

A. Application Submission (Proposed § 1114.5)

Proposed § 1114.5 explains that if an applicant seeks a marketing order under the PMTA pathway for its new tobacco product, it would be required to submit a PMTA to FDA and receive a marketing 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 proposed § 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 of proposed § 1114.7(e) in section VII.B.5. Submitting a complete application as part of an initial submission is important because, as explained in the discussion of proposed § 1114.27 in section VIII.B, FDA may refuse to accept or file an incomplete application for review.

B. Required Content and Format (Proposed § 1114.7)

1. General

Proposed § 1114.7(a) would require 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)); and
- Certification statement (as described in § 1114.7(l)).

As described in the discussion of proposed § 1114.27(a)(1) in section VIII.B, 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. As described in section VIII.B on proposed § 1114.27(b)(1), 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.

2. Format

Proposed § 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 (Ref. 6). Proposed § 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 proposing 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 proposed § 1114.49, FDA is proposing that the PMTA and all supporting documents must 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 would be permitted to obtain a waiver from the electronic filing requirement, in accordance with § 1114.49. FDA has provided information on our website about technical specifications, including electronic formats that would allow FDA to process, review, and archive the

application.[7] FDA intends to update this information as needed to accommodate changes in technology.

FDA is proposing 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 proposed § 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 submissions have not been in a static format, and thus, the pages reformat, renumber, rebullet, or re-date each time the document is accessed. Receiving applications with these issues affects our ability to cross-reference, share (internally), and efficiently evaluate information. Lastly, because 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*), proposed § 1114.7(b) would ensure that these files can be managed, opened, and read by the Agency for the duration of the retention period.

Finally, proposed § 1114.7(b)(2) would 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 (21 U.S.C. 387k). 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 master files, please consult the guidance for industry ''Tobacco Product Master Files.'' [8]

Applicants may also include content in a PMTA by cross-reference to a pending MRTPA for the same tobacco product.[9] FDA recommends that applicants seeking to market a new tobacco product that has not previously received marketing authorization as a modified risk tobacco product submit a single application under section 911(l)(4) of the FD&C Act (*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 only one application and include it in the other by cross-reference. This approach would prevent any transcription errors and would also 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 the proposed rule, except as described in subpart B, FDA would 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 would be required to include the full text of such information in its PMTA. FDA is proposing this restriction because cross-referencing 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. 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.

3. General Information

Proposed § 1114.7(c) lists the information that would be required to 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. The table, as set forth in proposed § 1114.7(c), would include requirements to submit general information related to electronic nicotine delivery systems (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 guidance ''Premarket Tobacco Product Applications for Electronic Nicotine Delivery Systems.''

The PMTA would be required to include the following information using the FDA-provided form (Ref. 6), as appropriate:

- Applicant name, address, and contact information;
- The name, address, and contact information for the authorized

[7] For more information on electronic submission, including electronic submission file formats and specification, please visit FDA's web page at: *https://www.fda.gov/industry/fda-esubmitter/using-esubmitter-prepare-tobacco-product-submissions.*

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

[9] 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 an order 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. Such an approach would 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.

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.

- 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 would include:
  - The manufacturer;
  - Product name(s), including the brand and subbrand (or other commercial name(s) used in commercial distribution);
  - Product category; product subcategory; and product properties, as provided by the tables in proposed § 1114.7(c). The applicant would select and provide the appropriate category, subcategory, and product properties for the new tobacco product. This product-specific information is required under sections 910(b)(1)(B) and (G) of the FD&C Act and the proposed rule would require its inclusion in the general information section 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 would be a required part of an application, see the discussion of proposed § 1114.7(i)(1) in section VII.B.9. It is important to note that for the characterizing flavor product property, the applicant would be required to state ''none'' if it does not consider the product to have a characterizing flavor. Applicants that have questions regarding how to describe their product's characterizing flavor are encouraged 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 proposed § 1114.27(a)(1), it would likely slow down the substantive review process.

- The type of PMTA. The applicant would be 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 submission tracking numbers (STNs), where applicable. The types of prior submissions may 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;
- Address and the Facility Establishment Identifier (FEI) number(s) of the establishment(s) involved in the manufacturer of the new tobacco product. This information would 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 would allow FDA to more quickly locate application content necessary to determine whether a PMTA should be accepted and filed for further review under proposed § 1114.27;
- A brief description of how permitting the marketing of the new tobacco product is expected to be appropriate for the protection of the public health (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
- 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.

4. Descriptive Information

Proposed § 1114.7(d) would require applicants to provide descriptive information in this section that outlines the major aspects of the new tobacco product, which is required to be submitted under sections 910(b)(1)(A), (D), and (G) of the FD&C Act. This information would include:

- 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 proposed rule would require 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. If there are previous or similar versions that are the subject of studies in the application or were marketed, the proposed rule would require the applicant to include a bibliography of all reports regarding the previous or similar version of the product, whether adverse or supportive. FDA would require 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;

- 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 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 would be required to explicitly state that it proposes no restrictions. As described in proposed § 1114.31, FDA will consider these proposed restrictions during its review of the PMTA and, where appropriate, include the restrictions in the marketing order for the product together with any additional restrictions FDA may require.

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. Proposed § 1114.7(e) would require 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 no marketing 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 is proposing to have applicants submit samples as required by FDA after acceptance of an application rather than as part of an initial submission. This would allow FDA to determine the need for samples, allow the samples to be tracked and identified as part of the correct application, and submitted to testing facilities that are adequately prepared to accept the samples (*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. As described in proposed § 1114.27, if required by FDA, product samples would 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.

6. Labeling and Marketing Plans

Proposed § 1114.7(f) of the FD&C Act would require that a PMTA contain specimens of labeling and 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. Proposed § 1114.7(f)(1) would elaborate on this requirement and require the application to contain specimens of all proposed labeling for the new tobacco product, including labels, inserts, onserts, instructions, and other accompanying information. The specimens of labeling would be 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.

As described in proposed § 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 proposed § 1114.7(k)(1)(iv).

b. *Marketing Plan.* Proposed § 1114.7(f)(2) would require a PMTA to contain a description of the applicant's marketing plans for the tobacco product that an applicant has developed by the time of submission and concerning at least the first year of marketing after an applicant receives a marketing order, including information relating to labeling, advertising, marketing, promotion, and sales and distribution of its new tobacco product. FDA is proposing to require the submission of marketing plans as part of a PMTA under its authority in section 910(b)(1)(G) of the FD&C Act to require other information relevant to the subject matter of the application because marketing plans can provide important information regarding whether permitting the marketing of the new tobacco product would be APPH. Specifically, marketing plans can inform FDA's consideration under section 910(c)(4) of the FD&C Act of the potential risks and benefits of the tobacco product to the population as a whole, including whether the marketing of the product would increase or decrease the likelihood that those who do not use tobacco products, including youth and young adults, will start using them.

FDA is proposing to require the submission of marketing plans to help it understand and prevent or minimize the potential harm that could be caused by the marketing of a new tobacco product. Consistent with its mission to protect the public health, FDA seeks to limit youth exposure to the labeling, advertising, marketing, or promotion of a new tobacco product in order to limit uptake of the new tobacco product by nonusers of tobacco products, especially youth. FDA must also assess potential uptake of the new tobacco product by current tobacco product users who

would have otherwise stopped using tobacco products and how use of the new tobacco product may affect poly use behaviors and subsequent tobacco use. Applicants may have information that allows them to carefully target the marketing for a particular product to reach only its intended consumers of legal age. In reviewing the marketing plans contained in a PMTA, FDA intends to consider how an applicant will target the marketing of its new tobacco product to reach its intended consumers of legal age and to assess potential effect on nonusers. FDA will also consider how the applicant intends to minimize the extent to which youth can access the product and are exposed to its marketing. Where FDA determines that restrictions on the sales and distribution of the new tobacco product (including access to, and the advertising and promotion of, the tobacco product) would be APPH, FDA can impose such restrictions under the terms of a marketing order as described in section VIII.D.

The applicant's marketing plans will help FDA determine whether permitting the marketing of the new tobacco product would be APPH because they will provide input that is critical to FDA's determination of the likelihood of changes in tobacco product use behavior, especially when considered in conjunction with other information contained in the application. FDA will review the marketing plan to evaluate potential youth access to, and youth exposure to the labeling, advertising, marketing, or promotion of, a new tobacco product. For example, heavy use of online social media to promote a tobacco product without access restrictions, as opposed to actions such as paper mailings directed only to current smokers of legal age, indicates the potential for youth to be exposed to the promotion of the product. This information would help FDA make its APPH determination by showing whether a PMTA fully or accurately accounts for the likelihood of changes in tobacco product use behavior that may occur as a result of marketing the new tobacco product. For example, if the PMTA does not address youth access to the product, youth exposure to the product's labeling, advertising, marketing, and promotion, and youth initiation, such as describing how it proposes to restrict the sale or distribution of its product to limit potential youth access to the product (*e.g.,* selling the tobacco product in adult-only establishments) or exposure to advertising (*e.g.,* using age verification controls for digital advertising), FDA may be unable to determine that the applicant has made a showing that permitting the marketing of the new tobacco product would be APPH. FDA expects that companies seeking authorization will have prepared plans for potential marketing that they expect to undertake during at least an initial period of marketing, such that providing these plans as part of the application would not require significant resources.

Additionally, as set forth in proposed § 1114.41, FDA would require each applicant that receives a marketing order to continue to report its marketing plans, along with items such as copies of the product's labeling, advertising, marketing, and promotion, and the results of the implementation of such plans. Continuing to monitor the marketing plans for the new tobacco product once on the market is important to help FDA evaluate both the potential for changes to tobacco product use behavior and the implementation of any restrictions in the marketing order. As described in section VIII.F., where FDA finds that the continued marketing of a new tobacco product is no longer APPH, such as where changes in the marketing of a new tobacco product result or are likely to result in a significant increase in youth initiation not foreseen in FDA's review of a PMTA, FDA would withdraw the marketing order for a product.

There is a well-established body of scientific evidence regarding the effect of advertising and marketing on tobacco product initiation (*see e.g.,* Refs. 7–10), which FDA must consider as part of its basis for determining whether permitting the marketing of a product would be appropriate for the protection of the public health under section 910(c)(4) of the FD&C Act. The impact of tobacco advertising and marketing on youth and young adult tobacco use behavior has been well documented. The 2012 Surgeon General's report, *Preventing Tobacco Use Among Youth and Young Adults,* synthesizes more than 30 years of research on the topic and 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. 12). The National Cancer Institute made a similar conclusion it 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. 8). 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. 13–21). 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. 22–24) 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. 12).

Marketing plans would provide information about the ways and frequency with which consumers would be exposed to tobacco product advertising, marketing, promotion, and other communication activities. This information can provide valuable insight into the likelihood that nonusers, particularly youth, would initiate tobacco product use. 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. 21 and 25). 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. 25–27).

Proposed § 1114.7(f)(2) would require, as part of the description of the marketing plans, that the PMTA specify information such as the intended target audience(s), media and distribution channels, specific tactics, total dollar amount(s) of media buys and marketing and promotional activities, and timing for the activities, including, but not limited to, information describing the items listed below. As used in proposed § 1114.7(f)(2), other consumer-directed activities include any other types of action regarding the new tobacco product that may reach consumers, such as communications that are intended to

inform retailers' communications with consumers. If an applicant does not intend to use any advertising, marketing, promotion, or other communication activities directed at consumers regarding its new tobacco product, or the applicants has not developed marketing plans by the time of filing, the PMTA must contain a statement to that effect in this section of the application. The types of information that the marketing plan section would be required to contain include, but are not limited to:

- Any plans to use competent and reliable data sources, tools, technologies, and methodologies to establish, maintain, and monitor highly targeted marketing plans and media buys. This could include, for example, use of and sources of first and second-party age-verified data, public records, industry-standard syndicated research services, and embedded tracking pixels in digital advertising;
- A description of the target adult audiences by age-range(s) (including young adult audiences ages 18–24) and other demographic and psychographic characteristics. Examples of demographic characteristics include, but are not limited to race, ethnicity, and geographic location (*e.g.,* urban, rural). Examples of types of psychographic characteristics include, but are not limited to hobbies, interests, risk-taking behaviors, tobacco use behaviors, purchase behaviors, and online search behaviors;
- A description of the target audience insights (*e.g.,* demographics, psychographics, findings from consumer research) the applicant is using to inform its marketing plans, including its strategic approach, key messages and themes, creative direction, and potential tactics or marketing channels. FDA generally expects that applicants will have conducted market or consumer research to determine, and gain information regarding, its target audience. This could include product-specific insights (*e.g.,* target audience 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 a manufacturers approach to marketing the product. This could also include information regarding where the target audience tends to consume marketing and advertising (*e.g.,* television programs the target audience watches, social media influencers the target audience follows, websites and retail locations the target audience frequents) that can be used to tailor its approach, select relevant marketing tactics, and use relevant marketing channels. The applicant should describe such insights in this section of the application;
- Any means by which youth-access to the tobacco product or youth-exposure to the tobacco product labeling, advertising, marketing, and promotion would be limited. FDA expects that applications will contain information regarding how the applicant intends to prevent sales or distribution to individuals below the legal purchasing age. Such information could include, for example, whether and how the company intends to: utilize independent, third-party age and identity-verification software on its website(s); distribute its product only to age-restricted locations; and limit the quantity of its product that an adult customer may purchase within a given period of time;
- Plans to use owned, earned, shared, or paid social media to advertise or promote the tobacco product. While media categories often overlap, owned media typically consists of a company's own media properties they control, such as the company's product-branded website. Earned media typically consists of unpaid media publicity, consumer interest or pick up of advertising or promotion, such as a news article about the product or a social media influencer talking about a company's product or sharing's a company's social media post without payment. Shared media typically consists of a company's social media properties, such as a company's social media accounts and content. Paid media consists of advertising and promotion that a company pays for, such as advertising appearing on television and radio, in and around retail stores, and in digital media, including content shared by a social media influencer who a company pays to promote to the tobacco product;
- Plans to use partners, sponsors, influencers (*e.g.,* celebrities, cultural icons, individuals with substantial followers on social media), bloggers, or brand ambassadors to create labeling for, market, advertise or promote the tobacco product;
- Plans to conduct in-person consumer engagements, including events at which the tobacco product will be demonstrated or sampled. Applicants planning to conduct in-person engagements should include a description of how access would be restricted to individuals at or above the Federal minimum age of purchase; and
- Plans to use earned media, public relations, or other communications outreach to promote the tobacco product. Earned media could consist of actions such as plans to pitch stories about the new tobacco product to newspapers without compensation. 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.

FDA invites comment on the specific information in the proposed marketing plans section, and whether FDA should require additional information related to marketing plans and the basis for any such additional provisions.

At this time, FDA is not proposing to require the submission of advertising for application filing, except where used as stimuli in studies (*e.g.,* stimuli in perception studies). Specifically, in addition to the marketing plan requirements in this section, proposed § 1114.7(k)(1)(iv) would require a PMTA to contain full reports of information concerning investigations that are published, known to, or should be known to, the applicant regarding the impact of the tobacco product's label, labeling, and advertising on perceptions of the product and tobacco product use intentions.

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 the substantial equivalence premarket pathway, not for PMTAs. If the applicant believes the action would qualify for an available categorical exclusion, the applicant would be required to 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.

If the new tobacco product resulted from modification(s) to a legally marketed predecessor product (*i.e.,* a grandfathered tobacco product or a product that has received marketing authorization from FDA), the environmental assessment also would be required to include a statement indicating whether the new tobacco product is intended to: (1) Replace the predecessor tobacco product once the new tobacco product receives market authorization and is commercially marketed; (2) be a line extension of the predecessor tobacco product; (3) be marketed along with the predecessor product by the same manufacturer; and/or (4) be marketed along with the predecessor tobacco product by a different manufacturer (*e.g.,* by a manufacturer other than the manufacturer of the predecessor tobacco product). The change in what is available in the marketplace is a factor FDA considers in determining whether the issuance of a marketing order may significantly affect the quality of the human environment as part of its NEPA review, *e.g.,* the new product may present different disposal issues if more product remains after consumer use or if the materials that the new product is composed of degrade differently.

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 order. (See the discussion of proposed §§ 1114.27 and 1114.29 in section VIII.)

8. Summary

Proposed § 1114.7(h) would require 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 is proposing to require the summary under authority of sections 701(a) and 910(b)(1)(G) of the FD&C Act because it will provide FDA with an understanding of the information contained in the PMTA and allow FDA to plan and conduct a more efficient review of the detailed technical information the summary describes. The summary would also help reviewers understand the product and the accompanying scientific data more quickly and would allow applicants to highlight information they believe demonstrates their product should receive a marketing order. The summary should discuss all aspects of the PMTA and synthesize the application into a well-structured, unified document. The summary should serve as a briefing document that highlights the most important aspects of the application, with each section consisting of a page or two focused on information that the applicant believes contributes to a finding that permitting the marketing of the product would be APPH. The applicant would be required to 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 section would be required to contain a discussion of the following items, where applicable, and explicitly identify areas in which there is a lack of information, if any:

- 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 proposed § 1114.7(i) in section VII.B.9;
- 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 highlighting 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 proposed § 1114.7(j) in section VII.B.12.;
- 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 health risks of the tobacco product to both users and nonusers of the product 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 proposed § 1114.7(k)(1)(i) in section VII.B.13.a.i.;
  - The impact the product and its marketing will have on the likelihood of changes in tobacco use behavior of tobacco product users, including cessation, switching (*i.e.,* to a different tobacco product), and poly use (*i.e.,* using the new tobacco product in conjunction with one or more other tobacco products). See the discussion of proposed § 1114.7(k)(1)(ii) in section VII.B.13.a.ii.;
  - The impact the product and its marketing will have on the likelihood of tobacco use initiation by tobacco products nonusers, especially youth and young adults, including among never users and former users, and the likelihood of poly use and switching behaviors. See the discussion of proposed § 1114.7(k)(1)(iii) in section VII.B.13.a.iii.;
  - How users and nonusers perceive the tobacco product and its label, labeling, and advertising, how the label, labeling, and advertising affect use intentions, and 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 proposed § 1114.7(k)(1)(iv) in section VII.B.13.a.iv.; 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 proposed § 1114.7(k)(1)(v)) in section VII.B.13.a.v.

The proposed rule also would require 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. 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 the product's marketing has or may have on overall tobacco-related morbidity and mortality. 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. As an illustration, an applicant may make an overall assessment of whether the product will 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 the marketing of a new tobacco product is 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 VIII.D. regarding proposed § 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. Proposed § 1114.7(i) would implement 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, constituents, and additives. Under the proposed rule, the application would be 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. Proposed § 1114.7(i)(1)(i) would require 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 would require:

- 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.

This information is especially important as it may not be readily apparent from the component or part's identity what function and purpose it may serve. For example, software used in or with a product may have functions and purposed 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.

ii. Materials. Proposed § 1114.7(i)(1)(ii) would require that the application include the following information for each material in the product because materials can affect the performance of the product. 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 would require:

- The material name and common name (if applicable);
- The component or part where it is located;
- The subcomponent or subpart where it is located (if applicable);
- The function of the material;
- Quantities (including ranges or means and acceptance limits);
- Specifications (including quality, grades, and suppliers) 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 proposed § 1114.27(a)(1), it may slow down the substantive review process.

iii. Ingredients other than tobacco. Proposed § 1114.7(i)(1)(iii) would require that the application contain information on ingredients other than tobacco (information on tobacco ingredients is addressed in proposed § 1114.7 (i)(1)(iv)). The required information would include:

- 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 would be 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, with the unit of measure (including ranges or means, and acceptance limits);
• The specifications (including purity or grade and supplier); and
• For complex purchased ingredients, each single chemical substance would be required to be 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 proposed § 1114.27(a)(1), it may slow down the substantive review process.

iv. Tobacco ingredients. Proposed § 1114.7(i)(1)(iv) would require information regarding tobacco ingredients, including:

• The type(s) of tobacco, including grade(s) and variety or varieties. This information is important to determining the public health impact of the products because different grades and varieties have different constituent profiles. The application would also need to contain information on the applicant's grading system so that FDA understands the meaning of the grade;
• The quantity, with the unit of measure (including ranges or means, and acceptance limits), of each tobacco ingredient in the new tobacco product;
• 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, such as the constituent profile.

Additionally, FDA recommends a PMTA also contain any other information about tobacco ingredients to fully characterize the new tobacco product, as applicable, such as country of origin, which can affect constituent levels (Ref. 28). 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 proposed § 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 would be required to specifically state that the product does not contain tobacco.

FDA is proposing 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 would allow 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 ''Listing of Ingredients in Tobacco Products.''

v. Constituents. Proposed § 1114.7(i)(1)(v) would require 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, proposed § 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 is currently seeking public comment on its proposal to add 19 constituents to the established list of HPHCs.[10] An application would not be required to contain testing for all HPHCs on the initial list; rather, it would be required to 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. 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 a 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 ''Guidance for Industry, Premarket Tobacco Product Applications for Electronic Nicotine Delivery Systems.'' Constituent testing data FDA is proposing that a PMTA contain for all products includes:

• The constituent names in alphabetical order;
• The common name(s);
• The CAS number;
• The mean quantity and variance with unit of measure;
• The number of samples and measurement replicates for each sample. As stated in proposed § 1114.7(i)(4)(iv), the testing would be required to 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 would be 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 would be required by § 1114.7(i)(4)(i));
• The length of time between dates of manufacture and date(s) of testing (as would be 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

[10] 84 FR 38032 (August 5, 2019).

(as would be required by § 1114.7(i)(4)(iii));

- Reports of constituent testing that include test protocols, any deviation(s) from the test protocols, quantitative acceptance criteria, line data, and a summary of the results, for each applicable parameter (as would be 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 would be required by § 1114.7(i)(4)(vii).

For combusted or inhaled tobacco products, constituent smoke or aerosol yields from the new product would be required to be determined using intense and nonintense smoking or aerosol-generating regimens, where established. Two smoking or aerosol-generating regimens are required, where established, in order 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 (Ref. 29–30). By requiring both an intense and a nonintense smoking or aerosol generating regimen, where established, FDA would have a better understanding of quantities of each constituent that may be produced by the tobacco product when used under different conditions. If an alternative to the established smoking regimens (*e.g.,* International Organization for Standardization (ISO) and Health Canada Intense (HCI) regimens for cigarettes) is used, such as where intense and nonintense smoking or aerosol generating regimens have not been established, the applicant would be required to provide an explanation of why the alternative provides comparable results to the intense and nonintense smoking regimens.

vi. Container closure system. Proposed § 1114.7(i)(1)(vi) would require that the application contain a description of the container closure system for the new tobacco product, if applicable, 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 would also need to describe 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 will 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 also provide information regarding whether the container closure system has any features that could prevent accidental exposure (*e.g.,* a feature that prevents e-liquid from being accidentally ingested by children). Additionally, evidence demonstrates that the container closure system used can change the characteristics of the product. Packaging materials constitute the container closure system if substances within that packaging are intended or reasonably expected to 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. Another example of this is when menthol or other ingredients are applied to the inner foil to become incorporated into the consumed product (Ref. 2). 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 also diffuse into snuff and affect its characteristics (Ref. 3). 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 versus 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 that may support a finding that permitting an ENDS to be marketed would be APPH, see the ''Guidance for Industry, Premarket Tobacco Product Applications for Electronic Nicotine Delivery Systems.''

vii. Statement of tobacco blending, reconstitution, manipulation. Finally, the proposed rule would require a full statement of the tobacco blending, reconstitution, or manipulation, where applicable. This may include manufacturer specifications, and tobacco types, quantities, and tobacco grading systems. This information is important because it helps FDA understand the characteristics of the tobacco product. Information on tobacco grades and grading systems used by an applicant (where applicable) will help FDA understand the quality of tobacco used, which can provide important information since the specified tobacco grades may impact the tobacco chemistry (*e.g.,* the nicotine content) and, thereby, the chemical composition of the tobacco product (Ref. 31).

b. Other properties. Proposed 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), would require 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 proposed definition for finished tobacco product (which includes all components and parts, sealed in final packaging), the dimensions and schematic drawings would be 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. 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. Tables 1 through 20 in proposed § 1114.7(i)(2)(ii)(B) provide the parameters that would be required for different categories of tobacco products. As part of the full description of the properties of the tobacco product, the proposed rule would also require, as included in the tables, a quantitative description of the performance criteria, including test protocols, line 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. The proposed parameters and their importance to understanding their impact on public health are described below.

Note that in addition to the parameters listed in tables 8 to 20 of the draft codified, FDA is also providing additional design parameters that it recommends including in a PMTA for certain types of deemed tobacco products in just the preamble. FDA is considering whether it should require the submission of these additional design parameters as part of the final rule and is requesting public comment regarding whether FDA should include these parameters as requirements in the final rule, whether FDA should recommend or require additional design parameters, and, if so, the basis for including additional design parameters.

Table 1 in proposed § 1114.7(i)(2)(ii)(B) describes the design parameters and information on performance criteria to be provided for cigarettes. These parameters 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 mass may affect smoke constituent yields (Ref. 32).
- Cigarette length may alter tobacco biomarker levels (Ref. 33).
- Cigarette diameter may affect filter efficiency and, in turn, smoke constituent yields (Ref. 34).
- Puff count can directly affect smoke constituent yields (Ref. 35).
- Cigarette draw resistance may result in differences in the difficulty of pulling air through the tobacco rod and, in turn, affect smoke constituent yields (Ref. 36).
- Tobacco rod length may alter tobacco biomarker levels (Ref. 33).
- Tobacco filler mass may affect smoke constituent yields (Ref. 32).
- Tobacco rod density may modify burn properties and smoke constituent yields (Refs. 37 and 38).
- Tobacco cut size alters the size of the tobacco pieces, which may result in more particulate matter (Ref. 39).
- Tobacco moisture may affect puff count (Ref. 40).
- Cigarette paper length and cigarette paper width may affect smoke constituent yields (Ref. 32).
- Cigarette paper base paper basis weight may affect puff count and smoke constituent yields (Ref. 41).
- Cigarette paper base paper porosity may affect smoke constituent yields (Ref. 41).
- Cigarette 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. 42).
- Cigarette paper band diffusivity may affect smoke constituent yields because it mimics air flow during smoldering (Ref. 43).
- Cigarette paper band width may affect ventilation and, in turn, smoke constituent yields (Ref. 44).
- Cigarette paper band space may affect ignition propensity and, in turn, puff count (Ref. 45).
- Filter efficiency may affect smoke constituent yields (Ref. 44).
- Filter diameter, filter mass, filter tow crimping index, denier per filament, total denier, filter density, and filter length may affect filter efficiency and, in turn, smoke constituent yields (Ref. 46).
- Filter pressure drop may affect smoke constituent yields (Ref. 47).
- Plug wrap, including length, width, basis weight, porosity, and caliper, contributes to the overall ventilation (Ref. 44).
- Tipping paper, including length, width, and basis weight, may affect smoke constituent yields (Ref. 48).
- Filter ventilation, including location and number of holes and rows, may affect smoke constituent yields (Ref. 34).

Table 2 in proposed § 1114.7(i)(2)(ii)(B) describes the design parameters and information on performance criteria to be provided for new portioned and non-portioned smokeless tobacco products. These parameters 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. 49).
- Tobacco moisture may affect microbial growth in the product, extraction efficiency, and total exposure to nicotine, NNN, and NNK (Refs. 4 and 5).
- Portion mass may affect user exposure to a tobacco product and, in turn, HPHCs contained in each portion (Ref. 50).
- Portion length may affect the constituents in each portion (Ref. 50).
- Portion width may result in a surface area difference, which is proportional to the amount and rate of constituents released from the product (Ref. 51).
- Portion thickness may result in a surface area difference, which is directly proportional to the amount and rate of constituents released from the product (Ref. 51).
- Pouch material basis weight, pouch material air permeability, and pouch material caliper influences the interactions between the tobacco and oral cavity, thereby potentially affecting the amount and rate of constituents released from the product (Ref. 52).
- Pouch material 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. 53).
- Pouch material nicotine dissolution extent is a function of the initial release and duration of the ongoing release, thereby potentially affecting the amount and rate of constituents released from the product (Refs. 52 and 54).

Table 3 in proposed § 1114.7(i)(2)(ii)(B) describes the design parameters and information on performance criteria to be provided for new roll-your-own (RYO) tobacco rolling paper products. These parameters 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. 47).
- RYO paper 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. 41 and 47).
- RYO paper base paper basis weight may affect puff count and smoke constituent yields (Ref. 41).
- RYO paper base paper porosity may affect smoke constituent yields (Ref. 41).
- 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. 42).
- RYO paper band diffusivity may affect smoke constituent yields because it mimics air flow during smoldering (Ref. 43).
- RYO paper band width may affect ventilation and, in turn, smoke constituent yields (Ref. 44).

- RYO paper band space may affect ignition propensity and, in turn, puff count (Ref. 45).

Table 4 in proposed § 1114.7(i)(2)(ii)(B) describes the design parameters and information on performance criteria to be provided for new RYO tobacco tubes. These parameters 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. 32).
- Tube length may alter tobacco biomarker levels (Ref. 33).
- Tube diameter may affect filter efficiency and, in turn, smoke constituent yields (Ref. 34).
- Tube paper length and tube paper width may affect smoke constituent yields (Ref. 32).
- Tube paper base paper basis weight may affect puff count and smoke constituent yields (Ref. 41).
- Tube paper base paper porosity may affect smoke constituent yields (Ref. 41).
- 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. 42).
- Tube paper band diffusivity may affect smoke constituent yields because it mimics air flow during smoldering (Ref. 43).
- Tube paper band width may affect ventilation and, in turn, smoke constituent yields (Ref. 44).
- Tube paper band space may affect ignition propensity and, in turn, puff count (Ref. 45).

Table 5 in proposed § 1114.7(i)(2)(ii)(B) describes the design parameters and information on performance criteria to be provided for new RYO tobacco filtered tubes. These parameters 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. 32).
- Tube length may alter tobacco biomarker levels (Ref. 33).
- Tube diameter may affect filter efficiency and, in turn, smoke constituent yields (Ref. 34).
- Tube paper length directly correlates to non-filter tube length, which may affect smoke constituent yields (Ref. 32).
- Tube paper width may affect smoke constituent yields (Ref. 32).
- Tube paper base paper basis weight may affect puff count and smoke constituent yields (Ref. 41).
- Tube paper base paper porosity may affect smoke constituent yields (Ref. 41).
- 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. 42).
- Tube paper band diffusivity may affect smoke constituent yields because it mimics air flow during smoldering (Ref. 43).
- Tube paper band width may affect ventilation and, in turn, smoke constituent yields (Ref. 44).
- Tube paper band space may affect ignition propensity and, in turn, puff count (Ref. 45).
- Filter efficiency may affect smoke constituent yields (Ref. 44).
- Filter diameter, filter mass, filter tow crimping index, and denier per filament may affect filter efficiency and, in turn, smoke constituent yields (Ref. 46).
- Total denier, filter density, and filter length may affect filter efficiency and, in turn, smoke constituent yields (Ref. 30).
- Filter pressure drop may affect smoke constituent yields (Ref. 47).
- Plug wrap, including length, width, basis weight, porosity, and caliper, contributes to the overall ventilation (Ref. 44).
- Tipping paper, including length, width, and basis weight, may affect smoke constituent yields (Ref. 48).
- Filter ventilation, including location and number of holes and rows, may affect smoke constituent yields (Ref. 34).

Table 6 in proposed § 1114.7(i)(2)(ii)(B) describes the design parameters and information on performance criteria to be provided for RYO tobacco. These RYO tobacco parameters 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 filler mass may affect smoke constituent yields when used with rolling paper (Ref. 32).
- Tobacco cut size alters the size of the tobacco pieces, which may result in more particulate matter (Ref. 39).
- Tobacco moisture may affect puff count when used with rolling paper (Ref. 40).

Table 7 in proposed § 1114.7(i)(2)(ii)(B) describes the design parameters and information on performance criteria to be provided for new RYO tobacco paper tips. These parameters 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. 47).
- 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. 41 and 47).
- RYO paper base paper basis weight may affect puff count and smoke constituent yields (Ref. 41).
- RYO paper base paper perforation may affect smoke constituent yields (Ref. 41).
- RYO paper tip ventilation may affect smoke constituent yields (Ref. 34).

Table 8 in proposed § 1114.7(i)(2)(ii)(B) describes the design parameters and information on performance criteria to be provided for filtered, sheet-wrapped cigars. These parameters 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 length and diameter can directly affect the amount of tobacco that is burned and, in turn, affect smoke constituent yields (Ref. 55).
- Tobacco filler mass may affect smoke constituent yields (Ref. 56).
- Tobacco rod density may modify burn properties and smoke constituent yields (Refs. 37 and 38).
- Tobacco cut size alters the size of the tobacco pieces, which may result in more particulate matter (Ref. 39).
- Tobacco moisture may affect puff count (Ref. 40).
- Cigar wrapper and binder porosity may affect smoke constituent yields (Refs. 58 and 59).
- Filter efficiency may affect smoke constituent yields (Ref. 44).
- Filter diameter and filter length may affect filter efficiency and, in turn, smoke constituent yields (Ref. 46).
- Filter pressure drop may affect smoke constituent yields (Ref. 47).
- Tipping paper length may affect smoke constituent yields (Ref. 48).
- Ventilation may affect smoke constituent yields (Ref. 56).

In addition to the parameters that would be required by the proposed rule, FDA recommends a PMTA for a filtered, sheet-wrapped cigar also contain the following additional design parameters in table 8a and is specifically requesting

public comments on whether these parameters should be required in the final rule.

TABLE 8a—ADDITIONAL DESIGN PARAMETERS RECOMMENDED TO BE PROVIDED 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 draw resistance (mm H_2O). • Cigar burn rate (mm/s). • Cigar wrapper length (mm). • Cigar wrapper width (mm). • Cigar wrapper basis weight (g/m^2). • Cigar binder length (mm). • Cigar binder width (mm). • Cigar binder basis weight (g/m^2). • Filter mass (mg). • Filter density (g/cm^3). • Filter tow crimping index. • Filter total denier (g/9000m). • Filter denier per filament (dpf). • Plug wrap length (mm). • Plug wrap width (mm). • Plug wrap basis weight (g/m^2). • Plug wrap porosity (CU). • Tipping paper width (mm). • Tipping paper basis weight (g/m^2). • Tipping paper perforation (CU). • Filter ventilation position of holes. • Filter ventilation number of holes. • Filter ventilation number of rows.	• Cigar mass (mg). • Cigar draw resistance (mm H_2O). • Cigar burn rate (mm/s). • Puff count. • Cigar wrapper length (mm). • Cigar wrapper width (mm). • Cigar wrapper basis weight (g/m^2). • Cigar binder length (mm). • Cigar binder width (mm). • Cigar binder basis weight (g/m^2). • Filter mass (mg). • Filter density (g/cm^3). • Filter tow crimping index. • Filter total denier (g/9000m). • Filter denier per filament (dpf). • Plug wrap length (mm). • Plug wrap width (mm). • Plug wrap basis weight (g/m^2). • Plug wrap porosity (CU). • Tipping paper width (mm). • Tipping paper basis weight (g/m^2). • Tipping paper perforation (CU).

FDA recommends including these parameters as part of the application because they may help fully characterize the product and may affect its impact on public health:

- Cigar mass reflects the amount of tobacco in a cigar, which may affect smoke constituent yields (Ref. 56).
- Cigar puff count can directly affect smoke constituent yields (Ref. 56).
- Cigar draw resistance may result in differences in the difficulty of pulling air through the tobacco rod and, in turn, affect smoke constituent yields (Ref. 36).
- Burn rate may affect puff count and, in turn, affect smoke constituent yields (Ref. 57).
- Cigar wrapper and binder basis weight may affect puff count and smoke constituent yields (Refs. 36 and 58).
- 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 (Ref. 36).
- Filter mass, filter tow crimping index, denier per filament, total denier, and filter density may affect filter efficiency and, in turn, smoke constituent yields (Ref. 46).
- Plug wrap, including length, width, basis weight, porosity, and caliper, contributes to the overall ventilation (Ref. 39).
- Tipping paper, including width, and basis weight, may affect smoke constituent yields (Ref. 48).
- Ventilation, including location and number of holes and rows, may affect smoke constituent yields (Ref. 56).

Table 9 in proposed § 1114.7(i)(2)(ii)(B) describes the design parameters and information on performance criteria to be provided for unfiltered, sheet-wrapped cigars. These parameters 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. 56).
- Cigar length and diameter can directly affect the amount of tobacco that is burned and, in turn, affect smoke constituent yields (Ref. 55).
- Tobacco filler mass may affect smoke constituent yields (Ref. 56).
- Cigar wrapper porosity may affect smoke constituent yields (Refs. 58 and 59).
- Cigar tip dimensions directly influence the overall cigar draw resistance and in turn, puff count (Ref. 60).

In addition to the parameters that would be required by the proposed rule, FDA recommends a PMTA for an unfiltered, sheet-wrapped cigar also contain the following additional design parameters as described in Table 9a and is specifically requesting public comments on whether these parameters should be required under the final rule.

TABLE 9a—ADDITIONAL DESIGN PARAMETERS RECOMMENDED TO BE PROVIDED 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 draw resistance (mm H_2O). • Cigar burn rate (mm/s). • Tobacco rod density (g/cm^3). • Tobacco cut size (mm). • Tobacco moisture (%).	• Cigar draw resistance (mm H_2O). • Cigar burn rate (mm/s). • Puff count. • Tobacco rod density (g/cm^3). • Tobacco cut size (mm).

TABLE 9a—ADDITIONAL DESIGN PARAMETERS RECOMMENDED TO BE PROVIDED FOR UNFILTERED SHEET-WRAPPED CIGARS—Continued

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/m^2). • Cigar binder length (mm). • Cigar binder width (mm). • Cigar binder basis weight (g/m^2). • Cigar binder porosity (CU). • Cigar tip mass (mg) (if applicable).	• Tobacco moisture (%). • Cigar wrapper length (mm). • Cigar wrapper width (mm). • Cigar wrapper basis weight (g/m^2). • Cigar binder length (mm). • Cigar binder width (mm). • Cigar binder basis weight (g/m^2). • Cigar binder porosity (CU). • Cigar tip mass (mg) (if applicable).

FDA recommends including these parameters as part of the application because they may help fully characterize the product and changes may affect its impact on public health:

- Cigar puff count can directly affect smoke constituent yields (Ref. 56).
- Cigar draw resistance may result in differences in the difficulty of pulling air through the tobacco rod and, in turn, affect smoke constituent yields (Ref. 36).
- Burn rate may affect puff count and, in turn, affect smoke constituent yields (Ref. 57).
- Tobacco rod density may modify burn properties and smoke constituent yields (Refs. 37 and 38).
- Tobacco cut size alters the size of the tobacco pieces, which may result in more particulate matter (Ref. 39).
- Tobacco moisture may affect puff count (Ref. 40).
- Cigar wrapper and binder basis weight may affect puff count and smoke constituent yields (Refs. 36 and 58).
- 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 (Ref. 36).
- Cigar binder porosity may affect smoke constituent yields (Refs. 58 and 59).

Table 10 in proposed § 1114.7(i)(2)(ii)(B) describes the design parameters and information on performance criteria to be provided for leaf-wrapped cigars. These parameters 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. 56).
- Cigar length and diameter can directly affect the amount of tobacco that is burned and, in turn, affect smoke constituent yields (Ref. 55).
- Tobacco moisture may affect puff count (Ref. 40).

In addition to the parameters that would be required by the proposed rule, FDA recommends a PMTA for a leaf-wrapped cigar also contain the following additional design parameters as described in Table 10a. FDA is gaining experience reviewing the design parameters of deemed tobacco products and is specifically requesting public comments on whether these parameters should be required under the final rule.

TABLE 10a—ADDITIONAL DESIGN PARAMETERS RECOMMENDED TO BE PROVIDED 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 draw resistance (mm H_2O). • Cigar burn rate (mm/s). • Tobacco filler mass (mg). • Tobacco rod density (g/cm^3). • Tobacco cut size (mm). • Cigar wrapper length (mm). • Cigar wrapper minimum width (mm). • Cigar wrapper maximum width (mm). • Cigar wrapper basis weight (g/m^2). • Cigar wrapper porosity (CU). • Cigar binder length (mm). • Cigar binder minimum width (mm). • Cigar binder maximum width (mm). • Cigar binder basis weight (g/m^2). • Cigar binder porosity (CU).	• Cigar draw resistance (mm H_2O). • Cigar burn rate (mm/s). • Puff count. • Tobacco filler mass (mg). • Tobacco rod density (g/cm^3). • Tobacco cut size (mm). • Cigar wrapper length (mm). • Cigar wrapper minimum width (mm). • Cigar wrapper maximum width (mm). • Cigar wrapper basis weight (g/m^2). • Cigar wrapper porosity (CU). • Cigar binder length (mm). • Cigar binder minimum width (mm). • Cigar binder maximum width (mm). • Cigar binder basis weight (g/m^2). • Cigar binder porosity (CU).

FDA recommends including these parameters as part of the application because changes they may help fully characterize the product and may affect its impact on public health as follows:

- Cigar draw resistance may result in differences in the difficulty of pulling air through the tobacco rod and, in turn, affect smoke constituent yields (Ref. 36).
- Burn rate may affect puff count and, in turn, affect smoke constituent yields (Ref. 57).
- Filler mass (mg) may affect smoke constituent yields (Ref. 56).
- Tobacco rod density may modify burn properties and smoke constituent yields (Refs. 37 and 38).
- Tobacco cut size alters the size of the tobacco pieces, which may result in more particulate matter (Ref. 39).

• Cigar wrapper and binder basis weight may affect puff count and smoke constituent yields (Refs. 36 and 58).
• Cigar wrapper and binder porosity may affect smoke constituent yields (Refs. 58 and 59).
• Cigar wrapper and binder length, minimum width, and maximum 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 (Ref. 36).

Table 11 in proposed § 1114.7(i)(2)(ii)(B) describes the design parameters and information on performance criteria to be provided for cigar tobacco. These parameters 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:

• Tobacco cut size alters the size of the tobacco pieces, which may result in more particulate matter (Ref. 39).
• Tobacco moisture may affect puff count (Ref. 40).

In addition to the parameters that would be required by the proposed rule, FDA would recommend applicants include filler mass (mg) as additional design parameter in a PMTA for cigar tobacco because it may affect smoke constituent yields (Ref. 56). FDA is gaining experience reviewing the design parameters of cigar tobacco and other deemed tobacco products and is specifically requesting public comments on whether this parameter should be required in the final rule.

Table 12 in proposed § 1114.7(i)(2)(ii)(B) describes the design parameters and information on performance criteria to be provided for a cigar wrapper. These parameters 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:

• Cigar wrapper length, and its minimum width and maximum 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 (Ref. 36).

In addition to the parameters that would be required by the proposed rule, FDA also recommends a PMTA for a cigar wrapper also contain the following additional design parameters as described in Table 12a and is specifically requesting public comments on whether these parameters should be required under the final rule.

TABLE 12a—ADDITIONAL DESIGN PARAMETERS RECOMMENDED TO BE PROVIDED 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 basis weight (g/m^2). • Cigar wrapper porosity (CU).	• Cigar wrapper basis weight (g/m^2). • Cigar wrapper porosity (CU).

FDA recommends including these parameters as part of the application because changes they may help fully characterize the product and may affect its impact on public health as follows:
• Cigar wrapper basis weight may affect puff count and smoke constituent yields (Refs. 36 and 58).
• Cigar wrapper porosity may affect smoke constituent yields (Refs. 58 and 59).

Table 13 in proposed § 1114.7(i)(2)(ii)(B) describes the design parameters and information on performance criteria to be provided for a waterpipe. The number of hoses and the waterpipe bowl volume are a necessary part of the application because they are needed to fully characterize the product.

In addition to the parameters that would be required by the proposed rule, FDA recommends a PMTA for a waterpipe also contain the following additional design parameters as described in Table 13a and is specifically requesting public comments on whether these parameters should be required under the final rule.

TABLE 13a—ADDITIONAL DESIGN PARAMETERS RECOMMENDED TO BE PROVIDED 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 material (mm). • Hose internal diameter (mm). • Stem length (mm). • Stem internal diameter (mm). • Hose Permeability (CU). • Bowl diameter (mm). • Bowl shape. • Pressure drop (mm H_2O). • Water filter efficiency (%). • Foil length (mm). • Foil width (mm). • Ventilation hole distribution. • Number of ventilation holes. • Ventilation (%). • Heating source type.	• Hose length (mm). • Hose internal diameter (mm). • Stem length (mm). • Stem internal diameter (mm). • Hose Permeability (CU). • Bowl diameter (mm). • Pressure drop (mm H_2O). • Water filter efficiency (%). • Foil length (mm). • Foil width (mm). • Ventilation (%).

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. FDA recommends including these parameters as part of the application

because they can help fully characterize the product and changes may affect its impact on public health:

- Hose dimensions (length and diameter) are directly proportional to air infiltration and affects toxicant yields (Ref. 61).
- Hose material may affect hose permeability, which may affect smoke constituent yields (Ref. 61).
- Water filtering efficiency is directly proportional to mainstream smoke and can increase exposure to HPHCs (Ref. 62).
- Pressure drop may result in differences in the difficulty of pulling air through the waterpipe and, in turn, affect smoke constituent yields (Ref. 36).
- Waterpipe components or parts, including stem, bowl, windscreen (foil), and purge valve, impact puffing behavior and toxicant exposure; therefore, the foil dimensions and ventilation may affect smoke constituent yields (Ref. 63).
- The diameter of the flow path is directly related to the resistance to draw, which may affect smoke constituent yields (Ref. 63).
- The aluminum foil perforation pattern (size, number and distribution of holes) impacts the path of hot gases through the tobacco mixture, which may affect smoke constituent yields (Ref. 63).

Table 14 in proposed § 1114.7(i)(2)(ii)(B) describes the design parameters and information on performance criteria to be provided for waterpipe tobacco. These parameters are necessary to fully characterize the product and changes may affect its impact on public health as follows:

- 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. 39 and 40).
- Tobacco moisture may affect puff count. Moisture contributes to packing density, thus decreasing void volume (Ref. 40).

In addition to the parameters that would be required by the proposed rule, FDA is recommending PMTAs for a waterpipe tobacco also include the filler mass (mg) because it may affect smoke constituent yields (Ref. 56) and is specifically requesting public comments on whether this parameter should be required in the final rule.

Table 15 in proposed § 1114.7(i)(2)(ii)(B) describes the design parameters and information on performance criteria to be provided for a waterpipe heating source. These parameters are necessary to fully characterize the product and changes may affect its impact on public health because 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 temperature may affect smoke constituent yields (Ref. 64).

In addition to the parameters that would be required by the proposed rule, FDA recommends a PMTA for a waterpipe heating source also include the additional design parameters as described in Table 15a and is specifically requesting public comments on whether these parameters should be required under the final rule.

TABLE 15a—ADDITIONAL DESIGN PARAMETERS RECOMMENDED TO BE PROVIDED 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:
• Charcoal burn rate (mm/s) (if applicable).	• Charcoal temperature (°C) (if applicable).
• Charcoal mass (mg) (if applicable).	• Charcoal burn rate (mm/s) (if applicable).
• Charcoal density (g/cm^3) (if applicable).	• Charcoal mass (mg) (if applicable).
• Electrical heater coil resistance (ohms) (if applicable).	• Charcoal density (g/cm^3) (if applicable).
• Number of coils (if applicable).	• Electrical heater coil resistance (ohms) (if applicable).
• Coil configuration (if applicable).	• Coil diameter (gauge) (if applicable).
• Coil diameter (gauge) (if applicable).	• Coil failure testing (if applicable).
• Coil failure testing (if applicable).	• Battery mAh rating (mAh) (if applicable).
• Battery mAh rating (mAh) (if applicable).	• Battery voltage operating range (volts) (if applicable).
• Battery voltage operating range (volts) (if applicable).	• Battery current operating range (amps) (if applicable).
• Battery current operating range (amps) (if applicable).	• Power delivery unit (PDU) voltage operating range (volts) (if applicable).
• Power delivery unit (PDU) voltage operating range (volts) (if applicable).	• PDU current operating range (amps) (if applicable).
• PDU current operating range (amps) (if applicable).	• PDU wattage operating range (watts) (if applicable).
• PDU wattage operating range (watts) (if applicable).	• PDU temperature cut-off (°C) (if applicable).
	• PDU wattage deviation (watts).
	• PDU temperature control deviation (°C).

FDA recommends including these parameters (as applicable to the heating source) as part of the application because they may help fully characterize the product and changes may affect its impact on public health:

- 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, temperature, and burn rate may affect smoke constituent yields (Ref. 64).

Table 16 in proposed § 1114.7(i)(2)(ii)(B) describes the design parameters and information on performance criteria to be provided for waterpipe foil. The waterpipe foil length and width are necessary to fully characterize the product and changes may affect its impact on public health because waterpipe components or parts windscreen (foil) impact smoke's puffing behavior and toxicant exposure. Therefore, the foil dimensions may affect smoke constituent yields. (Ref. 63).

In addition to the parameters that would be required by the proposed rule, FDA recommends a PMTA for waterpipe foil also include the following additional design parameters as described in Table 16a and is specifically requesting public comments on whether these parameters should be required under the final rule.

TABLE 16a—ADDITIONAL DESIGN PARAMETERS RECOMMENDED TO BE PROVIDED 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). • Foil width (mm). • Ventilation hole distribution. • Number of ventilation holes. • Ventilation (%).	• Foil length (mm). • Foil width (mm). • Ventilation (%).

FDA recommends including these parameters as part of the application because they may help fully characterize the product and changes may affect its impact on public health:

- Waterpipe components or parts, including the windscreen (foil) impact smoke's puffing behavior and toxicant exposure. Therefore, the foil dimensions and ventilation may affect smoke constituent yields (Ref. 63).
- The aluminum foil perforation pattern (size, number and distribution of holes) impacts the path of hot gases through the tobacco mixture, which may affect smoke constituent yields (Ref. 63).

Table 17 in proposed § 1114.7(i)(2)(ii)(B) describes the design parameters and information on performance criteria to be provided for a pipe. The bore diameter, bit length and diameter, and stem length and diameter are design parameters are necessary to fully characterize the product.

In addition to the parameters that would be required by the proposed rule, FDA recommends a PMTA for a pipe also include the following additional design parameters as described in Table 17a. FDA is issuing this list of pipe parameters, which are based upon similar parameters in other categories of tobacco products, for consideration and public comment. We are particularly interested in scientific investigations that support keeping or removing these parameters, or adding different parameters to the table.

TABLE 17a—ADDITIONAL DESIGN PARAMETERS RECOMMENDED TO BE PROVIDED 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:
• Moisture drain volume (ml). • Moisture drain location. • Bowl chamber cover outer diameter (mm). • Bowl chamber cover inner diameter (mm). • Draught hole diameter (mm). • Bottom screen. • Draught hole shape. • Draught hole location. • Bowl chamber diameter (mm). • Bowl chamber hole shape. • Bow chamber volume (cm^3). • Pipe pressure drop (mm H_2O). • Two-phase smoke flow (cc/min). • Airway volume (cm^3). • Filter length (mm). • Filter pressure drop (mm H_2O). • Filter efficiency (%). • Pipe ventilation (%).	• Moisture drain volume (ml). • Bowl chamber cover outer diameter (mm). • Bowl chamber cover inner diameter (mm). • Draught hole diameter (mm). • Bowl chamber diameter (mm). • Bow chamber volume (cm^3). • Pipe pressure drop (mm H_2O). • Two-phase smoke flow (cc/min). • Airway volume (cm^3). • Filter length (mm). • Filter pressure drop (mm H_2O). • Filter efficiency (%). • Pipe ventilation (%).

Table 18 in proposed § 1114.7(i)(2)(ii)(B) describes the design parameters and information on performance criteria to be provided for pipe tobacco. Tobacco cut size and moisture are design parameters that are necessary to fully characterize the product.

In addition to the parameters that would be required by the proposed rule, FDA recommends a PMTA for pipe tobacco also include filler mass (mg). FDA recommends the inclusion of this pipe tobacco parameter based upon similar parameters in other categories of tobacco products for consideration and public comment. We are particularly interested in scientific investigations that support keeping or removing this parameter, or adding different parameters.

Table 19 in proposed § 1114.7(i)(2)(ii)(B) describes the design parameters and information on performance criteria to be provided for an ENDS. These parameters 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 temperature, e-liquid consumption, and aerosol characteristics such as particle number concentration, count median diameter, and $PM_{2.5}$, which impact aerosol exposure (Ref. 65).
- Coil resistance may affect overall heating element resistance, thereby influencing heating element temperature. The heating element temperature may affect toxicant emissions and nicotine delivery (Refs. 66–70).
- Coil 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. 68 and 70).
- 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. 69).

- The temperature of the coil can affect the chemical and physical characteristics of the aerosol delivered to the user. An increase in coil temperature can increase HPHC levels in the aerosol, therefore, maximum coil temperature and temperature control deviation from this maximum coil temperature can affect toxicant emissions and nicotine delivery (Refs. 67–70).

In addition to the parameters that would be required by the proposed rule, FDA recommends a PMTA for an ENDS also include the following additional design parameters as described in Table 19a and is specifically requesting public comments on whether these parameters should be required under the final rule.

TABLE 19a—ADDITIONAL DESIGN PARAMETERS RECOMMENDED TO BE PROVIDED 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) (dimensionless). • Atomizer tank/cartridge volume (mL). • Number of coils (dimensionless). • Coil diameter (gauge). • Coil failure testing (cycles to failure). • Mass of wicking material (mg). • Wicking rate (mm/min). • Battery voltage operating range (V). • Battery current operating range (mA). • Power Delivery Unit (PDU) voltage operating range (V). • PDU current operating range (mA).	• Draw resistance (mm H_2O). • Puff count (for full tank/cartridge) (dimensionless). • Atomizer tank/cartridge volume (mL). • Coil diameter (gauge). • Coil failure testing (cycles to failure). • Mass of wicking material (mg). • Wicking rate (mm/min). • Battery voltage operating range (V). • Battery current operating range (mA). • PDU voltage operating range (V). • PDU current operating range (mA). • PDU wattage deviation (W).

FDA recommends including these parameters (as applicable to the ENDS product) as part of the application because they may help fully characterize the product and changes may affect its impact on public health:

- Coil and solder, as well as coil coatings, can transfer to the e-liquid and lead to increased toxicant emissions (Refs. 71 and 72).
- Number of coils present can affect overall atomizer resistance and distribution of heat dissipation (Ref. 73).
- The position of the coil can increase the possibility of dry puff conditions and subsequent increased toxicant emissions (Ref. 68).
- E-liquid absorbency of the wick and wicking rate can lead to dry puff conditions and increased toxicant emissions (Ref. 73 and 74).
- Wicking materials can transfer to the e-liquid and lead to increased toxicant emissions (Ref. 72).
- Atomizer and cartridge components of e-cigarettes may be heated repeatedly and aerosolized and can contribute to increased toxicant emissions (Ref. 66).
- 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. 74).
- E-liquid capacity of the atomizer tank/cartridge can affect total puff volume, which in turn can affect total toxicant emissions (Refs. 74 and 75).
- Battery/PDU voltage or voltage operating range may affect the heating element temperature, thereby affecting toxicant emissions and nicotine delivery (Refs. 67–70).
- Battery wattage or wattage operating range may affect the heating element temperature, thereby affecting toxicant emissions (Refs. 68 and 70).
- Coil 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. 68 and 70).
- Atomizer coil temperature (heating element temperature) may affect toxicant emissions and nicotine delivery (Refs. 67–70).
- PDU wattage deviation may influence heating element temperature, thereby affecting toxicant emissions (Refs. 68 and 70).
- The temperature of the coil can affect the chemical and physical characteristics of the aerosol delivered to the user. An increase in coil temperature can increase HPHC levels in the aerosol, therefore, maximum coil temperature and temperature control deviation from this maximum coil temperature can affect toxicant emissions and nicotine delivery (Refs. 67–70).
- Coil resistance, number of coils, coil gauge, and coil configuration may affect overall heating element resistance, thereby influencing heating element temperature. The heating element temperature may affect toxicant emissions and nicotine delivery (Refs. 66–70).
- 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. 66 and 76).
- Battery power impacts the delivery of nicotine and the total emissions of volatile aldehydes (Refs. 77 and 78).
- Battery and PDU voltage impacts the amount of e-liquid consumed, the vapor temperature, and the total emissions of volatile aldehydes (Ref. 78).
- The type and amount of wicking material can affect the e-liquid absorbency of the wick and wicking rate, possibly leading to dry puff conditions and increased toxicant emissions (Refs. 73 and 74).
- 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. 79).

Table 20 in proposed § 1114.7(i)(2)(ii)(B) describes the design parameters and information on performance criteria to be provided for an e-liquid. These parameters 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 (Ref. 74 and 75).

In addition to the parameters that would be required by the proposed rule, FDA recommends a PMTA for an e-liquid also contain the following additional design parameters as described in Table 20a and is specifically requesting public comments on whether these parameters should be required under the final rule.

TABLE 20a—ADDITIONAL DESIGN PARAMETERS RECOMMENDED TO BE PROVIDED 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 boiling point (°C). • E-liquid viscosity (at 20 °C) • E-liquid volume (ml). • Particle number concentration (#/cm^3). • Count median diameter (nm). • $PM_{2.5}$ (μg/m^3).	• E-liquid boiling point (°C). • E-liquid viscosity (at 20 °C). • E-liquid volume (ml). • Particle number concentration (#/cm^3). • Count median diameter (nm). • $PM_{2.5}$ (μg/m^3).

These parameters are a necessary part of the application because they may help fully characterize the product and changes may affect the its impact on public health:

• E-liquid solvent composition can cause variations in e-liquid boiling point. E-liquid composition, and subsequently e-liquid boiling point, can affect aerosol particle size distribution and amount of aerosol produced (Ref. 80).

• Aerosol parameters such as particle number concentration, count median diameter, and $PM_{2.5}$ 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. 81 and 82).

• E-liquid viscosity and boiling point impact the proportion of nicotine that is aerosolized (Ref. 83). E-liquid viscosity can also affect the e-liquid absorbency through the wick and wicking rate, possibly leading to dry puff conditions and increased toxicant emissions. Also, the e-liquid viscosity can affect the electronic cigarette nicotine and other toxicant delivery to the user (Refs. 73 and 74).

• The e-liquid volume can affect the delivery of nicotine and other toxicants to the user (Refs. 74 and 75).

iv. Function. The proposed rule would require 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).

v. pH of product and nicotine formulation. The proposed rule would require 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. 84 and 85).

The proposed rule would also require the PMTA to specify the formulation of the nicotine in the product. The nicotine formulation would be 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. 86 and 87). 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. 88–90).

vi. Fermentation process. For those products that contain fermented tobacco, the proposed rule would require an application to contain information on the fermentation process. The proposed rule would require this information because the fermentation process can result in different degrees of change in the chemical constituents of the tobacco (Ref. 91 and 92) and also affect the type and number of microorganisms in the final product, (Ref. 93) which could potentially affect the levels of TSNAs and stability of the products during storage. In addition, the type and amount of the fermentation inoculum can change the product as a result of directed fermentation (Ref. 94). Therefore, the application must contain the following information regarding 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 present during product processing (*e.g.,* cleaning of product contact surfaces);

• Specifications and test data for pH, temperature, moisture content, and water activity;

• Frequency of aeration or turning (if applicable);

• Duration of fermentation;

• Added ingredients; and

• Method used to stabilize or stop fermentation (if applicable), including parameters of the method (*e.g.,* length of treatment, temperature) and method validation data to demonstrate that fermentation is adequately suppressed to preclude further in-package fermentation that could lead to increases in TSNAs and microbial content in the final product. Having a process in place to suppress microbial activity to preclude further in-package fermentation is important because failing to do so could result in a product that may have different constituent levels than are specified in the application; and

• Storage conditions of the fermented tobacco prior to packaging and duration of storage (if applicable).

vii. Storage and stability information. The proposed rule would also require a PMTA to contain product storage and stability information that establishes the microbial and chemical stability of the product throughout the stated shelf life. Product storage and stability information is important for FDA's review of a tobacco product because

bacterial communities and constituents in tobacco products can change over time. Information obtained through stability testing could be used to ensure that the tobacco product is chemically and microbiologically stable during the expected product storage period and does not result in changes that could affect the product's potential health risks. If no shelf life is indicated, an applicant should provide details of stability over a specified amount of time and justify why that time period is appropriate. For example, if an applicant believes that 2 years after the date of manufacture is an appropriate time because that is the typical period of time in which their product is sold to consumers, an applicant should describe such.

The proposed rule would require this stability testing information because product stability is affected by factors such as the fermentation and stabilization processes (if applicable), addition of chemical additives to control microbial activity (*e.g.,* preservatives, metabolic inhibitors, humectants), and water activity (a_w) of the product (Refs. 91 and 95–98). Additionally, factors such as nitrate/nitrite concentrations, moisture content, microbial content, storage temperature, and pH are reported to influence the microbial stability and TSNA formation during storage of tobacco products (Refs. 99–104).

An application would be required to contain the following storage and stability information:

- A description of how the shelf life is indicated on the tobacco product, if applicable. The proposed 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 indicated. For example, if the tobacco product labeling has a 'use by,' 'best by,' or expiration date, a PMTA would have to describe how the date is determined (*e.g.,* a certain number of days after packaging).
- Testing on the tobacco product in the same container closure system that will be used if granted a marketing order performed at the beginning (zero time), middle, and end of the expected storage time for the chemical and microbial endpoints for the following items:
  - Microbial content data, including total aerobic microbial count and total yeast and mold count, along with identification of detected microbiological organisms by genus and species names (if applicable);
  - pH;
  - moisture content;
  - water activity;
  - TSNAs. The data specifying TSNAs would be required to be reported as separate amounts for a total TSNAs, NNN, and NNK.
  - nitrate and nitrite levels;
  - preservatives and microbial metabolic inhibitors (if any); and
  - method of heat treatment or pasteurization used to reduce microbial loads.

Accelerated studies, 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 tentative expiration dates provided full shelf life studies are not available and are being conducted. Where data from accelerated studies are used to project a tentative expiration date that is beyond a date supported by actual shelf life studies, stability studies must be conducted, including tobacco product testing at appropriate intervals, until the tentative expiration date is verified or the appropriate expiration date is determined.

As would be required by proposed § 1114.7(i)(4), the reported stability testing would need to 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. Proposed § 1114.7(i)(4) would also require the test data to contain:

- 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 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; and
- A description of method procedure, method validation information and rationale for selecting each test method, including relevant voluntary testing standard; and
- Reports of product formulation testing that include test protocols, quantitative acceptance criteria, line data, and a summary of the results, for each applicable parameter.

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 would be required to 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: 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, software errors or flaws (*i.e.,* bugs) that occasionally result in the product performing differently than designed; failure of a safety switch to shutoff a product if it exceeds a certain temperature; and the failure of a battery design feature to prevent battery from overcharging. The PMTA would have to 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 is requesting public comment regarding the scope of design risks and misuse hazards that would be required to be included in this section. Specifically, FDA is requesting input regarding whether the design risks or misuse hazards for which an application would be required to contain a review and assessment should be (1) those not normally associated with the tobacco product, (2) those not normally associated with the category of tobacco products; or (3) those not normally associated with all tobacco products generally.

10. Principles of Operation

Proposed § 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 would require the PMTA to contain full narrative descriptions 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, 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;
- The length of time it takes for a user to consume a single unit of the product. This may be characterized in multiple ways depending on the product type, for example, a single unit may include, but not be limited to one cigarette, one tobacco pouch, or a specified volume of e-liquid used. FDA requests public comment on appropriate metrics for determining what should constitute a single unit for various product types and also whether FDA should require the average time for all users to consume a single unit, the median time to consume a single until, or the range of time it takes users 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.

11. Product Testing and Analysis Information

Proposed § 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. FDA is proposing this requirement under its authority in 910(b)(1)(G) because the testing requirements described in this section are relevant to the subject matter of the application in that it helps 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). FDA notes that the sample size and number of replicates necessary to substantiate the type of testing may vary according to the type of testing. FDA recommends that a PMTA contain an explanation of why the applicant believes the sample size and number of replicates used is sufficient to support the reliability of the results. Additionally, the applicant would be required to 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 would be required to retain source data under proposed § 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 would need to contain complete description of the regimen.

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. Proposed § 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 order under section 910(c)(1)(i)(A) of the FD&C Act.[11] 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 this evaluation, FDA may conduct inspections as described in proposed § 1114.27 to verify the information and data submitted in the application.

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

[11] 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.

use of the product as characterized in the PMTA. Additionally, a nonconforming tobacco product constitutes a different tobacco product than the one authorized in the marketing 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. This proposed regulation provides requirements for how manufacturers would be required to handle complaints in similar situations, as well as the subsequent investigation, evaluation, and corrective and preventive actions they would need to take to address such issues.

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. 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. 105). 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 that contains a nicotine concentration higher than the established specification can be more addictive (Refs. 106 and 107). 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. 45). 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. 108).

Given the dangers associated with nonconforming (including contaminated) tobacco products, FDA is proposing to 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 proposed § 1114.7(j) and to help FDA determine if it conforms to the requirements of section 906(e) of the FD&C Act:

- 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. Proposed § 1114.7(k) sets forth FDA's proposed interpretation of this requirement, together with its authority in section 910(b)(1)(G), in three parts: (1) The types of investigations that would be 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 would be required to contain to demonstrate that the application contains all published investigations; and (3) the information that would constitute a full report of an investigation.

a. Types of investigations and analyses. 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 proposed § 1114.7(k)(1). Under the proposed rule, applicants would be required to submit full reports (as described in proposed § 1114.7(k)(3)) of all information published or known to, or which should reasonably be known to, the applicant regarding the types of investigations described in proposed § 1114.7(k)(1). Applicants would be 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.

Proposed § 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 proposed requirement would ensure that FDA understands the full scope of the health risk investigations for a new tobacco product. It does not require a PMTA to contain each type of health risk investigation described in this section beyond what is published, known to, or should reasonably be known to, an applicant and, applicants should not interpret this proposed section to be a list of investigations that it must conduct to receive a marketing order. 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., 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. Applicants may want to review the areas of scientific investigation listed in this proposed section in an effort 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 order.

An applicant may choose to conduct one of the health risk investigations described in § 1114.7(k)(1) to help demonstrate the health risks of a new tobacco product; however, it should be clear that the proposed rule is not requiring applicants to conduct these studies beyond what may be necessary to generate substantive information to meet the filing requirements set forth in proposed § 1114.27(b)(1)(ii). While the proposed rule is not requiring applicants to conduct studies beyond what may be necessary to generate substantive information to meet the filing requirements set forth in § 1114.27(b)(1)(ii), if such studies, together with other information in the PMTA, do not show that permitting the marketing of the new tobacco product would be APPH, FDA would issue an no marketing order. Applicants have some flexibility in the particular studies that they may conduct; an application would not necessarily need to contain each type of study described in § 1114.7(k) for filing or to receive an order.

Proposed § 1114.7(k) would interpret section 910(b)(1)(A) 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 no marketing orders (proposed § 1114.33) in section VIII.E. describes circumstances where FDA intends to issue a no marketing order. The description of the issuance of marketing order (proposed § 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.

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

- *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 and is not required under the proposed rule. 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. If an applicant chooses to bridge data from a

studied tobacco product to the subject new tobacco product, FDA recommends that the application contain the rationale and justification to support the use of bridging studies.

Where an applicant chooses to bridge to data from a general study or a study conducted using a different tobacco product, it should 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 would 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 below.

- *Comparison Products.* As part of FDA's consideration under 910(c)(4) of the FD&C Act of the risks and benefits of 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, poly use, cessation) that may occur with the marketing of the new tobacco product. We recommend an applicant 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. It is helpful for FDA to understand 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 proposed § 1114.27(b)(1)(ii), a PMTA would be required to 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 between your proposed 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 1:1 comparison as in a substantial equivalence report under section 905(j), rather, it is meant to demonstrate how the proposed new 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 your 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 proposed new 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.

- *Foreign Data.* 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 applicant should 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.[12] 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.

Foreign clinical studies should be performed by clinical investigators so that the rights, safety, and welfare of human subjects have been 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 proposed § 1114.7(k) that an application contain all published studies regarding a new tobacco product. 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.

i. Health risks of the product. Proposed § 1114.7(k)(1)(i)(A) would require 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 would include 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 is proposing to include these investigations under its interpretation of the requirements of

[12] 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.

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 would be required to 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.

The proposed rule would 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; however, as set forth in proposed § 1114.27(b)(1)(ii) and described in section VIII.B., an application would be required to contain substantive information regarding the health risks of the new tobacco product to be filed. Where an applicant chooses to conduct its own investigations, FDA is providing the following discussion of non-binding recommendations for consideration.

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 that would be required by proposed § 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 would recommend 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 supports reducing the reliance on animal testing where adequate and scientifically valid non-animal 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 non-animal 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 proposed § 1114.7(k)(1)(i)(B), a PMTA would be required to 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. 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 place and to use this comparison in the decision about whether permitting the marketing of the product would be APPH. The toxicological profile investigations covered by the proposed rule would also include 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 is proposing to include the toxicological profile of the tobacco 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 would be required to contain if published or known to, or should reasonably be known to, an applicant would 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 proposed § 1114.7(i)(1)(v), the constituent reporting section. The types of studies or information required by the proposed 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 toxicological profile includes 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 proposed § 1114.33, 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 proposed § 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 proposed 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 proposed § 1114.27(b)(1)(ii) and described in section VIII.B.. Information about the product's toxicity and a comparison of its toxicity to other tobacco products could satisfy this threshold 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 no marketing order for the new tobacco product.

Under proposed § 1114.7(k)(1)(i)(C), a PMTA would be required to 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 would also be required to 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. FDA is proposing to include the pharmacological profile of the tobacco product as 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 would be required to 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 would be required to 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 would be required to 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.

The pharmacological profile of the product provides important information about the health risks of the product because it is directly related to the health risks of the product as well as its risk relative to other products. The pharmacological profile of nicotine, for example, is particularly important for assessing product health risk because its pharmacokinetic properties can enhance or reduce the product's associated health risks. 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. 109–112).

Under proposed § 1114.7(k)(1)(i)(D), a PMTA would be required to 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. FDA is proposing under section 910(b)(1)(G) of the FD&C Act to require 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 is proposing that applicants 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 is also proposing to require 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 as part of the required information because existing data indicates that a significant number (approximately 40 percent or more by some estimates) of individuals who currently use tobacco products use more than one type of tobacco product (Refs. 113 and 114). 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. 115 and 116).

The types of investigations that a PMTA would be required to 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 from 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 proposed § 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. An applicant should consider the appropriate comparative health information a PMTA may need beyond this threshold requirement 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 no marketing order for the new tobacco product.

For demonstrating the health risks that are posed by the product in comparison to using other tobacco products, FDA recommends a 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 between your proposed 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 comparing the health risks of the product to categories of products that have a substantial market share (*e.g.,* cigarettes, smokeless tobacco, cigars). 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.

ii. Impacts on tobacco use behavior of tobacco product users. FDA interprets health risk investigations under section 910(b)(1)(A) of the FD&C Act to include the effect of the product and its label, labeling, and advertising 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).

Proposed § 1114.7(k)(1)(ii)(A) would require 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 proposed § 1114.27(b)(1)(ii) and described in section VIII.B., 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, 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 compulsive and continued use despite harm or risk of harm, and craving of the product. FDA proposes to require the submission of abuse liability information under its interpretation of section 910(b)(1)(A) 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 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 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 no marketing 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 only a threshold amount of abuse liability information under proposed § 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 would want to 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.

Section 1114.7(k)(1)(ii)(B) of the proposed rule would require 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 is proposing to require 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. Under proposed § 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, and how such use affects the health risks of the product to individual users. This means 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.

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. 69). 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.

Section 1114.7(k)(1)(ii)(C) of the proposed rule would also require 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. Data indicate that a substantial number of tobacco product users are poly-users of tobacco products (Ref. 113 and 114). FDA is proposing to require information regarding the likelihood of dual or poly-use because such use may increase or decrease known health risks and may pose risks that are not currently known (Refs. 115 and 116). 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 poly use, will help FDA determine the health risks that poly users may encounter.

Section 1114.7(k)(1)(ii)(D)–(F) of the proposed rule would also require 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 or switch back 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 proposed § 1114.7(k)(1)(ii)(c)–(f) would require a PMTA to contain only information published, known to, which would reasonably be known to the applicant, as set forth in proposed § 1114.27(b)(1)(ii), if a PMTA does not contain a threshold amount of 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. And while 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 order for the product. If a PMTA lacks sufficient information needed for FDA to make these determinations, FDA intends to issue a no marketing order for the new tobacco product.

FDA is proposing to require 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 otherwise 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 is also proposing to require information regarding current tobacco product user behavior because to determine whether the product is appropriate for the protection of public health, FDA must under section 910(c)(4)(A) of the FD&C Act take into account the increased or decreased likelihood that current tobacco product users will stop using tobacco products. 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.

iii. Impacts on tobacco use initiation by nonusers, including youth and young adults. The proposed rule would also require 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 and young adults, 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 proposed § 1114.27(b)(1)(ii), if a PMTA does not contain a threshold amount of information regarding the likelihood of changes to 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. And while the rule would not require an application to contain more than a threshold amount of relevant information for filing, FDA must be able to determine the potential risks and benefit 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 in order to issue a marketing order for the product. If FDA lacks sufficient information to make these determinations, it intends to issue a no marketing order for the new tobacco product.

FDA is proposing to require 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 proposed product would be APPH, FDA will need to understand how youth may use or intend to use the proposed product because youth are a population of particular concern for initiating tobacco use. However, FDA does not require research to be conducted on youth. Inferences regarding youth may potentially be extrapolated from young adults, as well as derived from existing sources of data, reviews of published scientific literature, and/or bridging information obtained from other sources. Providing data from the published literature or marketing information in your application with appropriate bridging information may be one useful approach. If you take such an approach, FDA recommends that you clearly explain how such data can be extrapolated to the target population or populations of interest, including youth, for the product that is the subject of the PMTA.

If an applicant chooses to conduct a study in the United States using minors, they 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, have been 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 minors should have a narrow research scope and be as focused as possible given sensitivities around the conduct of research in youth populations. Specifically, research priorities for youth 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 use/susceptibility among non-users. Studies conducted among youth focusing on issues beyond these key questions (*e.g.,* exposing youth to advertisements or marketing material for tobacco products) would warrant 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.

The proposed rule would also require 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 is proposing to include information regarding likelihood of re-initiation by former users as part of its interpretation of the requirements of section 910(b)(1)(A) of the FD&C Act and under its authority of 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.

iv. Perceptions and use intentions. The proposed rule would require 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 impact of the product and its label, labeling, and advertising on individuals' perception of the risks of the product, and the ability of individuals to understand the labeling and instructions for use and use the product in accordance with those instructions; however, as set forth in proposed § 1114.27(b)(1)(ii), if a PMTA does not contain substantive information regarding the potential impact of the product and its label, labeling, and advertising on individuals' perception of the product, and their use intentions, FDA intends refuse to file the application. This means where there is no published information or information that is otherwise known to the applicant regarding the potential impact of the product and its label, labeling, and 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 investigations and include a full report of the results in its PMTA for filing. And while the rule would not require an application to contain more than a threshold amount of relevant information for filing, FDA must be able to determine the potential risks and benefit 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 in order to issue a marketing order for the product. 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, and promotion of the new tobacco product may have on consumer perceptions and use intentions, FDA intends to issue a no marketing order for the new tobacco product.

FDA is proposing to include 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. 117). If an applicant uses advertising as stimuli in a tobacco product perception and use intention study, the PMTA would be required to indicate, as part of the full report of the study under proposed § 1114.7(k)(3), whether it is representative of advertising that the applicant intends to use in marketing the product that is required by proposed § 1114.7(f)(2). If the advertising is not representative of the advertising an applicant intends to use in marketing the product, the applicant would be required to 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 also relevant to determining whether the labeling is misleading, which is a reason for which FDA would have to 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. Additionally, 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.

v. Human factors. The proposed rule would also require 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; however, as set forth in proposed § 1114.27(b)(1)(ii), if a PMTA does not contain a threshold amount of information regarding the potential impact of human factors on the health risks of the product, FDA intends to refuse to file the application. This means where there is no published information or information that is otherwise known to the applicant regarding the potential impact of human factors on product risk, 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. And while the rule would not require an application to contain more than a threshold amount of relevant 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. If FDA lacks sufficient information to make this determination, it intends to issue a no marketing order for the new tobacco product. FDA is proposing to require human factors information as part of its interpretation of the requirements of section 910(b)(1)(A) 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 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 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 actually be prohibited (*e.g.,* laws prohibiting use of a product in the workplace, public spaces, airplanes).

FDA recommends that human factors investigations be conducted in the form of actual 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. If errors or failures or new findings are identified in the 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. Proposed § 1114.7(k)(2) would require an applicant to conduct a literature search for each type of information described in proposed § 1114.7(k)(1) and require the application 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 would also be required to 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 would also be required to contain a statement to that effect. FDA is proposing to require 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 proposing to include these requirements in the rule under authority of sections

701(a) and 910(b)(1)(G) of the FD&C Act because it would help FDA to determine whether the application contains reports of all published investigations in an efficient manner by helping FDA determine whether the application contains all relevant published studies, rather than having to follow up with the applicant about the inclusion or exclusion of specific studies. FDA must determine whether the application contains all published investigations because FDA 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 also why some investigations that do not initially appear to be relevant were included in the application. 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.

c. Study reports. Proposed § 1114.7(k)(3) would set requirements for the full report of each investigation that must be included as part of an application. An application would be required to contain each type of documentation listed in proposed § 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 obtaining the document is unduly burdensome due to the effort or expense involved. Where an applicant considers a document that would be required by this section to not be reasonably available, the application would be required 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 would be required to contain:

i. Full copies of any published articles and other reference materials. FDA is proposing to require that an application contain full copies of published articles and other reference materials to facilitate the review process. FDA is proposing this requirement to enable it to review an application more quickly.

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 would be required to include 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. FDA is proposing this requirement to help enable it to determine whether the study's findings are accurate and reliable. While this rule on its own would not require compliance with the GLP regulations found in part 58,[13] FDA would consider a nonclinical laboratory investigation that contains the documentation required by part 58 to satisfy the requirements of proposed § 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;
- 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 proposed rule would require 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 satisfy the financial disclosure requirements of the proposed rule. Financial conflicts information is important for FDA to consider because it addresses 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

[13] 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.

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 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 is proposing to require the protocol, investigator instructions, and statistical analysis plan as 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.

vi. Line data. To facilitate FDA's review, the application should contain line data in 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*);

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. A list of all sites that had early termination and the reason for early termination, along with any audit certificates and inspection results, if applicable;

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; and

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 proposed rule would require 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 would be required is where a clinical biomarker study on a product that is similar to the proposed product in terms of design, ingredients, and HPHCs is used to provide information about the anticipated health risks of the proposed product. As described in proposed § 1114.45, applicants would be required to keep each questionnaire and case report form from the study as part of its own internal records, which FDA may inspect, as described in proposed § 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 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 vulnerable subjects. 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 the 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 recommends, but does not currently require, maintaining 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, or advertising as stimuli, the proposed rule would require the full report of the study to contain a statement regarding whether the label, labeling, or advertising used is representative of advertising that 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 would be required to 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 proposed § 1114.7(k)(1)(iv) in section VII.B.13.a.iv.

d. The effect on the population as a whole. The proposed rule would require a PMTA to contain an in-depth analysis and discussion of how the data and information contained in the application establish that the proposed product is 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 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 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. FDA is proposing this requirement because it directly informs FDA's determination under section 910(c)(2)(A) of the FD&C Act of whether permitting the marketing of the new tobacco product would be APPH.

e. Certification statements. Proposed § 1114.7(m) would require that the application contain a specific statement certifying that the applicant would maintain all records to substantiate the accuracy of the application consistent with the record retention requirements in proposed § 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 would 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 (Proposed § 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 proposed 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, is proposing § 1114.9 to allow the submission of amendments to a pending application.

Proposed § 1114.9 provides that FDA may request, and an applicant may submit, an amendment to a pending PMTA together with the appropriate form (Ref. 11). Because FDA tracks PMTAs using the STN, an amendment must specify the STN that is assigned to the PMTA. An amendment would also be required to include 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 proposed § 1114.13.

Proposed § 1114.9(b) describes how the submission of an amendment may affect the time required for the review (as described in proposed § 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 may 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. 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 which FDA receives the amendment. Because section 910(c)(1) of the FD&C Act requires FDA to complete its review of an application meeting the requirements of section 910(b)(1) within 180 days of its receipt, under proposed § 1114.9(b)(1) a new 180-day review period would begin on the date FDA receives a major amendment.

Proposed § 1114.9(b)(2) describes the effect that minor amendments would 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 will not require substantial review time. 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 order without the amendment, it would issue a no marketing 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 180 days of FDA's request, FDA may, as described in proposed § 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. FDA is proposing § 1114.9(c) under authority of 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 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, proposed § 1114.9(d) would prevent the applicant from amending the application. 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 (Proposed § 1114.11)

Proposed § 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 proposed § 1114.29), the applicant may request to withdraw its application by using the appropriate form (Ref. 11) to specify the name of the new tobacco product, the STN of the application, and stating 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 would require 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 would allow 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 would issue an acknowledgment letter to the applicant, at which time the application would be considered withdrawn. Withdrawing an application would not prejudice a future submission.

The application is an Agency record even if withdrawn. Thus, under proposed § 1114.11(c), FDA would retain the withdrawn application consistent with Agency record retention schedules and policies and, under the Agency's public information regulations in 21 CFR part 20 (part 20), would provide a copy to the applicant upon request subject to § 20.45.

E. Change in Ownership of an Application (Proposed § 1114.13)

Proposed § 1114.13 describes the steps that an applicant would be required to take when it transfers ownership of a PMTA. This proposed 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. Under proposed § 1114.13, at the time of the transfer, the new and former applicants (or owners) of the PMTA would be required to use the appropriate form (Ref. 11) and submit certain information to the Agency. First, the former applicant would be required to 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 would be required to 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 proposed § 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 would have a copy of the PMTA from the former applicant, if the new applicant requests a copy of the PMTA filed with FDA, FDA would provide a copy to the new applicant, subject to the FOIA requirements as implemented by FDA at 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 (proposed § 1114.45 would impose a recordkeeping requirement).

F. Supplemental Application Submission (Proposed § 1114.15)

Proposed § 1114.15 discusses the availability of supplemental PMTAs. Supplemental PMTAs are an alternative format of submitting a PMTA that meets the requirements of proposed § 1114.7 that would reduce the burden associated with the submission and review of an application. 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 of the FD&C Act for submissions that are based on a PMTA that FDA has previously reviewed. Applicants that have received a marketing 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 order. The applicant would be able to submit a supplemental PMTA only for a modification or modifications that require the submission of limited information or revisions to the PMTA to make it apply to the modified tobacco product. FDA is proposing to restrict 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 would 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.

As discussed in proposed § 1114.15(a), an applicant would not be able to 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. Because supplemental PMTAs are based on a cross-referencing system that is supposed to reduce the burden of preparing and reviewing a PMTA, FDA is proposing 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.

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.

Potentially Appropriate for Supplemental PMTA Format
• Changes in connection type/thread size (*e.g.,* 510).
• Minor Software Changes not affecting device functionality.
○ Changes to user interface.
○ Changes in recording/data capture properties.
• 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.
• Changes to amount of wicking material.
• Minor changes in wick ignition temperature.

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.
• 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, FDA is proposing two other limitations on the submission of a supplemental PMTA. Under proposed § 1114.15(a), a supplemental PMTA could not be submitted where the marketing 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 following a presubmission meeting. FDA is proposing to restrict the submission of supplemental PMTAs in this situation because it can signal that the PMTA for the original tobacco product contains information that is not sufficient or reliable such that a marketing order could be issued. 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.

1. Required Format

Under proposed § 1114.15(b) the supplemental PMTA format would be the same as the format for standard PMTAs submitted under § 1114.7(b), except that applicants would be required to 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. A supplemental PMTA must contain the full text or a cross-reference to text in a master file for the following new content sections under proposed § 1114.15(c)(1):

- General information (as described in § 1114.7(c));
- New product information (as described in § 1114.15(c));
- Statement of compliance with 21 CFR 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(d)); and
- Certification statement (as described in § 1114.15(e)).

A supplemental PMTA must also contain application sections that comprise information included by cross-reference to the PMTA for the original tobacco product. 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 product information section. For example, if a new health risk investigation on the product is published and it is not contained in the new product information section, a full report (as described in § 1114.7(k)(3)) of the investigation must be included in full text together with a cross-reference to the health risk investigations section in the PMTA for the original tobacco product. The cross-reference-based sections that must be included under proposed § 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 proposed § 1114.15(d), the application 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 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 would be 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.
- A concluding summary of how the new tobacco product meets the requirements to receive a marketing 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 order.

4. Postmarket Information

Under proposed § 1114.15(e), a supplemental PMTA would be required to contain postmarket information. 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 that would otherwise be required in a report under proposed § 1114.41, covering the period in time from when it received its marketing order for the original tobacco product to when it submitted the supplemental PMTA. Because information that is contained in a postmarket report is likely to 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

Proposed § 1114.15(f) would require the application to contain a specific certification statement signed by an authorized representative that, in addition to the certification required under § 1114.7(m) for a standard PMTA, certifies that the modifications identified in the certification are the only modification(s) to the original tobacco product.

G. Resubmissions (Proposed § 1114.17)

Proposed § 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 no marketing order. An applicant may submit a resubmission for the same tobacco product that received a no marketing order or for a different new tobacco product that results from changes necessary to address the deficiencies outlined in a no marketing order. This application format allows an applicant to address the deficiencies described in a no marketing order without having to undertake the effort of submitting a standard PMTA. The resubmission format is available to resubmit an application that received a no marketing order because FDA has completed its review of such PMTAs 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 proposed § 1114.33, while FDA will identify the deficiencies that resulted in the no marketing 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 would not be able to 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 no marketing order would require 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 no marketing order if an applicant may not pursue a resubmission to address the identified flaws.

1. Format

Under proposed § 1114.17(b) the resubmission format requirements would be the same as the format in § 1114.7(b) for standard PMTAs, except that applicants would be required to 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 applications because the referenced information will be presented in the proper context and format, and will facilitate application review.

2. Content

The required content for resubmission is divided into two general categories: new content sections and cross-referenced content sections. The resubmission must contain the full text or cross-referenced text from a master file of the following new content sections under proposed § 1114.17(c)(1):

- 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. 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 no marketing order. The cross-reference-based sections that must be included under proposed § 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 proposed § 1114.17(d), the application must contain a section that lists and provides a separate response to each deficiency described by FDA in the no marketing 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 no marketing order, followed by applicant-identified deficiencies. Where an applicant modifies the original tobacco product to address the deficiencies outlined in the no marketing order, the applicant must also include: (a) 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 (b) all data and information relating to each modification to the product that would be required in an application under § 1114.7.

4. Certification Statement

Proposed § 1114.17(e) would require the applicant to include one of two certification statements signed by an authorized representative that, in addition to the certification required under § 1114.7(l) for standard PMTA, certifies either: (a) That the application addresses all deficiencies specified in the no marketing order and is being submitted for a tobacco product that is identical to the product for which FDA issued a no marketing order or (b) 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.

5. Resubmission Meeting

Under proposed § 1114.17(f), 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 no marketing order may contact FDA for more information.

VIII. FDA Review (Proposed Part 1114, Subpart C)

A. Communications Between FDA and Applicants (Proposed § 1114.25)

Proposed § 1114.25 would set forth general principles for the communications between FDA and applicants and is intended to provide more information to applicants about FDA communications. Proposed § 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 may use a variety of methods to communicate with applicants such as telephone conversations, letters, emails, or face-to-face meetings depending on the circumstances and issues. FDA would document 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 order or the date and time at which FDA will act on an application.

B. Review Procedure (Proposed § 1114.27)

Proposed § 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 it acceptance review of all premarket submissions based upon the criteria set forth in § 1105.10. The proposed rule would incorporate and build upon these general criteria to set PMTA-specific acceptance criteria. Under the proposed 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 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 in-depth, 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. This means that 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.

- May otherwise be refused under § 1105.10.

Once FDA has completed its acceptance review under proposed § 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 proposed § 1114.7. Because FDA is not issuing a no marketing order under § 1114.33 when it refuses to accept a submission, an applicant would not be able to utilize the resubmission format described in proposed § 1114.17 to address the flaws outlined by FDA.

FDA is proposing to implement 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 would have to meet to be accepted for review will ensure that FDA will be able to efficiently review applications and consider only applications that meet quality and content standards. 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) and will 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 an existing reason for which FDA may refuse to file an application under § 25.15. The filing requirements would 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 quality elements and appears to be facially complete, the filing review is a more in-depth review to ensure the technical elements contain sufficient information for initiating substantive review. For example, during acceptance review, FDA would check whether the PMTA appears to contain product design parameters, but during filing review, FDA would 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 is proposing to conduct the filing review 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 technical 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 would 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 that would be required by proposed § 1114.7(k)(2)). Proposed § 1114.27(b)(1)(ii) would require a PMTA to contain substantive information regarding certain categories of investigations described in proposed § 1114.7(k)(1). While FDA retains discretion to file applications as set forth in proposed § 1114.27(b)(1), we generally intend to refuse to file each application that does not meet the information threshold 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.[14]

FDA is proposing this application filing requirement under its authority in sections 910(b)(1)(G) 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 risk and benefits to the population the health of the population under section 910(c)(4) of the FD&C Act. Refusing to file PMTAs that contain no information regarding these broad categories of information would allow 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 order. FDA expects that this efficiency would significantly

[14] Information that is available to applicants includes, for example, the studies FDA has funded, published, and made available to the public, which are consolidated FDA's 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.*

benefit those applicants seeking timely consideration of complete, high-quality applications.

Proposed § 1114.27(b)(1)(ii) would require PMTAs to contain substantive information regarding:

- The health risks of the new tobacco product (as described in § 1114.7(k)(1)(i)(A)–(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 and 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 portions of § 1114.7(k)(1)(i)(D)). This would require a comparison to the risks generally presented by a product category as a whole. However, a comparison to 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) would also be sufficient. 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 use 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 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 or switch back to other tobacco products that may present increased risks to individual health (as described in § 1114.7(k)(1)(ii)(C)–(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 that the marketing of the new tobacco product would have on tobacco product initiation by current nonusers of tobacco products (as 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, and advertising 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.

FDA invites comment on the information threshold requirements in proposed § 1114.27(b)(1)(ii), including comments on: Whether the information would be best included in the final rule as a request or a requirement; whether FDA should request or require additional information as a threshold for filing and the basis for any such additional provisions; and how these and other potential requests or requirements related to the information threshold requirement for filing relate to specific provisions of the FD&C Act, as well as other applicable law(s).

- 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, although administratively complete, does not meet the requirements 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 proposed § 1114.15(a), FDA may also refuse to file a supplemental PMTA where the marketing order for the original tobacco product has been temporarily suspended (except where authorized in writing by FDA) or has been withdrawn. As described in proposed § 1114.17(a), FDA would refuse to file a resubmission where the no marketing 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.

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 proposed § 1114.29, act on the application, except as described in proposed §§ 1114.9 and 1114.27(c)(4) & (5). 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 would also include information required by the proposed rule including product samples if required. Because the proposed rule would require the submission of samples in accordance with FDA instructions that are likely to be issued after a PMTA is accepted by FDA, the review clock would begin, at the earliest, when FDA receives product samples if it has required samples and those samples are the last piece needed

to complete an application. Similarly, if an application is missing other pieces of required information, the review clock 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 begins, as well as notice of when it is paused, resumed, or reset.

FDA is proposing four instances in which the 180-day review period after receipt of a complete PMTA would not run over a period of 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 VII.C., the submission of a major amendment would be considered to be the submission of a new PMTA, which would reset the 180-day review clock.

The second instance in which FDA's 180-day review period would not run over 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).[15] 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 clock until any violation of the user fee requirement of part 1150 is resolved. FDA is proposing 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 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 would 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 would not complete its review of a PMTA until the applicant is in compliance with part 1150. FDA is proposing 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.

The third instance in which FDA's 180-day review period would not run over 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 and the sites and entities involved with the clinical and nonclinical research (including third parties and contract research organizations) that would 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 calendar days.

The fourth instance in which FDA's 180-day review period may not run over 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 21 CFR part 25. Under § 25.15(a), failure to submit an adequate EA is grounds for refusing to file or authorize an application. Consistent with § 25.15(a), FDA would refuse to authorize the marketing of a new tobacco product where a PMTA contains an inadequate EA.

As described in proposed § 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. Inspecting sites and entities involved with clinical and nonclinical research, including their records (such as those required to be kept under proposed § 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 order. Under proposed § 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 no marketing 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 US commercial distribution, FDA can view the product being manufactured.

C. FDA Action on an Application (Proposed § 1114.29)

Proposed § 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

[15] Currently, only the manufacturers of cigarettes, cigars, snuff, chewing tobacco, pipe tobacco, and roll-your-own 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.

fails to respond to a request for an amendment within 180 days under § 1114.9(b) or requests to withdraw an application under § 1114.11;

- Third, FDA could issue a letter canceling the application if FDA finds it mistakenly acknowledged 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 order as described in § 1114.31; or
- Sixth, FDA could issue a no marketing order as described in § 1114.33.

D. Issuance of a Marketing Order (Proposed § 1114.31)

Under section 910(c)(1)(A)(i) of the FD&C Act, FDA will issue a marketing 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 order for a new tobacco product, FDA must be able to determine the following:

1. 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 marketing order withdrawal criteria in section 910(d)(1)(A) of the FD&C Act, FDA must continue to find the product meets the APPH standard over time. Generally, 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. Because the APPH standard requires a balancing of product-specific potential risks and benefits, 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 potentially 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. On the other hand, where a PMTA for the same new 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 could potentially result in the issuance of a no marketing order because the product is not likely to have a net benefit to the population as a whole.

Additionally, the factors that could demonstrate 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. 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. As the tobacco product market changes over time, the potential risks and benefits to the population as a whole of marketing a new tobacco product might also change. A new tobacco product that receives a marketing 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. FDA requests comment on its interpretation of the APPH standard set forth in section 910(c) of the FD&C Act, including how it should apply the standard over time as the tobacco product marketplace and tobacco product use behaviors change.

It is important to note that in order for FDA to issue a marketing 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. regarding proposed § 1114.33, failure to submit sufficient information that FDA needs to be able to make its required findings would result in the issuance of a no marketing order.

This proposed 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 order. The proposed rule would create 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 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 order, FDA relies upon only valid scientific evidence to determine whether the marketing of the new tobacco product would be APPH. 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 also 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 it has 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 its 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 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 proposed § 1114.27(b)(1)(ii)), FDA expects that PMTAs would provide sufficient evidence to support the issuance of a marketing order where they contain 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 its product and the U.S. population or provides adequate justification for how the information is relevant. FDA recognizes that this type of long-term 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 and its label, labeling, and advertising 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 no marketing order for the product because it would lack 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.

2. 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 proposed § 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 order under section 910(a)(1)(i)(A) of the FD&C Act. Until such a time as 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.

3. Based on a fair evaluation of all material facts, the proposed labeling is not false or misleading in any particular.

4. 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 proposed rule would be required by proposed § 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 would need to 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 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.

Proposed § 1114.31(b) describes restrictions and additional requirements that FDA may include as part of a marketing 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. Proposed § 1114.31(b)(1) reiterates this authority as part of the rule and proposed § 1114.31(b)(2) would allow FDA to include restrictions on sales and distribution proposed by the applicant as part of its PMTA as part of a marketing order.

Proposed § 1114.31(b)(3) would allow 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, including but 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., 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 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 would allow FDA to ensure it can appropriately track and monitor the impact that the use of such information. FDA anticipates it would 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 No Marketing Order (Proposed § 1114.33)

Proposed § 1114.33 describes the circumstances under which FDA would issue a no marketing order for a new tobacco product after PMTA review. Proposed § 1114.33(a)(1) specifies that FDA would issue a no marketing order if any of the grounds for denial listed in 910(c)(2) of the FD&C Act apply to the application. As mentioned in the discussion of the issuance of a marketing order, meeting the requirements for application acceptance and filing does not mean that an application has sufficient information to receive a marketing order. For example, while FDA may accept and file an application that contains the information in proposed § 1114.7(k), FDA would not issue a marketing order unless that information also makes a showing that the marketing of a new tobacco product would be APPH. While the proposed 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 its potential health risks or face the possibility of receiving a no marketing order. 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 may receive a no marketing order.

Examples of when FDA would be required to issue a no marketing 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 to 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 and outside of the new tobacco product's 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 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.

Proposed § 1114.33(a) would also allow FDA to issue a no marketing 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 order. FDA is proposing to issue a no marketing 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 proposed § 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 proposed § 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 order. As stated in proposed § 1114.45, the records would be required to be legible and written in English.

If FDA issues a no marketing 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 no marketing order, the deficiencies specified in the order might not be an exhaustive listing of all deficiencies contained in the PMTA.

F. Withdrawal of a Marketing Order (Proposed § 1114.35)

Proposed § 1114.35 describes the grounds and procedures for withdrawing a marketing order for a new tobacco product. FDA would 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:

- 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 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 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.

FDA also interprets section 910(d)(1)(A) of the FD&C Act to provide for the withdrawal of a marketing order where changes to the tobacco product marketplace result in FDA finding that the marketing of a product is no longer APPH. FDA interprets the APPH standard to require ongoing consideration of the public health impact of the marketing of a new tobacco product and thus what is necessary to satisfy the standard changes with the tobacco product marketplace. 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 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 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 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. FDA requests public comments on its interpretation of 910(d)(1)(A) of the FD&C Act. FDA requests comment on its interpretation of the APPH standard, including how it should apply the standard over time as the tobacco product marketplace and tobacco product use behaviors change.

- 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.

2. Any postmarket requirement imposed by the marketing 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. FDA is proposing this requirement to allow the withdrawal of a marketing order where an applicant fails to meet requirements imposed by a marketing 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 may seek advice on scientific matters from any appropriate FDA advisory committee in deciding whether to withdraw a marketing order and may use information other than that submitted by the applicant in deciding whether to withdraw a marketing order. Prior to withdrawing a marketing order, FDA will notify the holder of the marketing order of the opportunity for an informal hearing under 21 CFR part 16. If the holder of the marketing order does not request an informal hearing or if FDA decides to withdraw the marketing order after the informal hearing is held, FDA will issue an order withdrawing the marketing order. FDA will notify the public that the marketing order for the product has been withdrawn and state the basis for the withdrawal.

G. Temporary Suspension of a Marketing Order (Proposed § 1114.37)

Proposed § 1114.37 describes the grounds and procedures by which FDA will temporarily suspend a marketing 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 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 proposed rule, FDA will notify the holder of the marketing order of the opportunity to hold an informal hearing. If FDA determines after the opportunity for the informal hearing that the marketing order for the tobacco product should be temporarily suspended, the Agency will issue an order temporarily suspending the marketing 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 order, it will proceed expeditiously to initiate order withdrawal proceedings.

IX. Postmarket Requirements (Proposed Part 1114, Subpart D)

A. Postmarket Changes (Proposed § 1114.39)

Proposed § 1114.39 describes the scope of a marketing order. FDA issues marketing orders for the specific new tobacco product described in the PMTA. An applicant may not make any modification to the product that is the subject of the order, as any modification to the tobacco product would result 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, would be required to be reported under proposed § 1114.41. Applicants seeking to make modifications to the tobacco product may submit a standard PMTA, a supplemental PMTA, or a request for an exemption from substantial equivalence for the modified product, where appropriate, to FDA to seek marketing authorization for the new tobacco product, but may not market the new tobacco product until FDA has authorized the marketing of the new tobacco product. 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 subject to an FDA enforcement action.

B. Reporting Requirements (Proposed § 1114.41)

Proposed § 1114.41 would require applicants that receive a marketing 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 order. Proposed § 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 proposed § 1114.41 to submit two types of reports after receiving a marketing order: Periodic reports and adverse experience reports. Applicants would need to submit periodic reports within 60 calendar days of the reporting date specified in the marketing order (or potentially sooner if they choose to use the application as the basis for a supplemental PMTA under proposed § 1114.15). FDA anticipates that the reports would be required 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 (*e.g.,* the novelty of the type of product). Applicants would have to submit the following information electronically together with the appropriate form (Ref. 11) as part of each periodic report under proposed § 1114.41(a)(1):

- 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 description of the changes made to the manufacturing, facilities, or controls, if any, during the reporting period. This description would be required to include sufficient information for FDA to determine whether a change to the manufacturing, facilities, and controls results in a new tobacco product or could potentially require the marketing order to be withdrawn. This information would include a comparison to the manufacturing, facilities, or controls described in the PMTA, the rationale for marking 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 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 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 proposed § 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 proposed § 1114.7(k)(1) not previously submitted as part of the PMTA or previous postmarket reports, as well as significant findings from publications not previously reported. 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;
- 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. This information 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 and whether the marketing order should be temporarily suspended under section 910(d)(3) of the FD&C Act;
- 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 proposed § 1114.47 and 21 CFR 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, and tobacco use status.

FDA would require 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 product continues to be APPH. The volume of sales, demographics of purchasers, and other sales data provide information that can help indicate trends in tobacco use behavior for the product, such as whether nonusers are initiating tobacco product use with the product and current tobacco product users are using the product. These data are especially important for FDA to review because the data inform a determination of whether the marketing of the new tobacco product continues to be APPH. 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 higher rates of youth initiation with the tobacco product than anticipated in the PMTA could result in FDA finding that continued marketing of the tobacco product is no longer APPH and the marketing order should be withdrawn under section 910(d)(1)(A) of the FD&C Act.

- 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 applicants to submit advertising because it can indicate the potential for trends in tobacco use behavior for the product, such as whether nonusers are likely to initiate tobacco product use with the product and current tobacco product users are likely to use the product (see section VII.B.6 regarding proposed § 1114.7(f) for a discussion of the impact of advertising);
- A description of the implementation of all advertising and marketing plans, including strategic creative briefs and paid media plans (whether conducted by you, on your behalf, or at your direction) 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:

○ Use of competent and reliable data sources, methodologies, and technologies to establish, maintain, and monitor highly targeted advertising and marketing plans and media buys;

○ Targeting of specific adult audiences by age-range(s), including young adults, ages 18–24, and other demographic or psychographic characteristics that reflect the intended target audience, including a list of all data sources used to target advertising and marketing plans and media buys;

○ Actions taken to restrict youth-access and limit youth-exposure to the products' labeling, advertising, marketing, or promotion;

○ Use of owned, earned, shared, or paid media to create labeling for, advertise, market, and/or promote the products;

○ Use of partners, influencers, bloggers, or brand ambassadors to create labeling for, advertise, market, and/or promote the products;

○ Consumer engagements—whether conducted by you, on your behalf, or at your direction—including events at which the products are intended to be demonstrated; and

○ Use of earned media or public-relations outreach to create labeling for, advertise, market, or promote the products;

- A report or summary of the actual delivery of advertising impressions, by channel, by product (if applicable), and by audience demographics (*e.g.,* age, gender, race/ethnicity, geographic location), including a breakout by age-group (*i.e.,* adults, ages 25+; young adults, ages 18–24; and youth, ages 12–17 and ages 11 and under), not previously submitted. This report or summary must be verified against post-launch delivery-verification reports submitted to the tobacco product company from an accredited source; and
- An overall assessment of how the marketing of the tobacco product continues to be APPH.

Applicants would also be 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 proposed § 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 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.

As part of its review of a postmarket report, FDA would be able to 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 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 order, requiring the submission of a new PMTA under § 1114.7 or a supplemental PMTA under § 1114.15 and issuance of a marketing 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 could be subject to enforcement action.

FDA notes that the proposed periodic reporting requirements in § 1114.41 apply most appropriately to new tobacco products that are being actively manufactured, sold, distributed, or consumed. Where an applicant temporarily ceases the introduction, or delivery for introduction, of its new tobacco product into interstate commerce, FDA is seeking public comment regarding whether it should include a provision in the rule that would allow: (1) An applicant to temporarily stop submitting periodic reports, upon notice to, and agreement by, FDA, during the period of time in which it does not introduce, or deliver for introduction, its new tobacco product into interstate commerce; and (2) an applicant to resume the introduction, or delivery for introduction, of is new tobacco product into interstate commerce, upon notice to, and agreement by, FDA, after submitting a periodic report to FDA meeting the requirements of § 1114.41 that covers the period in time since it last submitted a period report or received its order if reports had yet to be submitted. In this scenario, an applicant that fails to submit a

postmarket report and receive FDA agreement prior to resuming the introduction, or delivery for introduction, of its new tobacco product into interstate commerce may be marketing a product in violation of section 902(6)(B) of the FD&C Act, rendering their product adulterated and making it subject to enforcement action. FDA is specifically seeking comment on factors FDA should consider in determining whether the applicant should be allowed to temporarily cease its periodic reporting, including whether product has ceased being manufactured, sold, or distributed either in the United States or abroad.

FDA is also seeking public comment regarding whether it should, rather than creating a provision in a final rule, consider exercising enforcement discretion regarding periodic reporting requirements on a case-by-case basis after receiving the notice under 905(i)(3) of the FD&C Act. Under the requirements of section 905(i)(3), an applicant that receives a marketing order would be required to provide notice to FDA in the event that it discontinues the manufacture, preparation, compounding or processing for commercial distribution of the new tobacco product.

X. Miscellaneous (Proposed Part 1114, Subpart E)

Proposed subpart E describes other procedures and requirements related to PMTAs, including record retention, electronic submission requirements, and confidentiality considerations.

A. Record Retention (Proposed § 1114.45)

Consistent with the authority to require recordkeeping under sections 909 and 910(f) of the FD&C Act, proposed § 1114.45 would require 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 and ensure that such records remain readily available to the Agency upon request. The records would be required to be legible, written in English, and available for inspection and copying by officers or employees designated by the Secretary. This proposed requirement would help 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 order in addition to the requirements in the proposed rule.

1. Record Retention by the Applicant

Under proposed § 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 proposed § 1114.7(k)(3). One way that an applicant may satisfy this requirement is to retain all of the documentation described in part 58.
- 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 would also be required to 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 would also be required to 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.

2. Record Format and Availability

The proposed rule would require 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 would have to retain the records as described in proposed § 1114.45(a)(3). Records relating to the PMTA would have to be retained for a period of no less than 4 years from the date the marketing order is issued. Records relating to the postmarket reports, including both periodic reporting and adverse experience reporting would have to 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 section 704 and 905(g) of the FD&C Act.

B. Confidentiality (Proposed § 1114.47)

Proposed § 1114.47 states that FDA would determine the public availability of any part of any PMTA and other content related to a PMTA as provided under this proposed 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) (21 U.S.C. 387f(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.

Like with drugs and devices, the intent to market a tobacco product is often considered confidential commercial information, as premature disclosure could result in a competitive advantage to competitors. Therefore, FDA is proposing § 1114.47(b), which would address the confidentiality of a PMTA prior to the issuance of a marketing order. Under the proposed

regulation and consistent with part 20, FDA would 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. Proposed § 1114.47(b)(2) provides that FDA would 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 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. Proposed § 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 (which concerns the public disclosure of advisory committee records), except information that has been shown to fall within the exemption established for trade secrets and confidential commercial or financial information in § 20.61, or personal privacy in § 20.63.

Proposed § 1114.47(c) describes the information that FDA will make available after issuing a marketing order consistent with the requirements of § 20.61. Under proposed § 1114.47(c), FDA would 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 that are not exempted from disclosure under § 20.61 for trade secrets and confidential commercial information, or in § 20.63 for personal privacy.

Even after receipt of a no marketing order, the intent to market may still constitute confidential commercial information, as the applicant may still have the goal to market the new tobacco product that is the subject of the PMTA. Under proposed § 1114.47(d), FDA may also make certain information available after it issues a no marketing order unless the information is otherwise exempt from disclosure under part 20. The information that FDA may disclose would include product category, subcategory, package size, and the basis for the no marketing order.

C. Electronic Submission (Proposed § 1114.49)

Consistent with FDA's authority to issue regulations for the efficient enforcement of the FD&C Act, proposed § 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. Reasons that an applicant might request a waiver would include that the applicant has no access to email or a computer. Under proposed § 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 is proposing § 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 quickly than a submission submitted on paper through postal mail. FDA intends to provide 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*). FDA intends to update this information as needed (*e.g.,* to accommodate changes in technology).

XI. Paperwork Reduction Act of 1995

This proposed 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. 3501–3520). A description of these provisions is given in the *Description* section of this document with an estimate of the annual reporting and recordkeeping. 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.

FDA invites comments on these topics: (1) Whether the proposed collection of information is necessary for the proper performance of FDA's functions, including whether the information will have practical utility; (2) the accuracy of FDA's estimate of the burden of the proposed collection of information, including the validity of the methodology and assumptions used; (3) ways to enhance the quality, utility, and clarity of the information to be collected; and (4) ways to minimize the burden of the collection of information on respondents, including through the use of automated collection techniques, when appropriate, and other forms of information technology.

Title: Premarket Tobacco Product Applications and Recordkeeping Requirements, OMB Control Number 0910–0768.

Description: This proposed rule would interpret and codify requirements related to the content and format of PMTAs, the procedure by which FDA would review PMTAs, and the maintenance of records regarding the legal marketing of certain tobacco products without PMTAs. The proposed 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 proposed 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.

FDA is proposing 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 proposing recordkeeping requirements regarding the legal marketing of grandfathered 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 proposed § 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. Proposed § 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 21 CFR part 25, a summary, product formulation, manufacturing, health risk investigations, and a certification statement.

Proposed § 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 proposed 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, is proposing § 1114.9 to allow the submission of amendments to a pending application.

Proposed § 1114.13 describes the steps that an applicant would be required to take when it changes ownership of a PMTA. This proposed 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.

Proposed § 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 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 order. FDA is proposing to restrict 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 would 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.

Proposed § 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 no marketing order. An applicant may submit a resubmission for the same tobacco product that received a no marketing order or for a different new tobacco product that results from changes necessary to address the deficiencies outlined in a no marketing order. This application format allows an applicant to address the deficiencies described in a no marketing order without having to undertake the effort of submitting 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.

Proposed § 1114.41 would require 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. Proposed § 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 proposed § 1114.41 to submit two types of reports after receiving a marketing order: Periodic reports and adverse experience reports.

Applicants would need to submit periodic reports within 60 calendar days of the reporting date specified in the marketing order. FDA anticipates that the reports would be required 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 would also be 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 proposed § 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.

Proposed § 1114.45 would require 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 proposed § 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.

Proposed § 1100.200 states that subpart C of part 1100 would establish requirements for the maintenance of records by tobacco product manufacturers who introduce a grandfathered tobacco product, or deliver it for introduction, into interstate commerce

Proposed § 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.

Proposed § 1114.49 would require an applicant to submit a PMTA and all supporting and related documents to FDA in electronic format. Under proposed § 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 is proposing § 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 quickly than a submission submitted on paper through postal mail.

FDA estimates the burden of this collection of information as follows:

TABLE 21—ESTIMATED ANNUAL REPORTING BURDEN [1]

Activity	Number of respondents	Number 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.

TABLE 22—ESTIMATED ANNUAL REPORTING BURDEN [1]

"21 CFR part"; activity	Number of respondents	Number 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
Premarket Tobacco Product Application (PMTA) Submission (FDA Form 4057)	24	1	24	.50	12
Premarket Tobacco Product Application Amendment And General Correspondence Submission (FDA Form 4057a)	24	14	336	.083	28
1114.41 Reporting Requirements (periodic reports)	3	1	3	50	150
1114.9 Amendments	24	4	96	188	18,048
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	.60	11
1114.49(b) and (c) Waiver from Electronic Submission	1	1	1	.25	.25
Total					22,514

[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 distinct products.

FDA has based these estimates on the full analysis of economic impacts and experience with current PMTA submissions. Table 21 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 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 22 describes the estimated annual reporting burden per the requirements that the proposed 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 Rule was published. For originally regulated products we expect to receive one full PMTA submission for a total of 1,713 hours.

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 .50 (30 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 FDA Form 4057a for use when firms are submitting amendments and other general correspondence. Our estimate is 0.83 (5 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 estimates under proposed § 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 preliminary regulatory impact analysis (PRIA) 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 proposed § 1114.9 firms would prepare amendments to PMTA bundles in response to deficiency letters. These amendments contain additional information that we need to complete substantive review. In the PRIA we state in our limited history reviewing PMTAs, we on average issue four deficiency letters. Based on this, we would anticipate four responses back per bundle. Therefore, we estimate that 24 respondents will submit 96 amendments (24×4). 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 18,048 hours.

Proposed § 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.

Proposed § 1114.15 is an alternative format of submitting a PMTA that meets the requirements of proposed § 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 proposed § 1114.17 an applicant may submit a resubmission for the same tobacco product that received a no marketing order or for a different new tobacco product that results from changes necessary to address the deficiencies outlined in a no marketing order. Based on the PRIA, we are estimating that out of all bundles received in 2020, 2021, and 2022, that an average of 3 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 proposed § 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. Proposed § 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 (15 minutes) per waiver for a total of .25.

TABLE 23—ESTIMATED ANNUAL RECORDKEEPING BURDEN [1]

"21 CFR part" and "activity"	Number of recordkeepers	Number of records per recordkeeper	Total annual records	Average burden per recordkeeping	Total Hours
1114.45 PMTA Records	24	1	24	2	48
1100.204 Grandfathered products 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 23 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 proposed rule, if finalized, would require that firms establish and maintain records related to SE Exemption Requests and Grandfathered products. We expect the burden hours of this proposed 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 proposed rule to be negligible for any Grandfathered products that have already submitted Standalone Grandfathered Submissions, because firms would have established the required records when submitting the Standalone Grandfathered 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 22,514 reporting hours and 52 recordkeeping hours for a total of 22,566.

To ensure that comments on information collection are received, OMB recommends that written comments be faxed to the Office of Information and Regulatory Affairs, OMB (see **ADDRESSES**). All comments should be identified with the title of the information collection.

In compliance with the Paperwork Reduction Act of 1995 (44 U.S.C. 3407(d)), the Agency has submitted the information collection provisions of this proposed rule to OMB for review. These requirements will not be effective until FDA obtains OMB approval. FDA will publish a notice concerning OMB approval of these requirements in the **Federal Register**.

XII. Executive Order 13132: Federalism

We have analyzed this proposed 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 (21 U.S.C. 387p) 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, if this proposed rule is made final, the final rule would create requirements that fall within the scope of section 916(a)(2) of the FD&C Act.

XIII. Consultation and Coordination With Indian Tribal Governments

We have analyzed this proposed rule in accordance with the principles set forth in Executive Order 13175. We have tentatively determined that the rule does not contain policies that would have a substantial direct effect 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. The Agency solicits comments from tribal officials on any potential impact on Indian Tribes from this proposed action.

XIV. 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.

XV. Preliminary Economic Analysis of Impacts

We have examined the impacts of the proposed 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 proposed rule is a significant regulatory action as defined by Executive Order 12866.

The Regulatory Flexibility Act requires us to analyze regulatory options that would minimize any significant impact of a rule on small entities. Because the proposed rule, if finalized, would generate net benefits or negligible costs for most affected small entities, we propose to certify that the proposed rule would 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 $154 million, using the most current (2018) Implicit Price Deflator for the Gross Domestic Product. This proposed rule would not result in an expenditure in any year that meets or exceeds this amount.

The proposed rule, if finalized, would add a requirement that tobacco manufacturers of grandfathered tobacco products and products that are exempt from the requirements of demonstrating substantial equivalence maintain records to demonstrate that they can legally market their products. For products that receive a PMTA marketing order, the proposed rule, if finalized, would require certain postmarket reporting, including recordkeeping, periodic reporting and adverse experience reporting. The proposed rule also sets forth requirements for the content and format of PMTA and the procedures we follow to review the PMTA.

If finalized, the proposed rule would create cost savings for firms and for us by reducing the number of follow-on submissions for PMTAs. The proposed rule would also create cost savings for us by reducing the cost of review, reducing the number of deficiency letters we would issue during substantive scientific review, and eliminating the need to process unnecessary data. In Table 24, we present the total benefits of the proposed rule. We estimate that average annualized benefits over 20 years would equal $5.54 million at a 7 percent discount rate and $5.44 million at a 3 percent discount rate.

If finalized, the proposed rule would create costs for firms and for us by increasing the number of complete PMTA submissions for deemed and originally regulated tobacco products. Moreover, because this is the first regulation to account for the costs of the PMTA requirements for originally regulated products, we also include the costs to submit and review PMTAs for these tobacco products; we already included the costs to submit and review PMTAs for deemed tobacco products in the final regulatory impact analysis for the Deeming Rule. Firms would incur costs to maintain and submit postmarket reports, and we would incur costs to review postmarket reports. Finally, firms would incur costs to read and understand the rule and costs to maintain records for some grandfathered products. In Table 24, we present the total costs of the proposed rule. We estimate that average annualized costs over 20 years would equal $7.05 million at a 7 percent discount rate and $6.76 million at a 3 percent discount rate.

TABLE 24—SUMMARY OF BENEFITS, COSTS, AND DISTRIBUTIONAL EFFECTS OF THE PROPOSED RULE

	Category	Primary estimate	Low estimate	High estimate	Units			Notes
					Year dollars	Discount rate (percent)	Period covered (years)	
Benefits	Annualized Monetized ($m/year).	$5.54	$2.57	$9.23	2017	7	20	All quantified benefits are cost savings.
		5.44	2.54	9.03	2017	3	20	
	Annualized Quantified					7		
						3		
	Qualitative							
Costs	Annualized Monetized ($m/year).	7.05	3.18	11.65	2017	7	20	
		6.76	3.12	11.05	2017	3	20	
	Annualized Quantified					7		
						3		
	Qualitative							

TABLE 24—SUMMARY OF BENEFITS, COSTS, AND DISTRIBUTIONAL EFFECTS OF THE PROPOSED RULE—Continued

	Category	Primary estimate	Low estimate	High estimate	Units			Notes
					Year dollars	Discount rate (percent)	Period covered (years)	
Transfers	Federal Annualized Monetized ($m/year).	From:			To:			
	Other Annualized Monetized ($m/year).	From: Products without marketing orders.			To: Products with marketing orders.			
Effects	State, Local, or Tribal Government: None Small Business: None Wages: None Growth: None							

In line with Executive Order 13771, in Table 15 we estimate present and annualized values of costs and cost savings over an infinite time horizon.

TABLE 15—E.O. 13771 SUMMARY TABLE

[In $ millions 2016 dollars, over an infinite time horizon] [a]

	Primary estimate (7%)	Lower bound (7%)	Upper bound (7%)	Primary estimate (3%)	Lower bound (3%)	Upper bound (3%)
Present Value of Costs	$104.04	$47.84	$170.31	$214.04	$101.20	$349.33
Present Value of Cost Savings	83.18	38.76	138.98	177.26	82.15	296.89
Present Value of Net Costs	20.86	(0.23)	44.29	36.78	(14.19)	91.71
Annualized Costs	3.03	1.39	4.96	6.23	2.95	10.17
Annualized Cost Savings	2.42	1.13	4.05	5.16	2.39	8.65
Annualized Net Costs	0.61	(0.01)	1.29	1.07	(0.41)	2.67

[a] Only the primary estimates (mean) sum in simulation results.

We have developed a comprehensive Preliminary Economic Analysis of Impacts that assesses the impacts of the proposed rule. The full analysis of economic impacts is available in the docket for this proposed rule (Ref. 118) and at *https://www.fda.gov/about-fda/reports/economic-impact-analyses-fda-regulations.*

XVI. Proposed Effectivre Date

FDA proposes that any final rule that issues based on this proposal become effective 30 days after the final rule publishes in the **Federal Register**.

XVII. 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 (see **ADDRESSES**). 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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118. *Preliminary Regulatory Impact Analysis; Initial Regulatory Flexibility Analysis; Unfunded Mandates Reform Act Analysis, Premarket Tobacco Product Applications and Recordkeeping Requirements; Proposed Rule.

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, it is proposed that chapter I of title 21 of the Code of Federal Regulations be 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.

§§ 1100.1, 1100.2, 1100.3, and 1100.5 [Desingated as Subpart A]

■ 3. Designate §§ 1100.1, 1100.2, 1100.3, and 1100.5 as subpart A under the following heading:

Subpart A—Tobacco Products Subject to FDA Authority

Subpart B [Reserved]

■ 4. Add reserved 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.

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 grandfathered tobacco product, or deliver it for introduction, into interstate commerce.

§ 1100.202 Definitions.

For the purposes of this part:

Commercially marketed means the offering of a tobacco product for sale to consumers in all or parts of the United States. Factors FDA may consider include advertising or any other manner used to communicate, that the tobacco product is available for purchase. Tobacco products that are exclusively in a test market are not commercially marketed.

Grandfathered tobacco product means 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 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.

(a) Any tobacco product manufacturer that introduces a grandfathered 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:

(1) Dated copies of advertisements;
(2) Dated catalog pages;
(3) Dated promotional material;
(4) Dated trade publications;
(5) Dated bills of lading;
(6) Dated freight bills;
(7) Dated waybills;

(8) Dated invoices;
(9) Dated purchase orders;
(10) Dated customer receipts;
(11) Dated manufacturing documents;
(12) Dated distributor or retailer inventory lists; or
(13) Any other dated document that demonstrates that the tobacco product was commercially marketed (not exclusively in test markets) in the United States as of February 15, 2007.

(b) 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.

(c) 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 grandfathered 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 ''grandfathered tobacco product'' means a tobacco product that was commercially marketed in the United States on February 15, 2007. The term 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 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) Product labeling.

(vi) Documents related to product packing and storage conditions.

(vii) Analytical test method records, including:

(A) Performance criteria.

(B) Validation or verification documentation; and

(C) Reports/results from these test methods.

(viii) Source data and related summaries.

(2) An applicant that submits an abbreviated report for a modification to a grandfathered tobacco product must also maintain records demonstrating that the grandfathered 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 received 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, or a substantial equivalence (SE) or premarket tobacco product application marketing order must maintain a copy of the exemption order or marketing order.

(4) An applicant that submits an abbreviated report for a modification to a tobacco product marketed consistent with section 910(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act, but for which an SE order has not been granted, 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 order.
1114.33 Issuance of a no marketing order.
1114.35 Withdrawal of a marketing order.
1114.37 Temporary suspension of a marketing 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 under section 911(l)(4) of

the Federal Food, Drug, and Cosmetic Act seeking both a marketing 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.

§ 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 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.

Component or *part* means

(1) Any software or assembly of materials intended or reasonably expected:

(i) To alter or affect the tobacco product's performance, composition, constituents, or characteristics; or

(ii) To be used with or for the human consumption of a tobacco product.

(2) 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 or in tobacco smoke or emission that is or potentially is inhaled, ingested, or absorbed into the body.

Container closure system means any packaging materials that are a component or part of the 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).

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 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 the 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.

No marketing 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.

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.

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.

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.

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 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.

§ 1114.7 Required content and format.

(a) *General.* 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 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 (as described in paragraph (f) of this section);

(5) Statement of compliance with part 25 of this chapter (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 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 § 1114.7(c)(3)(iii)

Tobacco product category:	Tobacco product subcategory:	Product properties:
(A) Cigarettes	*(1)* Combusted, Filtered	—Package type (*e.g.,* hard pack, soft pack, clam shell). —Product quantity (*e.g.,* 20 cigarettes). —Length (*e.g.,* 89 millimeters (mm), 100 mm). —Diameter (*e.g.,* 6 mm, 8.1 mm).

TABLE 1 TO § 1114.7(c)(3)(iii)—Continued

Tobacco product category:	Tobacco product subcategory:	Product properties:
		—Ventilation (*e.g.,* 0%, 10%, 25%). —Characterizing flavor(s) (*e.g.,* none, menthol). —Additional properties needed to uniquely identify the tobacco product (if applicable).
	(2) Combusted, Nonfiltered	—Package type (*e.g.,* hard pack, soft pack, clam shell). —Product quantity (*e.g.,* 20 cigarettes). —Length (*e.g.,* 89 mm, 100 mm). —Diameter (*e.g.,* 6 mm, 8.1 mm). —Characterizing flavor(s) (*e.g.,* none, menthol). —Additional properties needed to uniquely identify the tobacco product (if applicable).
	(3) Combusted, Bidi, and Other	—Package type (*e.g.,* hard pack, soft pack, clam shell). —Product quantity (*e.g.,* 20 cigarettes). —Length (*e.g.,* 89 mm, 100 mm). —Diameter (*e.g.,* 6 mm, 8.1 mm). —Ventilation (*e.g.,* 0%, 10%, 25%) (if applicable). —Characterizing flavor(s) (*e.g.,* none, menthol). —Additional properties needed to uniquely identify the tobacco product (if applicable).
	(4) Noncombusted (*e.g.,* heated tobacco).	—Package type (*e.g.,* hard pack, soft pack, clam shell). —Product quantity (*e.g.,* 20 cigarettes, 25 cigarettes). —Length (*e.g.,* 89 mm, 100 mm). —Diameter (*e.g.,* 6 mm, 8.1 mm). —Ventilation (*e.g.,* 0%, 10%, 25%). —Characterizing flavor(s) (*e.g.,* none, menthol). —Source of energy (*e.g.,* charcoal, electrical heater). —Additional properties needed to uniquely identify the tobacco product (if applicable).
	(5) Cigarette, Co-Package	—For a new co-packaged tobacco product composed of multiple cigarette tobacco products, include, as applicable, all properties for each individual tobacco product, as identified above.
(B) Roll-Your-Own Tobacco Products.	*(1)* Roll-Your-Own Tobacco Filler	—Package type (*e.g.,* bag, pouch). —Product quantity (*e.g.,* 20 g, 40 grams (g)). —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.,* bag, box, booklet). —Product quantity (*e.g.,* 200 papers). —Length (*e.g.,* 79 mm, 100 mm, 110 mm). —Width (*e.g.,* 45 mm, 60 mm, 78 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 mm, 100 mm). —Diameter (*e.g.,* 6 mm, 8.1 mm). —Ventilation (*e.g.,* 0%, 10%, 25%). —Characterizing flavor(s) (*e.g.,* none, menthol). —Additional properties needed to uniquely identify the tobacco product (if applicable).
	(4) Cigarette Tube, Nonfiltered	—Package type (*e.g.,* bag, box). —Product quantity (*e.g.,* 100 tubes, 200 tubes). —Length (*e.g.,* 89 mm, 100 mm). —Diameter (*e.g.,* 6 mm, 8.1 mm). —Characterizing flavor(s) (*e.g.,* none, menthol). —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 mm, 12 mm). —Diameter (*e.g.,* 6 mm, 8.1 mm). —Ventilation (*e.g.,* 0%, 10%, 25%). —Characterizing flavor(s) (*e.g.,* none, menthol). —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 mm, 15 mm). —Width (*e.g.,* 27 mm). —Characterizing flavor(s) (*e.g.,* none, menthol).

TABLE 1 TO § 1114.7(c)(3)(iii)—Continued

Tobacco product category:	Tobacco product subcategory:	Product properties:
		—Additional properties needed to uniquely identify the tobacco product (if applicable).
	(7) Roll-Your-Own, Co-Package ...	—For a new tobacco product composed of multiple roll-your-own tobacco products, include all applicable properties for each tobacco product (*e.g.,* roll-your own tobacco, rolling paper, filtered cigarette tube, nonfiltered cigarette tube, filter, paper tip) as identified above.
		—Additional properties needed to uniquely identify the tobacco product (if applicable).
	(8) Other	—Package type (*e.g.,* bag, box). —Product quantity. —Characterizing flavor(s) (*e.g.,* none, menthol). —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 g, 30 g). —Tobacco cut size (*e.g.,* 5 mm, 7 mm). —Characterizing flavor(s) (*e.g.,* none, menthol, cherry, wintergreen). —Additional properties needed to uniquely identify the tobacco product (if applicable).
	(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 g). —Portion count (*e.g.,* 15 pouches, 20 pieces). —Portion mass (*e.g.,* 1.5 g/pouch, 2 g/piece). —Portion length (*e.g.,* 15 mm, 20 mm). —Portion width (*e.g.,* 10 mm, 15 mm). —Portion thickness (*e.g.,* 5 mm, 7 mm). —Tobacco cut size (*e.g.,* 5 mm, 7 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 g, 2 ounces). —Tobacco cut size (*e.g.,* 5 mm, 7 mm). —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 g). —Portion count (*e.g.,* 15 pouches, 20 pieces). —Portion mass (*e.g.,* 1.5 g/pouch, 2 g/piece). —Portion length (*e.g.,* 15 mm, 20 mm). —Portion width (*e.g.,* 10 mm, 15 mm). —Portion thickness (*e.g.,* 5 mm, 7 mm). —Tobacco cut size (*e.g.,* 5 mm, 7 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 g, 2 ounces). —Tobacco cut size (*e.g.,* 0.05 mm, 0.07 mm). —Characterizing flavor(s) (*e.g.,* none, menthol, cherry, wintergreen). —Additional properties needed to uniquely identify the tobacco product (if applicable).
	(6) Dry Snuff, Portioned	—Package type (*e.g.,* plastic can with metal lid, plastic can with plastic lid). —Product quantity (*e.g.,* 22.5 g, 20 g). —Portion count (*e.g.,* 15 pouches, 20 pieces). —Portion mass (*e.g.,* 1.5 g/pouch, 2 g/piece). —Portion length (*e.g.,* 10 mm, 15 mm). —Portion width (*e.g.,* 5 mm, 8 mm). —Portion thickness (*e.g.,* 3 mm, 4 mm). —Tobacco cut size (*e.g.,* 5 mm, 7 mm). —Characterizing flavor(s) (*e.g.,* none, menthol, cherry, wintergreen).
	(7) Dissolvable	—Package type (*e.g.,* plastic can with metal lid, plastic can with plastic lid). —Product quantity (*e.g.,* 22.5 g, 20 g).

TABLE 1 TO § 1114.7(c)(3)(iii)—Continued

Tobacco product category:	Tobacco product subcategory:	Product properties:
		—Product form (*e.g.,* strip, tablet, stick). —Portion count (*e.g.,* 15 sticks, 20 tablets). —Portion mass (*e.g.,* 1.5 g/strip, 1.0 g/piece). —Portion length (*e.g.,* 10 mm, 15 mm). —Portion width (*e.g.,* 5 mm, 8 mm). —Portion thickness (*e.g.,* 3 mm, 4 mm). —Tobacco cut size (*e.g.,* 0.05 mm, 0.07 mm). —Characterizing flavor(s) (*e.g.,* none, menthol, cherry, wintergreen). —Additional properties needed to uniquely identify the tobacco product (if applicable).
	(8) Chewing Tobacco, Loose	—Package type (*e.g.,* bag, pouch). —Product quantity (*e.g.,* 20 g, 40 g). —Tobacco cut size (*e.g.,* 0.05 mm, 0.07 mm). —Characterizing flavor(s) (*e.g.,* none, menthol, cherry, wintergreen). —Additional properties needed to uniquely identify the tobacco product (if applicable).
	(9) Chewing Tobacco, Portioned ..	—Package type (*e.g.,* plastic can with metal lid, plastic can with plastic lid). —Product quantity (*e.g.,* 20 g). —Product form (*e.g.,* plug, twist, portioned chewing tobacco). —Portion count (*e.g.,* 1 plug, 3 twists, 10 bits). —Portion mass (*e.g.,* 2 g/bit). —Portion length (*e.g.,* 8 mm, 10 mm). —Portion width (*e.g.,* 6 mm, 8 mm). —Portion thickness (*e.g.,* 5 mm, 7 mm). —Characterizing flavor(s) (*e.g.,* none, menthol, cherry, wintergreen). —Additional properties needed to uniquely identify the tobacco product (if applicable).
	(10) Smokeless Co-Package	—For a new tobacco product composed of multiple smokeless tobacco products, include all applicable properties for each individual tobacco product as identified above. —Additional properties needed to uniquely identify the tobacco product (if applicable).
	(11) Other	—Package type (*e.g.,* bag, box). —Product quantity. —Characterizing flavor(s) (*e.g.,* none, menthol). —Additional properties needed to uniquely identify the tobacco product.
(D) ENDS (Electronic Nicotine Delivery System).	*(1)* E-Liquid, Open	—Package type (*e.g.,* bottle, box). —Product quantity (*e.g.,* 1 bottle, 5 bottles). —Characterizing flavor(s) (*e.g.,* none, tobacco, menthol, cherry, wintergreen). —E-liquid volume (*e.g.,* 10 milliliter (ml)). —Nicotine concentration (*e.g.,* 0, 0.2 mg/ml). —Propylene glycol/vegetable glycerin (PG/VG) ratio (*e.g.,* N/A, 0/100, 50/50). —Additional properties needed to uniquely identify the tobacco product (if applicable).
	(2) E-Liquid, Closed	—Package type (*e.g.,* cartridge). —Product quantity (*e.g.,* 1 cartridge, 5 cartridges). —Characterizing flavor(s) (*e.g.,* none, tobacco, menthol, cherry, wintergreen). —E-liquid volume (*e.g.,* 10 ml). —Nicotine concentration (*e.g.,* 0, 0.2 mg/ml). —PG/VG ratio (*e.g.,* N/A, 0/100, 50/50). —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). —Characterizing flavor(s) (*e.g.,* none, tobacco, menthol, cherry, wintergreen). —Length (*e.g.,* 100 mm, 120 mm). —Diameter (*e.g.,* 6 mm, 8 mm). —E-liquid volume (*e.g.,* 2 ml, 5 ml). —Nicotine concentration (*e.g.,* 0, 0.2 mg/ml). —PG/VG ratio (*e.g.,* N/A, 0/100, 50/50). —Wattage (*e.g.,* 100 W, 200 W). —Battery capacity (*e.g.,* 100 mAh, 200 mAh). —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).

TABLE 1 TO § 1114.7(c)(3)(iii)—Continued

Tobacco product category:	Tobacco product subcategory:	Product properties:
		—Characterizing flavor(s) (*e.g.,* none, tobacco, menthol, cherry, wintergreen). —Length (*e.g.,* 100 mm, 120 mm). —Diameter (*e.g.,* 8 mm, 14 mm). —E-liquid volume (*e.g.,* 2 ml, 5 ml). —Wattage (*e.g.,* 100 W, 200 W). —Battery capacity (*e.g.,* 100 mAh, 200 mAh). —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 e-cigarette, 5 e-cigarettes). —Characterizing flavor(s) (*e.g.,* none, tobacco, menthol, cherry, wintergreen). —Additional properties needed to uniquely identify the tobacco product (if applicable).
	(6) ENDS Co-Package	—For a new tobacco product composed of multiple ENDS tobacco products, include all applicable properties for each individual tobacco product as identified above. —Additional properties needed to uniquely identify the tobacco product (if applicable).
	(7) ENDS Other	—Package type (*e.g.,* bag, box). —Product quantity. —Characterizing flavor(s) (*e.g.,* none, 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). —Characterizing flavor (*e.g.,* none, menthol). —Length (*e.g.,* 89 mm, 100 mm). —Diameter (*e.g.,* 6 mm, 8.1 mm). —Ventilation (*e.g.,* none, 10%, 25%). —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). —Characterizing flavor (*e.g.,* none, menthol). —Length (*e.g.,* 100 mm, 140 mm). —Diameter (*e.g.,* 8 mm, 10 mm). —Tip (*e.g.,* none, wood tips, plastic tips). —Additional properties needed to uniquely identify the tobacco product (if applicable).
	(3) Cigar, Leaf-Wrapped	—Package type (*e.g.,* box, film, sleeve, none). —Product quantity (*e.g.,* 1 cigar, 5 cigars). —Characterizing flavor (*e.g.,* none, whiskey). —Length (*e.g.,* 150 mm, 200 mm). —Diameter (*e.g.,* 8 mm, 10 mm). —Wrapper material (*e.g.,* burley tobacco leaf, Connecticut shade grown tobacco leaf). —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 g, 16 ounces). —Characterizing flavor (*e.g.,* none, menthol, cherry). —Tobacco cut size (*e.g.,* 15 cuts per inch). —Additional properties needed to uniquely identify the tobacco product (if applicable).
	(6) Cigar Co-Package	—For a new tobacco product composed of multiple cigar tobacco products, include all applicable properties for each individual tobacco product as identified above. —Additional properties needed to uniquely identify the tobacco product (if applicable).
	(7) Other	—Package type (*e.g.,* bag, box). —Product quantity. —Characterizing flavor(s) (*e.g.,* none, menthol). —Additional properties needed to uniquely identify the tobacco product.
(F) Pipe Tobacco Products	*(1)* Pipe	—Package type (*e.g.,* box, none).

TABLE 1 TO § 1114.7(c)(3)(iii)—Continued

Tobacco product category:	Tobacco product subcategory:	Product properties:
		—Product quantity (*e.g.,* 1 pipe). —Length (*e.g.,* 200 mm, 300 mm). —Diameter (*e.g.,* 25 mm). —Characterizing flavor(s) (*e.g.,* none, menthol). —Additional properties needed to uniquely identify the tobacco product (if applicable).
	(2) Pipe Tobacco Filler	—Package type (*e.g.,* bag, pouch). —Product quantity (*e.g.,* 20 g, 16 ounces). —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.,* bowl, shank, stem, screen, filter). —Product quantity (*e.g.,* 1 bowl, 1 stem, 100 filters). —Characterizing flavor(s) (*e.g.,* none, menthol). —Additional properties needed to uniquely identify the tobacco product (if applicable).
	(4) Pipe Co-Package	—For a new tobacco product composed of multiple pipe tobacco products, include all applicable properties for each individual tobacco product as identified above. —Additional properties needed to uniquely identify the tobacco product (if applicable).
	(5) Other	—Package type (*e.g.,* bag, box). —Product quantity. —Characterizing flavor(s) (*e.g.,* none, menthol). —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). —Length (*e.g.,* 200 mm, 500 mm). —Width (*e.g.,* 100 mm, 300 mm). —Number of hoses (*e.g.,* 1, 2, 4). —Characterizing flavor(s) (*e.g.,* none, menthol). —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 g, 16 ounces). —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 g, 680 g). —Characterizing flavor(s) (*e.g.,* none, menthol, apple). —Portion count (*e.g.,* 20 fingers, 10 discs, 1 base). —Portion mass (*e.g.,* 15 g/finger). —Portion length (*e.g.,* 40 mm, 100 mm). —Portion width (*e.g.,* 10 mm, 40 mm). —Portion thickness (*e.g.,* 10 mm, 40 mm). —Source of energy (*e.g.,* charcoal, battery, electrical). —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, apple). —Additional properties needed to uniquely identify the tobacco product (if applicable).
	(5) Waterpipe Co-Package	—For a new tobacco product composed of multiple waterpipe tobacco products, include all applicable properties for each individual tobacco product as identified above. —Additional properties needed to uniquely identify the tobacco product (if applicable).
	(6) Waterpipe Other	—Package type (*e.g.,* bag, box). —Product quantity. —Characterizing flavor(s) (*e.g.,* none, tobacco, menthol). —Additional properties needed to uniquely identify the tobacco product (if applicable).
Other	Other	—Package type (*e.g.,* bag, box). —Product quantity. —Characterizing flavor(s) (*e.g.,* none, tobacco, menthol). —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) Address and the Facility Establishment Identifier (FEI) number(s), if available, of the establishment(s) involved in the manufacture of the new tobacco product;

(9) A brief statement regarding how the PMTA satisfies the content requirements of section 910(b)(1) of the Federal Food, Drug, and Cosmetic Act;

(10) A brief description of how marketing of the new tobacco product would be appropriate for the protection of the public health; and

(11) 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 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 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) *Marketing plans.* A PMTA must contain a description of the applicant's plans for labeling, advertising, marketing, promotion, and other consumer-directed activities regarding the new tobacco product developed by the time of filing. Such marketing plans must contain descriptions of actions that would be taken by the applicant, on behalf of the applicant, or at the applicant's direction for at least the first year the product would be marketed after receiving an order. If an applicant does not intend to use any advertising, marketing, promotion, or other communication activities directed at consumers, or has not developed marketing plans by the time of submission, the PMTA must contain a statement to that effect. As part of the description of the marketing plan, the PMTA must specify items such as the intended target audience(s), media and distribution channels, particular tactics, total dollar amount(s) of media buys and marketing and promotional activities (where applicable), and timing for the activities, including, but not limited to, information describing:

(i) The use of competent and reliable data sources, tools, technologies, and methodologies to establish, maintain, and monitor highly targeted marketing plans and media buys;

(ii) The target adult audiences by age-range(s) (including young adult audiences ages 18 to 24), and other demographic or psychographic characteristics;

(iii) The insights into the target audience the applicant is using to inform its marketing plans, including its strategic approach, key messages and themes, creative direction, and potential marketing tactics or channels.

(iv) Any means by which youth-access or youth-exposure to the products' labeling, advertising, marketing, and promotion would be limited;

(v) The use of owned, earned, shared, or paid media to advertise or promote the products;

(vi) The use of partners, sponsors, influencers, bloggers, or brand ambassadors to advertise or promote the products;

(vii) The use of consumer engagements, including events at which the products will be demonstrated or sampled; and

(viii) The use of earned media, public-relations, or other communications outreach to promote the products.

(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.

(2) Where the new tobacco product results from modifications to a legally marketed predecessor product, the environmental assessment must state whether the new tobacco product is intended to replace the predecessor tobacco product once the new tobacco product receives market authorization and is commercially marketed, be a line extension of the predecessor tobacco product, be marketed along with the predecessor product by the same manufacturer, or be marketed along with the predecessor tobacco product by a different manufacturer.

(h) *Summary.* The application must include a summary of all information contained in the application, including the following items, and identify areas in which there is a lack of information, where applicable:

(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:

(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, of tobacco product users;

(iii) The impact the product and its marketing will have on the likelihood of tobacco use initiation by tobacco products nonusers;

(iv) How users and nonusers perceive the risk of the tobacco product based upon its labeling, packaging, and marketing;

(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.

(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;

(F) The specification(s) (including quality/grades and suppliers) used for the new tobacco product; 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);

(C) The function of the ingredient;

(D) The quantity with the unit of measure (including ranges or means and acceptance limits) of the material(s) of the ingredients in the tobacco product reported as mass per gram of tobacco for nonportioned tobacco products and as mass per portion for portioned tobacco products;

(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), including grade(s) and variety/varieties;

(B) The quantity with the unit of measure (including ranges or means, acceptance limits) of tobacco 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) The analytical methods used and associated reference(s);

(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; and

(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 regimens.

(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 20 of this paragraph as applicable; 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 20 of this paragraph for the product category as applicable:

TABLE 1 TO § 1114.7(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 mass (mg). • Cigarette length (mm). • Cigarette diameter (mm). • Cigarette draw resistance (mm H_2O). • Tobacco rod length (mm). • Tobacco filler mass (mg). • Tobacco rod density (g/cm^3). • Tobacco cut size (mm). • Tobacco moisture (%). • Cigarette paper length (mm). • Cigarette paper width (mm). • Cigarette paper base paper basis weight (g/m^2). • Cigarette paper base paper porosity (CU). • Cigarette paper band porosity (CU). • Cigarette paper band diffusivity (cm^2/s). • Cigarette paper band width (mm). • Cigarette paper band space (mm). • Filter length (mm). • Filter diameter (mm). • Filter mass (mg) • Filter density (g/cm^3). • Filter tow crimping index. • Filter pressure drop (mm H_2O). • Filter efficiency (%). • Filter total denier (g/9000m). • Filter denier per filament (dpf) • Plug wrap length (mm). • Plug wrap width (mm). • Plug wrap basis weight (g/m^2). • Plug wrap porosity (CU). • Tipping paper length (mm). • Tipping paper width (mm). • Tipping paper basis weight (g/m^2). • Tipping paper perforation (CU). • Filter ventilation (%). • Filter ventilation position of holes. • Filter ventilation number of holes. • Filter ventilation number of rows.	• Cigarette mass (mg). • Cigarette length (mm). • Cigarette diameter(mm). • Cigarette draw resistance (mm H_2O). • Puff count. • Tobacco rod length (mm). • Tobacco filler mass (mg). • Tobacco rod density (g/cm^3). • Tobacco cut size (mm). • Tobacco moisture (%). • Cigarette paper length (mm). • Cigarette paper width (mm). • Cigarette paper base paper basis weight (g/m^2). • Cigarette paper base paper porosity (CU). • Cigarette paper band porosity (CU). • Cigarette paper band diffusivity (cm^2/s). • Cigarette paper band width (mm). • Cigarette paper band space (mm). • Filter length (mm). • Filter diameter (mm). • Filter mass (mg). • Filter density (g/cm^3). • Filter tow crimping index. • Filter pressure drop (mm H_2O). • Filter efficiency (%). • Filter total denier (g/9000m). • Filter denier per filament (dpf). • Plug wrap length (mm). • Plug wrap width (mm). • Plug wrap basis weight (g/m^2). • Plug wrap porosity (CU). • Tipping paper length (mm). • Tipping paper width (mm). • Tipping paper basis weight (g/m^2). • Tipping paper perforation (CU). • Filter ventilation (%).

TABLE 2 TO § 1114.7(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). • Tobacco moisture (%). • Portion length (mm). • Portion width (mm). • Portion mass (mg). • Portion thickness (mm). • Pouch material basis weight (g/m^2). • Pouch material air permeability (L/m^2/s). • Pouch material nicotine dissolution rate (%/min). • Pouch material nicotine dissolution extent (mg). • Pouch material thickness (μm).	• Tobacco cut size (mm). • Tobacco moisture (%). • Portion length (mm). • Portion width (mm). • Portion mass (mg). • Portion thickness (mm). • Pouch material basis weight (g/m^2). • Pouch material air permeability (L/m^2/s). • Pouch material nicotine dissolution rate (%/min). • Pouch material nicotine dissolution extent (mg). • Pouch material thickness (μm).
Nonportioned Smokeless Tobacco Products	
• Tobacco cut size (mm).	• Tobacco cut size (mm).

TABLE 2 TO § 1114.7(i)(2)(ii)—REQUIRED DESIGN PARAMETER INFORMATION FOR PORTIONED AND NONPORTIONED SMOKELESS TOBACCO PRODUCTS—Continued

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 moisture (%).	• Tobacco moisture (%).

TABLE 3 TO § 1114.7(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 paper mass (mg). • RYO paper base paper basis weight (g/m^2). • RYO paper base paper porosity (CU). • RYO paper band porosity (CU). • RYO paper band diffusivity (cm^2/s). • RYO paper band width (mm). • RYO paper band space (mm).	• RYO paper length (mm). • RYO paper width (mm). • RYO paper mass (mg). • RYO paper base paper basis weight (g/m^2). • RYO paper base paper porosity (CU). • RYO paper band porosity (CU). • RYO paper band diffusivity (cm^2/s). • RYO paper band width (mm). • RYO paper band space (mm).

TABLE 4 TO § 1114.7(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 diameter (mm). • Tube paper length (mm). • Tube paper width (mm). • Tube paper base paper basis weight (g/m^2). • Tube paper base paper porosity (CU). • Tube paper band porosity (CU). • Tube paper band diffusivity (cm^2/s). • Tube paper band width (mm). • Tube paper band space (mm).	• Tube mass (mg). • Tube length (mm). • Tube diameter (mm). • Tube paper length (mm). • Tube paper width (mm). • Tube paper base paper basis weight (g/m^2). • Tube paper base paper porosity (CU). • Tube paper band porosity (CU). • Tube paper band diffusivity (cm^2/s). • Tube paper band width (mm). • Tube paper band space (mm).

TABLE 5 TO § 1114.7(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 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 (CU). • Tube paper band porosity (CU). • Tube paper band diffusivity (cm^2/s). • Tube paper band width (mm). • Tube paper band space (mm). • Filter length (mm). • Filter diameter (mm). • Filter mass (mg). • Filter density (g/cm^3). • Filter tow crimping index. • Filter pressure drop (mm H_2O). • Filter efficiency (%). • Filter total denier (g/9000m). • Filter denier per filament (dpf). • Plug wrap length (mm). • Plug wrap width (mm). • Plug wrap basis weight (g/m^2). • Plug wrap porosity (CU). • Tipping paper length (mm). • Tipping paper width (mm). • Tipping paper basis weight (g/m^2).	• Tube mass (mg). • Tube length (mm). • Tube 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 (CU). • Tube paper band porosity (CU). • Tube paper band diffusivity (cm^2/s). • Tube paper band width (mm). • Tube paper band space (mm). • Filter length (mm). • Filter diameter (mm). • Filter mass (mg). • Filter density (g/cm^3). • Filter tow crimping index. • Filter pressure drop (mm H_2O). • Filter efficiency (%). • Filter total denier (g/9000m). • Filter denier per filament (dpf). • Plug wrap length (mm). • Plug wrap width (mm). • Plug wrap basis weight (g/m^2). • Plug wrap porosity (CU). • Tipping paper length (mm). • Tipping paper width (mm). • Tipping paper basis weight (g/m^2).

TABLE 5 TO § 1114.7(i)(2)(ii)—REQUIRED DESIGN PARAMETER INFORMATION FOR RYO TOBACCO FILTERED TUBES—Continued

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:
• Tipping paper perforation (CU). • Filter ventilation (%). • Filter ventilation position of holes. • Filter ventilation number of holes. • Filter ventilation number of rows.	• Tipping paper perforation (CU). • Filter ventilation (%).

TABLE 6 TO § 1114.7(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 filler mass (mg). • Tobacco cut size (mm). • Tobacco moisture (%).	• Tobacco filler mass (mg). • Tobacco cut size (mm). • Tobacco moisture (%).

TABLE 7 TO § 1114.7(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 perforation (CU). • RYO paper tip ventilation (%).	• 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 perforation (CU). • RYO paper tip ventilation (%).

TABLE 8 TO § 1114.7(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 length (mm). • Cigar diameter (mm). • Tobacco filler mass (mg). • Tobacco rod density (g/cm^3). • Tobacco cut size (mm). • Tobacco moisture (%). • Cigar wrapper porosity (CU). • Cigar binder porosity (CU). • Filter length (mm). • Filter diameter (mm). • Filter pressure drop (mm H_2O). • Filter efficiency (%). • Tipping paper length (mm). • Filter ventilation (%).	• Cigar length (mm). • Cigar diameter (mm). • Tobacco filler mass (mg). • Tobacco rod density (g/cm^3). • Tobacco cut size (mm). • Tobacco moisture (%). • Cigar wrapper porosity (CU). • Cigar binder porosity (CU). • Filter length (mm). • Filter diameter (mm). • Filter pressure drop (mm H_2O). • Filter efficiency (%). • Tipping paper length (mm). • Filter ventilation (%).

TABLE 9 TO § 1114.7(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 minimum diameter (mm). • Cigar maximum diameter (mm). • Tobacco filler mass (mg). • Cigar wrapper porosity (CU). • Cigar tip length (mm) (if applicable). • Cigar tip inner diameter (mm) (if applicable). • Cigar tip width (mm) (if applicable).	• Cigar mass (mg). • Cigar length (mm). • Cigar minimum diameter (mm). • Cigar maximum diameter (mm). • Tobacco filler mass (mg). • Cigar wrapper porosity (CU). • Cigar tip length (mm) (if applicable). • Cigar tip inner diameter (mm) (if applicable). • Cigar tip width (mm) (if applicable).

TABLE 10 TO § 1114.7(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). • Cigar minimum diameter (mm). • Cigar maximum diameter (mm). • Tobacco moisture (%).	• Cigar mass (mg). • Cigar length (mm). • Cigar minimum diameter (mm). • Cigar maximum diameter (mm). • Tobacco moisture (%).

TABLE 11 TO § 1114.7(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 (mm). • Tobacco moisture (%).	• Tobacco cut size (mm). • Tobacco moisture (%).

TABLE 12 TO § 1114.7(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 minimum width (mm). • Cigar wrapper maximum width (mm).	• Cigar wrapper length (mm). • Cigar wrapper minimum width (mm). • Cigar wrapper maximum width (mm).

TABLE 13 TO § 1114.7(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:
• Number of hoses. • Bowl volume (ml).	• Bowl volume (ml).

TABLE 14 TO § 1114.7(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 (mm). • Tobacco moisture (%).	• Tobacco cut size (mm). • Tobacco moisture (%).

TABLE 15 TO § 1114.7(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 source type. • Charcoal temperature (°C) (if applicable). • Coil temperature range (°C) (if applicable). • Power delivery unit (PDU) temperature cut-off (°C) (if applicable).	• Charcoal temperature (°C) (if applicable). • Coil temperature range (°C) (if applicable). • PDU temperature cut-off (°C) (if applicable).

TABLE 16 TO § 1114.7(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). • Foil width (mm).	• Foil length (mm). • Foil width (mm).

TABLE 17 TO § 1114.7(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:
• Bore minimum diameter (mm). • Bore maximum diameter (mm). • Bit length (mm).	• Bore minimum diameter (mm). • Bore maximum diameter (mm). • Bit length (mm).

TABLE 17 TO § 1114.7(i)(2)(ii)—REQUIRED DESIGN PARAMETER INFORMATION FOR PIPES—Continued

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:
• Bit diameter (mm). • Stem length (mm). • Stem diameter (mm).	• Bit diameter (mm). • Stem length (mm). • Stem diameter (mm).

TABLE 18 TO § 1114.7(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 (mm). • Tobacco moisture (%).	• Tobacco cut size (mm). • Tobacco moisture (%).

TABLE 19 TO § 1114.7(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:
• Airflow rate (cc/min). • Coil resistance (ohms). • Overall atomizer resistance (ohms). • Wick ignition temperature (°C). • Battery mAh rating (mAh). • PDU wattage operating range (W). • Coil temperature cut-off (°C). • Coil temperature range (°C).	• Airflow rate (cc/min). • Coil resistance (ohms). • Overall atomizer resistance (ohms). • Wick ignition temperature (°C). • Battery mAh rating (mAh). • PDU wattage operating range (W). • Coil temperature cut-off (°C). • Coil temperature range (°C).

TABLE 20 TO § 1114.7(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 volume (ml).	• E-liquid volume (ml).

(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 those products that contain fermented tobacco, information on the fermentation process, including the following:

(A) Composition of the inoculum (starter culture) with genus and species name(s) and concentration(s) (if applicable);

(B) Any step(s) taken to reduce endogenous microbes (*e.g.,* cleaning of product contact surfaces);

(C) Specifications and test data for pH, temperature, moisture content, and water activity;

(D) Frequency of aeration or turning (if applicable);

(E) Duration of fermentation;

(F) Added ingredients; and

(G) Method used to stabilize or stop (if applicable), fermentation, including data to demonstrate that the process is effective at reducing microbial content of the product and to suppress microbial activity of residual microorganisms to preclude further in-package fermentation.

(vi) *Storage and stability information.* The application must contain product storage and stability information that establishes the microbial and chemical stability of the product throughout the shelf life, including:

(A) A description of the shelf life and how it is indicated on the tobacco product, if applicable; and

(B) Testing on the tobacco product in the same container closure system that will be used if granted a marketing order that was performed at the beginning (zero time), middle, and end of the expected storage time for the chemical and microbial endpoints for the following items: Microbial content data, including total aerobic microbial count and total yeast and mold count along with identification of detected microbiological organisms by genus and species names, if applicable; pH; moisture content; water activity; tobacco-specific nitrosamines (TSNAs) (reported as separate amounts for the total TSNAs, NNN (N′-nitrosonornicotine), NNK (4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone)); nitrate and nitrite levels; preservatives and microbial metabolic inhibitors (if any); and method of heat treatment, pasteurization, or other method used to reduce microbial loads.

(vii) *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 and, where applicable, can change the product design and add or subtract ingredients;

(ii) The length of time it takes for a user to consume a single unit of the product; 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 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 facilities 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, including the substantive information required by § 1114.27(b)(1)(ii) for application filing, 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, which have been made to show:

(i) *Health risks of the product.* The potential health risks of the tobacco product to users and nonusers, including potential exposures, 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, including those 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 will affect the tobacco use behavior of tobacco product users, 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 and young adults.* The impact of the tobacco product, its label, labeling, and advertising on tobacco use initiation by nonusers, including:

(A) The likelihood that consumers who have never used tobacco products, particularly youth and young adults, 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 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 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. For studies involving human subjects, to the extent reasonably available or obtainable, the application must contain a certification that clinical 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;

(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, along with any audit certificates and inspection results, 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 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), FDA may 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 180 days of 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 § 20.45 of this chapter.

§ 1114.13 Change in ownership of an application.

An applicant may transfer of 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 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 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 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 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. 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 order for the original tobacco product has been withdrawn; or

(3) The marketing 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 following a presubmission meeting.

(b) *Required format.* The supplemental PMTA must comply with format requirements of § 1114.7(b), except that an applicant must include 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 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 part 25 of this chapter (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 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 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 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 on 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 of all information required under § 1114.41 covering the period of time from when it received a marketing order 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 no marketing order. The resubmission must contain new information necessary to address application deficiencies and cross-reference applicable content from the PMTA that received the no marketing order. An applicant may utilize the resubmission format for the same tobacco product for which FDA issued a no marketing order or a new tobacco product that results from modifications to the product necessary to address the deficiencies described in a no marketing 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 no marketing 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

no marketing order. 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 no marketing order by cross-reference and contain all 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));

(iv) Statement of compliance with part 25 of this chapter (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 no marketing order, including all data and information necessary to complete each response, and 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 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 the following certification 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 no marketing 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 no marketing 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 include sufficient information required by section 910(b)(1)(A) through (b)(1)(F) 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 information, including information from published literature or bridged from an investigation of another tobacco product, regarding:

(A) The health risks of the new tobacco product (as described in § 1114.7(k)(1)(i)(A) through (C));

(B) 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 (as set forth 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, including 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));

(E) The impact that marketing 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 or switch back to other tobacco products that may present increased risks to individual health (as set forth in § 1114.7(k)(1)(ii)(C) through (F));

(F) The impact that the marketing of the new tobacco product would have on tobacco product use behavior of current nonusers of tobacco products (as described in § 1114.7(k)(1)(iii)); or

(G) The impact of the product and its label, labeling, and advertising on individuals' perception of the product and their use intentions (as described in § 1114.7(k)(1)(iv));

(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, 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 order as described in § 1114.31; or

(f) Issue a no marketing order as described in § 1114.33.

§ 1114.31 Issuance of a marketing order.

(a) FDA will issue a marketing 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 order becomes effective on the date it is issued.

(b) FDA may include, as part of the marketing 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 order under section 910(c)(1)(B) of the Federal Food, Drug, and Cosmetic Act to help FDA make the finding 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 no marketing order.

(a) *Issuance.* FDA will issue a no marketing order if:

(1) 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 no marketing order will, where practicable, identify measures to remove the application from deniable form.

§ 1114.35 Withdrawal of a marketing order.

(a) *Grounds for withdrawal.* FDA may withdraw a marketing 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 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 order.

(2) FDA may use information other than that submitted by the applicant in deciding whether to withdraw a marketing order.

(c) *Informal hearing.* Prior to withdrawing a marketing order, FDA will offer the holder of the marketing 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 order an order withdrawing the marketing order for the new tobacco product.

(e) *Public notice.* FDA will give the public notice of an order withdrawing a marketing order for a tobacco product and will announce the basis of the withdrawal.

§ 1114.37 Temporary suspension of a marketing order.

(a) FDA will temporarily suspend a marketing 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 order of a tobacco product, FDA will offer the holder of the marketing order an opportunity for an informal hearing under part 16 of this chapter.

(c) If, after offering the holder of the marketing 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 order for a tobacco product.

(d) After issuing an order temporarily suspending the marketing order, FDA will proceed expeditiously to initiate proceedings to withdraw the marketing order for the tobacco product.

Subpart D—Postmarket Requirements

§ 1114.39 Postmarket changes.

A marketing 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 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.* Except as specified in § 1114.43, each applicant that receives a marketing order must submit to FDA all information required by the terms of the marketing 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 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 order and will not result in a finding that the marketing 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 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, as well as 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, and tobacco use status;

(vii) 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;

(viii) 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;

(ix) A description of the implementation of all advertising and marketing 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:

(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;

(B) Targeting of specific adult audiences by age-range(s), including young adults, ages 18 to 24, and other demographic or psychographic characteristics that reflect the intended target audience, including a list of all data sources used to target advertising and marketing plans and media buys;

(C) Actions taken to restrict youth-access and limit youth-exposure to the products' labeling, advertising, marketing, or promotion;

(D) Use of owned, earned, shared, or paid social media to create labeling for, advertise, market, or promote the products;

(E) Use of partners, influencers, bloggers, or brand ambassadors to create labeling for, advertise, market, or promote the products;

(F) Consumer engagements conducted by the applicant, on its behalf, or at its direction, including events at which the products were demonstrated; and

(G) Use of earned media or public-relations outreach to create labeling for, advertise, market, or promote the products;

(x) An analysis of the actual delivery of advertising impressions, by channel, by product (if applicable), and by audience demographics, including a breakout by age-group, that have not been previously submitted, verified against post-launch delivery-verification reports submitted to the applicant from an accredited source;

(xi) Additional information required to be reported under the terms of a marketing order (if applicable); and

(xii) 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 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 order, requiring the submission of a new PMTA under § 1114.7 or a supplemental PMTA under § 1114.15 and issuance of a marketing 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 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 order, including records related to both the application and postmarket reports, and ensure that such records remain readily available to the Agency upon request. 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 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 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) 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 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. If the applicant has publicly disclosed or acknowledged, or authorized FDA in writing to publicly disclose or acknowledge, the existence of that particular information contained in an application, FDA may disclose the existence of that particular information.

(4) If FDA refers an application to TPSAC, the contents of the application will be available for public disclosure under part 20 of this chapter, except information that has been shown to fall within the exemption established for trade secrets and confidential commercial or financial information in § 20.61, or personal privacy in § 20.63.

(c) *Disclosure of data and information after issuance of a marketing order.* After FDA issues a marketing 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 no marketing order.* After FDA issues a no marketing 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 no marketing 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 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/tobaccoproducts*). 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: July 24, 2019.

Norman E. Sharpless,

Acting Commissioner of Food and Drugs.

Dated: September 3, 2019.

Eric D. Hargan,

Deputy Secretary, Department of Health and Human Services.

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