

Premarket Tobacco Product Applications for Electronic Nicotine Delivery Systems

Guidance for Industry

Comments may be submitted at any time for Agency consideration. Electronic comments may be submitted to <https://www.regulations.gov>. Alternatively, submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Room 1061, Rockville, MD 20852. All comments should be identified with Docket No. FDA-2015-D-2496.

For questions regarding this guidance, contact the Center for Tobacco Products at 1-877-CTP-1373 (1-877-287-1373) Monday - Friday, 9 a.m. – 4 p.m. ET.

Additional copies are available online at <https://www.fda.gov/tobacco-products/compliance-enforcement-training/small-business-assistance-tobacco-product-industry>. You may send an e-mail request to SmallBiz.Tobacco@fda.hhs.gov to receive an electronic copy of this guidance. You may send a request for hard copies to U.S. Food and Drug Administration, Center for Tobacco Products, Attn: Office of Small Business Assistance, Document Control Center, Bldg. 71, Rm. G335, 10903 New Hampshire Ave., Silver Spring, MD 20993-2000.

**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Tobacco Products**

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Premarket Tobacco Product Applications for Electronic Nicotine Delivery Systems

Guidance for Industry¹

This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance is intended to assist persons submitting premarket tobacco product applications (PMTAs) for electronic nicotine delivery systems (ENDS) under section 910 of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) (21 U.S.C. 387j). This guidance communicates FDA's current thinking on these applications to improve the efficiency of application submission and review; however, the recommendations in this guidance are non-binding. When FDA reviews PMTAs for ENDS, it will base decisions on the obligations that arise from the FD&C Act and its implementing regulations. FDA anticipates that the experience gained through the publication of this guidance and review of PMTAs may contribute to future rulemaking and guidances.

The guidance explains, among other things:

- Products to which this guidance applies;
- When a PMTA is required under the statute and regulations;
- General procedures for review of an ENDS PMTA;
- What information the FD&C Act requires you to submit in a PMTA; and
- What information FDA recommends you submit in an ENDS PMTA to show that permitting your new tobacco product to be marketed would be appropriate for the protection of the public health (APPH).

¹ This guidance was prepared by the Office of Science and Office of Regulations in the Center for Tobacco Products at FDA.

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FDA is committed to helping industry better understand the tobacco product review process and the requirements of the law and will continue holding public webinars and meetings with industry to assist manufacturers of deemed tobacco products. FDA has published guidance on meetings with industry² and has had many productive meetings to address companies' specific questions on their development of tobacco products. Throughout this document, we identify additional assistance (including support offered by the Office of Small Business Assistance within the Center for Tobacco Products (CTP)) available to applicants preparing to submit a PMTA for ENDS.³ We have also provided related resources and compliance periods for small-scale tobacco product manufacturers.⁴ FDA's web site and guidance documents provide information about the three pathways available to market products (including PMTA).

FDA has also held a series of public workshops to gather scientific information on ENDS products and the public health, and to provide more information about application review.⁵ As specified in the preamble to the final deeming rule, manufacturers will benefit from additional assistance with their marketing applications, including the designation of a Regulatory Health Project Manager so that they have a single point of contact in CTP's Office of Science for questions about their marketing applications. They also will have access to an appeals process in the event that FDA denies their marketing applications. FDA expects that these steps will help streamline the PMTA submission process for applicants and reduce the time it will take the Agency to review premarket submissions for ENDS and other deemed products.

If an applicant wishes to discuss its development of a PMTA, the applicant may request a meeting as set forth in the research and development (R&D) meetings guidance. See section XII of this document for additional discussion related to meetings with FDA.

The recommendations made in this guidance document are substantially similar to those set forth in the draft guidance issued on May 5, 2016. If you have taken measures consistent with the draft guidance, they will generally be consistent with the recommendations herein.

² Information about how to request meetings with CTP can be found in FDA's guidance, *Meetings with Industry and Investigators on the Research and Development of Tobacco Products* (R&D meetings guidance), available on the Internet at <https://www.fda.gov/tobacco-products/rules-regulations-and-guidance/guidance>. For additional information on requesting a meeting with FDA in the context of preparing for a PMTA submission, see section XII of this document.

³ See section XIII of this document for more information on CTP's Office of Small Business Assistance.

⁴ The final deeming rule outlines the various compliance periods for each of the pathways to market a new product, including additional relief available for small-scale tobacco product manufacturers. FDA has since updated the compliance periods; the updated compliance periods can be found in FDA's guidance titled "Extension of Certain Tobacco Product Compliance Deadlines Related to the Final Deeming Rule" available at <https://www.fda.gov/tobacco-products/rules-regulations-and-guidance/guidance>. Interested manufacturers may contact CTP's call center at 1-877-CTP-1373 for questions regarding this compliance policy.

⁵ Information and transcripts from CTP's series of public workshops on "Electronic Cigarettes and the Public Health" (conducted December 10-11, 2014; March 9-10, 2015; and June 1-2, 2015) and "Tobacco product Application Review – A Public Meeting" (conducted October 22-23, 2018) are available on CTP's Public Meetings and Conferences Web page at <https://www.fda.gov/TobaccoProducts/NewsEvents/default.htm>.

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FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

The Family Smoking Prevention and Tobacco Control Act (Tobacco Control Act) (Public Law 111-31) was enacted on June 22, 2009, amending the FD&C Act and providing FDA with the authority to regulate tobacco products. Specifically, section 101(b) of the Tobacco Control Act amends the FD&C Act by adding a new chapter that provides FDA with authority over tobacco products. Section 901 of the FD&C Act (21 U.S.C. 387a), as amended by the Tobacco Control Act, states that the new chapter in the FD&C Act (chapter IX—Tobacco Products) (21 U.S.C. 387 through 387t) applies to all cigarettes, cigarette tobacco, roll-your-own tobacco, and smokeless tobacco and to any other tobacco products that the Secretary of Health and Human Services by regulation deems to be subject to this chapter.

On May 10, 2016, FDA issued a 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” (final deeming rule) (81 FR 28973). The final deeming rule extended FDA's tobacco product authorities to all products, other than accessories of deemed tobacco products, that meet the statutory definition of “tobacco product” in section 201(rr) of the FD&C Act (21 U.S.C. 321(rr)). In the final deeming rule, FDA clarifies that all ENDS (including, but not limited to, e-cigarettes, e-pens, e-cigars, e-hookah, vape pens, personal vaporizers, and electronic pipes) are subject to FDA's chapter IX authorities on the effective date of the final deeming rule.⁶ ENDS products include both the e-liquid and e-cigarette used as an ENDS, whether sold as a unit or separately.

Products deemed under the final deeming rule are now subject to most of the same FD&C Act provisions to which cigarettes, cigarette tobacco, roll-your-own tobacco, and smokeless tobacco are subject, including premarket review requirements and the adulteration and misbranding provisions. FDA has issued a draft guidance for public comment explaining FDA's compliance policy for investigational tobacco products, which discusses circumstances in which FDA generally intends not to enforce the premarket review requirements for tobacco products used for investigational purposes.⁷ Further, deemed products will be subject to the modified risk tobacco product restrictions in section 911 of the FD&C Act. If the applicant seeks to market its new

⁶ If an ENDS manufacturer wishes to make a cessation claim or otherwise market its product for therapeutic purposes, the company must submit an application for its ENDS to be marketed as a medical product. Please see section IV.B.1 for further discussion.

⁷ When finalized, the draft guidance *Use of Investigational Tobacco Products* will represent FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA Tobacco Products Guidance Web page at <https://www.fda.gov/tobacco-products/rules-regulations-and-guidance/guidance>.

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tobacco product as a modified risk tobacco product, the applicant will also have to submit a modified risk tobacco product application and receive FDA's authorization.⁸ In addition, these products are also subject to certain other restrictions set out in the final deeming rule and may be subject to other requirements or restrictions established in future regulations.

Under section 910 of the FD&C Act, persons wanting to market a new tobacco product (one that was not commercially marketed in the United States as of (i.e., on) February 15, 2007, or any modified tobacco product that was commercially marketed after February 15, 2007) must first obtain an order to do so (referred to in this guidance as a marketing order) under section 910(c)(1)(A)(i) unless a report pursuant to section 905(j) of the FD&C Act has been submitted for the new tobacco product and FDA has issued an order under section 910(a)(2) that the new tobacco product is substantially equivalent to a tobacco product commercially marketed in the United States as of (i.e., on) February 15, 2007 (the 905(j) pathway), or the new tobacco product is exempt from the substantial equivalence requirements.⁹ When a new product is not found to be substantially equivalent to an appropriate predicate product or exempt from the substantial equivalence requirements, you must submit a PMTA under section 910(b) and receive a marketing order under section 910(c)(1)(A)(i) prior to marketing the product.

All deemed products that meet the definition of a "new tobacco product," including ENDS, are subject to the requirements of premarket review in sections 910(a)(2) of the FD&C Act. Given the expected difficulty in identifying valid ENDS predicate products (products commercially marketed on February 15, 2007, or previously determined to be substantially equivalent to an appropriate predicate product) for use in the substantial equivalence pathway, FDA expects to receive PMTA submissions from manufacturers of deemed ENDS products. Section 910(b)(1) of the FD&C Act contains the requirements for a PMTA submission. This guidance is intended to provide information to assist applicants in submitting a PMTA to apply for a marketing order under section 910(c)(1)(A)(i).

To the extent that an eligible predicate product (one marketed as of February 15, 2007, or previously determined to be substantially equivalent to an appropriate predicate product) is available for ENDS products, and firms are interested in utilizing the 905(j) pathway to market for their new ENDS tobacco products, we refer you to sections 905(j) and 910(a) of the FD&C Act, 21 CFR sections 1105.10 and 1107.1, and FDA's relevant guidance documents located at <https://www.fda.gov/tobacco-products/rules-regulations-and-guidance/guidance>. You can find a list of marketing orders where FDA determined a product to be substantially equivalent at <https://www.fda.gov/TobaccoProducts/Labeling/TobaccoProductReviewEvaluation/ucm339928.htm>.

⁸ When finalized, the draft guidance *Modified Risk Tobacco Product Applications* will represent FDA's current thinking on this topic, including submission of a combined PMTA and MRTPA, available at <https://www.fda.gov/tobacco-products/rules-regulations-and-guidance/guidance>.

⁹ FDA has interpreted "as of February 15, 2007" to mean any tobacco product that was commercially marketed in the United States on February 15, 2007. For additional discussion, see FDA's guidance for industry *Establishing That a Tobacco Product Was Commercially Marketed in the United States as of February 15, 2007*, available on the Internet at <https://www.fda.gov/tobacco-products/rules-regulations-and-guidance/guidance>. FDA guidance states that "[i]f you cannot provide documentation specifically dated on February 15, 2007, FDA suggests you provide documentation of commercial marketing for a reasonable period of time before and after February 15, 2007."

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This guidance represents FDA’s non-binding recommendations on some appropriate means of addressing the premarket authorization requirements for deemed ENDS products. If an applicant wishes to discuss the development of a product application, the applicant may request a meeting with FDA as described in section XII of this document and further discussed in the R&D meetings guidance document.

III. DEFINITIONS

This section provides definitions of certain terms as they are used in this guidance document.

A. Accessory

The term *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 (21 CFR 1100.3).

For purposes of this guidance, the term “composition,” in this definition means the manner in which the materials, including, for example, ingredients, additives, and biological organisms (e.g., micro-organisms added for fermentation in smokeless products), are arranged and integrated.

Examples of products that FDA considers accessories for an ENDS product include screwdrivers, lanyards, and decorative cases.

B. Additive

An *additive* is 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 (section 900(1) of the FD&C Act).

C. Component or Part

Component or part means any software or assembly of materials intended or reasonably expected: 1) to alter or affect the tobacco product’s performance, composition, constituents, or characteristics; or 2) to be used with or for the human consumption of a tobacco product.

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Component or part excludes anything that is an accessory of a tobacco product. (21 CFR 1100.3).

The following is a nonexhaustive list of examples of components or parts of ENDS (including e-cigarettes): e-liquids, atomizers, batteries (with or without variable voltage), cartomizers (atomizer plus replaceable fluid-filled cartridge), digital display/lights to adjust settings, clearomizers (refillable e-liquid cartridges with built-in atomizer and wicking system), tank systems, flavors, bottles that contain e-liquids, and programmable software.

D. Covered Tobacco Product

Under 21 CFR 1143.1, the term *covered tobacco product* means any tobacco product deemed to be subject to the FD&C Act under 21 CFR 1100.1, but excludes any component or part of a tobacco product that is not made or derived from tobacco. Examples of covered tobacco products include, but are not limited to, cigars, pipe tobacco, and e-liquids.¹⁰

E. E-cigarette

For the purposes of this guidance, *e-cigarette* refers to an electronic device that delivers e-liquid in aerosol form into the mouth and lungs when inhaled; it is also referred to as an aerosolizing apparatus. For example, FDA considers vapes or vape pens, personal vaporizers, cigalikes, e-pens, e-hookahs, e-cigars, and e-pipes to be e-cigarettes. For the purposes of this guidance, e-cigarettes may either be open e-cigarettes or closed e-cigarettes. 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. Also, for the purposes of this guidance, if an e-cigarette contains e-liquid it is referred to as a prefilled e-cigarette.

F. E-liquids

For the purposes of this guidance document, *e-liquids* include liquid nicotine, nicotine-containing liquids (i.e., liquid nicotine combined with colorings, flavorings, and/or other ingredients), and liquids that do not contain nicotine or other material made or derived from tobacco, but that are intended or reasonably expected to be used with or for the human consumption of a tobacco product.

An e-liquid that contains nicotine made or derived from tobacco meets the definition of a tobacco product and, therefore, is subject to FDA's chapter IX authorities. Liquids that do not contain nicotine or other material made or derived from tobacco, but that are intended or reasonably expected to be used with or for the human consumption of a tobacco product, may be components or parts and, therefore, subject to FDA's tobacco control authorities. For example, where a "zero nicotine" or "nicotine free" e-liquid (e.g., a zero nicotine flavored e-liquid) is intended or reasonably expected to be mixed with liquid nicotine, that e-liquid may be a component or part of a tobacco product and subject to FDA's tobacco control authorities. Such e-

¹⁰ For additional restrictions on covered tobacco products, see 21 CFR 1140.14 and part 1143.

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liquids would be tobacco products even if sold separately from an e-cigarette. E-liquids containing zero nicotine that are not otherwise made or derived from tobacco and are not intended or reasonably expected to be mixed with liquid nicotine or other materials made or derived from tobacco are not tobacco products and thus are not subject to FDA's tobacco control authorities under the FD&C Act.

G. Finished Tobacco Product

For purposes of this guidance document, the term *finished tobacco product* refers to a tobacco product, including all components and parts, sealed in final packaging. For example, an e-liquid sealed in final packaging that is to be sold or distributed to a consumer for use is a finished tobacco product, but in contrast, an e-liquid that is sold or distributed for further manufacturing into a finished ENDS product is not itself a finished tobacco product.

H. New Tobacco Product

The term *new tobacco product* is defined in section 910(a)(1) of the FD&C Act as:

- (A) any tobacco product (including those products in test markets) that was not commercially marketed in the United States as of February 15, 2007; or
- (B) 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, 2007.¹¹

I. Tobacco Product

A *tobacco product* is “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)” (section 201(rr) of the FD&C Act). This term does not include an article that is a drug, device, or combination product as defined in the FD&C Act (21 CFR 1100.3). The term is not limited to products containing tobacco or tobacco derivatives, and also includes components, parts, or accessories of tobacco products, whether they are sold for further manufacturing or for consumer use. For example, e-liquids, e-cigarettes, atomizers, and batteries used in ENDS are tobacco products, whether they are sold to consumers for use in an ENDS or are sold for further manufacturing into another product sold to a consumer.

IV. DISCUSSION

A. Products to Which This Guidance Applies

As noted above, the final deeming rule extended FDA's tobacco product authorities to all products, other than accessories of deemed tobacco products, that meet the statutory definition of “tobacco product” in section 201(rr) of the FD&C Act (21 U.S.C. 321(rr)). Currently, FDA

¹¹ See note 7.

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generally considers ENDS to be electronic nicotine delivery systems that deliver aerosolized e-liquid when inhaled.¹² Because ENDS products fall within the definition of “tobacco product” under section 201(rr) of the FD&C Act and are not accessories of deemed products, the tobacco product authorities (including the PMTA authorities) apply to ENDS products. ENDS include the components and parts of ENDS products, but not their related accessories. Therefore, such components and parts are also subject to FDA’s authority, including premarket review. Overall, the ENDS category thus includes a variety of products, such as vape pens or personal vaporizers, cigalikes, e-pens, e-hookahs, e-cigars, e-pipes, e-liquids, atomizers, batteries (with or without variable voltage), cartomizers (atomizer plus replaceable fluid-filled cartridge), digital display/lights to adjust settings, clearomizers (refillable e-liquid cartridges with built-in atomizer and wicking system), tank systems, flavors, and programmable software. Because it is a rapidly changing industry and new ENDS products may be developed in the future this is a non-exhaustive list of examples of ENDS products.

Subsequent sections of this guidance refer to three subcategories of ENDS products:

- E-liquids
- E-cigarettes
- ENDS products that package e-liquids and e-cigarettes together

We detail our recommendations in sections VI through VIII regarding the type of information that should be submitted for these three subcategories of products. FDA recognizes that with the innovation in the ENDS market, there may be ENDS products that do not fit neatly into one of these categories. If you have questions about which recommendations you should follow for your ENDS product, please contact CTP’s call center at 1-877-CTP-1373 (1-877-287-1373). Small businesses may also contact CTP’s Office of Small Business Assistance by email at smallbiz.tobacco@fda.hhs.gov or by phone at 1-877-CTP-1373 to discuss questions regarding PMTA content. Questions about a specific premarket tobacco application should reference your Submission Tracking Number (STN) and may be directed to CTP’s Office of Science. For additional information on small business assistance, see section XIII of this document.

B. When Are PMTAs Required and What Enforcement Policies Apply?

1. Considerations for All Applicants

Section 910 of the FD&C Act requires a marketing order for new tobacco products. At this time, FDA intends to limit enforcement of the requirements of section 910 to finished tobacco products, including components and parts of ENDS products sold or distributed separately for consumer use. FDA does not, at this time, intend to enforce these requirements for components and parts of deemed products that are sold or distributed solely for further manufacturing into finished tobacco products, and not sold separately to the consumer. For example, an e-liquid that is sold or distributed for further manufacturing into a finished ENDS product is not itself a finished tobacco product and, at this time, FDA does not intend to enforce against such e-liquids

¹² Manufacturers of products that use an electronic heating source in conjunction with substances other than e-liquids, such as tobacco, should also consider whether the recommendations in this guidance could help them prepare a PMTA for their product.

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that are sold or distributed without a marketing order. In contrast, an e-liquid sealed in final packaging that is to be sold or distributed to a consumer for use is a finished tobacco product.

If an ENDS product is marketed for tobacco cessation or for any other therapeutic purpose, the product is a drug or device, rather than a tobacco product, under the authorities of FDA's Center for Drug Evaluation and Research or Center for Devices and Radiological Health, and appropriate approval must be sought to market a product as a drug or device.¹³

Please note that if you are seeking to market your new tobacco product as a modified risk tobacco product, you will also have to submit a modified risk tobacco product application for FDA's review and receive authorization.¹⁴ See section VI of this document for information on submitting a single application to seek authorization to market a new tobacco product as a modified risk tobacco product, rather than submitting a separate PMTA and MRTPA.

2. *ENDS Retailers Who Mix or Prepare Their Own E-Liquids or Create or Modify E-cigarettes from Various Components*

An ENDS retail establishment that mixes or prepares combinations of liquid nicotine, flavors, or other e-liquids for direct sale to consumers for use in ENDS, or creates or modifies e-cigarettes for direct sale to consumers for use in ENDS (sometimes known as a vape shop) meets the definition of "tobacco product manufacturer" in section 900(20)¹⁵ of the FD&C Act. Section 910(a)(1) defines a "new tobacco product" as "any tobacco product (including those products in test markets) that was not commercially marketed in the United States as of February 15, 2007," or "any modification (including a change in design, any component, any part, or any constituent, including a smoke constituent, or in the content, delivery or form of nicotine, or any other additive or ingredient) of a tobacco product where the modified product was commercially marketed in the United States after February 15, 2007." Therefore, those establishments engaged in mixing and/or preparing combinations of liquid nicotine, flavors, and/or other e-liquids or creating or modifying e-cigarettes for direct sale to consumers for use in ENDS are both tobacco product manufacturers and retailers, and consequently are subject to all the requirements applicable to manufacturers and retailers including the PMTA requirements.¹⁶

¹³ 21 CFR 1100.3; see, e.g., sections 505 (21 U.S.C. 355) (drugs) and 515 (21 U.S.C. 360e) (devices) of the FD&C Act and *Sottera, Inc. v. Food & Drug Administration*, 627 F.3d 891 (D.C. Cir. 2010).

¹⁴ 21 USC 387k. When finalized, the guidance *Modified Risk Tobacco Product Applications* will represent FDA's current thinking on this topic.

¹⁵ A "tobacco product manufacturer" means "any person, including any repacker or relabeler, who manufactures, fabricates, assembles, processes, or labels a tobacco product; or imports a finished tobacco product for sale or distribution in the United States" (section 900(20) of the FD&C Act, 21 U.S.C. 387(20)).

¹⁶ The guidance *Interpretation of and Compliance Policy for Certain Label Requirement; Applicability of Certain Federal Food, Drug, and Cosmetic Act Requirements to Vape Shops* represents FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA Tobacco Products Guidance Web page at <https://www.fda.gov/tobacco-products/rules-regulations-and-guidance/guidance>.

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C. General Procedures for ENDS PMTA Review

The time it takes to review a PMTA depends on the complexity of the product. FDA intends to act as expeditiously as possible with respect to all new applications, while ensuring that statutory standards are met.

FDA will review an ENDS PMTA consistent with the requirements of section 910(c) of the FD&C Act. Under section 910(c)(1)(A), FDA must act on a PMTA “as promptly as possible, but in no event later than 180 days after the receipt of an application.” To determine when the 180-day period begins, FDA generally relies on the date of receipt of a complete application by CTP’s Document Control Center (DCC) (or, if samples are the last part of the application submitted, the location to which samples are sent), not the date that the applicant sent it. To be complete, a PMTA must include all information specified in section 910(b)(1) (and discussed further in Section VI below). As noted in the next paragraph, FDA may refuse to file an incomplete application. If FDA refuses to file an application, FDA will issue a letter to the applicant identifying the deficiencies that prevented FDA from filing the application.

In addition, we are clarifying that FDA distinguishes among an application that has been “accepted,” an application that has been “filed,” and an application that is “complete.”

- **Accepted:** An application has been “accepted” after the Agency completes a preliminary review and determines that the application appears on its face to contain information required by the statutory provisions and any applicable regulations.¹⁷
- **Filed:** After FDA accepts a PMTA, an application has been “filed” after FDA completes a filing review and determines that the application is sufficiently complete to permit a substantive review. This filing review occurs only for a premarket tobacco application or a modified risk application and results in either a filing letter or a refusal to file letter.
- **Substantive Review of a Complete Application:** An application is considered complete when it contains the information required by section 910(b)(1) of the FD&C Act, including product samples, which starts the 180-day review period as set forth in section 910(c)(1)(A) of the FD&C Act. If there are deficiencies identified during the review of the filed PMTA, CTP may issue letters requesting additional information or clarification on deficiencies identified within the application. Issuance of such a letter would pause the 180-day review period until CTP receives a complete response to all the deficiencies identified within the letter.

In addition to the information required by section 910(b)(1) of the FD&C Act, FDA may also request information about your PMTA as necessary to support FDA’s review of your application under its authority in section 910(b)(1)(G), which requires a PMTA to contain such other information relevant to the subject matter of the application as FDA may require. FDA may also want to inspect your manufacturing, clinical research, or nonclinical research sites, including all records and information regarding your research related to your PMTA. Inspections of these sites allow FDA to assess the accuracy and validity of the information provided, including clinical and

¹⁷ FDA’s basic acceptance criteria are codified at 21 CFR 1105.10, which describes when FDA will refuse to accept a tobacco product submission (or application) because the application has not met a minimum threshold for acceptability for FDA review.

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nonclinical information, confirm whether the tobacco product meets applicable product standards under section 907 of the FD&C Act (if any), and confirm that the product can be manufactured according to defined standards outlined in the PMTA. Inspections will also provide important information regarding whether the manufacturing, processing, or packing of the tobacco product conform to tobacco product manufacturing practices, which will be set forth in a future rulemaking.¹⁸

Under section 910(b)(2) of the FD&C Act, FDA has the discretion, upon your request or on its own initiative, to refer your PMTA to the Tobacco Product Scientific Advisory Committee (TPSAC). FDA Advisory committees are used to obtain independent, expert advice on scientific, technical, and policy matters. TPSAC reviews and evaluates safety, dependence, and health issues relating to tobacco products and provides appropriate advice, information, and recommendations to the Commissioner of Food and Drugs.¹⁹ If you wish to request that FDA refer your PMTA to TPSAC, you should include the request in the cover letter of your initial PMTA submission. If you would like to request that FDA refer your PMTA to TPSAC after your PMTA has been submitted, please contact CTP to discuss this option.

D. Public Health Considerations for ENDS Products

1. Section 910(c)(2)(A) Standard: A Showing That the New Tobacco Product Is Appropriate for the Protection of the Public Health

Section 910(c)(2)(A) of the FD&C Act requires that FDA deny a PMTA where it finds “there is a lack of a showing that permitting such tobacco product to be marketed would be appropriate for the protection of the public health.”²⁰ FDA’s finding of whether there is a showing that permitting a product to be marketed would be appropriate for the protection of the public health (APPH) must be determined with respect to the risks and benefits to the population as a whole, including users and nonusers of the tobacco product, and taking into account:

- (A) the increased or decreased likelihood that existing users of tobacco products will stop using such products; and
- (B) the increased or decreased likelihood that those who do not use tobacco products will start using such products.

¹⁸ FDA intends to issue regulations under section 906(e) of the FD&C Act that will contain the requirements for tobacco product manufacturing practices. At that time, each new PMTA will also be expected to demonstrate that the methods, facilities, or controls used conform to these regulations (section 910(c)(2)(B)).

¹⁹ For more information, please visit the TPSAC website:

<https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/TobaccoProductsScientificAdvisoryCommittee/default.htm>

²⁰ In addition, the statute provides that FDA shall deny PMTAs under section 910(c)(2) of the FD&C Act where:

- (B) the methods used in, or the facilities or controls used for, the manufacture, processing, or packing of such tobacco product do not conform to the requirements of section 906(e);
- (C) based on a fair evaluation of all material facts, the proposed labeling is false or misleading in any particular; or
- (D) such tobacco product is not shown to conform in all respects to a tobacco product standard in effect under section 907, and there is a lack of adequate information to justify the deviation from such standard.

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(Section 910(c)(4) of the FD&C Act.) We provide information in this section to assist applicants in submitting an ENDS PMTA that could support a showing that the marketing of a new tobacco product would be APPH.

Throughout this guidance document, we recommend providing specific information pertaining to different topic areas and scientific disciplines to enable FDA to make a determination of whether your PMTA supports a showing that permitting the marketing of your new tobacco product would be APPH. For example, knowing the full assessment of the toxicological effects of your ENDS (e.g., ingredients, components, use of the product) is important to assess the health effects on users and nonusers under Section 910(b). As such, FDA assesses the toxicology of the product to determine whether product use would have a detrimental effect on users' and nonusers' health. FDA weighs all of the potential benefits and risks from the information contained in the PMTA to make an overall determination of whether the product should be authorized for marketing.

You may propose specific restrictions on sale and distribution that can help support a showing that permitting the marketing of the product would be APPH (e.g., a restriction that decreases the likelihood that those who do not use tobacco products will start using tobacco products). FDA may consider your product in that context and may include your proposed restrictions as mandatory conditions in your marketing order. These restrictions would be in addition to any other restrictions that FDA may require on the sale and distribution of the tobacco product, or any postmarket records and reports FDA may find necessary.

The following sections highlight several broad categories of issues that applicants should consider to help demonstrate that permitting the marketing of their products would be APPH and, consequently, should be authorized for marketing.

2. Valid scientific evidence

The FD&C Act states that the finding of whether permitting the marketing of a product would be APPH will be determined, when appropriate, on the basis of well-controlled investigations²¹ (section 910(c)(5)(A)). However, section 910(c)(5)(B) of the FD&C Act also allows the Agency to consider other "valid scientific evidence" if found sufficient to evaluate the tobacco product. Given the relatively new entrance of ENDS on the U.S. market, FDA understands that limited data may exist from scientific studies and analyses.²² If an application includes, for example, information on other products (e.g., published literature, marketing information) with appropriate bridging studies, FDA intends to review that information to determine whether it is valid scientific evidence sufficient to demonstrate that the marketing of a product would be APPH. Nonclinical studies alone are generally not sufficient to support a determination that permitting the marketing of a tobacco product would be appropriate for the protection of the public health.

²¹ Well-controlled investigations are generally those that are designed and conducted in such a way that minimizes or controls for bias, confounding variables, and other factors that may render the results unreliable.

²² As discussed in section VI.H.2., due to the limited nonclinical or clinical research conducted on specific ENDS products, it is likely that applicants will conduct certain investigations themselves and submit their own research findings as a part of their PMTA.

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Nonetheless, in general, FDA does not expect that applicants will need to conduct long-term studies to support an application.²³ As an example for nonclinical assessments, long-term studies such as carcinogenicity bioassays are not expected to be included in an application. For clinical assessments, instead of conducting clinical studies that span months or years to evaluate potential clinical impact, applicants could demonstrate possible long-term health impact by including existing longer duration studies in the public literature with the appropriate bridging information (i.e., why the data used are applicable to the new tobacco product) and extrapolating from short-term studies.²⁴ In addition, nonclinical in vitro assays that assess the toxicities that are seen following long-term use of tobacco products may be supportive of these clinical assessments. These studies, used as a basis to support a PMTA, should be relevant to the new tobacco product and address, with robust rationale, acute toxicological endpoints or other clinical endpoints that may relate to long-term health impacts. In this context, FDA considers long-term studies to be those studies that are conducted over six months or longer.

FDA recommends that you provide a detailed explanation of how the data and information provided in your PMTA (including the information required by section 910(b)(1) of the FD&C Act) constitute valid scientific information that would support a finding by FDA that marketing your new tobacco product is APPH.

If an applicant has questions about investigations, including alternatives to well-controlled investigations it would like to utilize, we recommend that the applicant meet with FDA to discuss the approach prior to preparing and submitting an application.²⁵ For additional information regarding alternatives to well-controlled investigations please see section X of this guidance.

3. 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, dual use, cessation) that are likely to 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 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.

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. For tobacco products that are within the same category and subcategory, we recommend applicants consider products that consumers are most likely to be considered interchangeable between your proposed product and other similar products.

²³ See section X for additional discussion.

²⁴ See section X of the guidance for more information about alternatives to conducting long-term studies.

²⁵ See the R&D meetings guidance.

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For example, for a PMTA for an e-liquid, FDA recommends the product's health risks be compared to those health risks presented by other e-liquids used in a similar manner. This comparison of health risks is not meant to be a 1:1 product 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. We recommend as part of the evaluation of the new product's risk compared to other tobacco products that you include those characteristics (materials, ingredients, design, composition, heating source, or other features) that contribute to the new product presenting the same, less, or different health risks than other tobacco products of similar category and subcategory.

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 products for demonstrating the health risks of the new product in comparison to other tobacco products. For example, in the 2018 tobacco market conditions, some ENDS product manufacturers market their products as replacements for combusted cigarettes. In this case, it could be appropriate to evaluate the risks of ENDS products in relation to the risks of both cigarettes and other similar ENDS products. Poly tobacco use risks should also be considered.

4. Nicotine exposure warnings

Section 910(b)(1)(F) of the FD&C Act requires a PMTA to contain specimens of the labeling proposed to be used for the new tobacco product. Warning statements are an important part of the product's labeling. Given the health risks and hazards associated with exposure to e-liquids (including oral, dermal, and ocular dangers), nicotine exposure warnings on labels or labelling of finished ENDS products that contain nicotine can help establish that permitting the marketing of the product would be APPH. FDA believes a nicotine exposure warning is important to aid in the prevention of, or decrease in, the risk of acute toxicity by warning consumers and the public about the risk of inadvertent exposure to nicotine (up to and including potentially deadly nicotine poisoning), especially by children. To that end, FDA recommends that a nicotine exposure warning be included in specimens of the labels or labeling that are submitted.

Nicotine exposure warnings should accurately and truthfully communicate the health risks and hazards of e-liquid use in a clear and simple manner. To best help your product meet the standard for authorization, we recommend that nicotine exposure warnings:

- Be clear, conspicuous, prominent, understandable, factual, and not false or misleading;
- Be indelibly printed on the label/labeling of the tobacco product on the side that is most likely to be viewed by a consumer (if the packaging is too small to accommodate a legible warning, FDA recommends that these warnings be permanently affixed on the product's carton or other outer container, wrapper, or a tag otherwise permanently affixed to the tobacco product package);

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- Include bold colorings and markings containing pictographs — that could be understood by a child who cannot read — to discourage opening and ingesting the package contents;
- Provide a statement regarding nicotine being a dangerous substance and the potential for nicotine poisoning;
- Describe the mode or process of possible accidental exposure;
- Include a specific statement about keeping e-liquids out of the reach of children and pets; and
- Include instructions to seek medical help if accidental contact occurs.

The text below are examples of a textual nicotine exposure warning. These examples are not necessarily applicable to all ENDS products, and we recommend that applicants use text that is appropriate for their product.

WARNING: Contains nicotine, which can be poisonous. Avoid contact with skin and eyes. Do not drink. Keep out of reach of children and pets. In case of accidental contact, seek medical help.

or

WARNING: Contains nicotine. Do not get on skin or in eyes. Do not drink. Store in original container and keep away from children and pets. In case of accidental contact, call the Poison Control Center at 1-800-222-1222.

5. Warning statement regarding the addictiveness of nicotine

In accordance with 21 CFR 1143.3(a)(1), it is unlawful for any person to manufacture, package, sell, offer to sell, distribute, or import for sale or distribution within the United States any cigarette tobacco, roll-your-own (RYO) tobacco, or covered tobacco product other than cigars, unless the package label bears the following warning statement: “WARNING: This product contains nicotine. Nicotine is an addictive chemical.” Alternatively, under 21 CFR 1143.3(c), such tobacco products that do not contain nicotine (i.e., no nicotine at detectable levels) must include the following statement: “This product is made from tobacco.” Manufacturers of products that do not contain nicotine must submit a self-certification that their RYO tobacco, cigarette tobacco, or covered tobacco products other than cigars do not contain nicotine. Because any ENDS product that contains nicotine or another substance derived from tobacco (e.g., e-liquids containing nicotine, closed delivery systems sold with e-liquids containing nicotine) is a covered tobacco product, it must comply with the requirement that the package label bear the appropriate warning statement under 21 CFR part 1143. The specimens of labeling included in a PMTA for a product containing nicotine under section 910(b)(1)(F) of the FD&C Act must include package labels with the required warning statement on the addictiveness of nicotine.

The provision at 21 CFR § 1143.3(d) requires that if a tobacco product is too small or otherwise unable to accommodate a label with sufficient space to bear the warning statement regarding the addictiveness of nicotine, the warning must appear on the carton or other outer container or wrapper if the carton, outer container, or wrapper has sufficient space to bear such information,

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or appear on a tag otherwise permanently affixed to the tobacco product package.²⁶ For new tobacco products too small or otherwise unable to accommodate the warning on the label, you must submit specimens of the outer container or wrapper or the tag otherwise permanently affixed to the tobacco product package and explain how the outer container, wrapping, or tag will be attached to the tobacco product.

6. Protective packaging

Given the health risks and hazards associated with exposure to e-liquids (including oral, dermal, and ocular dangers), especially to infants and children, FDA recommends that manufacturers provide sufficient information describing the kind of packaging in which their ENDS product will be sold to support a finding that the marketing of the product is APPH. While various types of packaging may help support such a finding, examples of packaging that may mitigate risks of accidental exposure to e-liquids include child-resistant packaging²⁷ and exposure-limiting packaging (e.g., flow restrictors). An example of child-resistant packaging that would help show the marketing of the product would be APPH is, depending on the circumstances, packaging that is significantly difficult for children 5 years of age and under to open, use, or obtain a toxic, potentially addicting, or otherwise harmful amount of the tobacco product or any of its constituents within a reasonable time and that is not unreasonably difficult for a majority of adults to use properly.²⁸ The description should also include information regarding the tamper-resistant and tamper-evident²⁹ properties of the packaging.

V. HOW TO SUBMIT A PMTA

FDA strongly encourages you to submit your PMTA in an electronic format to facilitate efficiency and timeliness of data submission and processing. We recommend you submit your application online using the CTP Portal, which can be found online at <https://www.fda.gov/tobacco-products/manufacturing/submit-documents-ctp-portal>.

You can also securely submit your PMTA via the FDA Electronic Submissions Gateway (ESG). Information about the eSubmitter tool can be found online at <https://www.fda.gov/ForIndustry/FDAeSubmitter/ucm189469.htm>.

²⁶ See 21 CFR part 1143 for the complete list of requirements for the required warning statement regarding the addictiveness of nicotine that must appear on the package labels and advertisements for cigarette tobacco, roll-your-own tobacco, and covered tobacco products other than cigars.

²⁷ The Child Nicotine Poisoning Prevention Act of 2015 (Pub. L. 114-116) (CNPPA) requires any nicotine provided in a liquid nicotine container sold, offered for sale, manufactured for sale, distributed into commerce, or imported into the United States to be packaged in accordance with the standards provided in 16 CFR 1700.15, as determined through testing in accordance with the method described in 16 CFR 1700.20, and any subsequent changes to such sections adopted by the Consumer Product Safety Commission (CPSC). The CNPPA excludes “a sealed, pre-filled, and disposable container of nicotine in a solution or other form in which such container is inserted directly into an e-cigarette or other similar product, if the nicotine in the container is inaccessible through customary or reasonably foreseeable handling or use, including reasonably foreseeable ingestion or other contact by children.”

²⁸ See, e.g., 15 U.S.C. 1471.

²⁹ Tamper-evident packaging is designed to provide visible evidence to consumers that tampering has occurred, such as a torn label or a tear in a blister pack.

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If you submit your application in an electronic format, FDA recommends that you follow the information set forth in the technical specifications document, Electronic Submission File Formats and Specifications, which is available on the FDA Web site (<https://www.fda.gov/TobaccoProducts>). Following the technical specifications document is one way you can help ensure that your application is in an electronic format that FDA can process, read, review, and archive.

Additionally, to help prepare for a potential referral of your PMTA to the TPSAC, FDA recommends that you identify information that you believe to be a trade secret or confidential commercial information that is contained in your PMTA. You can identify this information by submitting two separate and complete versions of the PMTA: one un-redacted version and one marked-for-redaction version. The marked-for-redaction version should denote the content that is the subject of a proposed redaction at the place where the text is located in the document in a manner that allows the text to remain legible, such as placing a box around the content. FDA also recommends that you submit an index that lists the location of each proposed redaction in the PMTA by page number, and that you explain in detail why you believe that each proposed redaction qualifies as a trade secret or confidential, commercial information³⁰ that is not available for disclosure under 21 CFR 20.61. Doing the above will speed the process if FDA refers your application to TPSAC.

You may withdraw your PMTA at any time until FDA issues an order granting or denying a marketing order. Please notify FDA in writing if you wish to withdraw your PMTA. This notification should be clearly labeled as a PMTA withdrawal and submitted through the electronic system (CTP Portal or ESG) or sent to the following address:

Food and Drug Administration
Center for Tobacco Products
Document Control Center
Building 71, Room G335
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

As described in section IV.C, for the purposes of beginning FDA's 180-day review period, an application is considered "received" on the date that a complete application is received by CTP's DCC (or the location to which samples are submitted).

³⁰ Per part 20.61 "[a] trade secret may consist of any commercially valuable plan, formula, process, or device that is used for the making, preparing, compounding, or processing of trade commodities and that can be said to be the end product of either innovation or substantial effort. There must be a direct relationship between the trade secret and the productive process" and "[c]ommercial or financial information that is privileged or confidential means valuable data or information which is used in one's business and is of a type customarily held in strict confidence or regarded as privileged and not disclosed to any member of the public by the person to whom it belongs. (§20.61(a)-(b)).

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VI. CONTENT AND FORMAT OF A PREMARKET TOBACCO PRODUCT APPLICATION FOR ENDS PRODUCTS

Your PMTA must include all information that is required by section 910(b)(1) of the FD&C Act. Under section 910(b)(1), the application must contain:

- (A) full reports of all information, published or known to, or which should reasonably be known to, the applicant, concerning investigations that have been made to show the health risks of such tobacco product and whether such tobacco product presents less risk than other tobacco products;
- (B) a full statement of the components, ingredients, additives, and properties, and of the principle or principles of operation, of such tobacco product;
- (C) a full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and, when relevant, packing and installation of, such tobacco product;
- (D) an identifying reference to any tobacco product standard under section 907, which would be applicable to any aspect of such tobacco product, and either adequate information to show that such aspect of such tobacco product fully meets such tobacco product standard or adequate information to justify any deviation from such standard;
- (E) such samples of such tobacco product and of components thereof as the Secretary may reasonably require;
- (F) specimens of the labeling proposed to be used for such tobacco product; and
- (G) such other information relevant to the subject matter of the application as the Secretary may require.

This section discusses the mandatory requirements in section 910, provides FDA's general recommendations for PMTA content, and explains FDA's current thinking on well-controlled investigations and other valid scientific information.

To improve the efficiency of the PMTA submission and review processes, FDA recommends that you organize your PMTA content in the following order:

- General Information
- Table of Contents
- Descriptive Information
- Product Samples
- Labeling
- Environmental Assessment
- Summary of All Research Findings
- Scientific Studies and Analyses

See sections VII through IX of this guidance document for additional recommendations for PMTA content for certain types of ENDS products.

FDA anticipates that a single premarket submission may cover multiple products and may include a single, combined cover letter and table of contents across all products. When FDA receives a premarket submission that covers multiple, distinct new tobacco products, we intend to consider information on each product as a separate, individual PMTA. Therefore, it is important that you clearly identify what content pertains to each distinct product and show that you have satisfied the requirements of section 910(b)(1) for each product. For example, FDA considers each ENDS product with a differing flavor variant and/or nicotine strength to be a

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different product. In such a case, an applicant may submit a single premarket submission for the group of ENDS products, clearly delineating which information overlaps and is applicable to all products and which information is specific to a single product (e.g., a specific flavoring or nicotine strength).

Additionally, you may submit a single application for any tobacco product that is a new tobacco product under section 910 of the FD&C Act and which you seek to commercially market as a modified risk tobacco product. Accordingly, if you are seeking a PMTA marketing order as discussed in this guidance and a modified risk order for the same product, you may submit a single application. The single application should include the information required under section 910 for a PMTA, as well as the information required under section 911 of the FD&C Act for a modified risk tobacco product application. If you choose to submit a single application, it is important that you clearly identify what content pertains to the PMTA and show that you have satisfied the requirements of section 910(b)(1).

As specified in 21 CFR 1105.10, FDA may refuse to accept a submission unless it meets certain basic criteria, which are noted throughout the document. Your application must be in English or contain complete English translations of any information submitted within (21 CFR 1105.10(a)(2)). For any documents written in a language other than English, we recommend that you provide the original document, the English translation, and certification that the translation into English is accurate. FDA also recommends that your PMTA be legible and well organized.

If you submit your application electronically, it must be in a format that FDA can process, read, review or archive under 21 CFR 1105.10(a)(3). To facilitate review, FDA recommends that you follow the information set forth in the technical specifications document, Electronic Submission File Formats and Specifications, which is available on the FDA Web site (<https://www.fda.gov/TobaccoProducts>) and also recommends your PMTA:

- Be static, that is, the pages should not reformat, renumber, or re-date each time the document is accessed;
- Provide accurate cross-links to other sections when referenced;
- Enable the user to print each document page by page, as it would have been provided in paper, maintaining fonts, special orientations, table formats, and page numbers; and
- Allow the user to copy text, images, and data electronically into other common software formats.

A. General Information

FDA recommends that you include a cover letter that contains basic information identifying yourself as the applicant and the specific product(s) for which you are seeking a marketing order. This cover letter should prominently identify the submission with “Premarket Tobacco Product Application (PMTA) – [Name of New Tobacco Product]” and include information such as:

- The name and address of your company (required by 21 CFR 1105.10(a)(4));

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- Your authorized U.S. agent or representative's name and address (required by 21 CFR 1105.10(a)(4)-(5)). FDA also recommends you provide their title, phone number, email, and fax number;
- Basic information identifying the new product (required by 21 CFR 1105.10(a)(7)). FDA also recommends this information include the unique identification information described in section VI.C;
- Identifying information regarding prior submissions for the new product, such as substantial equivalence reports or previous PMTAs;
- Dates and purpose of any prior meetings with FDA regarding the new tobacco product;
- A brief statement regarding how the PMTA satisfies the content requirements of section 910(b)(1) of the FD&C Act, such as a table specifying which PMTA sections satisfy each statutory requirement;
- A list identifying all enclosures and labeling being submitted with the PMTA; and
- The signature of a responsible official, authorized to represent the applicant, who either resides in or has a place of business in the United States (required by 21 CFR 1105.10(a)(9)).

B. Table of Contents

FDA recommends that you include a comprehensive table of contents that specifies the section and page number for each item included in the PMTA with hyperlinks to relevant pages in the application. Your PMTA and any amendments also should contain a comprehensive index (i.e., a list of files and metadata).

C. Descriptive Information

Section 910(b)(1) of the FD&C Act requires that you provide information describing the major aspects of the new tobacco product. For this we recommend including the following:

- A unique identification of the new tobacco product;
- A concise but complete description of the new tobacco product;
- An identifying reference to any tobacco product standard under section 907 of the FD&C Act that would be applicable to your new tobacco product and either information that shows your new tobacco product meets the tobacco product standard or adequate information justifying any deviation from such standard, as required in section 910(b)(1)(D);
- An overview of the product's formulation and design, as part of the full statement of properties required by section 910(b)(1)(B);
- The name and description of any characterizing flavor the product contains, if applicable (as required by 21 CFR 1105.10(a)(7));
- The nicotine strength;
- The conditions for using the product or instructions for use, as part of the full statement of the principle or principles of operation required by section 910(b)(1)(B), and, if known, problems with use in previous or similar versions of the new product; and

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- If applicable, any restrictions on the sales and distribution of the new tobacco product that you propose to be included as part of a marketing order under section 910(c)(1)(B) to help support a showing that the marketing of the product would be APPH.

FDA recommends that the unique identification of the product include:

- For E-liquids:
 - Product name
 - Category: ENDS
 - Subcategory: E-Liquid
 - Package type
 - Package quantity (e.g., 1 bottle, 5 cartridges)
 - Characterizing flavor (for a product that is not identified with a characterizing flavor, the unique identification should affirmatively state there is no characterizing flavor; e.g., “Characterizing flavor: none”)
 - E-liquid volume per package (milliliter (mL))
 - Nicotine concentration (mg/ml or %)
 - Propylene glycol (PG)/vegetable glycerin (VG) ratio
- For a Closed E-cigarette or a Prefilled Open E-cigarette:
 - Product name
 - Category: ENDS
 - Subcategory: Closed E-cigarette or Prefilled Open E-cigarette
 - Package type
 - Package quantity (e.g., 1 e-cigarette, 5 e-cigarettes)
 - Characterizing flavor (for a product that is not identified with a characterizing flavor, the unique identification should affirmatively state there is no characterizing flavor; e.g., “Characterizing flavor: none”)
 - Length
 - Diameter
 - Nicotine concentration (mg/ml or %)
 - PG/VG ratio
 - E-liquid volume (mL)
 - Wattage
 - Battery capacity (milliamp hours (mAh))
- For an Open E-cigarette that is not prefilled (e.g., a refillable e-cigarette that does not contain e-liquid):
 - Product name
 - Category: ENDS
 - Subcategory: Open E-cigarette
 - Package type
 - Package quantity (e.g., 1 e-cigarette, 5 e-cigarettes)
 - Characterizing flavor (for a product that is not identified with a characterizing flavor, the unique identification should affirmatively state there is no characterizing flavor; e.g., “Characterizing flavor: none”)
 - Length
 - Diameter

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- Wattage
- Battery capacity (mAh)
- For ENDS Co-Package:
 - Product name
 - Category: ENDS
 - Subcategory: ENDS Co-Package
 - Package type
 - Package quantity (e.g., 1 e-cigarette, 5 e-cigarettes)
 - Characterizing flavor (for a product that is not identified with a characterizing flavor, the unique identification should affirmatively state there is no characterizing flavor; e.g., “Characterizing flavor: none”)
 - Length
 - Diameter
 - Nicotine concentration (mg/ml or %)
 - PG/VG ratio
 - E-liquid volume (mL)
 - Wattage
 - Battery capacity (mAh)

D. Product Samples

Section 910(b)(1)(E) of the FD&C Act requires that a PMTA contain samples of the new tobacco product and its components as FDA may reasonably require. FDA will conduct a review of the PMTA for filing and preliminarily determine whether samples are required and, if so, the number of samples to be submitted for FDA to conduct its own testing and analysis. FDA anticipates that samples will be required in most instances, but we generally intend to inform an applicant if samples will not be required for application filing. FDA will send the applicant a letter that requests the number of samples to be submitted and instructions on how the applicant can submit those samples. Samples should be submitted according to the instructions in the letter and sent directly to the address specified in the letter. As discussed in Section IV.C., a complete application includes the appropriate number of samples, if requested by FDA during filing review or by previous agreement. Thus, if the samples are the last part of the submission to make it complete, FDA’s review period begins when FDA receives the sample or samples. Discussing product samples at a presubmission meeting may help speed up the sample submission process.³¹

E. Labeling

As required by section 910(b)(1)(F) of the FD&C Act, your PMTA must include specimens of all proposed labeling for your new tobacco product. The term *labeling* is defined in section 201(m) of the FD&C Act as “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,” and includes labels, inserts, onserts, instructions, and other accompanying information or materials. The

³¹ See the guidance for industry guidance entitled *Meetings with Industry and Investigators on the Research and Development of Tobacco Products* and section V of the ENDS PMTA Submission Guidance for more information on presubmission meetings.

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submitted specimens of proposed labeling for all product panels should be legible and reflect the actual size and color for use with the new tobacco product as part of your PMTA. All labeling you submit also should include any warning statements appropriate for the product class where applicable, such as the required addiction warning and recommended nicotine exposure warnings described in section IV.D.2 of this guidance and must comply with all other applicable labeling requirements under the FD&C Act.

To help establish that a product is not misbranded and that permitting the marketing of a product would be APPH, FDA recommends that your product labeling include text or graphic elements (in addition to the required warning statement regarding the addictiveness of nicotine and the recommended nicotine exposure warning) to minimize risks associated with use of the product and text or graphic elements to identify the product. Text or graphic elements to minimize risks should be directed at both users and nonusers of the tobacco product and should include directions for use, storage, and recharging, if applicable. For example, the text or graphic could help to show that risk of battery failure would be minimized by recharging the product only with specified chargers or that the product's composition is stabilized by certain storage conditions. Identification elements can include information on your label, such as the batch number, expiration date, and unique identifier bar codes. FDA encourages applicants to use font types and sizes and organizational formats (such as bulleted lists) that are legible and conspicuous, making it easy for consumers to read and understand.

F. Environmental Assessment

An environmental assessment must be included in an ENDS PMTA for FDA's review. Under 21 CFR 25.15, an applicant must include an environmental assessment prepared in accordance with 21 CFR 25.40, unless the action qualifies for a categorical exclusion. Per 21 CFR 25.35, the only categorical exclusion that applies to PMTA submissions is an issuance of an order that a new tobacco product may not be introduced or delivered for introduction into interstate commerce (i.e., a denial of a marketing authorization after FDA's review of a PMTA). More information on environmental assessments can be found in 21 CFR part 25.³²

G. Summary of All Research Information

Section 910(b)(1)(A) of the FD&C Act requires that your PMTA contain full reports of all information published, known to, or which should reasonably be known to you, concerning investigations that have been made to show the health risks of your new tobacco product and whether it presents less risk than other tobacco products. While not required, we recommend that your PMTA contain a well-structured summary to provide FDA with an adequate understanding of the data and information in the PMTA, including the quantitative aspects of the data. This summary will facilitate and help expedite FDA's review. FDA recommends that the summary include a description of the operation of the new tobacco product as well as a section summarizing all research information in your PMTA, including the health risks (e.g.,

³² The Small Entity Compliance Guide (SECG), *National Environmental Policy Act; Environmental Assessments for Tobacco Products; Categorical Exclusions*, represents FDA's current thinking on this topic. For the most recent version of the SECG, check the FDA Tobacco Products Guidance Web page at <https://www.fda.gov/tobacco-products/rules-regulations-and-guidance/guidance>.

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toxicological testing outcomes) of the product, the product's effect on overall tobacco use behavior among current users, the product's effect on overall tobacco use initiation among nonusers, and the product's effect on the population as a whole. The discussion should include information such as:

- (1) A summary of the nonclinical and clinical studies relevant to your PMTA, regardless of whether you consider these studies favorable or unfavorable to the application. It would be helpful to include the specific product or products that were studied and how those products have similar characteristics (similar materials, ingredients, design, composition, heating source, or other features) to the applicant's product if used as a substitute or supplement for data for the product. It would also be helpful to include the study findings, such as whether the findings concern the product's health risks compared to other tobacco products and whether the product presents less risk than other tobacco products. If no relevant health information is available, we recommend that you state so in this section;
- (2) The relative health risks of the new tobacco product for both users and nonusers compared to other tobacco products on the market (e.g., other ENDS, combusted tobacco products such as cigarettes), including tobacco products within the same product category as it may be expected that consumers of current products within the same product category may switch to using a newly marketed product, and the health risks compared to never using tobacco products;
- (3) The chemical and physical identity and quantitative levels of the emission of aerosols under the range of operating conditions (e.g., various temperature, voltage, wattage settings) and use patterns (e.g., intense and non-intense use conditions) within which consumers are likely to use the new tobacco product;
- (4) The likelihood, based on the research information contained in your application, of current nonusers of tobacco products initiating or reinitiating tobacco use by using the new tobacco product;
- (5) The likelihood, based on the research information contained in your application, that consumers will adopt the new tobacco product and then switch to other tobacco products that may present higher levels of risk, such as cigarettes;
- (6) The likelihood, based on the research information contained in your application, of consumers using the new tobacco product in conjunction with other tobacco products;
- (7) The likelihood, based on the research information contained in your application, of current tobacco product users switching to the product instead of ceasing tobacco product use or using an FDA-approved tobacco cessation product (because use of ENDS products includes inherent risk above quitting altogether or the use of an FDA-approved nicotine-replacement therapy (NRT));
- (8) Assessment of abuse liability (i.e., the addictiveness, abuse, and misuse potential of the new product and the exposure to nicotine during product use);
- (9) Assessment of user topography (how individual users consume the product, e.g., the number of puffs, puff duration, puff intensity, duration of use), the frequency with which consumers use the product, and the trends by which users consume the product over time; and
- (10) A discussion demonstrating how the data and information contained in your PMTA establish that permitting the marketing of the new tobacco product would be APPH.

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As part of the discussion in item (10), FDA recommends that you provide an overall assessment of the effect that the new tobacco product may have on the health of the population as a whole. The assessment should synthesize all of the information regarding the product (as described in items numbered 1-9, above) and its potential effects on health, tobacco use behavior, and tobacco use initiation to infer the impact of the potential effect the product's marketing may have on tobacco-related morbidity and mortality. As an illustration, an applicant may make an overall qualitative assessment of whether the product will have a positive impact on the health of the population as a whole by accounting for potential reductions in disease risk (as 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 non-tobacco users to adopt use of the tobacco product and the accompanying potential increases in disease risks among those new users of the product.

H. Scientific Studies and Analyses

Section 901(b)(1)(A), (B), and (C) require that an application contain “full reports of all information . . . concerning investigations which have been made to show the health risks of [the] tobacco product and whether such tobacco product presents less risk than other tobacco products”; “a full statement of the components, ingredients, additives, and properties, and of the principle or principles of operation”; and “a full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and, when relevant, packing and installation of, such tobacco product.” This section provides FDA's recommendations concerning these requirements. FDA recommends organizing the full reports, full statements, and full descriptions of all scientific studies and analyses required by the FD&C Act and referenced elsewhere in the PMTA into a single section. For each study, you should indicate whether the product studied is identical to the new tobacco product, a different version of the new tobacco product (e.g., an earlier prototype), or another comparable product.

1. Product Analyses and Manufacturing

FDA recommends that this section contain the detailed technical information and analyses concerning your new tobacco product and its manufacturing that is required by section 910(b)(1)(B)-(C) of the FD&C Act.

Product analyses and testing should be conducted on the ENDS tobacco product that is the subject of the PMTA. Any product sample submitted (as discussed in section VI.D of this guidance) should be from one of the batches tested for purposes of this section if such a sample is still within its shelf life. Otherwise, a sample should be one with a shelf life current at the time of submission. FDA recommends that, for each product analysis or testing that is included in this section of your PMTA, you include full reports of all testing, including the following information, where applicable:

- Data sets that can reliably reflect the product and its manufacturing. For example, FDA recommends data sets spanning different batches (generally three or more) with multiple

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replicates per batch (generally seven or more), depending upon the variability demonstrated in the method validation, with date and time sampling points;

- Accreditation information for each testing laboratory;
- Validation information and rationale for selecting each test method, including any relevant voluntary testing standards; and
- Complete descriptions of any aerosol-generating regimens used for analytical testing.

At this time, FDA does not believe there is adequate scientific information or regulatory experience with ENDS products to support a PMTA authorization using only information on earlier or other versions of the product or similar products for descriptions of full product analysis as described in this section. If you feel that literature reviews may be an appropriate means for satisfying the requirements of section 910(b)(1)(B), please explain clearly how an adequate comparison (e.g., bridging) can be made between the products analyzed in the published material and the specific product that is the subject of your PMTA. If an applicant has questions or other alternatives to well-controlled investigations it would like to utilize, we recommend that the applicant meet with FDA to discuss the approach prior to preparing and submitting an application.³³

a. Components, ingredients, and additives

The chemistry of the product is a major indicator of the consumer's exposure to health risks. Section 910(b)(1)(B) of the FD&C Act requires a full statement of the components, ingredients, additives, and properties, and of the principle or principles of operation, of such tobacco product as part of your PMTA. FDA interprets this requirement to mean that you should provide a complete list of uniquely identified components, ingredients, and additives by quantity in the new product, as well as the applicable specifications and a description of the intended function for each.

FDA recommends listing information regarding the product's container closure system. The container closure system refers to any packaging materials that are a component or part of the tobacco product. For example, for e-liquids, this would include the container the liquid is in (e.g., a glass or plastic vial or a cartridge, including components of the vial or cartridge). The container closure system can often affect or alter the performance, composition, constituents, or characteristics of a tobacco product. The container closure system could, for example, intentionally or unintentionally, leach ingredients from the packaging into the product, as has previously occurred with other tobacco products.

This list should also specify the function(s) and grade or purity for each respective item. For guidance 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*.³⁴

b. Properties

³³ See the R&D meetings guidance.

³⁴ Available on the Internet at <https://www.fda.gov/tobacco-products/rules-regulations-and-guidance/guidance>.

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Properties of the product can influence a consumer's exposure to health risks. Section 910(b)(1)(B) of the FD&C Act requires that your PMTA include a full statement of the properties of the new tobacco product. We recommend that the "full statement of the properties" of the new tobacco product include a full narrative description of the tobacco product. The following information will aid in satisfying the statutory requirement under the FD&C Act and help FDA to determine whether permitting the marketing of the new tobacco product would be APPH.

- A description of 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);
- A description of all design features of the product, specifying the explicit range of or the nominal values of the design features as well as the design tolerance, where appropriate;
- A quantitative description of the performance specifications;
- A description of product container closure system. The description should include information on how the container closure system protects and preserves the product, such as from damage during transport, environmental contaminants, leaching, and migration of container closure system constituents into the products (FDA expects that this documentation may be generated by the applicant, by the supplier of the material of construction or the component, or by a laboratory under contract to either the applicant or the manufacturer);
- A description of how the product's properties (e.g., product design parameters, constituents) differ from similar, marketed tobacco products in the same category. For example, if your PMTA is for an e-liquid, we recommend a comparison to other e-liquids with similar nicotine content, flavors, and other ingredients, used in the same manner and under similar conditions. Because it is expected that consumers of current products that are of the same category may switch to using a newly marketed product, it is important that FDA be able to evaluate whether this switching would result in a lower or higher public health risk. You should describe both how your product may be similar and different from other products of the same category;
- Stability information for the new tobacco product. This information should include the established shelf life of the product and changes in pH and constituents (including HPHCs and other toxic chemicals) over the lifespan of the product, such as the factors that determine the shelf life (e.g., volume of e-liquid, power supply, atomizer, coil); how stability is affected by the storage conditions, such as moisture and temperature; full reports of all stability testing; and how the product's performance may significantly decline (e.g., decrease in aerosol flow rate or change in aerosol constituents) over the product's lifetime; and
- Assessments of product design hazards that could be expected to result in illness or injury from normal use and foreseeable misuse of the product, including actions taken or future plans that show how a design hazard is reduced, mitigated, or eliminated. For example, you could assess whether the consumer could tamper with the heating element and how the manufacturer has responded to such an assessment so the product is not misused. Similarly, you could describe how you plan to address the likelihood of battery use and foreseeable misuse leading to overheating, fire, and explosion during operation, charging, storage, and transportation.

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FDA also recommends that you include a complete list of uniquely identified constituents or chemicals, including those listed below, as appropriate for your product, and other toxic chemicals contained within the product or delivered by the product, such as a reaction product from leaching or aging and aerosol generated through the heating of the product. This type of information can be provided by measuring constituent or chemical yields from your product.

We recommend that this testing reflect the range of operating conditions (e.g., various temperature, voltage, wattage settings) and use patterns (e.g., intense and non-intense use conditions) within which consumers are likely to use your product, and the types of products that consumers are likely to use in conjunction with your products. For example, a refillable e-cigarette (i.e., an e-cigarette that includes an e-liquid reservoir that a consumer can refill) should be tested with a reasonable range of available e-liquids, particularly those available in different levels of nicotine; a replaceable e-cigarette (i.e., an e-cigarette that uses replaceable cartridges or pods) should be tested with a reasonable range of replaceable cartridges or pods with which it can be used; a closed e-cigarette that is not replaceable (i.e., an e-cigarette that includes an e-liquid reservoir that is not refillable) should be tested with the e-liquid with which it is packaged and sold; and components or parts should be tested with the reasonable range of products with which they could be used. FDA recommends that manufacturers of e-liquids test the constituent delivery in an e-cigarette that is designed to deliver low levels of aerosol (such as open refillable cigarette-like systems) as well as in an e-cigarette that is designed to deliver higher levels of aerosol with varying temperatures and voltage (such as a tank or mod system). Evaluating new tobacco products under a range of conditions, including both non-intense (e.g., lower levels of exposure and lower volumes of aerosol generated) and intense (e.g., higher levels of exposure and higher volumes of aerosol generated), enables FDA to understand the likely range of delivery of emissions. The two regimens are expected to provide the Agency with information about possible different deliveries of constituents, including the range of quantities of constituents.

In order to help FDA assess potential health risks and to enable FDA to make a finding that permitting the marketing of a new tobacco product would be APPH, FDA recommends that you consider the following constituents or chemicals³⁵ for analysis in e-liquids or aerosols, or both, as appropriate, for your product:

- Acetaldehyde
- Acetyl propionyl (also known as 2,3-pentanedione)

³⁵ These constituents include constituents that, to FDA's current thinking, potentially could cause health hazards depending on the level, absorption, or interaction with other constituents. FDA intends to establish a revised list of harmful and potentially harmful constituents (HPHCs) that include HPHCs in ENDS products and publish it in the *Federal Register*. While applicants should submit certain information about HPHCs as part of their applications, the requirement to submit HPHC listings under section 904 of the FD&C Act is separate and distinct from the premarket review requirements under section 910. HPHC information submitted under section 904 will assist FDA in assessing potential health risks and determining if future regulations to address a product's health risks are warranted. For PMTAs, FDA expects that applicants will report the levels of HPHCs as appropriate for each product, so the reported HPHCs will differ among different product categories. The Agency recommends that manufacturers consult with CTP's Office of Science about what is appropriate in the context of a specific application.

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- Acrolein
- Acrylonitrile
- Benzene
- Benzyl acetate
- Butyraldehyde
- Cadmium
- Chromium
- Crotonaldehyde
- Diacetyl
- Diethylene glycol
- Ethyl acetate
- Ethyl acetoacetate
- Ethylene glycol
- Formaldehyde
- Furfural
- Glycerol
- Glycidol
- Isoamyl acetate
- Isobutyl acetate
- Lead
- Menthol
- Methyl acetate
- N-butanol
- Nickel
- Nicotine from any source, including total nicotine, unprotonated nicotine, and nicotine salts
- NNK (4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone)
- NNN (N-nitrosornicotine)
- Propionic acid
- Propylene glycol
- Propylene oxide
- Toluene
- Other constituents, as appropriate for your particular product. For example, you might want to consider whether you should test for flavorants that can be respiratory irritants such as benzaldehyde, vanillin, and cinnamaldehyde.

FDA recognizes that some of the constituents or chemicals listed immediately above may be ingredients in e-liquids (e.g., menthol, propylene glycerol, glycerol, diethylene glycerol, ethylene glycerol). In such cases, it might be acceptable to provide the quantity added to the e-liquid in lieu of measuring constituent or chemical yields generated from the e-cigarette. If this approach is taken, FDA recommends you clearly state that the reported constituent or chemical quantity reflects the amount added to the product and not the quantity measured in the product. FDA also recommends that you explain why you believe the amount of ingredients or chemicals added to the product is an accurate measure of the constituent or chemical found in the product or aerosol

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(i.e., chemical reactions in the product will not change the chemical's amount) and, therefore, why testing is not warranted.

In addition to the constituents, FDA recommends that you report the pH of the e-liquids tested and the resulting aerosol.

FDA also recommends that you submit information regarding any relevant voluntary standards with which your product complies and why you believe the standard is relevant, as well as testing data to demonstrate conformance to such standards.

c. Principles of operation

Consumers may be able to alter an ENDS product's effects by changing the product design, the way the product is used, or adding or subtracting other ingredients. Section 910(b)(1)(B) of the FD&C Act requires you to submit as part of your PMTA "a full statement of the . . . principle or principles of operation" of the new tobacco product. FDA interprets a full statement of principle or principles of operation to include a full narrative description of the way in which a consumer will use the new tobacco product, including a description of how a consumer operates the product, how the manufacturer reasonably believes a consumer could change the product characteristics, adjust the performance, or add or subtract ingredients. This description also should include examples of the other types of ENDS products with which your product can be used and also show the range of conditions under which the product may operate.

d. Manufacturing

The manufacturing descriptions in your PMTA show how the product is made to conform to the product information provided in the PMTA. As required by section 910(b)(1)(C) of the FD&C Act, you must provide "a full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and, where relevant, packing and installation of the new tobacco product."³⁶

To help meet this statutory requirement, FDA recommends that you provide a listing of all manufacturing, packaging, and control sites for the product, including the facility names and addresses, the Facility Establishment Identifier number(s) (if available), and a contact name and telephone number for each facility. Moreover, we recommend that you provide 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, as applicable:

- Manufacturing and production activities at each facility, including a description of facilities and all production steps;

³⁶ The requirement to provide a full description of methods of manufacturing and processing is separate and distinct from tobacco product manufacturing practice requirements, which will be the subject of regulations under section 906(e) of the FD&C Act (21 U.S.C. 387f(e)). FDA intends to issue regulations under section 906(e) that will contain the requirements for tobacco product manufacturing practices. At that time, each PMTA will also be expected to demonstrate that the methods, facilities, or controls used conform to these regulations (section 910(c)(2)(B)).

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- Managerial oversight and employee training;
- Manufacturing processes and controls for product design, including a hazard analysis that details the correlation of the product design attributes with public health risk, and any mitigations for identified hazards that have been implemented;
- Activities related to identifying and monitoring suppliers and the products supplied (including, for example, purchase controls and materials acceptance activities);
- Validation and verification activities used to ensure that the new tobacco product matches specifications, including any voluntary standards with which your product complies;
- Test methods and procedures conducted before the new tobacco product is released for sale and distribution in the United States, including information on test parameters, such as the concentration of the standard solution, as well as a description of acceptance activities with protocol and acceptance criteria. If the product is manufactured without a solution, you should describe its performance characteristics (e.g., particle size, heating temperature); and
- Handling of complaints, nonconforming products and processes, and corrective and preventive actions.

FDA may request that you submit copies of selected SOPs if needed to enable FDA to more fully understand the methods used in, and the facilities and controls used for, the manufacturing and processing of the new tobacco product.

2. Nonclinical and Human Subject Studies

Section 910(b)(1)(A) of the FD&C Act requires that a PMTA contain “full reports of all information, published or known to, or which should reasonably be known to, the applicant, concerning investigations which have been made to show the health risks of such tobacco product and whether such tobacco product presents less risk than other tobacco products.” FDA interprets the information required under this provision to include not only investigations that support the PMTA, but also any investigations that do not support, or are adverse to, the PMTA. Information on both nonclinical and clinical investigations that must be provided, including, but not limited to, any studies assessing constituents of tobacco, aerosol, toxicology, consumer exposure, consumer use profiles, and consumer risk perception. Furthermore, information on investigations concerning products with novel components, ingredients, additives, or design features that are similar or related to those of the new tobacco product and investigations concerning products that share novel components, ingredients, additives, or design features with the new tobacco product should also be provided so that FDA may adequately assess the product’s health risks. To the extent the information is available, you should indicate the source of funding for all studies and provide a statement regarding any potential financial or other conflicts of interest on the part of the investigator(s). Due to the emerging nature of ENDS products within the general tobacco market, FDA acknowledges that there may be limited nonclinical or clinical research conducted on specific ENDS products. Thus, it is likely that applicants will conduct certain investigations themselves and submit their own research findings as a part of their PMTA. However, in general, FDA does not expect that applicants will have to conduct long-term studies to support an application.

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FDA interprets “full reports of all information, published or known to, or which should reasonably be known to, the applicant” to include all information from investigations conducted both within and outside the United States. While all clinical investigations (both within and outside the United States) submitted with your PMTA should be conducted to protect the rights, safety, and welfare of human subjects, you must (under section 910(b)(1)(A) of the FD&C Act) submit full reports of all information concerning relevant clinical investigations. Lack of adequate human subject protection procedures is not a justification for failing to include information on a relevant clinical investigation in your PMTA.

Where an applicant chooses to conduct studies, one way to protect the rights, safety, and welfare of human subjects is to ensure that clinical studies included in a PMTA are conducted in accordance with ethical principles acceptable to the international community (e.g., ICH E6 Good Clinical Practice standards).³⁷ Special attention should be paid to trials that may include vulnerable subjects.³⁸ Adequate procedures for human subject protection help protect the rights, safety, and welfare of human subjects in accordance with ethical principles acceptable to the research and health care communities and ensure that the data are scientifically valid.

Section 910(g) of the FD&C Act gives FDA the authority to issue regulations to exempt tobacco products intended for investigational use from the requirements of Chapter IX of the FD&C Act, including premarket submission requirements. To date, FDA has not issued such regulations, and consequently investigational tobacco products are not exempt from FD&C Act requirements, including premarket submission requirements. Until regulations governing the use of investigational tobacco products are issued and finalized, FDA intends to evaluate specific uses of investigational tobacco products on a case-by-case basis to make decisions about enforcing premarket review requirements with respect to such products.³⁹ FDA encourages persons who would like to study their new tobacco product to meet with the Office of Science in CTP to discuss their investigational plan. The request for a meeting should be sent in writing to the Director of CTP’s Office of Science and should include adequate information for FDA to assess the potential utility of the meeting and to identify FDA staff necessary to discuss agenda items.⁴⁰ Additional information related to meetings with FDA can be found in section XII of this document.

For published studies concerning investigations that have been conducted to show the health risks of your new tobacco product, you should provide a bibliography of the studies and a full copy of all articles stemming from each study in order to facilitate FDA’s review. You should

³⁷ For information on how good clinical practice standards have been used in other contexts, see FDA’s guidance for industry *E6 Good Clinical Practice: Consolidated Guidance*, available on the Internet at <https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm> (under ICH–Efficacy).

³⁸ For information on considerations on clinical trials with vulnerable subjects, see 21 CFR part 56.

³⁹ When finalized, the guidance for industry and investigators *Use of Investigational Tobacco Products* will represent FDA’s current thinking on this topic. For the most recent version of a guidance, check the FDA Tobacco Products Guidance Web page at <https://www.fda.gov/tobacco-products/rules-regulations-and-guidance/guidance>.

⁴⁰ See the R&D meetings guidance.

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also provide an explanation of the scope of the literature review you conducted to discover the relevant published studies, including how you identified, collected, and reviewed the studies. In addition, for studies that you conducted or that were conducted on your behalf, you should submit full study reports and data.

Your PMTA should include a summary of the results and methods of each study you submit. Information about studies' methodology and procedures help FDA assess the strength of the study. The summary should include, where available or reasonably obtainable:

- A description of the study objective;
- A description of the study design (or hypothesis tested);
- A description of any statistical analysis plan, including how data were collected and analyzed; and
- A brief description of the findings and conclusions (positive, negative, or inconclusive).

In addition, for each study regarding the health risks of the new tobacco product, we recommend that you include the following information, to the extent available or reasonably obtainable. Where information isn't available (e.g., it was never created) or reasonably obtainable (e.g., the expense or effort to obtain it far outweighs its usefulness), FDA recommends the applicant include an explanation of such in its application. It is important to note that failure to submit study report documents may affect the extent to which FDA is able to rely upon an investigation's findings during substantive application review.

- Copies of all study protocols and amendments that were used in the study;
- Copies of all investigator instructions;
- The statistical analysis plan, including a detailed description of the statistical analyses employed (i.e., all variables, confounders, and subgroup analyses and any amendments);
- A list of the sites where the study was conducted, including contact information and physical address(es);
- Line data or study data, consisting of an analyzable dataset of individual-level observations for each study participant (or laboratory animal or test replicate). FDA does not generally need case report forms other than those associated with participant deaths, other serious and unexpected adverse experiences, or discontinuations from the study. To facilitate our review, we request data in SAS-transport file in XPT format, created by a procedure that allows the files to be readily read by JMP software. We also request that you provide 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;
- The location of all data, if kept at the study site or elsewhere. As stated in the previous bullet, FDA is recommending the applicant submit only line data or study data for this section of their PMTA. FDA suggests the applicant retain all raw or source data, such as original records on a study's finding and all individual case report forms, rather than include it in the initial submission; FDA may want to inspect and review this data as necessary during the application's review;

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- The format of the records and data (e.g., electronic, hard copy);
- A list of all contractors who participated in the study, the role of each contractor, and the initiation and termination dates of the participation of each contractor; and
- A signed full report of the findings.

For nonclinical studies, we recommend you also include documentation of all actions taken to ensure the reliability of the study, such as appropriate good laboratory practices found in 21 CFR part 58.

For clinical studies, we recommend that you include, to the extent available or reasonably obtainable:

- Documentation of the protection of human subjects⁴¹ (e.g., documentation of study oversight by an Investigational Review Board duly constituted and operating under 21 CFR part 56; description of informed consent procedures, such as appropriate procedures found in 21 CFR part 50);
- All versions of questionnaires used;
- All versions of case report forms used; and
- All versions of informed consent forms.

Please note that individual subject case report forms and informed consent forms do not need to be submitted in the PMTA, but may be requested by FDA for further review if necessary to determine that permitting the marketing of the product would be APPH.

a. Nonclinical health risk information

Although nonclinical studies alone are generally not sufficient to support a determination that permitting the marketing of the product would be APPH (PMTAs would generally need clinical data), information from these nonclinical studies provides insight into the mechanisms of disease incidence caused by a tobacco product and, more generally, provides context for the data obtained from human studies regarding health risks, including addiction. Information on how manufacturers may want to address human study (clinical) information with new studies or existing studies, data, and literature is discussed in this guidance later in this section and in section X.

To help understand the health risks of a tobacco product, FDA recommends providing a full assessment of the toxicological and pharmacological profile associated with the new tobacco product including, if available:

- Toxicology data from the literature (i.e., all relevant publications);
- Analysis of constituents, including HPHCs and other toxicants, under both intense and non-intense use conditions as described in section VI.H.1.a;

⁴¹ If you are unable to provide information explaining how the rights, safety, and welfare of human subjects were protected, you should explain why (e.g., because you were not the sponsor of those studies the information is not reasonably available).

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- In vitro toxicology studies (e.g., genotoxicity studies, cytotoxicity studies);
- Computational modeling of the toxicants in the product (to estimate the toxicity of the product); and
- In vivo toxicology studies (to address unique toxicology issues that cannot be addressed by alternative approaches).

A thorough literature review, including publicly available toxicology databases, can provide valuable information on the toxicity of the ingredients in the e-liquid and aerosol by the expected route of exposure and level of exposure. We recommend that this section include:

- A description of the search methodology;
- All publications related to the toxicological evaluation of each of the ingredients (e.g., nicotine, glycerol, propylene glycol, flavors, metals) and the mixture of the ingredients in the e-liquid and aerosol produced from the ENDS;
- Particular attention to information regarding oral, inhalation, dermal, and ocular routes of exposure;
- Information concerning substances that may be solvent extractable from the container closure system or leachable into the e-liquid when the e-liquid is in contact with the container closure system (e.g., information on whether toxic substances present in the container closure system can potentially transfer into the e-liquid or aerosol);
- Toxicological endpoints such as cytotoxicity, genotoxicity, carcinogenicity, and respiratory, cardiac, reproductive, and developmental toxicity;
- Exposure kinetics, metabolism, and deposition and elimination profile of the ingredients, when available;
- A conclusion as to whether there is a toxicological concern with respect to the ingredients, constituents, flavors, humectants, and mixtures of humectants (glycerin, propylene glycol, and other ingredients) that will be delivered in the aerosol from the use of the new tobacco product; and
- Information on physiochemical changes of the mixture of ingredients in your product due to temperature, wattage, and/or voltage changes, if available.

Where a thorough literature review does not address these points, these topics may need to be addressed in separate studies conducted by the applicant.

Information generated from the new tobacco product itself also provides valuable insight into the toxicity profile of the product. This information may include analysis of constituents and other toxic compounds in the ENDS aerosol. It can also include in vitro studies, in vivo studies, or both with the ENDS product itself. These studies might be conducted if an applicant is unable to acquire publicly available toxicology information for specific aerosol ingredients. For any toxicity studies conducted prospectively, the following points should be considered:

- Studies should be based on the potential human exposure of the product. Exposures that mimic the highest consumer use scenario and one lower exposure level should be evaluated in the toxicology studies based on the results determined as described in section VI.H.1.a. Analysis of constituents and toxicant levels at the exposures tested should be included.

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- If the consumer can change the voltage and/or temperature of the heating element, we recommend that you provide any available data on the subsequent changes in the aerosol ingredients. Please also include any toxicity information relevant to these changes.
- We recommend that you provide aerosolization properties of each of the ingredients (e.g., constituents, humectants, metals, flavors included), particle size of these ingredients in the product, and deposition of these particles through inhalation. We also recommend that you discuss how these properties could affect the product's toxicity profile.
- In vitro assays can be used to evaluate the genotoxic potential of the ENDS in comparison to other tobacco products. We suggest using the ICH S2(R1) guidance⁴² and Organization for Economic Cooperation and Development protocols as a guide for genotoxicity assessment. We also recommend that you conduct these assays with multiple concentrations of your final product for validating your results. For appropriate hazard identification comparison, you should include the comparator products (e.g., products in the same category) in your in vitro assay.

FDA supports reducing, replacing, and/or refining the use of animal testing in research 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 the suitability and acceptability of non-animal tests for their particular new tobacco product. When animal-based nonclinical laboratory studies are conducted, investigators should use appropriate animal models, adhering to the best practices of refinement, reduction, and replacement of animals in research and following the applicable laws and regulations governing animal testing.

In addition to the available literature and any data generated on the specific product, a strong scientific justification for the potential daily exposure levels of users to an aerosol from an ENDS product should be included. This information is important to enable FDA to conduct a thorough evaluation of the toxicity potential of the new tobacco product. The aerosol exposure levels should reflect the best available science on how exposures will occur in consumers based on the intended use of the ENDS product. In addition, we recommend that you provide the scientific rationale for the selection of the daily exposure to any other tobacco products used as comparators. The assumptions used to determine the exposure levels from the ENDS product (including aerosol) versus other tobacco products should be clearly articulated. Your nonclinical information section should then use this exposure information to inform the comparisons of all ingredients (including constituents, flavors, metals, and other e-liquid additives such as propylene glycol and glycerol) between the ENDS product and the product used as a comparator in your PMTA submission.

FDA recommends that you identify the key features in the new tobacco product that affect the levels of toxicants contained in the aerosol and provide evidence that key parameters in the product are stable with batch-to-batch testing.

In the absence of toxicological data for a particular toxicant of concern, we recommend that you consider computational modeling using surrogate chemical structures. If computational modeling

⁴² FDA guidance for industry *ICH S2(R1) Genotoxicity Testing and Data Interpretation for Pharmaceuticals Intended for Human Use*, available on the Internet at <https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm> under ICH - Safety.

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is used, detailed modeling information should be provided including equations, assumptions, parameters (and data used to generate the parameters if such data were used), outputs, and references, as well a validation of the model. When you are using the model to evaluate the risk of a new tobacco product, we recommend that you utilize assumptions, equations, and parameters appropriate to the characteristics of the product and appropriate for the selected population of product users. If you plan to conduct any computational modeling, we suggest that you meet with CTP to specifically address this issue. Finally, we recommend that you provide an integrated summary discussing how permitting the marketing of the new tobacco product would be APPH from a toxicology perspective relative to any similar comparator tobacco products (when those products are used in the same manner, under similar conditions, and for the same duration and frequency).

b. Human health impact information

Your PMTA should provide data that adequately characterizes the potential impact of the new tobacco product on the health of both users and nonusers of tobacco products in order to support that permitting the marketing the new tobacco product would be APPH. This information can be gathered through your own studies or through alternatives, discussed in section X of this guidance. To evaluate the acute and chronic health effects associated with the product, FDA recommends including studies, other scientific evidence, or both, that identify biomarkers of exposure, biomarkers of harm, and health outcome measurements or endpoints. For example, biomarkers of toxicant exposure may include compounds such as cotinine, NNAL, and NNN. While long term studies are most useful for identifying chronic effects associated with use of a product, such studies are not routinely expected.

Considerations in addressing the human health impact of a new tobacco product may include, but are not limited to:

- Tobacco users who may switch from other tobacco products to the new tobacco product;
- Tobacco users and nonusers who, after adopting use of the new tobacco product, may switch to or switch back to other tobacco products that may present higher levels of individual health risk;
- Tobacco users who may opt to use the new tobacco product rather than cease tobacco use altogether;
- Tobacco users who may opt to use the new tobacco product rather than an FDA-approved tobacco cessation medication;
- Tobacco users who may use the new tobacco product in conjunction with other tobacco products;
- Nonusers, such as youth, never users, and former users, who may initiate or relapse tobacco use with the new tobacco product;
- The health effects in users of the new tobacco product; and
- Nonusers who experience adverse health effects from the new tobacco product.

Addressing these considerations in a full assessment of the health effects associated with your ENDS product may include evaluation of the following:

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i. Consumer perceptions and intentions

Consumer perception evaluations should address how consumers perceive product harms and include consideration of packaging and labeling. These evaluations should also address interest in and intentions to use the product, including among populations of non-users of tobacco products (e.g., vulnerable populations such as youth and young adults). Examples of information that may be considered in this analysis include published reports and data on consumer perceptions of the new tobacco product and its packaging and consumer intentions to use the product, and data you collect on consumer perceptions of the harms of the new tobacco product and of its proposed labeling or advertising and intentions to use the product, including among populations of non-users of tobacco products. If you are collecting data on consumer perceptions or intentions, we recommend evaluating perceptions of the product, both absolute and in comparison to other categories of tobacco products and to quitting all tobacco use. This evaluation should include the use intentions among current ENDS users, nonusers, and other tobacco product users, as well as reasons for use (e.g., complete substitution, use in environments where smoking is not allowed, fun and enjoyment).

ii. Likelihood of initiation and cessation by both users and nonusers of tobacco products

Evaluations of the likelihood of initiation among never-users and former users of tobacco products and cessation among current tobacco users should cover a range of tobacco use behaviors related to your new tobacco product. Examples of information that FDA recommends considering in these evaluations include:

- Published literature or applicant-initiated studies evaluating the effects of the ENDS on users, including effects on initiation, switching behavior, cessation, and dual use; and on nonusers' initiation of the product. Published literature or studies should be of the same or similar ENDS product. Where the ENDS product studied is similar to the new tobacco product, the applicant should explain why making such a comparison is appropriate; and
- Scientific information (e.g., information collected from peer-reviewed literature or data you collect on your product) on the likelihood of tobacco product use by nonusers, specifically youth and young adults, pregnant women, and other vulnerable populations.

Although randomized clinical trials could address cessation behavior of users of tobacco products, FDA believes this would also be true for observational studies (perception, actual use, or both) examining cessation behaviors.⁴³

iii. Product use patterns

Evaluation of product use patterns should consider the topography of how individual users consume the product (e.g., the number of puffs, puff duration, puff intensity, duration of use), the

⁴³ FDA recognizes that some clinical investigations examining cessation may require an investigational new drug application (IND). FDA encourages applicants to contact FDA with questions about whether the IND requirements apply to a particular clinical investigation.

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frequency with which consumers use the product, and the trends by which users consume the product over time. FDA recommends that information and data on product use, including use in conjunction with other tobacco products, be assessed, when possible, by factors that may be expected to influence such patterns, such as age group (including youth and young adults), sex, race, ethnicity, and education.

- If the product has not been previously marketed, such information could be collected from actual use studies.
- For previously marketed products, marketing data or company research conducted to understand the use patterns could be used as well. In addition, applicants may incorporate information from national surveys or the results of other published studies.
- Although most studies in the published scientific literature typically focus on general ENDS products and are not usually product-specific or type-specific, data from these studies can still be informative to assess overall ENDS product use information. Applicants using published studies of ENDS use to support their application should provide a scientific rationale and bridging information to allow FDA to assess whether the findings of such studies would be relevant to the product that is the subject of the application.
- In addition, applicants may need to supplement information from existing studies and surveys with applicant-specific perception surveys or actual use studies.

Section IV discusses FDA's current thinking on alternatives for obtaining study information and using bridging studies to apply existing studies to your product.

FDA also recommends sharing your marketing plan to enable FDA to better understand the potential consumer demographic. In addition, and if the product is currently marketed,⁴⁴ FDA recommends sharing sales data broken down by population demographics and tobacco use status. Sales data, if available, should be analyzed in regular (preferably 4-week or monthly) intervals and should include:

- The Universal Product Code that corresponds to the product(s) identified in the PMTA;
- 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 (e.g., convenience stores, food and drug markets, big box retailers, internet/online sales, tobacco specialty shops) promotional discounts (e.g., buy-one-get-one free or percentage discount);
- Demographic characteristics of product(s) purchasers, such as age, gender, and tobacco use status; and
- Information on top selling brands as a comparison for all recommended information, if available, so FDA can assess the market for the PMTA product to better estimate the potential impact on public health.

iv. Labeling comprehension and actual use

⁴⁴ FDA recognizes that some products covered by this guidance were on the market before FDA deemed all tobacco products subject to the FD&C Act and would expect that some would continue to be on the market during the final deeming rule's compliance period. These currently marketed products should provide data on current U.S. sales.

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FDA recommends that you include studies demonstrating that users and nonusers understand the product's labeling and instructions for use, and use the product according to its labeled instructions, including studies such as labeling comprehension studies, focus group studies, and surveys. FDA also recommends that you provide a description of how the product is actually used by the consumer, including both use as intended and use as not intended.

v. Human factors

Analyses to evaluate the impact of human factors may be helpful to identify risks associated with "real world" use of a new tobacco product and demonstrate that potential risks associated with use for both users and nonusers have been mitigated.

Human factors considerations and analyses should include studies, such as actual use studies, labeling comprehension studies, focus group studies, and surveys, that identify:

- Normal use and foreseeable misuse conditions (e.g., dripping);
- Product users and nonusers;
- Use environment, such as home, community settings, and mobile environments (e.g., cars, planes, other public forms of transportation);
- Use-related hazards and estimated use error risk (including misuse);
- Risk controls to ensure that harms and unintended consequences are minimized; and
- Adverse experiences.

vi. Abuse liability

Abuse liability evaluations, including pharmacokinetic evaluations, should consider the addictiveness and abuse and misuse potential of the new product and the exposure to nicotine during product use. These evaluations should consider:

- Published reports and data describing the abuse potential of the e-liquid or e-cigarette when used as an ENDS, as well as the abuse potential in comparison to other relevant tobacco products (such as cigarettes or other ENDS products); and
- Published reports and pharmacokinetic data (including published reports) examining the exposure to nicotine during use.

vii. Biomarkers of harm and biomarkers of exposure

Biomarkers of harm and biomarkers of exposure may include published reports or data on biomarkers of harm, biomarkers of exposure, and/or other intermediate health measures to users and nonusers. For example, biomarkers of toxicant exposure may include compounds such as cotinine, NNAL, and NNN. Section X discusses FDA's current thinking on alternatives for obtaining study information.

viii. Health outcomes

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Data to support the impact of the new tobacco product on the health of users and nonusers may include health effects related to specific constituents that have been identified in the aerosol delivered to the user. These constituents will vary depending on the product and may include glycerin, propylene glycol, nicotine, flavorings, and metals. These data should include health effects of aerosol exposures, including changes in physiological measurements, such as heart rate and blood pressure; changes in lung, cardiac, and metabolic function; adverse experiences, such as throat irritation and cough; and changes in laboratory values, such as mediators of inflammation and complete blood count indices.

FDA recommends that when you conduct studies, you ensure, to the extent possible, that the study findings are generalizable to the population of U.S. users and nonusers of your new tobacco product. If you are relying on published reports to support your PMTA, you should justify why the data from those reports can be bridged to your product and are appropriate for determining the impact of the new tobacco product on the U.S. population.

VII. ADDITIONAL RECOMMENDATIONS FOR PREMARKET TOBACCO PRODUCT APPLICATIONS FOR E-LIQUID PRODUCTS

Because e-liquids have different properties and characteristics than other e-cigarette components, there are additional health considerations that should be addressed in a PMTA for an e-liquid. In addition to the recommendations above for ENDS PMTAs in general, FDA recommends that you address the following additional information in the Product Analysis and Manufacturing section of a PMTA for an e-liquid.

A. Components, Ingredients, and Additives

In addition to the test analysis stated above in section VI.H.1.a, FDA recommends that you provide adequate information in the PMTA to characterize the ingredients (e.g., menthol, glycerol) in the e-liquid and identify characteristics of the e-liquid that may impact the constituents in the aerosol. FDA also recommends that you provide the e-liquid design parameters that would be affected by, and that would affect, e-cigarette performance, such as the e-liquid viscosity and boiling point.

B. Flavors

Because of the potential impact of flavors on product toxicity and appeal to youth and young adults, scientific reviews of flavors (e.g., toxicological analyses of flavor additives, chemistry analyses, clinical studies, literature reviews), should be included in a PMTA for an e-liquid. There may be significant differences in the health risk of flavors depending on their route of exposure as well as the formation of additional chemicals due to heating or burning of the flavors. Substances that are generally recognized as safe (GRAS) under sections 201(s) and 409 of the FD&C Act (21 U.S.C. 348) are defined as substances that are intentionally added to food and intended for oral ingestion. E-liquid is not food or intended for oral ingestion; therefore, the fact that some substances have been designated GRAS for food does not mean that they are safe for inhalation.

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Under section 910(b)(1)(A) of the FD&C Act, you must include in your PMTA full reports of all information, published or known to, or which should be reasonably known to you (the applicant) concerning investigations that have been made to show the health risks of the new tobacco product and whether the new tobacco product presents less risk than other tobacco products. FDA considers the appeal and use of ENDS product flavors important in ascertaining the health risks of these products. In this regard, FDA recommends that you describe research on flavor development including, but not limited to, market segmentation analysis or sensory testing. You should describe consumer perceptions among current ENDS users and other tobacco users for appeal and use intentions based on labeling and actual use of flavors, and product design. In addition to the recommended information contained throughout this guidance, it is also important for PMTAs for flavored products to examine the impact of the flavoring on consumer perception (see section VI.H.2.b.i, above, for a discussion of consumer perception evaluations), especially given the attractiveness of flavors to youth and young adults. Additionally, to provide a better understanding of the appeal of flavors to adults, FDA recommends examining adult appeal of such flavors in their decisions to initiate use, cease use of more harmful products, or dual use.

VIII. ADDITIONAL RECOMMENDATIONS FOR PREMARKET TOBACCO PRODUCT APPLICATIONS FOR E-CIGARETTES

E-cigarettes have different properties and characteristics than e-liquids and, consequently, present additional health considerations that are important for you to address in a PMTA for an e-cigarette. In addition to the general recommendations above for ENDS PMTAs, FDA recommends that you address the following additional information in a PMTA for an e-cigarette.

A. E-cigarette Design Factors to Consider

Section 910(b)(1)(B) of the FD&C Act requires that a PMTA include a full statement of the components, ingredients, additives, and properties, and the principle(s) of operation, of the new tobacco product. In addition, FDA recommends that in PMTAs for e-cigarettes and their components sold separately, you address both the items listed in this section of the guidance and the characteristics listed specifically for the batteries, atomizers, and software, as applicable.

ENDS users and nonusers are exposed to aerosols produced by the e-cigarette. Therefore, to understand the health impact of an ENDS product, it is important to understand how the e-liquid is heated as well as how the aerosol is generated and transmitted to the user. Information about the properties and principles of operation of an ENDS product will help FDA in determining the impact of the aerosol on health. FDA recommends that you provide a precise description of the e-cigarette, including detailed discussions of the following, if applicable:

- E-cigarette features;
- Material and/or ingredient functions;
- Capabilities to monitor product performance (e.g., temperature sensing, voltage sensing, battery life detection);
- Instructions and method of operation;
- Materials of all e-cigarette components;
- Operating ranges (e.g., lower and upper wattage, voltage limits that users can adjust);

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- Power supply, such as batteries (including whether it is rechargeable or replaceable);
- Charging source and the safety of using different charging sources; and
- Heating source (e.g., heating coil, chemical reaction).

FDA also recommends that your PMTA contain detailed e-cigarette schematics (e.g., CAD drawings) with dimensions, pictures, and labeling, accompanied by engineering design parameters.

Finally, electrical safety should be discussed, and applicable standards to which conformance have been demonstrated should be identified. This discussion should include appropriate data (e.g., test protocol, data, results). Additionally, you should provide a description of all built-in electrical safety features. Specific recommendations for batteries are listed in section VIII.B.1. If the product contains a controller, you should list and discuss the power management techniques used, such as pulse width modulation or direct current.

B. Possible Design Parameters for Subcategories of E-cigarette Components and Parts

FDA recognizes that there is no single set of engineering parameters that will characterize all e-cigarettes and that each subcategory may have additional design parameter information that is important in fully characterizing the health risk of the product. For example, battery characteristics such as alarm capabilities, voltage range, and battery type may affect the risk associated with using an ENDS product. The following sections provide examples of the information that FDA recommends you include for batteries, atomizers, and software. FDA recommends that this information be addressed in a PMTA for an e-cigarette that includes the components discussed below and in a PMTA for the component, if sold separately. In situations where a PMTA is for an e-cigarette that is not sold with other components (e.g., an e-cigarette sold without the battery included), FDA recommends discussing specifications for the components that can be used in the e-cigarette. As noted, FDA recognizes that there are many more subcategories of e-cigarette components than the three mentioned here, but we have included examples for these three components to help guide applicants in submitting the general information FDA recommends including for e-cigarette components. FDA recommends that a PMTA for an individual component (e.g., coil) that is a finished tobacco product identify the ENDS in which the applicant intends the component to be used, as well as provide information on how the component interacts with the intended product(s). For example, FDA recommends the data submitted for an individual coil reflect the coil's use in the ENDS in which the coil is intended to be used.

1. Batteries

FDA is concerned about the risk of harm related to batteries in ENDS. Many different aspects of batteries can cause health risks, such as leaching of battery materials into the product, battery explosion, or other defects. To enable FDA to assess the risks of a battery to be used in your tobacco product, we recommend that your PMTA include the following information:

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- Plans for addressing the likelihood of use and foreseeable misuse leading to overheating, fire, and explosion during operation, charging, storage, and transportation for distribution. For example, one approach would be to use a battery management system to monitor and control safety aspects of battery operation including charging and discharging. Then, in the application, you can explain how any battery management system incorporated into the product would function to reduce or mitigate any battery-related hazards. Battery management systems may reduce risks by ensuring: the battery only charges within manufacturer-specified operating regions for voltage, current, and ambient temperatures; the battery is only allowed to discharge within manufacturer-specified operating regions for voltage, current, duration, and ambient temperature limits; the battery voltage does not increase above the maximum voltage specified for the battery; the product cannot be used when a battery reaches specified end-of-life conditions; and the product cannot be used if the battery temperatures exceed safe operating limits due to other conditions.

If the e-cigarette includes the battery:

- Amperage rating (i.e., the maximum suggested amperage draw and duration for the battery and the maximum amperage draw and duration of the e-cigarette);
- Battery mAh rating (i.e., the milliamps per hour of the battery and its correlation to battery life);
- Battery type (including battery chemistry);
- Voltage output (at full charge and at low charge); and
- Testing certificates for any voluntary battery standards for the power supply. Examples of voluntary battery standards for non-rechargeable batteries include: (1) The series of standards from the International Electrotechnical Commission (IEC) (60086-1 12th Edition, 60086-2 13th Edition, 60086-4 4th Edition, and 60086-5 4th Edition,⁴⁵ and IEC 62133-1 and 2 Edition 1.0 2017-02⁴⁶) (2) Underwriters Laboratories Inc. (UL) Standard 2054 2nd Edition;⁴⁷ (3) UL Standard 1642 5th Edition.⁴⁸ Examples of voluntary battery standards for rechargeable batteries include: (1) IEC 62133 Edition 2.0 2012-12;⁴⁹ (2) UL 2054 2nd Edition;⁵⁰ or (3) UL's

⁴⁵ IEC International Standards for primary batteries: Part 1: General (60086-1 12th Ed., 2015); Part 2: Physical and electrical specifications (60086-2 13th Ed., 2015); Part 4: Safety of lithium batteries (60086-4 4th Ed., 2014); and Part 5: Safety of batteries with aqueous electrolyte (60086-5 4th Ed., 2016).

⁴⁶ IEC International Standards for Secondary Cells And Batteries Containing Alkaline Or Other Non-Acid Electrolytes – Safety Requirements For Portable Sealed Secondary Cells, And For Batteries Made From Them, For Use In Portable Applications – Nickel Systems and Lithium Systems (62133-1 and 2, Edition 1.0 2017-02)

⁴⁷ UL Standard for Household and Commercial Batteries (2054 2nd Ed., 2004).

⁴⁸ UL Standard for Lithium Batteries (1642 5th Ed., 2012).

⁴⁹ IEC International Standard for secondary cells and batteries containing alkaline or other non-acid electrolytes: Safety Requirements for Portable Sealed Secondary Cells, and for Batteries Made From Them, for Use in Portable Applications (62133 2nd Ed., 2012, including Corrigendum 1, 2013).

⁵⁰ UL Standard for Household and Commercial Batteries (2054 2nd Ed., 2004).

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Standard 1642 5th Edition.⁵¹ An additional example of a voluntary standard is the joint Canada-United States National Standards ANSI/CAN/UL 8139 – Electrical Systems of Electronic Systems and Vaping Devices --1st Edition 2018.

- If the e-cigarette uses a consumer-replaceable battery:
 - Battery specifications required by the e-cigarette; and
 - Voltage range and wattage range, if the e-cigarette alters or regulates the voltage.
- If the e-cigarette has alarm capabilities, indicate whether the product includes:
 - Reverse polarity protection (i.e., does it protect the battery from being placed in the e-cigarette backwards);
 - Under-voltage lock-out protection (i.e., does the power lock out in the event of the voltage dropping below the operational value);
 - Over-voltage lock out protection (i.e., does the power lock out when the voltage in the circuit is raised above the design limit);
 - Low resistance protection (i.e., does the e-cigarette lock out if the wire resistance is too low and, if so, what is the low resistance limit);
 - High controller temperature protection (i.e., does the e-cigarette detect the temperature of the controller and shut off when the temperature is too high); and
 - Unintended activation protection such as a maximum activation time limit, on/off capability, and locking capabilities.

2. *Atomizers and other similar parts (e.g., cartomizers)*

An atomizer is a component that uses a coil to electronically heat nicotine-containing e-liquid to produce an aerosol. FDA recommends that for PMTAs for e-cigarettes with atomizers and atomizers sold separately, you address the properties for each of the components of the product subject to the PMTA listed below.

- Atomizer:
 - Draw resistance (and operable range, if adjustable);
 - E-liquid capacity; and
 - Aerosol particle size across operable range.
- Coil:
 - Number of coils (either a set number or capability range, depending on e-cigarette design);
 - Coil gauge and material;
 - Coil resistance; and
 - Coil failure testing (i.e., cycles to failure).
- Wick:
 - Ignition temperature; and
 - Wicking absorbency (if refillable, we recommend that the absorbency be tested with low viscosity and high viscosity e-liquids).

⁵¹ UL Standard for Lithium Batteries (1642 5th Ed., 2012).

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3. *Software*

If the e-cigarette is software-driven, FDA recommends that you include the following:

- A software description, including a summary of the features, personal electronic devices with which it may be used (e.g., phones, tablets), and software operating environment;
- The function(s) for which the software is used (e.g., controlling temperature, nicotine content, flavor delivery);
- A hazard analysis of identified hardware/software hazards, including severity assessment and mitigations;
- A software requirements specification, including a summary of functional requirements;
- A traceability analysis, including traceability among requirements, specifications, identified hazards and mitigations, and verification and validation testing;
- Verification and validation documentation, including software functional test plan, pass/fail criteria, and results; and
- A revision level history, including revision history log with release version number and date.

IX. ADDITIONAL RECOMMENDATIONS FOR ENDS PRODUCTS THAT PACKAGE E-LIQUIDS AND E-CIGARETTES TOGETHER

FDA recognizes that many ENDS products will be packaged and sold together. For example, an open e-cigarette that does not contain e-liquids may be packaged and sold with separately contained e-liquids. Similarly, a closed e-cigarette will contain the e-liquid in the apparatus. In both cases, FDA recommends that, in addition to the information discussed in section VI, you address those items discussed in section VII for e-liquids and section VIII for e-cigarettes. Additionally, FDA recommends that product testing, such as testing aerosol particle size across the operable range, also be completed using the e-liquid solution and e-cigarette provided in the product package.

X. ADDITIONAL CONSIDERATIONS FOR SCIENTIFIC STUDIES AND ANALYSES

This guidance discusses FDA's current thinking on the types of information an applicant should include in a PMTA to help show that permitting the new tobacco product to be marketed would be APPH. Throughout this guidance, we reference suggestions for scientific studies and analyses to support this showing. FDA believes that in some cases, it may be possible to support a marketing order for an ENDS product without conducting new nonclinical or clinical studies. For example, if there is an established body of evidence regarding the health impact (individual or population) of your product or a similar product that can be adequately bridged to your product, such as data from the published literature or government-sponsored databases, these data may be sufficient to support a PMTA, as mentioned in the sections below.

In cases where a product has not yet been sufficiently reviewed, new nonclinical and clinical studies may be necessary to support a marketing order. The applicability of certain studies depends on what aspect of the statutory requirements of a PMTA the applicant intends to

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address. For example, to bridge to a completed study, if the PMTA product has been studied only in a certain demographic, the applicant would need to provide a scientific rationale for why the results of the study can be generalized to other demographic groups that are representative of the U.S. population as whole. 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 generalize to the broader U.S. population. Similarly, to use existing literature, if a product with similar characteristics (e.g., materials, ingredients, design, composition, heating source, other features) has been studied in a special population, this information may be used to support whether and how permitting the marketing of the product may be APPH by providing data relevant to the special population, which we would not otherwise have absent a new clinical trial. In these cases, you should explain why the study is relevant to use for the PMTA product (e.g., the similarities between the product, product use, or product market).

A. Alternatives to U.S.-Conducted Randomized Controlled Clinical Trials

Alternatives to U.S.-conducted randomized controlled clinical trials may be appropriate when potential bias associated with alternative controls can be addressed, including:

- Valid non-U.S. randomized controlled clinical trials data (when data can be generalized to the U.S. population);
- Study designs employing non-concurrent controls such as historical controls (e.g., literature, subject records) or objective performance criteria (i.e., performance criteria based on broad sets of data from historical databases (e.g., literature, registries) that are generally recognized as acceptable values (these criteria may be used for surrogate or clinical endpoints in demonstrating the risks or harm reduction for a tobacco product); or
- Observational studies.

Similarly, an effective use of incorporating by reference other PMTA submissions that have been previously authorized for the same applicant and similar product (rather than resubmitting duplicative information) may be done with cross-referencing. Alternatively, for information on master files, see section X.D.

B. Literature Reviews

Published literature reviews (including meta-analysis) or reports may be acceptable to support a PMTA, but are considered a less robust form of support for a PMTA. Additionally, applicants may conduct their own meta-analysis as appropriate. If a literature review is used to support a PMTA, FDA recommends that the PMTA:

- Describe the methodologies used in the literature review in detail and include the databases searched and the date of searches, search terms, reasons for inclusion/exclusion of documents, and the strategy for study quality assessment (systematic review is preferred);
- Identify the specific question(s) and issue(s) addressed by the literature review;
- Clearly identify the documents or manuscripts that address a specific question or issue;

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- Identify the funding source for included studies;
- Identify study design and methods;
- Identify characterization of study participants;
- Identify the year and geographical location of studies;
- Identify strengths and limitations of studies (e.g., study design elements including randomization details, potential biases, validity, variability, statistical models, and heterogeneity);
- Provide an interpretation of study findings;
- Provide adequate justification for bridging data from the product studied to your new tobacco product;
- Provide a summary of the evidence from the literature review;
- Document how the literature review findings support or do not support that permitting the marketing of your new tobacco product would be APPH;
- Include a bibliography and an appendix with the referenced publications; and
- Include comparative assessments of the health risks associated with use of your new tobacco product compared to the risks associated with quitting tobacco product use, using other tobacco products, and never using tobacco products.

In addition, when you submit a literature review to support an ENDS PMTA, FDA recommends that you consider the relevancy of the literature and adequacy of the study design in order to determine the likelihood that a particular body of literature will support a marketing order for the new tobacco product. For example, the following questions may be considered:

- Is the tobacco product in the literature comparable in terms of technology to the new tobacco product?
- Are there data (e.g., range of possible use, emissions under conditions of use, biomarkers of exposure) that can be used to adequately demonstrate comparability?
- Was the product in the literature used in a population that adequately represents the target population for the new tobacco product?
- Is the information in the literature sufficient to determine how the tobacco product was used?

We recommend that to strengthen the likelihood that the literature review will support your PMTA, you obtain additional information, such as full study methods, including randomization details.

C. Analysis of Published Literature and Public Datasets

You may consider conducting independent analyses of published studies. In these cases, FDA may review your analyses or publicly available analyses (for which there may be limited access to data, limited access to detailed study reports, or limited access to both) to partially or entirely support a PMTA. Please note, however, that if critical study details are not submitted, the studies may not be useful in FDA's review of your PMTA.

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If you cannot obtain the primary line or study data⁵² from the publicly available literature, we recommend that, to the extent possible, you obtain other information, such as the protocol, records of trial conduct and procedures, subject data listings for key variables, and documentation of the statistical analysis. If adverse or unintended experiences are being monitored, we recommend that, to the extent possible, you capture and document complete information for all serious adverse experiences (including deaths) and subject withdrawal related to adverse experiences, toxicity, or both.

D. Master Files

To reduce research burdens on manufacturers and increase efficiency of PMTA preparation and submissions, we encourage you to use tobacco product master files (TPMFs) whenever possible. TPMFs can be very useful when an applicant uses another company's component, part, or facility in the manufacturing, processing, or packaging of its ENDS product. Using a TPMF allows a company to submit trade secret or confidential commercial information to FDA without disclosing that information to an applicant that needs to include it as part of a regulatory submission. For example, a TPMF could be created by the company that sells liquid nicotine to downstream e-liquid manufacturers, then a variety of manufacturers that use that same supplier can be granted a right of reference to the supplier's master file for use in their applications. Another example where a TPMF could be useful includes an e-liquid manufacturer who establishes a TPMF for e-cigarette manufacturers to use in their PMTA. An e-cigarette manufacturer that purchases e-liquid could request that the e-liquid manufacturer establish a TPMF with CTP that contains information on the e-liquid to be used in PMTAs such as, but not limited to: components, ingredients, additives; properties; principles of operation; design parameters; manufacturing, controls, and quality processes; packaging; and stability. As long as the e-cigarette manufacturer has a letter from the TPMF owner with right to reference the file, CTP will consider the e-liquid specific information contained in the TPMF on behalf of the applicant as part of the applicant's PMTA. When an applicant submits a right of reference to a TPMF, CTP can access and review the confidential information in the TPMF as part of the PMTA, but the applicant relying on this information to support its submission does not see or have access to the proprietary information. This information will help applicants of deemed products prepare premarket and other regulatory submissions because they can reference information in TPMFs rather than develop the information on their own.

Given the anticipated availability and use of TPMFs, which allows manufacturers to rely on the data and analysis submitted to FDA by separate entities, FDA anticipates that manufacturers will, over time, benefit from significantly increased efficiencies and reduced costs for complying with the statute. Such a system prevents and reduces duplication and allows for manufacturer reliance on confidential or sensitive nonpublic information while maintaining its confidentiality, thus saving time and reducing burdens for multiple manufacturers. Because of the nature of upstream supply of many components for ENDS products, especially e-liquids, FDA anticipates that commercial incentives will be sufficient to drive manufacturer reliance on the system of master files.

⁵² Please see Section IV.H.2 for FDA's current thinking on line and study data.

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For more information on using TPMFs, refer to FDA's guidance for industry, *Tobacco Product Master Files*.⁵³

E. Bridging

Ideally, a PMTA will include studies conducted using the new tobacco product; however, bridging of data from one product to another may be feasible for a subset of products or for certain types of studies. For example, "X-flavor" e-liquids with nicotine concentrations ranging from 1 milligram per milliliter (mg/mL) to 24 mg/mL may not require unique studies 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 concentrations of "X-flavor" products. If you choose to bridge data from a studied tobacco product to your new tobacco product, you should provide the rationale and justification to support bridging (e.g., why the data used are applicable to your new tobacco product).

In addition, information that is available from earlier versions of an ENDS product or similar tobacco products may be used to bridge studies and analyses for the purposes of an ENDS PMTA. Earlier generations of a product line may provide important information that can reduce the need for large amounts of additional data.

While bridging your new tobacco product to existing data is a viable option, there may be circumstances when a bridging study may need to be conducted, such as when the product is sensitive to intrinsic factors (e.g., gender, race, age, pathology) and extrinsic factors (e.g., environmental, cultural). If the product is insensitive to these factors, a new bridging study may not be necessary. Another example of when 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.

XI. POSTMARKET REQUIREMENTS

A marketing order under section 910(c)(1)(A)(i) of the FD&C Act may require that the sale and distribution of the tobacco product be restricted, but only to the extent that the sale and distribution of a tobacco product may be restricted under a regulation under section 906(d). In addition, under section 910(f) of the FD&C Act, FDA may require that you establish and maintain certain postmarket records and make certain postmarket reports to FDA. Also, to the extent that your PMTA proposes specific restrictions on sale and distribution to help support a showing that permitting the marketing of the product would be APPH (e.g., a restriction that decreases the likelihood that those who do not use tobacco products will start using tobacco products), FDA may include such restrictions in a marketing order in addition to any other restrictions that FDA may require.

XII. REQUESTING MEETINGS WITH FDA

Tobacco manufacturers and importers intending to market products under the premarket tobacco application pathway may request meetings with FDA regarding the research and investigation of

⁵³ Available on the Internet at <https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

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tobacco products by submitting a formal meeting request to CTP. A formal industry meeting with FDA is a forum for the Agency to provide general assistance and guidance to applicants regarding their questions and challenges pertaining to compliance with regulations and requirements regarding the scientific data, information, and discussion needed for FDA to make a final decision on an application. Because these meetings often represent significant opportunities for assistance during the regulatory process, it is important for there to be efficient, consistent procedures for the timely and effective conduct of such meetings. In May 2012, CTP issued a guidance entitled *Meetings with Industry and Investigators on the Research and Development of Tobacco Products*⁵⁴ to assist persons in determining what to include in a meeting request; how and when to submit a meeting request; and what information is requested prior to the meeting. This guidance, updated in July 2016, focuses on tobacco product research and development and is therefore utilized by CTP for application-related meetings.

CTP has received meeting requests, from 2011 to present, for various topics such as questions related to study protocols for consumer perception, nonclinical studies, abuse liability evaluation, and models used to estimate population health impact related to a proposed marketing application. Many of these meetings have resulted in the submission of more complete applications that contain the scientific data, information, and discussion needed in premarket applications. FDA recommends that a meeting be held well in advance of the planned premarket submission so that the applicant has the opportunity to consider CTP feedback prior to preparing the application and to help ensure the application will be complete at the time of submission and likely to provide the data and information required for the Agency to make a final authorization decision. Considering the large number of anticipated applications and presubmission meetings for newly regulated tobacco products, in general, CTP intends to grant no more than one or two meetings per applicant. This will provide an opportunity for each applicant to receive feedback on its general approach for a complete application that addresses the scientific requirements for a PMTA.

To ensure a successful presubmission meeting for an application, before the meeting with FDA, the meeting requestor is expected to have a fully developed approach to meet the regulatory requirements for its planned application(s). There are many resources available to each applicant to aid in the development of a successful submission. Examples include, but are not limited to: FDA guidance related to applications, FDA Webinars, and documents posted on CTP's Web site regarding past FDA actions and the basis for those actions. Where it is considered appropriate, applicants may benefit from consulting with experts outside FDA prior to meeting with the Agency. These consultants may advise and/or assist applicants in developing the plan to address the regulatory requirements and preparing well-organized submissions. Once an applicant has developed a complete plan/approach, a meeting request should be submitted that focuses on: (1) the approach to the application; (2) its completeness; and (3) any significant challenges identified. During the meeting, FDA intends to discuss a general path forward on these three topics. The meeting request should include questions that have not been addressed through other avenues and for which the applicant needs a discussion with FDA in order to submit a well-developed and complete application. The presubmission meetings are not intended as a substitute for a full application review, nor are they intended to provide the level of detail that FDA would

⁵⁴ Available on the Internet at <https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

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consider during the course of scientific review. For example, in a presubmission meeting, FDA does not intend to address the adequacy of data (i.e., whether the data and information developed by the applicant are adequate to answer the regulatory standard “appropriate for the protection of the public health”). However, the presubmission meeting may provide helpful information to an applicant regarding the planned application so that it appears complete and well organized, and contains an approach that appears capable of addressing scientific requirements.

XIII. OFFICE OF SMALL BUSINESS ASSISTANCE

CTP’s Office of Small Business Assistance (OSBA) is available to assist manufacturers with general questions regarding statutory and regulatory requirements and will continue to provide support with respect to all deemed products, including ENDS. Questions about a specific premarket tobacco application should reference your STN and may be directed to CTP’s Office of Science.

FDA intends to expand the staffing for the OSBA to provide support for manufacturers who are newly regulated by FDA.

Small businesses may contact CTP by email at smallbiz.tobacco@fda.hhs.gov or by phone at 1-877-CTP-1373 to discuss questions regarding PMTA content, such as information necessary to satisfy the filing criteria under section 910(b) of the FD&C Act or ways to reduce burden by reference to another submission via the TPMF process. Additional information on Small Business Assistance can be found at <https://www.fda.gov/tobacco-products/compliance-enforcement-training/small-business-assistance-tobacco-product-industry>.