Premarket Tobacco Product Applications for Electronic Nicotine Delivery Systems

Guidance for Industry

DRAFT GUIDANCE

Comments may be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Electronic comments may be submitted to http://www.regulations.gov. Alternatively, submit written comments to the Division of Dockets Management (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For questions regarding this draft guidance, contact the Center for Tobacco Products at (Tel) 1-877-CTP-1373 (1-877-287-1373) Monday-Friday, 9 a.m. – 4 p.m. EDT.

Additional copies are available online at http://www.fda.gov/TobaccoProducts/Labeling/RulesRegulationsGuidance/default.htm. 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

May 2016

Table of Contents

Premarket Tobacco Product Applications for Electronic Nicotine Delivery Systems

Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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 explains, among other things:

- Products to which this guidance applies;
- When a PMTA is required;
- 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 whether permitting such new tobacco product to be marketed is appropriate for the protection of the public health.

FDA's draft guidance for industry, *Applications for Premarket Review of New Tobacco Products* (draft premarket review guidance),[2] discusses the general procedures for submitting a PMTA, including who can submit a PMTA, and when and how PMTAs should be submitted. Please note

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

[2] When finalized, the guidance *Applications for Premarket Review of New 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 http://www.fda.gov/TobaccoProducts/GuidanceComplianceRegulatoryInformation/ucm281147.htm.

that, when finalized, this guidance's focus on ENDS products may result in more specific recommendations for an ENDS PMTA than recommendations in FDA's draft premarket review guidance.

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 in order to assist manufacturers of newly deemed tobacco products. FDA also has published guidance on meetings with industry;[3] this has enabled FDA to have 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.

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.

Concurrently with issuing this guidance, FDA is publishing 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), to deem all products meeting the statutory definition of "tobacco product" in section 201(rr) of the FD&C Act (21 U.S.C. 321(rr)), except accessories of newly deemed tobacco products, to be subject to chapter IX of the FD&C Act. In the final deeming rule, FDA clarifies that all ENDS (including, but not limited to, e-cigarettes, e-cigars, e-hookah, vape pens, personal

[3] Information about how to request meetings with CTP can be found in FDA's final guidance, *Meetings with Industry and Investigators on the Research and Development of Tobacco Products*, available on the Internet at http://www.fda.gov/TobaccoProducts/Labeling/RulesRegulationsGuidance/ucm281147.htm. For additional information on requesting a meeting with FDA in the context of preparing for a PMTA submission, see section XII of this document.

vaporizers, and electronic pipes) are subject to FDA's chapter IX authorities on the effective date of the final deeming rule.[4] ENDS products include both the e-liquid and aerosolizing apparatus used as an ENDS, whether sold as a unit or separately. Products deemed under the final deeming rule will now be 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 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.[5] Further, newly 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 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.[6] 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.[7] When a new product is not found to be substantially equivalent to an appropriate predicate product or exempt from the substantial

[4] 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.

[5] 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 http://www.fda.gov/TobaccoProducts/GuidanceComplianceRegulatoryInformation/ucm281147.htm.

[6] When finalized, the draft guidance *Modified Risk Tobacco Product Applications* 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 http://www.fda.gov/TobaccoProducts/GuidanceComplianceRegulatoryInformation/ucm281147.htm.

[7] 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 http://www.fda.gov/TobaccoProducts/GuidanceComplianceRegulatoryInformation/ucm281147.htm. 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."

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 newly deemed products that meet the definition of a "new tobacco product," including ENDS, are subject to the premarket requirements in sections 910 and 905 (21 U.S.C. 387j and 387e) of the FD&C Act. Given the possible absence of valid predicates (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 newly deemed ENDS. 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 applying 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 FDA's relevant guidance documents located at http://www.fda.gov/TobaccoProducts/GuidanceComplianceRegulatoryInformation/ucm281147.htm. You can find a list of marketing orders where FDA determined a product to be substantially equivalent at http://www.fda.gov/TobaccoProducts/Labeling/TobaccoProductReviewEvaluation/ucm339928.htm.

This guidance represents FDA's current thinking on some appropriate means of addressing the premarket authorization requirements for newly 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 FDA's final guidance, *Meetings with Industry and Investigators on the Research and Development of Tobacco Products*.[8]

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

[8] Available on the Internet at http://www.fda.gov/TobaccoProducts/Labeling/RulesRegulationsGuidance/ucm281147.htm.

(2) is intended or reasonably expected to affect or maintain the performance, composition, constituents, or characteristics of a tobacco product but

(i) solely controls moisture and/or temperature of a stored product or

(ii) solely provides an external heat source to initiate (but not maintain) combustion of a tobacco product (21 CFR 1143.1).

"Composition," as used 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. Aerosolizing Apparatus

For the purposes of this guidance, *aerosolizing apparatus* refers to an electronic device that delivers e-liquid in aerosol form into the mouth and lungs when inhaled. For example, FDA considers cigalikes, e-pens, and e-hookahs to be aerosolizing apparatus.

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. Component or part excludes anything that is an accessory of a tobacco product.
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; clearomisers, tank systems, flavors, bottles that contain e-liquids, and programmable software.

D. Covered Tobacco Product

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. In addition to the provisions in the FD&C Act and implementing regulations that apply automatically to tobacco products, there are three restrictions for covered tobacco products: (1) the requirement for a minimum age of purchase in 21 CFR 1140.14 (which also applies to cigarettes, smokeless tobacco, cigarette tobacco, and roll-your-own tobacco); (2) the requirement for health warnings for product packages and advertisements in 21 CFR part 1143 (which also applies to cigarette tobacco and roll-your-own tobacco); and (3) the prohibition of vending machine sales of such products, unless the vending machine is located in a facility where the retailer ensures that individuals under 18 years of age are prohibited from entering at any time, in 21 CFR 1140.14 (which also applies to cigarettes, smokeless tobacco, cigarette tobacco, and roll-your-own tobacco).

E. E-liquids

For the purposes of this guidance document, liquid nicotine and nicotine-containing e-liquids (i.e., liquid nicotine combined with colorings, flavorings, and/or other ingredients) are generally referred to as *e-liquids*. 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.

F. Finished Tobacco Product

The term *finished tobacco product* refers to a tobacco product, including all components and parts, sealed in final packaging intended for consumer use. 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. At this time, FDA does not intend to enforce the premarket authorization requirements against e-liquids or other components and parts of newly deemed products that are not finished tobacco products. Finished tobacco products that are not covered tobacco products are not subject to the health warning statement requirements (21 CFR part 1143), age and identification restrictions (21 CFR 1140.14), and vending machine restrictions (21 CFR 1140.14) (see definition of covered tobacco product).

G. 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.[9]

H. 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,

[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 http://www.fda.gov/TobaccoProducts/GuidanceComplianceRegulatoryInformation/ucm281147.htm.

device, or combination product as defined in the FD&C Act. The term is not limited to products containing tobacco or tobacco derivatives, but also includes components, parts, or accessories of tobacco products, whether they are sold for further manufacturing or for consumer use. For example, e-liquids, aerosolizing apparatus, 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

There are many types of ENDS products (including, but not limited to, e-cigarettes, e-cigars, e-hookah, vape pens, personal vaporizers, and electronic pipes), all of which are subject to FDA's tobacco product authorities as of the effective date of the final deeming rule because they meet the definition of "tobacco product" under section 201(rr) of the FD&C Act and are not accessories of newly deemed products. In addition to ENDS products themselves, components and parts of ENDS products, but not their related accessories, are also subject to FDA's authority. 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, clearomisers, tank systems, flavors, and programmable software. The ENDS category includes a variety of products and, because it is a rapidly changing industry, new ENDS products may be developed in the future. Currently, FDA generally considers ENDS as tobacco products that use an electronic or other power source to heat e-liquids, tobacco, or other material derived from tobacco.

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

- E-liquids
- Aerosolizing apparatus
- ENDS products that package e-liquids and aerosolizing apparatus together

We provide a brief additional discussion of e-liquids below and detail our recommendations in section 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. For additional information on small business assistance, see section XIII of this document.

As stated in section 201(rr) of the FD&C Act, the definition of "tobacco product" includes any product made or derived from tobacco that is intended for human consumption that is not a drug or device, including any component, part, or accessory of a tobacco product. Upon the effective

date of the deeming rule, all products meeting this definition, except for accessories of newly deemed products, will be subject to FDA's chapter IX authorities. An e-liquid that contains nicotine made or derived from tobacco meets these criteria and, therefore, is subject to FDA's chapter IX authorities. For the purposes of this guidance document, *liquid nicotine* and *nicotine-containing e-liquids* (i.e., liquid nicotine combined with colorings, flavorings, and/or potentially other ingredients) are generally referred to as *e-liquids*. 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. 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-liquids would be tobacco products even if sold separately from an aerosolizing apparatus. 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 are thus not subject to FDA's tobacco control authorities under the FD&C Act.

B. When Are PMTAs Required?

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 newly 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 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. FDA intends to enforce against such finished e-liquids that are sold or distributed without a marketing order.

If an ENDS product is marketed for tobacco cessation or for any other therapeutic purpose, the product will be regulated as 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.[10]

[10] See 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).

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.[11]

FDA has taken several steps to assist manufacturers and industry to better understand the tobacco product premarket review process and the FD&C Act's statutory requirements, including:

(1) Encouraging meetings between CTP and the applicant; [12]

(2) assisting small businesses through CTP's Office of Small Business Assistance[13] and related resources and compliance periods for small-scale tobacco manufacturers;[14]

(3) providing information on FDA's Web site about the three pathways available to market products (including PMTA);

(4) developing public Webinars to explain the Agency's processes; and

(5) publishing guidance documents, such as this and other guidances referenced throughout this document. FDA also has held a series of public workshops to gather scientific information on ENDS products and the public health.[15] 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 newly deemed products.

FDA has had many productive meetings to address companies' specific questions on the development of tobacco products and, as the Agency reviews product applications for currently regulated and newly deemed categories of products, we intend to identify topics for which rulemaking or more product specific guidance is appropriate. If an applicant wishes to discuss its development of a PMTA, the applicant may request a meeting as set forth in FDA's final guidance, *Meetings with Industry and Investigators on the Research and Development of*

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[11] When finalized, the guidance *Modified Risk Tobacco Product Applications* 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 http://www.fda.gov/TobaccoProducts/GuidanceComplianceRegulatoryInformation/ucm281147.htm.

[12] For additional information on requesting a meeting with FDA in the context of preparing for a PMTA submission, see section XII of this document.

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

[14] 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 manufacturers. Interested manufacturers may contact CTP's call center at 1-877-CTP-1373 for questions regarding this compliance policy.

[15] 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) are available on CTP's Public Meetings and Conferences Web page at http://www.fda.gov/TobaccoProducts/NewsEvents/ucm238308.htm.

Tobacco Products.[16] See section XII of this document for additional discussion related to meetings with FDA.

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

An ENDS retail establishment that mixes and/or prepares combinations of liquid nicotine, flavors, and/or other e-liquids for direct sale to consumers for use in ENDS, or creates or modifies aerosolizing apparatus 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)[17] of the FD&C Act (21 U.S.C. 387(20)) and the combinations it mixes and/or prepares are "new tobacco products" within the meaning of section 910(a)(1). 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 aerosolizing apparatus for direct sale to consumers for use in ENDS are tobacco product manufacturers and, consequently, are subject to all of the requirements applicable to manufacturers.

C. General Procedures for ENDS PMTA Review

The time it takes to review a PMTA is dependent upon 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. If an applicant wishes to discuss how best to prepare a product application, the applicant may request a meeting as set forth in FDA's final guidance, *Meetings with Industry and Investigators on the Research and Development of Tobacco Products*.[18] Additional information related to meetings with FDA also can be found in section XII of this document.

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-

[16] Available on the Internet at http://www.fda.gov/TobaccoProducts/Labeling/RulesRegulationsGuidance/ucm281147.htm.

[17] 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)).

[18] Available on the Internet at http://www.fda.gov/TobaccoProducts/Labeling/RulesRegulationsGuidance/ucm281147.htm.

day period begins, FDA generally relies on the date of receipt of a complete submission by FDA's Document Control Center (DCC), not the date that the submitter sent it. A PMTA must include all information specified in section 910(b)(1) upon submission and FDA may refuse to file a submission if it is 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. FDA will have 180 days from the date of receipt to complete its review of a submission that meets the section 910(b)(1) requirements.

In addition, we are clarifying that FDA distinguishes between a marketing application that has been "submitted" to FDA, one that has been "accepted," and one that has been "filed."

- A marketing application has been "submitted" when a complete application is delivered and received electronically, through the mail, or through a courier to CTP's Document Control Center (DCC). Once a complete PMTA is submitted and received by CTP's DCC, FDA will have 180 days to consider the application as described in section 910(c)(A) of the FD&C Act.
- A marketing application "has been accepted" after the Agency completes a preliminary review and determined that the application on its face contains information required by the statutory and/or regulatory provisions applicable to that type of application.
- A marketing application has been "filed" after the Agency completes a threshold review and has determined that a complete, substantive review is warranted. 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.

Section 910(b)(1) of the FD&C Act states that an application shall contain:

(A) 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;
(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.

However, FDA may request additional information about your PMTA as necessary. FDA may also want to inspect your manufacturing, clinical research, or nonclinical research sites to support its review of your PMTA. Inspections of these sites allow FDA to assess the accuracy

and validity of the information provided, including clinical and non-clinical information, and confirm that the product can be manufactured in the way that the PMTA specifies. Inspections will also provide important information regarding whether the manufacturing, processing, or packing of the tobacco product conforms to tobacco product manufacturing practices, which will be set forth in a future rulemaking.[19]

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). 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 to refer your PMTA to TPSAC after your PMTA has been submitted, please contact the Center for Tobacco Products 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 PMTAs 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] 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 is appropriate for the protection of the public health. Our finding of whether there is a showing that permitting this product to be marketed would be appropriate for the protection of the public health 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.

(Section 910(c)(4) of the FD&C Act.)

[19] FDA intends to issue regulations under section 906(e) 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)).

[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.

Throughout this guidance document, we recommend providing specific information pertaining to different topic areas and disciplines in order to enable FDA to make a determination of whether your PMTA supports a showing that the marketing of your new tobacco product is appropriate for the protection of the public health. For example, knowing the full assessment of the toxicological effects of your ENDS product (e.g., ingredients, components, use of the product) is important to assess the health effects on users and nonusers. FDA will assess the toxicology of the product to determine whether the health effects of using the product would have a detrimental effect to users' and nonusers' health. FDA will weigh 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 marketed.

The FD&C Act states that this finding will be determined, when appropriate, on the basis of well-controlled investigations (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. Thus, if an application includes, for example, information (e.g., published literature, marketing information) with appropriate bridging studies, FDA will review that information to determine whether it is valid scientific evidence sufficient to demonstrate that a product is appropriate for the protection of the public health. 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.[21]

2. Specific Recommendations Concerning How to Support a Showing That Marketing of the New Tobacco Product Is Appropriate for the Protection of the Public Health

This guidance provides recommendations regarding what FDA considers important to include in an ENDS PMTA. Some of the recommendations discussed below are unique to ENDS, given the differences between ENDS and previously regulated products, like cigarettes. Some recommendations relate to basic resource and data limitations. The following sections highlight several broad categories of issues that applicants should address to help demonstrate that their products are appropriate for the protection of the public health and, consequently, should be authorized for marketing. Please note that this guidance's focus on ENDS products may result in more specific recommendations for an ENDS PMTA than the recommendations contained in FDA's draft premarket review guidance.

a. Scientific evidence

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) would support a finding by FDA that marketing your new tobacco product is appropriate for

[21] Information about how to request meetings with CTP can be found in FDA's final guidance, *Meetings with Industry and Investigators on the Research and Development of Tobacco Products*, available on the Internet at http://www.fda.gov/TobaccoProducts/Labeling/RulesRegulationsGuidance/ucm281147.htm.

the protection of the public health. Given the relatively new entrance of ENDS on the U.S. market, FDA understands that limited data may exist from scientific studies and analyses. Where human toxicity may be reliably predicted from nonclinical data, well-designed laboratory testing (in vitro and/or in vivo) may be the basis for this evaluation. (Please refer to section X.A of this guidance to review information that FDA considers when determining when scientific evidence may be used in lieu of clinical studies.)

FDA recommends that your explanation include a comparison of the new tobacco product to a representative sample of tobacco products legally on the market (i.e., either grandfathered or with a marketing authorization in effect) or those products that benefit from FDA's announced compliance policies at the time of your PMTA submission, including traditional combusted products (e.g., cigarettes, cigars). FDA suggests the applicant include a comparison to products with a substantial market share (e.g., cigarettes, smokeless tobacco, cigars) and a comparison between your product and other similar products within the same category. Because it is expected that consumers of current products that are in the same product category may switch to 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. As an example comparison between products within the same category, if your PMTA is for an e-liquid, we recommend a comparison to other e-liquids with similar nicotine content, similar flavors, or other similar ingredients. To completely assess whether your PMTA supports a showing that marketing the product would be appropriate for the protection of the public health, FDA will look at the product in the context of the current tobacco product market. FDA can do this by understanding the spectrum of risk of currently available tobacco products and assessing the new product within that spectrum.

Additionally, FDA understands that you may want to support certain topics in your PMTA (such as toxicology) with scientific data on tobacco products other than the proposed PMTA product. In this case, data from those products that are used in the same manner, under similar conditions, or for the same duration and frequency may be used to support your PMTA. Whether this information is appropriate depends on the specific products, the facts of the study or data, and the similarity of the product to your PMTA product. You should provide justification in your PMTA regarding why using evidence or data from other products to support your PMTA is appropriate based on these factors and other relevant considerations. Section X of this guidance describes FDA's thinking on options for manufacturers to obtain this scientific information (e.g., from published literature studies).

In sections VI.H, VII, VIII, and IX, we discuss the information that FDA recommends including in scientific studies and analyses to support a showing that permitting the new tobacco product to be marketed would be appropriate for the protection of the public health. An applicant may reference the same scientific evidence to demonstrate qualities of the tobacco product for different areas and disciplines, if applicable. In section X, we discuss the types of studies and research that may be appropriate to use in lieu of longitudinal clinical studies, given the limitations noted above. Also, to the extent that you propose specific restrictions on sale and distribution that can help support a showing that the marketing of the product is appropriate for the protection of the public health (e.g., a restriction that decreases the likelihood that those who do not 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. This is 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, as discussed in section XI.

b. Nicotine exposure warnings

Section 910(b)(1)(F) of the FD&C Act requires that PMTAs include specimens of the labeling proposed to be used for the new tobacco product. Warning statements are important parts of the product's labeling. Given the health risks and hazards associated with exposure to e-liquids (including oral, dermal, and ocular dangers), FDA recommends that, to help establish that marketing a product is appropriate for the protection of the public health, labels or labeling of the finished ENDS that contain nicotine include a nicotine exposure warning. Finished ENDS are those products, including all components and parts, sealed in final packaging intended for consumer use. FDA believes a nicotine exposure warning is important to aid in the prevention of and/or decrease 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 the nicotine exposure warning be included in specimens of the labels or labeling that are submitted.

The nicotine exposure warnings should accurately and truthfully communicate the health risks and hazards of e-liquid use in a clear and simple manner. These warnings should:

- 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);
- 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 is an example of a textual nicotine exposure warning, which should be modified as appropriate for your product. Although this example is not accompanied by pictographs, your warnings should also include pictographs as recommended above.

> 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.

c. 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 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), covered 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 must submit a self-certification that their covered tobacco products or tobacco-derived products do not contain nicotine. A covered tobacco product is any tobacco product deemed pursuant to 21 CFR 1100.1 to be subject to the FD&C Act, but excludes any component or part of a tobacco product that is not made or derived from tobacco. Therefore, any ENDS product that contains nicotine or tobacco (e.g., e-liquids containing nicotine, closed delivery systems sold with e-liquids containing nicotine) is a covered tobacco product and must comply with the requirement that the package label bear a warning statement regarding the addictiveness of nicotine. The specimens of labeling included in a PMTA 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, or appear on a tag otherwise permanently affixed to the tobacco product package.[22] 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.

d. Child-resistant 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 child-resistant packaging their ENDS product will be sold in to support a finding that the marketing of the product is appropriate for the protection of the public health. The description should also include information regarding the tamper-resistant and tamper-evident[23] properties of the packaging. An example of child-resistant

[22] 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.

[23] 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.

packaging that would help show the product is appropriate for the protection of the public health 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.

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. You can securely submit your PMTA via the FDA Electronic Submissions Gateway (ESG). Refer to the ESG website instructions for setting up a WebTrader account online at http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway/ucm114831.htm. Information about the eSubmitter tool can be found online at http://www.fda.gov/ForIndustry/FDAeSubmitter/ucm189469.htm.

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. You should also submit an index that lists the location of each proposed redaction in the PMTA by page number and you should explain, in detail, why you believe that each proposed redaction qualifies as a trade secret or confidential, commercial information that is not available for disclosure under 21 CFR 21.61.

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 (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 submission is received by the FDA's DCC.

VI. CONTENT 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.

Also, section 910(c)(5) requires FDA to base its determination to issue or not issue a marketing order on well-controlled investigations or other valid scientific evidence that is sufficient to evaluate the tobacco product.

This section discusses FDA's general recommendations for PMTA content, including the mandatory requirements discussed in section 910, other recommendations, and an explanation of FDA's current thinking on well-controlled investigations and other valid scientific information. FDA recommends that you organize your PMTA content in the following order to aid in the review of your PMTA. See sections VII through IX of this guidance document for additional recommendations for PMTA content for certain types of ENDS products.

You may submit a single premarket submission for multiple products and a single, combined cover letter and table of contents across all products; however, 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 differing flavor variants and nicotine strengths to be a 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).

FDA recommends that your PMTA be well organized, numbered using continuous pagination, legible, and written in the English language. For any foreign language documents, you should

also provide the original foreign language document, the English translations, and certification that the translation into English is accurate.

To facilitate review, each PMTA should:

- Be static, that is, the pages should not reformat, renumber, or re-date each time the document is accessed;
- 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.

You can find examples of acceptable file formats online at http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM347471.pdf.

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;
- Your authorized U.S. agent or representative's name, title, address, phone number, email address, and fax number;
- Basic information identifying the new product, including 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; and
- A list identifying all enclosures and labeling being submitted with the PMTA.

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

FDA recommends that you provide information describing the major aspects of the new tobacco product, such as the following items:

- 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 (21 U.S.C. 387g) 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;
- 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 910(b)(1)(B), and, if known, problems with use in previous or similar versions of the new product; and
- 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 is appropriate for the protection of the public health.

FDA recommends that the unique identification of the product include:

- For E-liquids:
  - Product name
  - Category: ENDS
  - Subcategory: E-Liquid
  - Package type
  - Package quantity (mL)
  - Characterizing flavor
  - Nicotine content (%)
- For Closed Aerosolizing Apparatus or a Prefilled Open Aerosolizing Apparatus:
  - Product name
  - Category: ENDS
  - Subcategory: Closed Aerosolizing Apparatus or Prefilled Open Aerosolizing Apparatus
  - Package type
  - Characterizing flavor
  - Nicotine content (%)
  - E-liquid capacity (mL)
  - Coil resistance (Ohms)
  - Battery capacity (mAh)

- For Open Aerosolizing Apparatus (Without E-liquid and Including Components and Parts of Open Aerosolizing Apparatus):
  - Product name
  - Category: ENDS
  - Subcategory: Open Aerosolizing Apparatus
  - Package type
  - E-liquid capacity (mL)
  - Coil resistance (Ohms)
  - Battery capacity (mAh)
- For ENDS Co-Package:[24]
  - Product name
  - Category: ENDS
  - Subcategory: ENDS Co-Package
  - Package type
  - Package quantity (mL)
  - Characterizing flavor
  - Nicotine content (%)
  - E-liquid capacity (mL)
  - Coil resistance (Ohms)
  - 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 recommends that applicants provide at least one sample of the new finished tobacco product that is the subject of the PMTA. FDA may conduct its own testing and analysis of the new tobacco product and its components and may request a reasonable number of additional samples for testing and analyses. FDA will send the applicant a letter acknowledging the receipt of the PMTA that includes information on how to submit the sample(s). Applicants should be ready to send a sample when they submit their PMTAs, and we recommend submitting the sample no later than 7 calendar days after the date of the acknowledgement letter. Samples should be submitted to the Southeast Regional Laboratory. The address and how to identify the sample or samples will be specified in the acknowledgement letter.

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

[24] An *ENDS Co-Package* refers to an open aerosolizing apparatus or a component or part that is sold or distributed to consumers in the same package as separately contained e-liquids or prefilled with e-liquid.

labels, inserts, onserts, instructions, and other accompanying information or materials (section 201(m) of the FD&C Act (21 U.S.C. 321(m)). The submitted specimens of proposed labeling for all product panels should 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 and recommended nicotine exposure warnings included in section IV.D.2 of this guidance, and should comply with all other applicable labeling requirements under the FD&C Act.

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 suggested 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.[25]

G. Summary of All Research Findings

Your PMTA should 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. FDA recommends that you include a description of the operation of the new tobacco product as well as a section summarizing all research findings in your PMTA, including the health risks (e.g., toxicological testing outcomes) of the product, the product's effect on tobacco use behavior among current users, the product's effect on tobacco use initiation among nonusers,

[25] 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 http://www.fda.gov/TobaccoProducts/GuidanceComplianceRegulatoryInformation/ucm281147.htm.

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. This should 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. The summary should also include the study findings, such as whether the findings concern health risks compared to other tobacco products and whether such product presents less risk than other tobacco products, if similar or not to the applicant's tobacco product. 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), 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., use conditions by light users, typical users, and heavy users) within which consumers are likely to use the new tobacco product;

(4) The likelihood, based on the research findings 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 findings 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 findings contained in your application, of consumers using the new tobacco product in conjunction with other tobacco products;

(7) The likelihood, based on the research findings contained in your application, of consumers 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 NRT);

(8) Assessment of abuse liability (i.e., the addictiveness and 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 the new tobacco product is appropriate for the protection of the public health.

FDA also 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 numbers 1-10, 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

FDA recommends organizing the full reports, full statements, and full descriptions of all scientific studies and analyses referenced elsewhere in the PMTA into this 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 sections 910(b)(1)(B)-(C) of the FD&C Act.

Product analyses and testing should be conducted on the ENDS tobacco product subject to the PMTA. The 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 the sample is still within its shelf life. Otherwise, the 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:

- Source data (please note that the data sets should span a minimum of three different batches with a minimum of 10 replicates per batch, 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.

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 products, as well as the applicable specifications and a description of the intended function for each. Components, ingredients, and additives include anything, other than accessories, that may reasonably be expected to directly or indirectly become part of, or affect the characteristics of, the finished new tobacco product (including, but not limited to, liquid reservoirs, solvents, flavor additives, heating coils, batteries, and pH modifiers). FDA recommends listing information regarding the product's container closure system. The container closure system refers to the packaging components that contain and protect a tobacco product, even if they are not in direct contact with the tobacco product, but are intended to provide protection to the product as it moves through the distribution system. For example, for e-liquids, this would include the container the liquid is in (e.g., a glass or plastic vial, a cartridge, etc.). The container closure system can often affect or alter the performance, composition, constituents, or characteristics of a tobacco product. For example, the container closure system could, 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*.[26]

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 it meet with FDA to discuss the approach prior to preparing and submitting an application.[27]

FDA also recommends that you include a complete list of uniquely identified constituents, 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 detected through constituent testing on your product. Your constituent testing should reflect the range of operating conditions (e.g., various temperature, voltage, wattage

[26] Available on the Internet at http://www.fda.gov/TobaccoProducts/GuidanceComplianceRegulatoryInformation/ucm281147.htm.

[27] Information about how to request meetings with CTP can be found in FDA's final guidance, *Meetings with Industry and Investigators on the Research and Development of Tobacco Products*, available on the Internet at http://www.fda.gov/TobaccoProducts/GuidanceComplianceRegulatoryInformation/ucm281147.htm.

settings) and use patterns (e.g., use conditions by light users, typical users, and heavy users) 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, an open aerosolizing apparatus (i.e., an aerosolizing apparatus that includes a refillable e-liquid reservoir) should be tested with a reasonable range of available e-liquids, particularly those available in different levels of nicotine; a closed aerosolizing apparatus (i.e., an aerosolizing apparatus that includes an e-liquid reservoir that is not refillable) should be tested with the e-liquids with which they are packaged and sold; and components or parts should be tested with the reasonable range of products with which they could be used. FDA recommends, at a minimum, that manufacturers of e-liquids test the constituent delivery in an aerosolizing apparatus that is designed to deliver low levels of aerosol (such as open refillable cigarette-like systems) as well as in an aerosolizing apparatus 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.

FDA recommends that you consider the following constituents[28] for analysis in e-liquids and aerosols, as appropriate, for your product:

- Acetaldehyde
- Acetyl Propionyl (also known as 2,3-pentanedione)
- Acrolein
- Acrylonitrile
- 4-Aminobiphenyl
- 1-Aminonaphthalene
- 2-Aminonaphthalene
- Ammonia
- Anabasine
- Benzene
- Benzo[a]pyrene
- 1,3-Butadiene

[28] These constituents are 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 in the *Federal Register*, issue guidance regarding constituent reporting (i.e., harmful or potentially harmful constituent (HPHC) reporting) under section 904(a)(3) of the FD&C Act, and later issue a testing and reporting regulation as required by section 915. 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 (21 U.S.C. 387d) 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.

- Cadmium
- Chromium
- Crotonaldehyde
- Diacetyl
- Diethylene glycol
- Ethylene glycol
- Formaldehyde
- Glycerol
- Isoprene
- Lead
- Menthol
- Nickel
- Nicotine, including total nicotine and unprotonated nicotine
- NNK (4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone)
- NNN (N-nitrosonornicotine)
- Propylene glycol
- Toluene
- Other constituents, as appropriate

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.

b. Properties

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. The "full statement of the properties" of the new tobacco product should include a full narrative description of the tobacco product, including:

- 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 (i.e., comparator products). 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;
- Storage and 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 operations, charging, storage, and transportation for distribution.

c. Principles of operation

Consumers may be able to alter an ENDS product's effect 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.

d. Manufacturing

The manufacturing descriptions show how the product is made to conform with 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, including e-liquids and aerosolizing apparatus."[29]

FDA recommends that you provide a listing of all manufacturing, packaging, and control sites for the product, including the facility names and addresses, 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:

- Manufacturing and production activities, including a description of facilities and all production steps;
- 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;
- Testing procedures conducted before the new tobacco product is released for sale and distribution in the U.S., including information 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

[29] The requirement to provide a full description of methods of manufacturing and processing is separate and distinct from good manufacturing practice requirements, the latter of which will be the subject of regulations under section 906(e) of the FD&C Act (21 U.S.C. 387f(e)). FDA will issue regulations under section 906(e) that will contain the requirements for demonstrating good 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)).

support the PMTA, but also any investigations that do not support, or are adverse to, the PMTA. Information on both nonclinical and clinical investigations should be provided, including, but not limited to, any studies assessing constituents of tobacco, tobacco smoke, or aerosol, toxicology, consumer exposure, and consumer use profiles. 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 conflicts of interest. 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.

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.[30] While all clinical investigations (both within and outside the United States) submitted with your PMTA should be conducted to ensure that the rights, safety, and welfare of human subjects have been protected, you must (under section 910(b)(1)(A) of the FD&C Act) submit full reports of all information concerning relevant clinical investigations even if the study did not protect the rights, safety, and welfare of human subjects. One way to ensure that the rights, safety, and welfare of human subjects are protected is to ensure that that clinical studies conducted or included in a PMTA are done so in accordance with ethical principles acceptable to the international community (e.g., ICH E6 Good Clinical Practice standards).[31] Special attention should be paid to trials that may include vulnerable subjects.[32]

Section 910(g) of the FD&C Act (21 U.S.C 387j(g)) 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

[30] As discussed in section X of this guidance, well-controlled investigations conducted outside the United States may be submitted to FDA in support of a PMTA. If you submit a study or studies conducted outside the United States in support of your PMTA, you should provide an explanation of how the rights, safety, and welfare of human subjects were protected or, if you do not know and are unable to provide this information, you should explain why (e.g., because you were not the sponsor of those studies).

[31] 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 http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm (under ICH–Efficacy).

[32] For information on considerations on clinical trials with vulnerable subjects, see 21 CFR 56.

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 and determine whether to enforce the premarket review requirements with respect to such products.[33] 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.[34] 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 article for each study. You should 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. However, 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, you should include, to the extent available or reasonably obtainable:

- Documentation of all actions taken to ensure the reliability of the study, such as appropriate good laboratory practices found in 21 CFR part 58, as applicable;
- Copies of all investigator instructions produced in addition to the protocol, if any;
- The statistical analysis plan, including a detailed description of the statistical analyses employed (i.e., all variables, confounders, and subgroup analyses and any amendments);

[33] 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 http://www.fda.gov/TobaccoProducts/GuidanceComplianceRegulatoryInformation/ucm281147.htm.

[34] Information about how to request meetings with CTP can be found in FDA's final guidance, *Meetings with Industry and Investigators on the Research and Development of Tobacco Products*, available on the Internet at http://www.fda.gov/TobaccoProducts/GuidanceComplianceRegulatoryInformation/ucm281147.htm.

- A list of the sites where a study was conducted, including contact information and physical address(es);
- Source data. 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 the 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;
- The location of all source data. If the site has not maintained all of the source data, indicate where the data are located;
- The format of the records and data (e.g., electronic, hard copy);
- A copy of any protocols and amendments that were used in the study;
- 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.

In addition, for clinical studies, you should include, to the extent available or reasonably obtainable:

- Documentation of all actions taken to ensure the reliability of the study and the protection of human subjects (e.g., documentation of study oversight by an Investigational Review Board duly constituted and operating under 21 CFR part 56; documentation of informed consent procedures, such as appropriate procedures found in 21 CFR part 50; and documentation of appropriate good laboratory practices, such as those found in 21 CFR part 58);
- 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 marketing of the product is appropriate for the protection of the public health.

a. Nonclinical health risk information

Although nonclinical studies alone are generally not sufficient to support a determination that marketing of the product is appropriate for the protection of the public health (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.

Nonclinical health risk information should provide a thorough toxicological and pharmacological evaluation of each of the ingredients, mixture of ingredients, and aerosols produced by the new tobacco product. FDA recommends that a full assessment of the toxicological profile associated with the new tobacco product include, if available:

- Toxicology data from the literature (i.e., all relevant publications);
- Analysis of constituents and other toxicants under both intense and non-intense use conditions as described in Section VI.H.1.a;
- In vitro toxicology studies (e.g., genotoxicity studies, cytotoxicity studies);
- In vivo toxicology studies (to address unique toxicology issues that cannot be addressed by alternative approaches); and
- Computational modeling of the toxicants in the product (to estimate the toxicity of the product).

A thorough literature review, including publically available toxicology databases, can provide valuable information on the toxicity of the ingredients in the e-liquid and aerosol by the expected route of administration and level of exposure. This section should include:

- A description of the search methodology;
- All publications related to the toxicological evaluation of each of the ingredients (nicotine, glycerol, propylene glycol, flavors, metals, and others) 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;
- Extractable leachable information from the aerosolizing apparatus;
- 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 the analyses 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 publically 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. At a minimum, 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.
- 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) guidance 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 the reliance on animal testing where adequate and scientifically valid non-animal alternatives can be substituted. FDA encourages sponsors to meet with CTP early in the development process to discuss what, if any, animal testing is appropriate and the suitability and acceptability of non-animal tests for their particular new tobacco product. When animal-based nonclinical laboratory studies are conducted, investigators should use appropriate animal models and adhere to the best practices of refinement, reduction, and replacement of animals in research and to applicable laws, regulations, and policies governing animal testing, such as the Animal Welfare Act (7 U.S.C. 2131 et seq.) and the Public Health Service Policy of Humane Care and Use of Laboratory Animals (available at http://grants.nih.gov/grants/olaw/references/phspol.htm).

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 is used, detailed modeling information should be provided including all source data, equations, assumptions, parameters, 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 the new tobacco product would be appropriate for the protection of the public health 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 likely impact of the new tobacco product on the health of both users and nonusers of tobacco products in order to support that marketing the new tobacco product would be appropriate for the protection of the public health. This information can be gathered through your own studies or through alternatives, discussed in Section X of this draft 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.

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 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:

i. Consumer perceptions

Consumer perception evaluations should address how consumers perceive product risk and include consideration of packaging and labeling. 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 data you collect on consumer perceptions of the harms of the new tobacco product and of its proposed labeling or advertising. If you are collecting data on consumer perceptions, we recommend evaluating perceptions of product risk, both absolute and in comparison to other categories of tobacco products, as well as 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 sponsor-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 will be responsible for providing justification for why making such a comparison is appropriate; and
- Scientific information on the likelihood of product use by youth, young adults, pregnant women, and other vulnerable populations.

Although randomized clinical trials could address cessation behavior of users of tobacco products, FDA will also accept observational studies (perception, actual use, or both) examining cessation behaviors.[35]

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 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 company's customer base could be used as well. In addition, applicants may incorporate information from national surveys or the results of other published studies. While most studies in the published scientific literature typically focus on general ENDS products and are not usually product-specific or type-specific, such data 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 X discusses FDA's current thinking on alternatives for obtaining study information. For example, section X.E discusses 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,[36] FDA recommends sharing sales data by population demographics and tobacco use status. Sales data, if available, should be analyzed in 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);

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

[36] 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 US sales.

- 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, self-selection, and actual use

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. 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 that identify:

- Normal use and foreseeable misuse conditions;
- 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 and aerosolizing apparatus independently as well as when the products are used together, as it relates to other tobacco 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 outcomes 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

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 should 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 aerosolizing apparatus 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 constituents and other chemical constituents (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 aerosolizing apparatus 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 review, including toxicological review on flavor additives, 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.

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 such new tobacco product presents less risk than other tobacco products. FDA considers the appeal and use of ENDS product flavors important to ascertain 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 draft 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 AEROSOLIZING APPARATUS

Aerosolizing apparatus 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 aerosolizing apparatus. In addition to the general recommendations above for ENDS PMTAs, FDA recommends that you address the following additional information in a PMTA for an aerosolizing apparatus.

A. Aerosolizing Apparatus 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 of the principle or principles of operation, of the new tobacco product. In addition, FDA recommends that in PMTAs for aerosolizing apparatus and their components sold separately, you address both the characteristics listed in this section of the guidance and the characteristics listed specifically for the batteries, atomizers, and software, as applicable.

ENDS product users and non-users are exposed to aerosols produced by the apparatus. 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 aerosolizing apparatus, including detailed discussions of the following, if applicable:

- Aerosolizing apparatus 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 aerosolizing apparatus components;
- Operating ranges (e.g., lower and upper wattage, voltage limits that users can adjust);
- 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 aerosolizing apparatus 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 Aerosolizing Apparatus Components and Parts

FDA recognizes that there is no single set of engineering parameters that will characterize all aerosolizing apparatus, 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 these characteristics be addressed in a PMTA for an aerosolizing apparatus that includes the components discussed below and in a PMTA for the component, if sold separately. In situations where a PMTA is for an aerosolizing apparatus that is not sold with other components (e.g., an aerosolizing apparatus sold without the battery included), FDA recommends discussing specifications for the components that can be used in the aerosolizing apparatus. As noted, FDA recognizes that there are many more subcategories of aerosolizing apparatus 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 aerosolizing apparatus components.

1. Batteries

FDA is concerned about the risk of the 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 the battery to be used in your product, we recommend that your PMTA include the following information:

- Plans for addressing the likelihood of use and foreseeable misuse leading to overheating, fire, and explosion during operations, charging, storage, and transportation for distribution.
- If the aerosolizing apparatus includes the battery:
  - Amperage rating (i.e., the maximum suggested amperage to pull from the battery);
  - 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.
- If the aerosolizing apparatus uses a consumer-replaceable battery:
  - Battery specifications required by the aerosolizing apparatus; and
  - Voltage range and wattage range, if the aerosolizing apparatus alters or regulates the voltage.
- If the aerosolizing apparatus has alarm capabilities, indicate whether the product includes:
  - Reverse polarity protection (i.e., does it protect the battery from being placed in the aerosolizing apparatus 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 aerosolizing apparatus 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 aerosolizing apparatus 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

FDA recommends that, for PMTAs for aerosolizing apparatus 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 aerosolizing apparatus 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).

3. Software

If the aerosolizing apparatus is software-driven, FDA recommends that you include the following:

- A software description, including a summary of the features and software operating environment;
- 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 AEROSOLIZING APPARATUS TOGETHER

FDA recognizes that many ENDS products will be packaged and sold together. For example, an open aerosolizing apparatus, which does not contain e-liquids, may be packaged and sold with separately contained e-liquids. Similarly, a closed aerosolizing apparatus 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 aerosolizing apparatus. 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 aerosolizing apparatus provided in the product package.

X. 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 such new tobacco product to be marketed would

be appropriate for the protection of the public health. 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's potential impact on the public health has not yet been sufficiently reviewed, new nonclinical and clinical studies may be required. The applicability of certain studies depends on what aspect of the statutory requirements of a PMTA the applicant intends to 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 the product may be appropriate for the protection of the public health 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);
- Observational studies; or
- Scientifically valid surrogate endpoints (e.g., 1- or 2-year data as a predictor for long-term experience or health effects).

Similarly, an effective use of incorporating by reference other PMTA submissions that have been previously authorized for the same applicant and same 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, the PMTA should:

- 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;
- 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 your new tobacco product is appropriate for the protection of the public health;
- 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 publically 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.

If you cannot obtain the primary source data from the publically 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 you capture and document complete information for all serious adverse experiences (including deaths) and subject withdrawal related to adverse experiences, toxicity, or both.

In addition, FDA intends to open public dockets for uniquely identified compounds likely to be used in an e-liquid product, such as propylene glycol, glycerin, nicotine, colorants, and flavoring agents. FDA intends to invite stakeholders to submit to the docket information regarding specific compounds, including data, studies, or other files, such as data on individual health effects of inhalation exposure, animal study data examining exposure to varying levels of compounds within e-liquids, or testing the impact of temperature on changes to the aerosol constituents. This information could then be used to support a PMTA for ENDS products.

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. FDA would then review the master file information as part of the PMTA as long as the applicant has

the right of reference to the master file information. This information will help applicants of newly 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 non-public 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.

For more information on using TPMFs, refer to FDA's guidance for industry, *Tobacco Product Master Files*.[37]

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.

[37] Available on the Internet at http://www.fda.gov/TobaccoProducts/GuidanceComplianceRegulatoryInformation/ucm281147.htm.

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.

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 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 final guidance entitled *Meetings with Industry and Investigators on the Research and Development of Tobacco Products*[38] 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 2012 guidance focuses on tobacco product research and development and is therefore utilized by CTP for application-related meetings; it is available on CTP's Web site at http://www.fda.gov/TobaccoProducts/Labeling/RulesRegulationsGuidance/ucm281147.htm.

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 pre-submission 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 their general approach for a complete submission that addresses the scientific requirements for a PMTA.

[38] Available on the Internet at http://www.fda.gov/TobaccoProducts/Labeling/RulesRegulationsGuidance/ucm281147.htm.

To ensure a successful pre-submission 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 pre-submission 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 consider during the course of scientific review. For example, in a pre-submission meeting, FDA will not address the adequacy of data (i.e., whether the data and information developed by the applicant is adequate to answer the regulatory standard "appropriate for the protection of the public health"). However, the pre-submission 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 any questions regarding statutory and regulatory requirements and will continue to provide support with respect to all newly deemed products, including ENDS. Staff from CTP's OSBA also will assist small manufacturers with identifying the types of documents that may be used to establish that their predicate products were on the market on February 15, 2007. This may include several calls or correspondence with the manufacturer as it submits different documents to the Agency.

FDA offered some assistance in the preamble to the final deeming rule, which announced an enforcement policy for small-scale tobacco product manufacturers that offers them targeted relief in certain areas to address concerns that small manufacturers may need additional time to comply with certain requirements of the FD&C Act. For purposes of this policy, FDA considers a "small-scale tobacco product manufacturer" to be a manufacturer of any regulated tobacco product that employs 150 or fewer full-time equivalent employees and has annual total revenues of $5,000,000 or less. (We note that FDA's thinking regarding "small-scale tobacco product manufacturer" here differs from the definition of "small tobacco product manufacturer" in section 900(16) of the FD&C Act.)

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 http://www.fda.gov/TobaccoProducts/GuidanceComplianceRegulatoryInformation/ucm189635.htm.