Premarket Tobacco Product Applications for Electronic Nicotine Delivery Systems

Guidance for Industry

DRAFT GUIDANCE

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

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Premarket Tobacco Product Applications for Electronic Nicotine Delivery Systems

Guidance for 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This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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;
- How FDA intends to review 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FDA's draft guidance for industry, *Applications for Premarket Review of New Tobacco Products* (draft premarket review guidance),[2] discusses the general procedures for submitting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 Product Guidance page at http://www.fda.gov/TobaccoProducts/GuidanceComplianceRegulatoryInformation/ucm281147.htm.

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

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 vaporizers, and electronic pipes) are subject to FDA's chapter IX authorities on the effective date of the final deeming rule.[3] 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. 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 on February 15, 2007, or any modified

[3] 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 their ENDS to be marketed as a medical product. Please see section IV.B.1 for further discussion.

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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 February 15, 2007 (the 905(j) pathway), or the new tobacco product is exempt from the substantial equivalence requirements. When a new product is not found to be substantially equivalent to an appropriate predicate product or exempt from the substantial equivalence requirements, you must submit a PMTA under section 910(b) and receive a marketing order under section 910(c)(1)(A)(i) prior to marketing the product.

All 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 limited availability of valid predicates 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 requirements for a PMTA submission. This guidance is intended to provide information to assist applicants in submitting a sufficient level of information to obtain 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.

This guidance represents FDA's current thinking on some appropriate means of addressing the premarket authorization requirements for newly deemed ENDS products.

III. DEFINITIONS

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

A. Accessory

The term *accessory* means any product that is intended or reasonably expected to be used with or for the human consumption of a tobacco product; does not contain tobacco and is not made or derived from tobacco; and meets either of the following: (1) is not intended or reasonably expected to affect or alter the performance, composition, constituents, or characteristics of a tobacco product; or (2) is intended or reasonably expected to affect or maintain the performance, composition, constituents, or characteristics of a tobacco product but (i) solely controls moisture and/or temperature of a stored 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

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this definition, means the manner in which the materials, including, for example, ingredients, additives, and biological organisms, are arranged and integrated.

B. 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.

C. Covered Tobacco Product

The term *covered tobacco product* means any tobacco product deemed to be subject to the FD&C Act under section 21 CFR § 1100.1, but excludes any component or part of a tobacco product that is not made or derived from tobacco.

D. 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.

E. 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.[4]

F. Tobacco Product

[4] FDA has interpreted "as of February 15, 2007" to mean any tobacco product that was not 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*.

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A *tobacco product* is "any product made or derived from tobacco that is intended for human consumption, including any component, part, or accessory of a tobacco product (except for raw materials other than tobacco used in manufacturing a component, part, or accessory of a tobacco product)" (section 201(rr) of the FD&C Act). This term does not include an article that is a drug, device, or combination product as defined in the FD&C Act. 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 briefly describe e-liquids and aerosolizing apparatus below and provide 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, [redacted]

1. E-Liquids

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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 also are referred to as e-liquids for the purposes of this guidance document. For example, where a "zero nicotine" or "nicotine free" 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. FDA considers such e-liquids to be a tobacco product even if sold separately from an aerosolizing apparatus.

2. Aerosolizing Apparatus

For the purposes of this guidance, *aerosolizing apparatus* refers to all components and parts (together or sold separately) of an ENDS product, other than the e-liquid itself, that interact directly or indirectly with e-liquid in the use of the tobacco product. For example, FDA considers an e-cigarette, e-pen, e-hookah without e-liquids, or a battery sold separately (to be used with an ENDS product) to be an aerosolizing apparatus.

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 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

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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.[5]

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 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)[6] 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 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. How Will FDA Review an ENDS PMTA?

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." A PMTA must include all information specified in 910(b)(1) upon submission and FDA may refuse to file incomplete applications. 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.

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.

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[5] 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).

[6] 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)).

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D. Public Health Considerations for ENDS Products

1. Section 910(c)(2)(A)'s 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."[7] 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.)

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 (i.e., 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. While FDA requests this information for particular topic areas and disciplines, FDA weighs all of the potential benefits and risks from the product to make an overall determination of whether the product should be marketed.

Under section 910(c)(5)(A) of the FD&C Act, FDA's finding must be determined "when appropriate . . . on the basis of well-controlled investigations." However, under section 910(c)(5)(B), if the Secretary determines that there exists valid scientific evidence (other than evidence derived from well-controlled investigations, as described in section 910(c)(5)(A)) that

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[7] In addition, the statute provides that FDA shall deny PMTAs under section 910(c)(2) of the FD&C Act where:
(B) the methods used in, or the facilities or controls used for, the manufacture, processing, or packing of such tobacco product do not conform to the requirements of section 906(e);
(C) based on a fair evaluation of all material facts, the proposed labeling is false or misleading in any particular; or
(D) such tobacco product is not shown to conform in all respects to a tobacco product standard in effect under section 907, and there is a lack of adequate information to justify the deviation from such standard.

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is sufficient to evaluate the new tobacco product, the Secretary may authorize that the determination under the public health standard be made on the basis of such evidence.

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 combusted 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 what is 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 support a finding that introducing your new tobacco product to the market is appropriate for the protection of the public health. Given the relatively new entrance of ENDS on the U.S. market, FDA understands that ENDS PMTA applicants may have limited data 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 range 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) and a comparison between your product and other similar products within the same category. 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. 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, flavors, or similar other ingredients.

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

[redacted]

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, 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 this warning is important to aid in the prevention of and/or decrease the risk of inadvertent exposure to nicotine, especially by children, which could lead to acute toxicity including potentially deadly nicotine poisoning. 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);

[redacted]

- 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." 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 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.

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 appears on a tag otherwise permanently affixed to the tobacco product package.[8] 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.

[8] See 21 CFR part 1143 for the complete list of requirements for the required warning statement regarding the addictiveness of nicotine.

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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[9] properties of the packaging. An example of child-resistant 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 [redacted] Information about the eSubmitter tool can be found online at [redacted]

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 unredacted 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, 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 or sent to the following address:

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

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Food and Drug Administration
Center for Tobacco Products

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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:

- 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;
- A full statement of the components, ingredients, additives, and properties, and of the principle or principles of operation, of such tobacco product;
- 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;
- An identifying reference to any tobacco product standard under section 907 that 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;
- Such samples of such tobacco product and of components thereof as the Secretary may reasonably require;
- Specimens of the labeling proposed to be used for such tobacco product; and
- 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 which 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

[redacted]

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 and delineate 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.

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

[redacted]

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.

[redacted]

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

[redacted]

- 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 Bundle[10]:
  - Product name
  - Category: ENDS
  - Subcategory: ENDS Bundle
  - 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 application 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

[10] An *ENDS Bundle* 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.

[redacted]

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 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

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. More information on environmental assessments can be found in 21 CFR 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 section summarizing all research findings in your PMTA, including a description of the operation of the new tobacco product, the health risks of the product, the product's effect on tobacco use behavior among current users, the product's effect on tobacco use initiation among nonusers, and the product's effect on the population as a whole. The discussion should include information such as:

[redacted]

- A summary of the nonclinical and clinical studies, both favorable and unfavorable, relevant to your PMTA, including which specific product or products were studied, how those products are similar to the applicant's product if used as a substitute or supplement for data for the product, the study findings, and if the findings concern health risks compared to other tobacco products, 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 this in this section;
- The 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) and the health risks compared to never using tobacco products;
- The chemical and physical identity and quantitative levels of the emission of aerosols under the range of operating conditions of the product;
- The likelihood, based on the research findings contained in your application, of consumers initiating or reinitiating tobacco use with the new tobacco product;
- 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;
- The likelihood, based on the research findings contained in your application, of consumers using the new tobacco product in conjunction with other tobacco products;
- 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;
- Assessment of abuse liability;
- Assessment of user topography; and
- 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 quantitative estimates of the effect that the new tobacco product may have on the health of the population as a whole. The estimates should integrate all of the information regarding the product and its potential effects on health, tobacco use behavior and tobacco use initiation to provide an overall assessment of the potential effect that the product's marketing may have on overall tobacco-related morbidity and mortality.

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

[redacted]

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 can, intentionally or unintentionally, leach ingredients from the packaging into the product. 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*.

FDA does not believe there is adequate scientific information or regulatory experience with ENDS products to support using only information on earlier or other versions of the product or

[redacted]

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 product that is the subject of your PMTA.

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. Your constituent testing should reflect the range of conditions under which consumers may use your product. For example, an open aerosolizing apparatus (an aerosolizing apparatus that includes a refillable e-liquid reservoir) should be tested with a wide range of available e-liquids; a closed aerosolizing apparatus (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; components or parts should be tested with the range of products with which they could be used; and e-liquids that can be used with a wide range of aerosolizing apparatus should be tested with such a range of aerosolizing apparatus with varying temperatures and voltage. FDA recommends that measurements of constituents, including those listed below and other toxic chemicals, as appropriate for your product, be evaluated under both nonintense use conditions and intense use conditions to enable FDA to understand the likely range of delivery of emissions.

FDA recommends that you consider the following constituents[11] 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
- Cadmium
- Chromium
- Crotonaldehyde
- Diacetyl

[11] 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.

[redacted]

- 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 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 criteria;
- 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.,

[redacted]

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. 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.

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 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.[12]

[12] 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)).

[redacted]

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 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 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.

[redacted]

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.[13] 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).[14] Special attention should be paid to trials that may include vulnerable subjects.[15]

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 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 according to potential public health concerns or other impacts on public health.[16] Applicants who would like to study their new tobacco products to support a premarket submission should contact the Office of Science at the Center for Tobacco Products to discuss submission of a study protocol and/or study endpoints.[17]

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[13] 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).

[14] 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/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm073122.pdf.

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

[16] 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 Product Guidance page at http://www.fda.gov/TobaccoProducts/GuidanceComplianceRegulatoryInformation/ucm281147.htm.

[17] Information about how to request meetings with CTP can be found in FDA's guidance for industry and investigators *Meetings with Industry and Investigators on the Research and Development of Tobacco Products*, available on the Internet at http://www.fda.gov/downloads/TobaccoProducts/GuidanceComplianceRegulatoryInformation/UCM305282.pdf.

[redacted]

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);
- 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:

[redacted]

- 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.

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;

[redacted]

- 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, and respiratory, cardiac, reproductive, and developmental toxicity;
- Hazard identification studies;
- 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.

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. 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 (i.e., products in the same category) in your in vitro assay.

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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. In all cases where animal testing is used, FDA advocates that research and testing derive the maximum amount of useful scientific information from the minimum number of animals, employ the most humane methods available within the limits of scientific capability, and comply with applicable laws, regulations, and policies governing animal testing.

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

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

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

[redacted]

health. 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:

[redacted]

- Published literature or sponsor-initiated studies evaluating the effects of the ENDS on users and nonusers, including effects on initiation, switching behavior, cessation, and dual use. 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, the likely impact of the tobacco product on cessation behavior instead could be evaluated through other types of studies, such as observational studies (perception, actual use, or both).[18]

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, the trends by which users consume the product over time, the switching and cessation rates for users of the product, and the potential for consumers to use the product in conjunction with other tobacco products (e.g., dual use). Descriptive data on product use, including use in conjunction with other tobacco products, should be broken down by demographic factors, such as age group (including youth and young adults), sex, race, ethnicity, and education; and by geographic regions (e.g., U.S. census regions).

FDA also recommends sharing your marketing plan for FDA to better understand the potential consumer demographic. In addition, and, if the product is currently marketed,[19] FDA recommends sharing sales data by population demographics and tobacco use status. If sales data are available, it should be analyzed in 4-week or monthly intervals, if data are available, and 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);

[18] 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.

[19] 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.

[redacted]

- 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

[redacted]

and nonusers. For example, biomarkers of toxicant exposure may include compounds such as cotinine, NNAL, and NNN.

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 you conduct studies to 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

[redacted]

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 PMTAs 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.

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:

- Aerosolizing apparatus features;
- Material and/or ingredient functions;
- Capabilities to monitor product performance (e.g., temperature sensing, voltage sensing, battery life detection);

[redacted]

- Instructions and method of operation;
- Materials of all aerosolizing apparatus components;
- Operating ranges;
- 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:

- If the aerosolizing apparatus includes the battery:

[redacted]

- 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 listed below.

- Overall atomizer:
  - Draw resistance (and operable range if adjustable);
  - E-liquid capacity; and
  - Aerosol particle size across operable range.
- Coils:
  - 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).

[redacted]

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 PMTA the applicant intends to

[redacted]

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 demonstrate how the elements specific to showing that the product is appropriate for the protection of the public health also apply to different demographics that would be representative of the U.S. population as whole. Similarly, to use existing literature, if a similar product 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;

[redacted]

- 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.

[redacted]

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 and increase efficiency of PMTA preparation and submissions, we encourage you to use tobacco product master files (TPMFs) whenever possible. A master file may contain detailed information on a specific manufacturing facility, process, methodology, or component used in the manufacturing, processing, or packaging of a tobacco product. By obtaining permission from a master file holder, you may reference extensive ingredient lists and constituent testing or other information that you otherwise would be required to perform or develop yourself to support your PMTA. Refer to FDA's guidance for industry, *Tobacco Product Master Files*, for more information on using TPMFs.

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 clinical 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, in certain circumstances, information that is available from earlier versions of the same ENDS product, or from marketing experience with 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.

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

XI. POSTMARKET REQUIREMENTS

A marketing order under section 910(c)(1)(A)(i) of the FD&C Act may require that the sale and distribution of the tobacco product be restricted, but only to the extent that the sale and distribution of a tobacco product may be restricted under a regulation under section 906(d). In addition, under section 910(f) of the FD&C Act, FDA may require that you establish and maintain certain postmarket records and make certain postmarket reports to FDA.

XII. OFFICE OF SMALL BUSINESS ASSISTANCE

Small businesses may contact [redacted] or by [redacted] 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.