Premarket Tobacco Product Applications for Electronic Nicotine Delivery Systems

Guidance for Industry

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

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

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

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

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Guidance for Industry[1]

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

I. INTRODUCTION

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

The guidance explains, among other things:

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

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

FDA is committed to helping industry better understand the tobacco product review process and the requirements of the law and will continue holding public webinars and meetings with industry to assist manufacturers of deemed tobacco products. FDA has published guidance on meetings with industry[2] and has had many productive meetings to address companies' specific questions on their development of tobacco products. Throughout this document, we identify additional assistance (including support offered by the Office of Small Business Assistance within the Center for Tobacco Products (CTP)) available to applicants preparing to submit a PMTA for ENDS.[3] We have also provided related resources and compliance periods for small-scale tobacco product manufacturers.[4] FDA's web site and guidance documents provide information about the three pathways available to market products (including PMTA).

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

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

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

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

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

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

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

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

II. BACKGROUND

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

On May 10, 2016, FDA issued a final rule, "Deeming Tobacco Products to Be Subject to the Federal Food, Drug, and Cosmetic Act, as Amended by the Family Smoking Prevention and Tobacco Control Act; Restrictions on the Sale and Distribution of Tobacco Products and Required Warning Statements for Tobacco Products" (final deeming rule) (81 FR 28973). The final deeming rule extended FDA's tobacco product authorities to all products, other than accessories of deemed tobacco products, that meet the statutory definition of "tobacco product" in section 201(rr) of the FD&C Act (21 U.S.C. 321(rr)). In the final deeming rule, FDA clarifies that all ENDS (including, but not limited to, e-cigarettes, e-pens, e-cigars, e-hookah, vape pens, personal vaporizers, and electronic pipes) are subject to FDA's chapter IX authorities on the effective date of the final deeming rule.[6] ENDS products include both the e-liquid and e-cigarette used as an ENDS, whether sold as a unit or separately.

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

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

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

C. General Procedures for ENDS PMTA Review

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

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

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

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

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

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

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

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

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

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

2. Valid scientific evidence

The FD&C Act states that the finding of whether permitting the marketing of a product would be APPH will be determined, when appropriate, on the basis of well-controlled investigations[21] (section 910(c)(5)(A)). However, section 910(c)(5)(B) of the FD&C Act also allows the Agency to consider other "valid scientific evidence" if found sufficient to evaluate the tobacco product. Given the relatively new entrance of ENDS on the U.S. market, FDA understands that limited data may exist from scientific studies and analyses.[22] If an application includes, for example, information on other products (e.g., published literature, marketing information) with appropriate bridging studies, FDA intends to review that information to determine whether it is valid scientific evidence sufficient to demonstrate that the marketing of a product would be APPH. Nonclinical studies alone are generally not sufficient to support a determination that permitting the marketing of a tobacco product would be appropriate for the protection of the public health.

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

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

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

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

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

3. Comparison Products

As part of FDA's consideration under 910(c)(4) of the FD&C Act of the risks and benefits of the marketing of the new tobacco product to the population as a whole, including users and nonusers of tobacco products, FDA reviews the health risks associated with changes in tobacco product use behavior (e.g., initiation, switching, dual use, cessation) that are likely to occur with the marketing of the new tobacco product. We recommend an applicant compare the health risks of its product to both products within the same category and subcategory, as well as products in different categories as appropriate. It is helpful for FDA to understand applicant's rationale and justification for comparators chosen within the same category or different categories of tobacco products. This comparative health risk data is an important part of the evaluation of the health effects of product switching.

Information about tobacco products in the same category or subcategory is important to FDA's evaluation of a tobacco product's potential effect on public health because current users may switch to other products within the same category. For tobacco products that are within the same category and subcategory, we recommend applicants consider products that consumers are most likely to considered interchangeable between your proposed product and other similar products.

[23] See section X for additional discussion.
[24] See section X of the guidance for more information about alternatives to conducting long-term studies.
[25] See the R&D meetings guidance.

For example, for a PMTA for an e-liquid, FDA recommends the product's health risks be compared to those health risks presented by other e-liquids used in a similar manner. This comparison of health risks is not meant to be a 1:1 product comparison as in a substantial equivalence report under section 905(j), rather, it is meant to demonstrate how the proposed new product may be evaluated in relation to similar products. We recommend as part of the evaluation of the new product's risk compared to other tobacco products that you include those characteristics (materials, ingredients, design, composition, heating source, or other features) that contribute to the new product presenting the same, less, or different health risks than other tobacco products of similar category and subcategory.

Information about tobacco products in different categories is important to FDA's evaluations because it can help demonstrate the changes in health risks current tobacco users could face if they switched to your new tobacco product or use it in conjunction with their current tobacco product. For tobacco products that are not in the same tobacco product category, but that may be appropriate for examining health risk, FDA recommends determining the likely users of the proposed new product to justify appropriate products for demonstrating the health risks of the new product in comparison to other tobacco products. For example, in the 2018 tobacco market conditions, some ENDS product manufacturers market their products as replacements for combusted cigarettes. In this case, it could be appropriate to evaluate the risks of ENDS products in relation to the risks of both cigarettes and other similar ENDS products. Polytobacco use risks should also be considered.

4. Nicotine exposure warnings

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

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

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

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

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

> WARNING: Contains nicotine, which can be poisonous. Avoid contact with skin and eyes. Do not drink. Keep out of reach of children and pets. In case of accidental contact, seek medical help.
>
> or
>
> WARNING: Contains nicotine. Do not get on skin or in eyes. Do not drink. Store in original container and keep away from children and pets. In case of accidental contact, call the Poison Control Center at 1-800-222-1222.

5. Warning statement regarding the addictiveness of nicotine

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

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

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

6. Protective packaging

Given the health risks and hazards associated with exposure to e-liquids (including oral, dermal, and ocular dangers), especially to infants and children, FDA recommends that manufacturers provide sufficient information describing the kind of packaging in which their ENDS product will be sold to support a finding that the marketing of the product is APPH. While various types of packaging may help support such a finding, examples of packaging that may mitigate risks of accidental exposure to e-liquids include child-resistant packaging[27] and exposure-limiting packaging (e.g., flow restrictors). An example of child-resistant packaging that would help show the marketing of the product would be APPH is, depending on the circumstances, packaging that is significantly difficult for children 5 years of age and under to open, use, or obtain a toxic, potentially addicting, or otherwise harmful amount of the tobacco product or any of its constituents within a reasonable time and that is not unreasonably difficult for a majority of adults to use properly.[28] The description should also include information regarding the tamper-resistant and tamper-evident[29] properties of the packaging.

V. HOW TO SUBMIT A PMTA

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

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

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

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

[28] See, e.g., 15 U.S.C. 1471.

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

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

Additionally, to help prepare for a potential referral of your PMTA to the TPSAC, FDA recommends that you identify information that you believe to be a trade secret or confidential commercial information that is contained in your PMTA. You can identify this information by submitting two separate and complete versions of the PMTA: one un-redacted version and one marked-for-redaction version. The marked-for-redaction version should denote the content that is the subject of a proposed redaction at the place where the text is located in the document in a manner that allows the text to remain legible, such as placing a box around the content. FDA also recommends that you submit an index that lists the location of each proposed redaction in the PMTA by page number, and that you explain in detail why you believe that each proposed redaction qualifies as a trade secret or confidential, commercial information[30] that is not available for disclosure under 21 CFR 20.61. Doing the above will speed the process if FDA refers your application to TPSAC.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

A. General Information

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

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

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

B. Table of Contents

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

C. Descriptive Information

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

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

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

FDA recommends that the unique identification of the product include:

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

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

D. Product Samples

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

E. Labeling

As required by section 910(b)(1)(F) of the FD&C Act, your PMTA must include specimens of all proposed labeling for your new tobacco product. The term *labeling* is defined in section 201(m) of the FD&C Act as "all labels and other written, printed, or graphic matter (1) upon any article or any of its containers or wrappers, or (2) accompanying such article," and includes labels, inserts, onserts, instructions, and other accompanying information or materials. The

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

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

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

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

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

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

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

In order to help FDA assess potential health risks and to enable FDA to make a finding that permitting the marketing of a new tobacco product would be APPH, FDA recommends that you consider the following constituents or chemicals[35] for analysis in e-liquids or aerosols, or both, as appropriate, for your product:

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

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

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

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

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

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

2. Nonclinical and Human Subject Studies

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

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

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

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

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

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

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

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

[40] See the R&D meetings guidance.

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

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

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

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

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

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

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

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

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

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

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

- 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[42] and Organization for Economic Cooperation and Development protocols as a guide for genotoxicity assessment. We also recommend that you conduct these assays with multiple concentrations of your final product for validating your results. For appropriate hazard identification comparison, you should include the comparator products (e.g., products in the same category) in your in vitro assay.

FDA supports reducing, replacing, and/or refining the use of animal testing in research where adequate and scientifically valid non-animal alternatives can be substituted. FDA encourages sponsors to meet with CTP early in the development process to discuss the suitability and acceptability of non-animal tests for their particular new tobacco product. When animal-based nonclinical laboratory studies are conducted, investigators should use appropriate animal models, adhering to the best practices of refinement, reduction, and replacement of animals in research and following the applicable laws and regulations governing animal testing.

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

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

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

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

3. Software

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

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

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

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

X. ADDITIONAL CONSIDERATIONS FOR SCIENTIFIC STUDIES AND ANALYSES

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

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

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

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

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

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

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

XIII. OFFICE OF SMALL BUSINESS ASSISTANCE

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

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

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