No. 23-1038

In the Supreme Court of the United States

FOOD AND DRUG ADMINISTRATION, PETITIONER

v.

WAGES AND WHITE LION INVESTMENTS, L.L.C., DBA TRITON DISTRIBUTION, ET AL.

ON WRIT OF CERTIORARI
TO THE UNITED STATES COURT OF APPEALS
FOR THE FIFTH CIRCUIT

JOINT APPENDIX

ELIZABETH B. PRELOGAR
Solicitor General
Department of Justice
Washington, D.C. 20530-0001
SupremeCtBriefs@usdoj.gov
(202) 514-2217

Counsel of Record
for Petitioner

ERIC N. HEYER
Thompson Hine LLP
1919 M Street, N.W.
Suite 700
Washington, D.C. 20036
eric.heyer@thompsonhine.com
(202) 331-8000

Counsel of Record
for Respondents

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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 email 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

June 2019

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Contains Nonbinding Recommendations

Premarket Tobacco Product Applications for Electronic Nicotine Delivery Systems

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.

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

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).

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

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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.

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

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[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.

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.

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.

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[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.

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

Under section 910 of the FD&C Act, persons wanting to market a new tobacco product (one that was not commercially marketed in the United States as of (i.e., on)

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[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.

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

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

All deemed products that meet the definition of a "new tobacco product," including ENDS, are subject to the requirements of premarket review in sections 910(a)(2) of the FD&C Act. Given the expected difficulty in identifying valid ENDS predicate products (products com-

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

mercially marketed on February 15, 2007, or previously determined to be substantially equivalent to an appropriate predicate product) for use in the substantial equivalence pathway, FDA expects to receive PMTA submissions from manufacturers of deemed ENDS products. Section 910(b)(1) of the FD&C Act contains the requirements for a PMTA submission. This guidance is intended to provide information to assist applicants in submitting a PMTA to apply for a marketing order under section 910(c)(1)(A)(i).

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

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

III. DEFINITIONS

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

A. Accessory

The term *accessory* means any product that is intended or reasonably expected to be used with or for the human consumption of a tobacco product; does not contain tobacco and is not made or derived from tobacco; and meets either of the following:

(1) is not intended or reasonably expected to affect or alter the performance, composition, constituents, or characteristics of a tobacco product; or

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

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

(ii) solely provides an external heat source to initiate but not maintain combustion of a tobacco product (21 CFR 1100.3).

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

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

B. Additive

An *additive* is any substance the intended use of which results or may reasonably be expected to result, directly or indirectly, in its becoming a component or otherwise affecting the characteristic of any tobacco product (including any substances intended for use as a flavoring or coloring or in producing, manufacturing, packing, processing, preparing, treating, packaging, transporting, or holding), except that such term does not include tobacco or a pesticide chemical residue in or on raw tobacco or a pesticide chemical (section 900(1) of the FD&C Act).

C. Component or Part

Component or part means any software or assembly of materials intended or reasonably expected: 1) to alter or affect the tobacco product's performance, composition, constituents, or characteristics; or 2) to be used with or for the human consumption of a tobacco product. Component or part excludes anything that is an accessory of a tobacco product. (21 CFR 1100.3).

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

D. Covered Tobacco Product

Under 21 CFR 1143.1, the term *covered tobacco product* means any tobacco product deemed to be subject to the

FD&C Act under 21 CFR 1100.1, but excludes any component or part of a tobacco product that is not made or derived from tobacco. Examples of covered tobacco products include, but are not limited to, cigars, pipe tobacco, and e-liquids.[10]

E. E-cigarette

For the purposes of this guidance, *e-cigarette* refers to an electronic device that delivers e-liquid in aerosol form into the mouth and lungs when inhaled; it is also referred to as an aerosolizing apparatus. For example, FDA considers vapes or vape pens, personal vaporizers, cigalikes, e-pens, e-hookahs, e-cigars, and e-pipes to be e-cigarettes. For the purposes of this guidance, e-cigarettes may either be open e-cigarettes or closed e-cigarettes. An open e-cigarette, also referred to as a refillable e-cigarette, is an e-cigarette that includes a reservoir that a user can refill with an e-liquid of their choosing. A closed e-cigarette is an e-cigarette that includes an e-liquid reservoir that is not refillable, such as a disposable cigalike, or that uses e-liquid contained in replaceable cartridges or pods that are not intended to be refillable. Also, for the purposes of this guidance, if an e-cigarette contains e-liquid it is referred to as a prefilled e-cigarette.

F. E-liquids

For the purposes of this guidance document, *e-liquids* include liquid nicotine, nicotine-containing liquids (i.e., liquid nicotine combined with colorings, flavorings, and/or other ingredients), and liquids that do not contain nicotine or other material made or derived from to-

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

bacco, but that are intended or reasonably expected to be used with or for the human consumption of a tobacco product.

An e-liquid that contains nicotine made or derived from tobacco meets the definition of a tobacco product and, therefore, is subject to FDA's chapter IX authorities. Liquids that do not contain nicotine or other material made or derived from tobacco, but that are intended or reasonably expected to be used with or for the human consumption of a tobacco product, may be components or parts and, therefore, subject to FDA's tobacco control authorities. For example, where a "zero nicotine" or "nicotine free" e-liquid (e.g., a zero nicotine flavored e-liquid) is intended or reasonably expected to be mixed with liquid nicotine, that e-liquid may be a component or part of a tobacco product and subject to FDA's tobacco control authorities. Such e-liquids would be tobacco products even if sold separately from an e-cigarette. E-liquids containing zero nicotine that are not otherwise made or derived from tobacco and are not intended or reasonably expected to be mixed with liquid nicotine or other materials made or derived from tobacco are not tobacco products and thus are not subject to FDA's tobacco control authorities under the FD&C Act.

G. Finished Tobacco Product

For purposes of this guidance document, the term *finished tobacco product* refers to a tobacco product, including all components and parts, sealed in final packaging. For example, an e-liquid sealed in final packaging that is to be sold or distributed to a consumer for use is a finished tobacco product, but in contrast, an e-liquid that is sold or distributed for further manufactur-

ing into a finished ENDS product is not itself a finished tobacco product.

H. New Tobacco Product

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

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

(B) any modification (including a change in design, any component, any part, or any constituent, including a smoke constituent, or in the content, delivery or form of nicotine, or any other additive or ingredient) of a tobacco product where the modified product was commercially marketed in the United States after February 15, 2007.[11]

I. Tobacco Product

A *tobacco product* is "any product made or derived from tobacco that is intended for human consumption, including any component, part, or accessory of a tobacco product (except for raw materials other than tobacco used in manufacturing a component, part, or accessory of a tobacco product)" (section 201(rr) of the FD&C Act). This term does not include an article that is a drug, device, or combination product as defined in the FD&C Act (21 CFR 1100.3). The term is not limited to products containing tobacco or tobacco derivatives, and also includes components, parts, or accessories of tobacco products, whether they are sold for further manufacturing or for

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[11] See note 7.

consumer use. For example, e-liquids, e-cigarettes, atomizers, and batteries used in ENDS are tobacco products, whether they are sold to consumers for use in an ENDS or are sold for further manufacturing into another product sold to a consumer.

IV. DISCUSSION

A. Products to Which This Guidance Applies

As noted above, the final deeming rule extended FDA's tobacco product authorities to all products, other than accessories of deemed tobacco products, that meet the statutory definition of "tobacco product" in section 201(rr) of the FD&C Act (21 U.S.C. 321(rr)). Currently, FDA generally considers ENDS to be electronic nicotine delivery systems that deliver aerosolized e-liquid when inhaled.[12] Because ENDS products fall within the definition of "tobacco product" under section 201(rr) of the FD&C Act and are not accessories of deemed products, the tobacco product authorities (including the PMTA authorities) apply to ENDS products. ENDS include the components and parts of ENDS products, but not their related accessories. Therefore, such components and parts are also subject to FDA's authority, including premarket review. Overall, the ENDS category thus includes a variety of products, such as vape pens or personal vaporizers, cigalikes, e-pens, e-hookahs, e-cigars, e-pipes, e-liquids, atomizers, batteries (with or without variable voltage), cartomizers (atomizer plus replaceable fluid-filled cartridge), digital display/lights to adjust settings, clearomizers (refillable e-liquid car-

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

tridges with built-in atomizer and wicking system), tank systems, flavors, and programmable software. Because it is a rapidly changing industry and new ENDS products may be developed in the future this is a non-exhaustive list of examples of ENDS products.

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

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

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

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

1. Considerations for All Applicants

Section 910 of the FD&C Act requires a marketing order for new tobacco products. At this time, FDA intends to limit enforcement of the requirements of section 910 to finished tobacco products, including components and parts of ENDS products sold or distributed separately for consumer use. FDA does not, at this time, intend to enforce these requirements for components and parts of deemed products that are sold or distributed solely for further manufacturing into finished tobacco products, and not sold separately to the consumer. For example, an e-liquid that is sold or distributed for further manufacturing into a finished ENDS product is not itself a finished tobacco product and, at this time, FDA does not intend to enforce against such e-liquids that are sold or distributed without a marketing order. In contrast, an e-liquid sealed in final packaging that is to be sold or distributed to a consumer for use is a finished tobacco product.

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

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

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

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

An ENDS retail establishment that mixes or prepares combinations of liquid nicotine, flavors, or other e-liquids for direct sale to consumers for use in ENDS, or creates or modifies e-cigarettes for direct sale to consumers for use in ENDS (sometimes known as a vape shop) meets the definition of "tobacco product manufacturer" in section 900(20)[15] of the FD&C Act. Section 910(a)(1) defines a "new tobacco product" as "any tobacco product (including those products in test markets) that was not commercially marketed in the United States as of February 15, 2007," or "any modification (including a change in design, any component, any part, or any constituent, including a smoke constituent, or in

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

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

the content, delivery or form of nicotine, or any other additive or ingredient) of a tobacco product where the modified product was commercially marketed in the United States after February 15, 2007." Therefore, those establishments engaged in mixing and/or preparing combinations of liquid nicotine, flavors, and/or other e-liquids or creating or modifying e-cigarettes for direct sale to consumers for use in ENDS are both tobacco product manufacturers and retailers, and consequently are subject to all the requirements applicable to manufacturers and retailers including the PMTA requirements.[16]

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

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

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)

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[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.

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

uct manufacturing practices, which will be set forth in a future rulemaking.[18]

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

D. Public Health Considerations for ENDS Products

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

Section 910(c)(2)(A) of the FD&C Act requires that FDA deny a PMTA where it finds "there is a lack of a showing that permitting such tobacco product to be

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

[19] For more information, please visit the TPSAC website: https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/TobaccoProductsScientificAdvisoryCommittee/default.htm

marketed would be appropriate for the protection of the public health."[20] FDA's finding of whether there is a showing that permitting a product to be marketed would be appropriate for the protection of the public health (APPH) must be determined with respect to the risks and benefits to the population as a whole, including users and nonusers of the tobacco product, and taking into account:

(A) the increased or decreased likelihood that existing users of tobacco products will stop using such products; and

(B) the increased or decreased likelihood that those who do not use tobacco products will start using such products.

(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

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

(B) the methods used in, or the facilities or controls used for, the manufacture, processing, or packing of such tobacco product do not conform to the requirements of section 906(e);

(C) based on a fair evaluation of all material facts, the proposed labeling is false or misleading in any particular; or

(D) such tobacco product is not shown to conform in all respects to a tobacco product standard in effect under section 907, and there is a lack of adequate information to justify the deviation from such standard.

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.

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

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[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.

[23] See section X for additional discussion.

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.

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

[25] See the R&D meetings 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. 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

[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.

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,

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[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."

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.

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

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[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.

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.

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[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)).

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).

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 (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 submitted specimens of proposed labeling for all product panels should be legi-

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[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.

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

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

F. Environmental Assessment

An environmental assessment must be included in an ENDS PMTA for FDA's review. Under 21 CFR 25.15, an applicant must include an environmental assessment prepared in accordance with 21 CFR 25.40, unless the action qualifies for a categorical exclusion. Per 21 CFR 25.35, the only categorical exclusion that applies to PMTA submissions is an issuance of an order that a new tobacco product may not be introduced or delivered for introduction into interstate commerce (i.e., a denial of a marketing authorization after FDA's review of a PMTA). More information on environmental assessments can be found in 21 CFR part 25.[32]

G. Summary of All Research Information

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

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

summary include a description of the operation of the new tobacco product as well as a section summarizing all research information in your PMTA, including the health risks (e.g., 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.

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

increases in disease risks among those new users of the product.

H. Scientific Studies and Analyses

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

1. Product Analyses and Manufacturing

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

Product analyses and testing should be conducted on the ENDS tobacco product that is the subject of the PMTA. Any product sample submitted (as discussed in

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

- Data sets that can reliably reflect the product and its manufacturing. For example, FDA recommends data sets spanning different batches (generally three or more) with multiple replicates per batch (generally seven or more), depending upon the variability demonstrated in the method validation, with date and time sampling points;
- Accreditation information for each testing laboratory;
- Validation information and rationale for selecting each test method, including any relevant voluntary testing standards; and
- Complete descriptions of any aerosol-generating regimens used for analytical testing.

At this time, FDA does not believe there is adequate scientific information or regulatory experience with ENDS products to support a PMTA authorization using only information on earlier or other versions of the product or similar products for descriptions of full product analysis as described in this section. If you feel that literature reviews may be an appropriate means for satisfying the requirements of section 910(b)(1)(B), please explain clearly how an adequate comparison (e.g., bridging) can be made between the products analyzed

in the published material and the specific product that is the subject of your PMTA. If an applicant has questions or other alternatives to well-controlled investigations it would like to utilize, we recommend that the applicant meet with FDA to discuss the approach prior to preparing and submitting an application.[33]

a. Components, ingredients, and additives

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

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

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[33] See the R&D meetings guidance.

This list should also specify the function(s) and grade or purity for each respective item. For guidance on uniquely identifying components, ingredients, and additives and reporting their quantities, please refer to FDA's guidance for industry, *Listing of Ingredients in Tobacco Products*.[34]

b. Properties

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;

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

- 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)
- Acrolein
- Acrylonitrile
- Benzene
- Benzyl acetate
- Butyraldehyde

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[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.

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

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

FDA also recommends that you submit information regarding any relevant voluntary standards with which your product complies and why you believe the stand-

ard is relevant, as well as testing data to demonstrate conformance to such standards.

c. Principles of operation

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

d. Manufacturing

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

where relevant, packing and installation of the new tobacco product."[36]

To help meet this statutory requirement, FDA recommends that you provide a listing of all manufacturing, packaging, and control sites for the product, including the facility names and addresses, the Facility Establishment Identifier number(s) (if available), and a contact name and telephone number for each facility. Moreover, we recommend that you provide a narrative description, accompanied by a list and summary of all standard operating procedures (SOPs) and examples of relevant forms and records, for the following categories of information, as applicable:

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

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

- 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

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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.

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 also provide an explanation of the scope of the literature review you conducted to discover the rel-

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[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.

evant 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;

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

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

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

- Documentation of the protection of human subjects[41] (e.g., documentation of study oversight by an Investigational Review Board duly constituted and operating under 21 CFR part 56; description of informed consent procedures, such as appropriate procedures found in 21 CFR part 50);
- All versions of questionnaires used;
- All versions of case report forms used; and
- All versions of informed consent forms.

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

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

a. Nonclinical health risk information

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

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

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

[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.

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

b. Human health impact information

Your PMTA should provide data that adequately characterizes the potential impact of the new tobacco product on the health of both users and nonusers of tobacco

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

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

- Tobacco users who may switch from other tobacco products to the new tobacco product;
- Tobacco users and nonusers who, after adopting use of the new tobacco product, may switch to or switch back to other tobacco products that may present higher levels of individual health risk;
- Tobacco users who may opt to use the new tobacco product rather than cease tobacco use altogether;
- Tobacco users who may opt to use the new tobacco product rather than an FDA-approved tobacco cessation medication;
- Tobacco users who may use the new tobacco product in conjunction with other tobacco products;

- Nonusers, such as youth, never users, and former users, who may initiate or relapse tobacco use with the new tobacco product;
- The health effects in users of the new tobacco product; and
- Nonusers who experience adverse health effects from the new tobacco product.

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

i. Consumer perceptions and intentions

Consumer perception evaluations should address how consumers perceive product harms and include consideration of packaging and labeling. These evaluations should also address interest in and intentions to use the product, including among populations of non-users of tobacco products (e.g., vulnerable populations such as youth and young adults). Examples of information that may be considered in this analysis include published reports and data on consumer perceptions of the new tobacco product and its packaging and consumer intentions to use the product, and data you collect on consumer perceptions of the harms of the new tobacco product and of its proposed labeling or advertising and intentions to use the product, including among populations of non-users of tobacco products. If you are collecting data on consumer perceptions or intentions, we recommend evaluating perceptions of the product, both absolute and in comparison to other categories of tobacco products and to quitting all tobacco use. This evaluation should include the use intentions among current ENDS users, nonusers, and other tobacco product

users, as well as reasons for use (e.g., complete substitution, use in environments where smoking is not allowed, fun and enjoyment).

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

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

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

Although randomized clinical trials could address cessation behavior of users of tobacco products, FDA believes this would also be true for observational studies

(perception, actual use, or both) examining cessation behaviors.[43]

iii. Product use patterns

Evaluation of product use patterns should consider the topography of how individual users consume the product (e.g., the number of puffs, puff duration, puff intensity, duration of use), the frequency with which consumers use the product, and the trends by which users consume the product over time. FDA recommends that information and data on product use, including use in conjunction with other tobacco products, be assessed, when possible, by factors that may be expected to influence such patterns, such as age group (including youth and young adults), sex, race, ethnicity, and education.

- If the product has not been previously marketed, such information could be collected from actual use studies.
- For previously marketed products, marketing data or company research conducted to understand the use patterns could be used as well. In addition, applicants may incorporate information from national surveys or the results of other published studies.
- Although most studies in the published scientific literature typically focus on general ENDS products and are not usually product-specific or type-specific, data from these studies can still be in-

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

formative to assess overall ENDS product use information. Applicants using published studies of ENDS use to support their application should provide a scientific rationale and bridging information to allow FDA to assess whether the findings of such studies would be relevant to the product that is the subject of the application.

- In addition, applicants may need to supplement information from existing studies and surveys with applicant-specific perception surveys or actual use studies.

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

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

- The Universal Product Code that corresponds to the product(s) identified in the PMTA;
- Total U.S. sales reported in dollars, units, and volume with breakdowns by U.S. census region, ma-

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

jor retail markets, and channels in which the product is sold (e.g., convenience stores, food and drug markets, big box retailers, internet/online sales, tobacco specialty shops) promotional discounts (e.g., buy-one-get-one free or percentage discount);

- Demographic characteristics of product(s) purchasers, such as age, gender, and tobacco use status; and
- Information on top selling brands as a comparison for all recommended information, if available, so FDA can assess the market for the PMTA product to better estimate the potential impact on public health.

iv. Labeling comprehension and actual use

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

v. Human factors

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

Human factors considerations and analyses should include studies, such as actual use studies, labeling com-

prehension studies, focus group studies, and surveys, that identify:

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

vi. Abuse liability

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

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

vii. Biomarkers of harm and biomarkers of exposure

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

viii. Health outcomes

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

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

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

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

A. Components, Ingredients, and Additives

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

B. Flavors

Because of the potential impact of flavors on product toxicity and appeal to youth and young adults, scientific reviews of flavors (e.g., toxicological analyses of flavor additives, chemistry analyses, clinical studies, literature reviews), should be included in a PMTA for an e-liquid. There may be significant differences in the health risk of flavors depending on their route of exposure as well as the formation of additional chemicals due to heating or burning of the flavors. Substances that are generally recognized as safe (GRAS) under sections

201(s) and 409 of the FD&C Act (21 U.S.C. 348) are defined as substances that are intentionally added to food and intended for oral ingestion. E-liquid is not food or intended for oral ingestion; therefore, the fact that some substances have been designated GRAS for food does not mean that they are safe for inhalation.

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

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

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

A. E-cigarette Design Factors to Consider

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

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

- E-cigarette features;
- Material and/or ingredient functions;
- Capabilities to monitor product performance (e.g., temperature sensing, voltage sensing, battery life detection);
- Instructions and method of operation;
- Materials of all e-cigarette components;
- Operating ranges (e.g., lower and upper wattage, voltage limits that users can adjust);
- Power supply, such as batteries (including whether it is rechargeable or replaceable);
- Charging source and the safety of using different charging sources; and
- Heating source (e.g., heating coil, chemical reaction).

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

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

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

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

1. Batteries

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

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

If the e-cigarette includes the battery:

- Amperage rating (i.e., the maximum suggested amperage draw and duration for the battery and the maximum amperage draw and duration of the e-cigarette);
- Battery mAh rating (i.e., the milliamps per hour of the battery and its correlation to battery life);
- Battery type (including battery chemistry);
- Voltage output (at full charge and at low charge); and
- Testing certificates for any voluntary battery standards for the power supply. Examples of voluntary battery standards for non-rechargeable batteries include: (1) The series of standards from the International Electrotechnical Commission (IEC) (60086-1 12th Edition, 60086-2 13th Edition, 60086-4 4th Edition, and 60086-5 4th Edition,[45] and IEC 62133-1 and 2 Edition 1.0 2017-02[46]) (2) Underwriters Laboratories

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

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

Inc. (UL) Standard 2054 2nd Edition;[47] (3) UL Standard 1642 5th Edition.[48] Examples of voluntary battery standards for rechargeable batteries include: (1) IEC 62133 Edition 2.0 2012-12;[49] (2) UL 2054 2nd Edition;[50] or (3) UL's Standard 1642 5th Edition.[51] An additional example of a voluntary standard is the joint Canada-United States National Standards ANSI/CAN/UL 8139—Electrical Systems of Electronic Systems and Vaping Devices—1st Edition 2018.

- If the e-cigarette uses a consumer-replaceable battery:
  - Battery specifications required by the e-cigarette; and
  - Voltage range and wattage range, if the e-cigarette alters or regulates the voltage.
- If the e-cigarette has alarm capabilities, indicate whether the product includes:

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

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

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

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

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

- Reverse polarity protection (i.e., does it protect the battery from being placed in the e-cigarette backwards);
- Under-voltage lock-out protection (i.e., does the power lock out in the event of the voltage dropping below the operational value);
- Over-voltage lock out protection (i.e., does the power lock out when the voltage in the circuit is raised above the design limit);
- Low resistance protection (i.e., does the e-cigarette lock out if the wire resistance is too low and, if so, what is the low resistance limit);
- High controller temperature protection (i.e., does the e-cigarette detect the temperature of the controller and shut off when the temperature is too high); and
- Unintended activation protection such as a maximum activation time limit, on/off capability, and locking capabilities.

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

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

- Atomizer:
  - Draw resistance (and operable range, if adjustable);

- E-liquid capacity; and
- Aerosol particle size across operable range.

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

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 address. For example, to bridge to a completed study, if the PMTA product has been studied only in a certain demographic, the applicant would need to provide a scientific rationale for why the results of the study can be generalized to other demographic groups that are representative of the U.S. population as whole. This could include a discussion of the factors that would be expected to influence study findings and whether they vary significantly across the U.S. population. The applicant should also clearly describe any reasons why study findings may not generalize to the broader U.S. population. Similarly, to use existing literature, if a product with similar characteristics (e.g., materials, ingredients, design, composition, heating source, other features) has been studied in a special population, this information may be used to support whether and how permitting the marketing of the product may be APPH by providing data relevant to the special population,

which we would not otherwise have absent a new clinical trial. In these cases, you should explain why the study is relevant to use for the PMTA product (e.g., the similarities between the product, product use, or product market).

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

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

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

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

B. Literature Reviews

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

- Describe the methodologies used in the literature review in detail and include the databases searched and the date of searches, search terms, reasons for inclusion/exclusion of documents, and the strategy for study quality assessment (systematic review is preferred);
- Identify the specific question(s) and issue(s) addressed by the literature review;
- Clearly identify the documents or manuscripts that address a specific question or issue;
- Identify the funding source for included studies;
- Identify study design and methods;
- Identify characterization of study participants;
- Identify the year and geographical location of studies;
- Identify strengths and limitations of studies (e.g., study design elements including randomization details, potential biases, validity, variability, statistical models, and heterogeneity);
- Provide an interpretation of study findings;

- Provide adequate justification for bridging data from the product studied to your new tobacco product;
- Provide a summary of the evidence from the literature review;
- Document how the literature review findings support or do not support that permitting the marketing of your new tobacco product would be APPH;
- Include a bibliography and an appendix with the referenced publications; and
- Include comparative assessments of the health risks associated with use of your new tobacco product compared to the risks associated with quitting tobacco product use, using other tobacco products, and never using tobacco products.

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

- Is the tobacco product in the literature comparable in terms of technology to the new tobacco product?
- Are there data (e.g., range of possible use, emissions under conditions of use, biomarkers of exposure) that can be used to adequately demonstrate comparability?

- Was the product in the literature used in a population that adequately represents the target population for the new tobacco product?
- Is the information in the literature sufficient to determine how the tobacco product was used?

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

C. Analysis of Published Literature and Public Datasets

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

If you cannot obtain the primary line or study data[52] from the publicly available literature, we recommend that, to the extent possible, you obtain other information, such as the protocol, records of trial conduct and procedures, subject data listings for key variables, and documentation of the statistical analysis. If adverse or unintended experiences are being monitored, we recommend that, to the extent possible, you capture and document complete information for all serious adverse

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

experiences (including deaths) and subject withdrawal related to adverse experiences, toxicity, or both.

D. Master Files

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

right of reference to a TPMF, CTP can access and review the confidential information in the TPMF as part of the PMTA, but the applicant relying on this information to support its submission does not see or have access to the proprietary information. This information will help applicants of deemed products prepare premarket and other regulatory submissions because they can reference information in TPMFs rather than develop the information on their own.

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

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

E. Bridging

Ideally, a PMTA will include studies conducted using the new tobacco product; however, bridging of data from one product to another may be feasible for a sub-

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

set of products or for certain types of studies. For example, "X-flavor" e-liquids with nicotine concentrations ranging from 1 milligram per milliliter (mg/mL) to 24 mg/mL may not require unique studies for each nicotine concentration of the "X-flavor" product if data from a subset of nicotine concentrations (e.g., low, middle, high) of "X-flavor" products may be bridged to other concentrations of "X-flavor" products. If you choose to bridge data from a studied tobacco product to your new tobacco product, you should provide the rationale and justification to support bridging (e.g., why the data used are applicable to your new tobacco product).

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

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

XI. POSTMARKET REQUIREMENTS

A marketing order under section 910(c)(1)(A)(i) of the FD&C Act may require that the sale and distribution of

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

XII. REQUESTING MEETINGS WITH FDA

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

ucts[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.

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

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 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 infor-

mation 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.

MEETING

Deemed Tobacco Product Applications—A Public Meeting

OCTOBER 28 - 29, 2019

Scheduled

Date:

October 28 - 29, 2019

Time:

8:30 AM - 4:30 PM ET

Location:

White Oak Campus: The Great Room
Conference Center
10903 New Hampshire Ave
Building 31, Room 1503
Silver Spring, MD 20993
United States

Organized By:

Center for Tobacco Products (/about-fda/fda-organization/center-tobacco-products)

On this page:

Meeting Objective

This meeting was intended to provide information on the agency's process for tobacco product application review with a particular focus on deemed tobacco prod-

ucts (e.g., cigars, waterpipe, and Electronic nicotine Delivery Systems (ENDS) including e-liquids and electronic cigarettes) including product review policies, procedures, and general scientific principles.

Agenda and Presentations

Transcripts

- Day 1 (/media/133498/download)
- Day 2 (/media/133499/download)

October 28, 2019

8:30 am (video (https://collaboration.fda.gov/phxcq4raw33u/?OWASP_CSRFTOKEN=7a8d148ac776ca8f3aec38aff7dee12ea4988c1caed05010cded06ab7496714f))

Welcome Address—Matthew Holman, Ph.D., CTP Office of Science

Opening Remarks—David Graham, M.P.A., NJOY

Overview of the Meeting—Anne Radway, M.S., CTP Office of Science

8:45 am—Communications & IT Resources

- CTP Website: What's New (/media/133449/download)—Stephanie Redus, M.S., CTP Office of Science (video (https://collaboration.fda.gov/phxcq4raw33u/?OWASP_CSRFTOKEN=7a8d148ac776ca8f3aec38aff7dee12ea4988c1caed05010cded06ab7496714f) begins at 11:15)
- Overview of Electronic Submissions: Preparation and Tools (/media/133500/download)—Crystal Allard, CTP Office of Science (video (https://collaboration.fda.gov/phxcq4raw33u/?OWASP CSRFTOKEN=7a8d148ac776ca8f3aec38aff7dee1

2ea4988c1caed05010cded06ab7496714f) begins at 36:52)

10:00 am—Panel Discussion on Communications and IT Resources (video (https://collaboration.fda.gov/phxcq4raw33u/? OWASP CSRFTOKEN=7a8d148ac776ca8f3aec38aff7dee12ea4988c1caed05010cded06ab7496714f) begins at 1:09:49)

Moderator: Anne Radway, M.S., CTP Office of Science

Panelists: Leanne Campbell, Ph.D., RAI Services, Co.; Anuschka Merson, M.S., ITG Brands, LLC; Crystal Allard, CTP Office of Science; Cristi Stark, M.S., CTP Office of Science

11:00 am—Premarket Tobacco Product Applications (PMTAs)—Review Process and Resources

- PMTA Review Process (/media/133443/download)—Emily Busta, M.S., CTP Office of Science (video (https://collaboration.fda.gov/ptf21jryjxyk/?OWASPCSRFTOKEN=7a8d148ac776ca8f3aec38aff7dee12ea4988c1caed05010cded06ab7496714f))
- Tobacco Product Master Files (TPMF) (/media/133501/download)—Sarah Amyot, M.P.H., CTP Office of Science (video (https://collaboration.fda.gov/ptf21jryjxyk/? OWASPCSRFTOKEN=7a8d148ac776ca8f3aec38aff7dee12ea4988c1caed05010cded06ab7496714f) begins at 37:14)

1:15 pm—Application-Related Inspections (/media/133442/download) (video (https://collaboration.fda.gov/pfef4ja21sv0/?OWASP CSRFTOKEN=7a8d148ac776ca8f3aec38aff7dee12ea4988c1caed05010cded06ab7496714f))

Chad Burger, M.S., CTP Office of Compliance and Enforcement

1:45 pm—Panel Discussion on PMTA Review Process (video (https://collaboration.fda.gov/pfef4ja21sv0/?OWASPCSRFTOKEN=7a8d148ac776ca8f3aec38aff7dee12ea4988c1caed05010cded06ab7496714f) begins at 13:25)

Moderator: Anne Radway, M.S., CTP Office of Science

Panelists: Kevin Burd, North America Nicotine; Michael Ogden, RAI Services, Co.; Cristi Stark, M.S., CTP Office of Science; Lillian Ortega, M.P.H., CTP Office of Compliance and Enforcement

2:30 pm—Premarket Tobacco Product Applications (PMTAs) Scientific Content

- PMTA Content Overview (/media/133445/download)—Ouida Holmes, M.P.H. (video (https://collaboration.fda.gov/pqa9tz9gez8k/?OWASPCSRFTOKEN=7a8d148ac776ca8f3aec38aff7dee12ea4988c1caed05010cded06ab7496714f)) &

  Priscilla Callahan-Lyon, M.D., CTP Office of Science (video (https://collaboration.fda.gov/pqa9tz9gez8k/?OWASP CSRFTOKEN=7a8d148ac776ca8f3aec38aff7dee12ea4988c1caed05010cded06ab7496714f) begins at 25:10)

- PMTA Post-Marketing Requirements (/media/133502/download)—Christine Saba, M.P.A., M.P.H., CTP Office of Science (video (https://collaboration.fda.gov/pqa9tz9gez8k/?OWASPCSRFTOKEN=7a8d148ac776ca8f3aec38aff7dee12ea4988c1caed05010cded06ab7496714f) begins at 35:29)

3:45 pm—Closing Remarks

Anne Radway, M.S., CTP Office of Science

October 29, 2019

8:30 am—Welcome (video (https://collaboration.fda.gov/pvoqa4eubefc/))

Todd Cecil, Ph.D., CTP Office of Science

8:45 am—PMTAs Scientific Content (Continued) (video (https://collaboration.fda.gov/pvoqa4eubefc/) begins at 5:35)

Lessons Learned from PMTA Reviews (/media/133444/download)—Hans Rosenfeldt, Ph.D., CTP Office of Science

9:30 am—Panel Discussion on PMTA Scientific Content (video (https://collaboration.fda.gov/pvoqa4eubefc/) begins at 36:22)

Moderator: Todd Cecil, Ph.D., CTP Office of Science

Panelists: Jason Flora, Ph.D., Altria; Elaine Round, Ph.D., RAI Services, Co.; Steve Seiferheld, M.S., Venebio; Iilun Murphy, M.D., CTP Office of Science; Emily Talbert, M.P.H., CTP Office of Health Communication and Education; Hans Rosenfeldt, Ph.D., CTP Office of Science

10:45 pm—Substantial Equivalence (SE) Scientific Content and Exemption Requests

- SE Program Overview (/media/133441/download)—Lauren DeBerry, M.P.H., CTP Office of Science (video (https://collaboration.fda.gov/pjdbn2np4rkl/?OWASP CSRFTOKEN=5e9b84f56d878dc93eae4b1184c6a148405a270ddb563cff072ebfebcf035eff))
- Grandfathered Tobacco Product Reviews (/media/133446/download)—Bryan Hills, J.D., CTP

Office of Compliance and Enforcement (video (https://collaboration.fda.gov/pjdbn2np4rkl/?_OWASP_CSRFTOKEN=5e9b84f56d878dc93eae4b1184c6a148405a270ddb563cff072ebfebcf035eff) begins at 25:10)

12:30 pm—Substantial Equivalence (SE) Scientific Content and Exemption Requests (Continued)

- SE Scientific Content, Including HPHC Testing & Reporting (/media/133448/download)—Salome Bhagan, M.S., Ph.D, (video (https://collaboration.fda.gov/p0odwd7xa3ue/?_OWASP_CSRFTOKEN=5e9b84f56d878dc93eae4b1184c6a148405a270ddb563cff072ebfebcf035eff)) & Melis Coraggio, M.S., CTP Office of Science (video (https://collaboration.fda.gov/p0odwd7xa3ue/?_OWASP_CSRFTOKEN=5e9b84f56d878dc93eae4b1184c6a148405a270ddb563cff072ebfebcf035eff) begins at 11:29)
- Request for Exemption from SE Marketing Pathway (/media/133447/download)—Jennifer Schmitz, M.P.H. (video (https://collaboration.fda.gov/p0odwd7xa3ue/?_OWASP_CSRFTOKEN=5e9b84f56d878dc93eae4b1184c6a148405a270ddb563cff072ebfebcf035eff) begins at 23:03) & Matt Walters, M.P.H., Ph.D., CTP Office of Science (video (https://collaboration.fda.gov/p0odwd7xa3ue/?_OWASP_CSRFTOKEN=5e9b84f56d878dc93eae4b1184c6a148405a270ddb563cff072ebfebcf035eff) begins at 36:33)

1:30 pm—Panel Discussion on SE Scientific Content (video (https://collaboration.fda.gov/p0odwd7xa3ue/?_OWASP_CSRFTOKEN=5e9b84f56d878dc93eae4b1184c6a148405a270ddb563cff072ebfebcf035eff) begins at 51:00)

Moderator: Todd Cecil, Ph.D., CTP Office of Science

Panelist: Christopher Junker, Ph.D., RAI Services, Co.; Gerald Long, M.S., ITG Brands LLC; Colleen Rogers, Ph.D., CTP Office of Science; Laurie Sternberg, J.D., CTP Office of Compliance and Enforcement; Matthew Walters, Ph.D., CTP Office of Science; Rosanna Beltre, M.P.H., CTP Office of Science

2:15 pm—Q&A Session (video (https://collaboration.fda.gov/pwzvunr3pcmc/? OWASP CSRFTOKEN=5e9b84f56d878dc93eae4b1184c6a148405a270ddb563cff072ebfebcf035eff))

Moderator: Todd Cecil, Ph.D., CTP Office of Science

Panelists: Glen Jones, PhD., CTP Office of Science; Iilun Murphy, M.D., CTP Office of Science; Cristi Stark, M.S., CTP Office of Science; Crystal Allard, CTP Office of Science; Swati Kabaria, Pharm.D., J.D., CTP Office of Compliance and Enforcement

3:15 pm—Closing Remarks

Brittani Cushman, J.D., Turning Point (video (https://collaboration.fda.gov/pwzvunr3pcmc/? OWASP CSRFTOKEN=5e9b84f56d878dc93eae4b1184c6a148405a270ddb563cff072ebfebcf035eff) begins at 1:41:00)

Julia McGinn-Rodriguez, M.S.P.P.M., CTP Office of Science (video (https://collaboration.fda.gov/pwzvunr3pcmc/? OWASP CSRFTOKEN=5e9b84f56d878dc93eae4b1184c6a148405a270ddb563cff072ebfebcf035eff) begins at 1:50:00)

Panelists

FDA invited panelists to address information pertaining to the following topics related to tobacco product marketing application review:

- **Application development and submission, including pre-submission meetings and use of Tobacco Product Master Files.**
- **Scientific content and evaluation of PMTAs**
- **Scientific content and evaluation of Exemption Requests and SE Reports**
- **Preparation of electronic submissions including FDA resources and tools available to support application submission**

Questions about your submissions?

Contact your Regulatory Health Project Manager

Additional Resources

- **Market and Distribute a Tobacco Product (/tobacco-products/products-guidance-regulations/market-and-distribute-tobacco-product)**
- **September 20, 2019—FDA issues proposed rule for premarket tobacco product applications as part of commitment to continuing strong oversight of e-cigarettes and other tobacco products (/news events/press-announcements/fda-issues-proposed-rule-prernarket-tobacco-product-applications-part- commitment-continuing-strong)**

Event Materials

Title	File Type/Size
Allard-ElectronicSubmissions.pdf (/media/133500/download)	pdf (5.38MB)
Amyot-TPMFS.pdf (/media/135019/download)	pdf (853.74 KB)

CTP-Website-Redus.pdf (/media/133449/download)	pdf (10.54 MB)
DeemedTobaccoProductApp-1028.pdf (/media/133498/download)	pdf (709.66 KB)
DeemedTobaccoProductApp-1029.pdf (/media/133499/download)	pdf (1.18 MB)
Saba-PMTA-NPRM-Market RptRegs.pdf (/media133502/download)	pdf (305.42 KB)
SE-2019Update-DeBerry.pdf (/media/133441/download)	pdf (654.40 KB)
Session2-AppRelatedInsp-Burger.pdf (/media/133442download)	pdf (326.88 KB)
Session2-PMTA-ReviewProc-Busta.pdf (/media/133443/download)	pdf (664.74 KB)
Session3-PMTA-Content-Holmes_0.pdf (/media/133445/download)	pdf (1.99 MB)
Session3-PMTA-Lesson-Rosenfeldt.pdf (/media/133444/download)	pdf (698.99 KB)
Session4-ExemptRequests-Schmitz.pdf (/media/133447/download	pdf (385.27 KB)
Session4-GF-ProductReview-Hills.pdf (/media/133446download)	pdf (382.38 KB)

Session4-SE-ScienceCont-Bhagan.pdf (/media/133448download)	pdf (1.09 MB)

UNITED STATES FOOD AND DRUG ADMINISTRATION

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DEEMED TOBACCO PRODUCT APPLICATIONS: A PUBLIC MEETING

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MONDAY
OCTOBER 28, 2019

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The public meeting met at the FDA White Oak Campus, Great Room, Room 1503, 10903 New Hampshire Avenue, Silver Spring, Maryland, at 8:30 a.m., Anne Radway, Moderator, presiding.

THIS TRANSCRIPT HAS NOT BEEN EDITED OR CORRECTED BUT APPEARS AS RECEIVED FROM THE COMMERCIAL TRANSCRIBING SERVICE.

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PRESENT:

ANNE RADWAY, MS, Moderator; Office of Science, CTP

CRYSTAL ALLARD, Office of Science, CTP

SARAH AMYOT, MPH, Office of Science, CTP

KEVIN BURD, North America Nicotine

CHAD BURGER, MS, Office of Compliance and Enforcement, CTP

EMILY BUSTA, MS, Office of Science, CTP

PRISCILLA CALLAHAN-LYON, MD, Office of Science, CTP

LEANNE CAMPBELL, PhD, RAI Services, Co.

DAVID GRAHAM, MPA, NJOY

MATTHEW HOLMAN, PhD, Office of Science, CTP

OUIDA HOLMES, MPH, Office of Science, CTP

ANUSCHKA MERSON, MS, ITG Brands, LLC

MICHAEL OGDEN, RAI Services, Co.

LILLIAN ORTEGA, MPH, Office of Compliance and Enforcement, CTP

STEPHANIE REDUS, MS, Office of Science, CTP

CHRISTINE SABA, MPA, MPH, Office of Science, CTP

CRISTI STARK, MS, Office of Science, CTP

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[63]

* * * product evidence that over their lifetime, youth aren't taking up or switching?

DR. MURPHY: I think people are looking at me to answer the question. So what I would say is that we know that youth use of electronic nicotine device systems is very problematic and concerning, right.

So that the, I think what's important is that applicants address how they are going to restrict youth access and youth use. Whether, you know, are there marketing—what are their marketing plans. What are the age verification plans.

I mean these are some of the kinds of things that you might want to take time to describe in your application to ensure to FDA that your product will not kind of exacerbate the current situation in methods to curb and improve limiting youth access.

MS. TALBERT: I would just add that tobacco product advertising can blend across categories. So in the advertising that you're * * *

* * * * *

[114]

* * * contact information for the regulatory health project manager assigned to their application.

The RHPM will be your main point of contact for any issues related to your application. They are the people that you should contact should you have any questions throughout the process. If the application is accepted by CTP, it moves to the next phase, filing review. As outlined in Section 910(b)(1), the purpose of the filing review is to determine if the application contains information to initiate substantive review.

During filing, CTP will conduct a more in-depth, multi-disciplinary review of the data as submitted, to determine if all statutory and regulatory requirements have been provided, as outlined in Section 910(b), Parts A through G, which are discussed on this and the following slide. Regulatory and scientific reviewers will determine if the application includes full reports of all information published or known to, or which should reasonably be known to the [115] applicant regarding the health risks of tobacco products, and whether the tobacco product presents less risk than other tobacco products.

This information should include, for example, comprehensive study results, case reports, complete data sets and analyses, as well as the analytic code used to analyze the results. Additional detail on the scientific contents to be included in a PMTA will also be discussed in a subsequent presentation. Applications should include a full statement of the components, ingredients, additives and properties and of the principle or principles of operation of the tobacco product.

For example, here a toxicology reviewer may look at the ingredients of the product to see if there is enough information to permit substantive review for their respective discipline. A full description of the methods used and the facilities and controls used for the manufacturer, processing and when relevant packaging and installation of the tobacco product [116] should also be included.

For example, an application should contain the addresses of the applicant's manufacturing facilities, process flows, descriptions of steps in the manufacturing process and others. PMTAs should also include an identifying reference to any tobacco product standard under Section 907 that applies, samples of the tobacco product and components thereof as reasonably may be required.

Samples allow for FDA to independently test the product that is the subject of the application. In general, a PMTA is considered incomplete until FDA confirms receipt of at least one sample of the proposed tobacco product. Generally, the number of samples CTP requires for testing will be identified in a separate sample request letter. If samples are not received, this may result in refusal to file.

Specimens of the proposed labeling to be used for the tobacco product should be included in the submission, as well as any other [117] information relevant to the subject matter of the application. Other information may be identified during the pre-submission meeting if held, that is specific to the tobacco product.

At the end of the filing phase, similar to the acceptance phase, CTP will issue one of two types of correspondence. If the submitted information is inadequate to continue with substantive review, the applicant will receive a refusal to file letter. In this letter, FDA will include the reasons for the refusal. If refused, the applicant has the option to submit a new application once they are able to meet the filing requirements for a PMTA.

If the application meets the filing requirements for a PMTA seeking a marketing order, CTP will issue a letter to notify the applicant that the application has been filed. If filed by CTP, the PMTA moves into Phase 3, which deals with substantive review and results in an action by CTP.

The substantive review phase is a [118] multidisciplinary approach to review the data submitted by the applicant and determine if such data is sufficient to demonstrate that authorizing the marketing of the new product would be appropriate for the protection of public health.

During the substantive review phase, CTP's Office of Science, in conjunction with the Office of Compliance and Enforcement, may conduct inspections of clinical or manufacturing facilities. You will hear more about inspections in a later presentation.

Additionally, CTP may conduct testing of the new product. At this phase, CTP should have received the samples requested in the sample request letter. An application may be referred to the Tobacco Products Scientific Advisory Committee, also known as TPSAC. If the applicant would like CTP to consider referral to TPSAC, they should include this request in the cover letter of their initial submission. Along this request, it would be helpful for the applicant to [119] provide a reason as to why TPSAC referral is being requested.

CTP has the discretion to refer a product under consideration to TPSAC, and will determine this during the substantive review phase.

CTP generally expects that when an applicant submits a PMTA, the submission will include all information required by Section 910(b)(1) of the FD&C Act. However, CTP recognizes that additional information may be needed to complete the review of a PMTA. If CTP determines additional information is needed to render a decision, the applicant will be notified by letter and given a period of time by which they will need to respond.

During this time, review of the application is suspended and the clock is stopped. If CTP receives an amendment to a PMTA that contains a substantial amount of new data that has not been previously submitted or reviewed by CTP, such as new data from a * * *

* * * * *

Enforcement Priorities for Electronic Nicotine Delivery Systems (ENDS) and Other Deemed Products on the Market Without Premarket Authorization (Revised)*

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 number FDA-2019-D-0661.

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

Additional copies are available online at https://www.fda.gov/tobacco-products/products-guidance-regulations/rules-regulations-and-guidance. 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.

* This is a revision to the first edition of this guidance, which issued in January 2020.

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

April 2020

Table of Contents

Enforcement Priorities for Electronic Nicotine Delivery Systems (ENDS) and Other Deemed Products on the Market Without Premarket Authorization (Revised)

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 document describes how we intend to prioritize our enforcement resources with regard to the marketing of certain deemed tobacco products that do not have premarket authorization.[2]

For ENDS products marketed without FDA authorization, FDA intends to prioritize enforcement against:

- Any flavored, cartridge-based ENDS product (other than a tobacco- or menthol-flavored ENDS product);

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[1] This guidance was prepared by the Office of Compliance and Enforcement, Office of Health Communication and Education, Office of Regulations, and Office of Science in the Center for Tobacco Products at FDA.

[2] As with FDA's prior compliance policies on deemed new tobacco products that do not have premarket authorization, this guidance document does not apply to any deemed product that was not on the market on August 8, 2016.

- All other ENDS products for which the manufacturer has failed to take (or is failing to take) adequate measures to prevent minors' access; and
- Any ENDS product that is targeted to minors or whose marketing is likely to promote use of ENDS by minors.[3]

Further, FDA intends to prioritize enforcement of any ENDS product that is offered for sale after September 9, 2020, and for which the manufacturer has not submitted a premarket application (or after a negative action by FDA on a timely submitted application).

This guidance does not in any way alter the fact that it is illegal to market any new tobacco product without premarket authorization. FDA is continuously evaluating new information and adjusting its enforcement priorities in light of the best available data, and it will continue to do so with respect to these products. FDA will take appropriate action regarding tobacco products that are marketed without premarket authorization, including as warranted based on changed circumstances, new information, or to better address minors' use of those products.

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[3] For purposes of this Final Guidance, FDA's use of the term "minor" refers to individuals under the age of 21. This is consistent with the Further Consolidated Appropriations Act, 2020 (H.R. 1865), signed into law on December 20, 2019, which included a provision amending section 906(d) of the Federal Food, Drug, and Cosmetic Act to increase the federal minimum age to purchase tobacco products from 18 to 21, and adding a provision that it is unlawful for any retailer to sell a tobacco product to any person younger than 21 years of age. In addition, FDA is working to update our regulations within 180 days, consistent with the timeline set forth in the law.

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

A. Statutory and Regulatory History

The Family Smoking Prevention and Tobacco Control Act (Tobacco Control Act) (Public Law 111-31) granted FDA the authority to regulate the manufacture, marketing, and distribution of cigarettes, cigarette tobacco, roll-your-own (RYO) tobacco, and smokeless tobacco products to protect the public health and to reduce tobacco use by minors. The Tobacco Control Act also gave FDA the authority to issue regulations deeming other products that meet the statutory definition of a tobacco product[4] to be subject to chapter IX of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 387 through 387u) (section 901(b) of the FD&C Act).

In accordance with that authority, on May 10, 2016, FDA issued a final rule deeming all products that meet the statutory definition of a tobacco product, except accessories of deemed tobacco products, to be subject to FDA's tobacco product authority. This included electronic nicotine delivery systems (ENDS), cigars, waterpipe (hookah) tobacco, pipe tobacco, nicotine gels, and

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[4] 21 U.S.C 321(rr) (section 201(rr) of the FD&C Act).

dissolvables that were not already subject to the FD&C Act (81 FR 28974 at 28976 (May 10, 2016)).

The requirements in Chapter IX of the FD&C Act now apply to deemed products. Particularly relevant to this guidance is section 910, which imposes certain premarket-review requirements for "new tobacco products" —*i.e.*, those that were not commercially marketed in the United States as of February 15, 2007. Accordingly, after the rule's effective date, deemed new tobacco products were required to obtain premarket authorization under Section 910. Deemed new tobacco products that remain on the market without marketing authorization are marketed unlawfully in contravention of the Tobacco Control Act. Through the premarket review process, FDA conducts a science-based evaluation to determine whether a new tobacco product meets the applicable statutory standard for marketing authorization—for example, whether the product is appropriate for the protection of public health with respect to the risks and benefits to the population as a whole, including users and nonusers, and taking into account, among other things, the likelihood that those who do not use tobacco products will start using them.

The preamble to the May 10, 2016, final deeming rule explained that FDA intended to defer enforcement for failure to have premarket authorization during two compliance periods related to premarket review: one for submission and FDA receipt of applications and one for obtaining premarket authorization. The first compliance period depended on the type of application. The compliance date was 12 months from the effective date of the rule for substantial equivalence exemption requests (EX REQs), 18 months for substantial equivalence reports (SE Reports), and 24 months for pre-

market tobacco applications (PMTAs). In addition, the preamble explained that under the second compliance period:

> Unless FDA has issued an order denying or refusing to accept the submission, products for which timely premarket submissions have been submitted will be subject to a continued compliance period for 12 months after the initial compliance period described previously. For such products, FDA does not intend to initiate enforcement for failure to have premarket authorization during this continued compliance period.[5]

The preamble further explained that this compliance policy did not apply to any new tobacco product that was not on the market on August 8, 2016. Significantly, this policy did not confer lawful marketing status on new tobacco products being marketed without the necessary premarket authorization.

In May 2017, FDA published a guidance document, *Three-Month Extension of Certain Tobacco Product Compliance Deadlines Related to the Final Deeming Rule*, under which the Agency, as a matter of enforcement discretion, stated its intention to defer enforcement for an additional three months for all future compliance dates for requirements under the final deeming rule.

In July 2017, FDA announced a new comprehensive plan for tobacco and nicotine regulation that would serve as a multi-year roadmap in an effort to significantly reduce tobacco-related disease and death. Prior to this announcement, nationally representative data

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[5] 81 FR at 29011.

suggested that youth use of e-cigarettes had declined beginning in 2016.[6] The comprehensive plan was announced in part to afford the Agency time to explore clear and meaningful measures to make combustible tobacco products less toxic, less appealing, and less addictive. One aspect of the plan involved striking a balance between regulation and encouraging development of innovative tobacco products that may be less harmful than cigarettes. The Agency announced that it planned to issue an updated compliance policy further deferring some enforcement timelines described in the final deeming rule.

In accordance with this comprehensive plan, in August 2017, FDA announced an extension of the period during which it did not intend to initiate enforcement action for premarket review requirements under the final deeming rule ("August 2017 Compliance Policy") for deemed tobacco products that were on the market on August 8, 2016. This revised policy stated that, for these products, FDA did not intend to initiate enforcement regarding submitting EX REQs, SE Reports, and PMTAs for newly regulated combusted tobacco products (such as most cigars) until August 8, 2021, and FDA did not intend to initiate enforcement regarding EX REQs, SE Reports, and PMTAs for newly regulated noncombusted tobacco products (such as most ENDS products) until August 8, 2022. In addition, FDA revised the compliance policy relating to the period after FDA receipt of EX REQs, SE Reports, and PMTAs for deemed to-

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[6] Jamal, A., A. Gentzke, S.S. Hu, et al., "Tobacco Use Among Middle and High School Students—United States, 2011-2016," Morbidity and Mortality Weekly Report, 66:597–603, 2017, available at: https://www.cdc.gov/mmwr/volumes/66/wr/mm6623a1.htm.

bacco products that were on the market on August 8, 2016. FDA stated that, under this policy, it intended to continue deferring enforcement until the Agency rendered a decision on an application (*i.e.*, issuance of: a Marketing Order; a No Marketing Order; a Refuse to File; or a Refuse to Accept) or the application was withdrawn.

In March 2018, the August 2017 Compliance Policy was challenged in the U.S. District Court for the District of Maryland, and on May 15, 2019, the court issued an order that vacated the guidance.[7] On July 12, 2019, the court issued a further order directing FDA to require that premarket authorization applications for all new—*i.e.*, not "grandfathered"[8]—deemed tobacco products be submitted to the Agency within 10 months, by May 12, 2020, and providing for a one-year period during which products with timely filed applications might remain on the market pending FDA review.[9] The court subsequently clarified that its order did not restrict FDA's

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[7] *American Academy of Pediatrics, et al. v. Food and Drug Administration, et al.*, 379 F. Supp. 3d 461, 496 (D. Md. 2019).

[8] A "grandfathered" product is one that was on the market as of February 15, 2007. Guidance, Establishing That a Tobacco Product Was Commercially Marketed in the United States as of February 15, 2007, dated September 2014, available at: https://www.fda.gov/media/123544/download.

[9] *American Academy of Pediatrics, et al. v. Food and Drug Administration, et al.*, No. 8:18-cv-883 (PWG), 2019 WL 3067492, at *7 (D. Md. July 12, 2019) (Dkt. No. 127). The court has granted intervention to vapor industry trade associations for purposes of appealing the court's decision and remedies order. *See American Academy of Pediatrics, et al. v. Food and Drug Administration, et al.*, No. 8:18-cv-883 (PWG), Dkt. No. 154 (Oct. 2, 2019). An appeal is pending. *See American Academy of Pediatrics v. Cigar Ass'n of America*, Nos. 19-2130, -2132, -2198, -2242 (4th Cir.).

authority to enforce the premarket review provisions against deemed products, or categories of deemed products, prior to the submission date or during the one-year review period.[10] On April 22, 2020, the court granted a motion for a 120-day extension (until September 9, 2020) in light of the global outbreak of respiratory illness caused by a new coronavirus.[11] As required by the court's order, deemed new tobacco products on the market as of August 8, 2016, for which premarket authorization applications are not filed by September 9, 2020, are subject to FDA enforcement actions, in the Agency's discretion.[12]

B. FDA Response to Evidence of Increasing Youth Use of ENDS Products

In late 2017, FDA started to see a marked increase in complaints about ENDS products. FDA initiated an investigation of these complaints, the majority of which pertained to minors' access to and use of these products. This new information indicated an alarming increase in the use of ENDS products by middle and high school students. In April 2018, FDA conducted a nationwide undercover enforcement effort that resulted in FDA issuing 56 warning letters to online retailers and 6 civil money penalty (CMP) complaints to retail establish-

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[10] *American Academy of Pediatrics, et al. v. Food and Drug Administration, et al.*, Case No. 8:18-cv-883 (PWG), (D. Md. Aug. 12, 2019), Dkt. No. 132.

[11] *American Academy of Pediatrics, et al. v. Food and Drug Administration, et al.,* Case No. 8:18-cv-883 (PWG), (D. Md. Apr. 22, 2020), Dkt. No. 182.

[12] *American Academy of Pediatrics, et al. v. Food and Drug Administration, et al.*, No. 8:18-cv-883 (PWG), 2019 WL 3067492, at *7 (D. Md. July 12, 2019) (Dkt. No. 127).

ments related to the illegal sales of certain ENDS products to minors. In addition, FDA sent an official request for information to manufacturers of certain ENDS products commonly used by minors requiring them to submit documents to facilitate the Agency's understanding of the reported high rates of youth use and the particular youth appeal of these products. FDA also took measures to address the sale of ENDS products to minors online by contacting eBay to raise concerns over several listings on its website. This resulted in listings for these ENDS products being removed from eBay.

In May 2018, FDA issued 17 warning letters to manufacturers, distributors, and retailers for selling e-liquids with labeling and/or advertising that resemble kid-friendly food products, such as juice boxes, candy, or cookies. The warning letters stated that failure to correct violations may result in FDA initiating further action such as seizure or injunctive relief. Of these warning letters, 13 were issued as part of a joint action with the Federal Trade Commission (FTC).

On September 12, 2018, FDA announced a series of enforcement and other regulatory actions related to the labeling and advertising of ENDS products, including that it had conducted nationwide, undercover investigations of brick-and-mortar and online stores over the summer of 2018 and issued more than 1,300 warning letters and CMP complaints to retailers who illegally sold ENDS products to minors. FDA also issued 12 warning letters to online retailers that were selling misleadingly labeled and/or advertised e-liquids resembling kid-friendly food products such as candy and cookies.

In addition, on September 12, 2018, FDA issued letters to five ENDS product manufacturers, requesting each

company to submit a plan describing how it would address minors' access to and use of its products.

In response to the September 12th letters to industry, manufacturers described safeguards that they could implement to help to restrict minors' access to ENDS products sold at brick and mortar retailers and online. Examples of potential safeguards included:

- Establishing or enhancing programs, such as mystery shopper programs, to monitor retailer compliance with age-verification and sales restrictions;
- Establishing and enforcing contractual penalties for contracted retailers that sell tobacco products to youth;
- Using age-verification technology to better restrict access to the manufacturer's website, such as through independent, third-party age- and identity-verification services that compare customer information against third-party data sources; and
- Limiting the quantity of ENDS products that a customer may purchase within a given period of time.

In conjunction with issuing the September 2018 letters, FDA announced in September 2018 that the Agency was considering whether, in light of current information, it would be appropriate to revisit the August 2017 Compliance Policy, which could result in withdrawing or revising the policy with respect to certain flavored products that may be contributing to the rise in youth use and having firms "remove some or all of [these] products . . . until they receive premarket au-

thorization and otherwise meet all of their obligations under the law."[13] Following the September 12th letters and announcement, FDA repeatedly publicly discussed[14] the fact that these compliance timelines were under reconsideration and solicited the view of stakeholders—including manufacturers, retail associations, and public interest organizations.[15]

Since the effective date of the Deeming Rule in August 2016, FDA has issued more than 10,000 warning letters and more than 1,400 CMP complaints to retailers for the sale of ENDS products to minors. Specifically, from April 2018 through August 2019, FDA issued over 6,000 warning letters and more than 1,000 CMP complaints to

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[13] FDA takes new steps to address epidemic of youth e-cigarette use, including a historic action against more than 1,300 retailers and 5 major manufacturers for their roles perpetuating youth access (Sept. 11, 2018), available at: https://www.fda.gov/news-events/press-announcements/fda-takes-new-steps-address-epidemic-youth-e-cigarette-use-including-historic-action-against-more.

[14] *See*, *e.g.,* Statement from FDA Commissioner Scott Gottlieb, M.D., on proposed new steps to protect youth by preventing access to flavored tobacco products and banning menthol in cigarettes, available at: https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm625884.htm; Scudder, L., "Vaping and E-Cigarettes in Kids: An Unprecedented Epidemic," Medscape, January 28, 2019, available at: https://www.medscape.com/viewarticle/908077?faf=1.

[15] *See, e.g.,* FDA Public Calendar—Meeting With FDA Officials, available at: https://www.fda.gov/newsevents/fda-meetings-conferences-and-workshops/public-calendar-meetings-fda-officials (noting meetings held on October 11, 16, 18, 29 and 30 of 2018; November 13, 2018; and December 19, 2018); February 6, 2019 Letters sent to JUUL Labs, Inc. and Altria Group Inc., requesting meetings to discuss concerns related youth addiction to tobacco products, available at: https://www.fda.gov/tobacco-products/rules-regulations-and-guidance/ctp-lettersindustry.

retailers for the sale of ENDS products to minors. Since May 2018, FDA has also issued over 40 warning letters to manufacturers, distributors, and retailers for selling e-liquids with false or misleading labeling and/or advertising that resemble kid-friendly products. In June 2019, the Agency issued joint FDA/FTC warning letters to four e-liquid manufacturers for violations related to online posts by social media influencers on the companies' behalf. In September 2019, FDA issued a warning letter to an ENDS manufacturer for marketing unauthorized modified risk tobacco products, including in outreach to youth.[16] FDA will continue to use all available tools to prevent youth use of all tobacco products, including ENDS products.

In 2018, FDA continued to receive information underscoring the problem of youth use of ENDS products. Current e-cigarette use had increased considerably among U.S. middle and high school students during 2017-2018, reversing a decline in e-cigarette use that had been observed in recent years and increasing overall tobacco product use in 2018. Specifically, among high school students, current e-cigarette use had increased by 78 percent in the past year (from 11.7 percent in 2017 to 20.8 percent in 2018, $p<0.001$), while among middle school students, current e-cigarette use had increased by 48 percent (from 3.3 percent in 2017 to 4.9 percent in 2018, $p = 0.001$).[17] Frequent use among

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[16] For more information, please see https://www fda.gov/news-events/press-announcements/fda-warns-juul-labsmarketing-unauthorized-modified-risk-tobacco-products-including-outreach-youth.

[17] Cullen, K.A., B.K. Ambrose, A.S. Gentzke, et al., "Notes from the Field: Increase in e-cigarette use and any tobacco product use among middle and high school students—United States, 2011-

high school students (defined as use on ≥ 20 of the past 30 days) also had increased, from 20.0 percent in 2017 to 27.7 percent in 2018 ($p = 0.008$).[18] Data from this study, as well as the concerns described above, prompted FDA to issue a draft guidance, "Modifications to Compliance Policy for Certain Deemed Tobacco Products" ("March 2019 Draft Guidance"), regarding the continued marketing of deemed tobacco products that have not obtained premarket authorization, and to call on industry to do more to keep their products out of the hands of minors.

In 2019, two of the largest surveys of tobacco use among youth found that e-cigarette use has hit the highest levels ever recorded. As detailed in Section IV below, data from both the National Youth Tobacco Survey (NYTS) and the Monitoring the Future (MTF) Study have documented a continued increase in youth use of ENDS products and further underscored the magnitude of the problem. These data, information conveyed to FDA in comments to the March 2019 Draft Guidance, and concern about health and safety issues connected to these products—*e.g.*, the harmful effects of nicotine on adolescent brain development, as well as battery explosions with ENDS products—continue to inform FDA's serious public health concerns regarding the sale of these products without premarket authorization. Repeated exposure to nicotine during adolescence induces long-lasting changes in brain regions involved in addiction, attention, learning, and memory.

2018," Morbidity and Mortality Weekly Report, 67(45);1276-1277, 2018.

[18] *Id.*

Furthermore, as of December 17, 2019, there have been approximately 2,506 reported cases of hospitalizations for lung injuries associated with use of vaping products ("hospitalized EVALI patients"), including 54 confirmed deaths.[19] Working closely with other federal and state agencies, FDA has not been able to determine the cause of this outbreak. It appears that most of the patients impacted by these illnesses reported using THC-containing products, with evidence suggesting that additive agents, specifically Vitamin E, may play a causative role. In many of the cases, individuals reported using multiple products, including some with nicotine. Many different substances and product sources are still under investigation.

Although this guidance does not address products that are not tobacco products, the outbreak of lung injuries associated with use of vaping products illustrates public health and safety concerns that may arise for products for which information related to product safety and health impact are lacking and affirms the importance of the premarket review process, as contemplated by the Tobacco Control Act, to scientifically evaluate products based on a public health standard.

Accordingly, FDA is issuing this Final Guidance to communicate its enforcement priorities with respect to ENDS products. FDA's decision to exercise its enforcement authorities with respect to particular products will be determined on a case-by-case basis, in-

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[19] *See* Centers for Disease Control and Prevention, "Outbreak of Lung Injury Associated with E-cigarette Use, or Vaping," available at https://www.cdc.gov/tobacco/basic information/e-cigarettes/severe-lung-disease.html#latest-outbreak-information.

formed by the enforcement priorities described in this Final Guidance and any other relevant factors.[20]

III. DEFINITIONS

For purposes of this guidance, FDA intends to use the following definitions:

Cartridge-based ENDS products are a type of ENDS product that consists of, includes, or involves a cartridge or pod that holds liquid that is to be aerosolized through product use. For purposes of this definition, a cartridge or pod is any small, enclosed unit (sealed or unsealed) designed to fit within or operate as part of an electronic nicotine delivery system.[21]

Electronic nicotine delivery systems (or ENDS) include devices, components, and/or parts that deliver aerosolized e-liquid when inhaled. For example, FDA considers vapes or vape pens, personal vaporizers, e-cigarettes, cigalikes, e-pens, e-hookahs, e-cigars, and e-pipes to be ENDS.

E-liquids are a type of ENDS product and generally refer to liquid nicotine and nicotine-containing e-liquids (*i.e.*, liquid nicotine combined with colorings, flavorings, and/or other ingredients). 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

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[20] *See Heckler v. Chaney*, 470 U.S. 821, 835 (1985) (providing that the FD&C Act's enforcement provisions commit broad discretion to the Secretary to decide how and when they should be exercised).

[21] An example of products that would not be captured by this definition include completely self-contained, disposable products.

product, may be components or parts and, therefore, subject to FDA's tobacco control authorities.

Label means a display of written, printed, or graphic matter upon the immediate container of any article. Section 201(k) of the FD&C Act.

Labeling means all labels and other written, printed, or graphic matter (1) upon any article or any of its containers or wrappers, or (2) accompanying such article. Section 201(m) of the FD&C Act.

New tobacco product means (1) any tobacco product (including those products in test markets) that was not commercially marketed in the United States as of February 15, 2007; or (2) any modification (including a change in design, any component, any part, or any constituent, including a smoke constituent, or in the content, delivery or form of nicotine, or any other additive or ingredient) of a tobacco product where the modified product was commercially marketed in the United States after February 15, 2007. Section 910(a) of the FD&C Act.

Tobacco product means any product made or derived from tobacco that is intended for human consumption, including any component, part, or accessory of a tobacco product (except for raw materials other than tobacco used in manufacturing a component, part, or accessory of a tobacco product). The term "tobacco product" does not mean an article that under the FD&C Act is a drug (section 201(g)(1) (21 U.S.C 321(g)(1))), a device (section 201(h)), or a combination product (section 503(g) (21 U.S.C 353(g))). Section 201(rr) of the FD&C Act.

IV. ENFORCEMENT PRIORITIES REGARDING CERTAIN ENDS PRODUCTS ON THE MARKET WITHOUT PREMARKET AUTHORIZATION

A. Overview

The Tobacco Control Act provides that new tobacco products (*i.e.*, non-grandfathered products) may not legally be marketed without premarket authorization. Accordingly, all deemed new tobacco products on the market without authorization are illegally marketed products.

Beginning February 6, 2020, FDA intends to prioritize enforcement of the premarket review requirements for certain ENDS products, including against retailers selling such products. Specifically, FDA intends to prioritize enforcement against:

(1) Flavored, cartridge-based ENDS products (except for tobacco- or menthol-flavored products);

(2) All other ENDS products for which the manufacturer has failed to take (or is failing to take) adequate measures to prevent minors' access; and

(3) Any ENDS products targeted to, or whose marketing is likely to promote use by, minors.

In addition, FDA intends to prioritize enforcement of any ENDS product that is offered for sale in the United States after September 9, 2020, and for which the manufacturer has not submitted a premarket application (or

after a negative action by FDA on a timely submitted application).[22]

FDA will make enforcement decisions on a case-by-case basis, recognizing that it is unable, as a practical matter, to take enforcement action against every illegally marketed tobacco product, and that it needs to make the best use of Agency resources. This guidance does not in any way alter the fact that it is illegal to market any new tobacco product without premarket authorization, or to sell any tobacco product to minors. The Agency also retains discretion to pursue enforcement action at any time against any deemed new tobacco product marketed without premarket authorization, regardless of whether it falls within one of these categories of enforcement priorities.

B. Data Show Substantial Increase in Youth Use of ENDS Products, Particularly Certain Flavored, Cartridge-Based ENDS Products

At the time FDA issued the August 2017 Compliance Policy to announce changes in its approach to enforcement regarding premarket authorization (as described in the preamble to the final deeming rule), data from the 2016 NYTS showed a decrease in prevalence of current e-cigarette use (*i.e.*, past 30-day use) among high school students, from 16 percent in 2015 to 11.3 percent in

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[22] We note that FDA would be enforcing the priorities discussed in Section IV of this guidance regardless of the court's decision in the *AAP* case. As discussed in this Final Guidance, FDA is implementing this policy to address the alarming increase in youth use of ENDS products as well as other recent health and safety issues regarding such products.

2016.[23] Results from the 2017 NYTS later confirmed that in regards to youth use there was no statistically significant rise at the time, with data suggesting that high school student use had leveled off between 2016 (11.3 percent)[24] and 2017 (11.7 percent).[25]

However, multiple survey results over the past several years demonstrate that there is significant initiation by youth. The recent surge in youth use of ENDS products has caused us to reevaluate our July 2017 assessment and to modify our enforcement priorities for ENDS products. Recent data show an alarming increase in youth use of ENDS products in the past two years. They also show youth are more likely to use certain flavored, cartridge-based ENDS products.

Overall, data showed that ENDS product use more than doubled among middle school and high school students from 2017 to 2019.[26] Data from MTF showed that from 2017 to 2018, current (past 30-day) e-cigarette use significantly increased from 6.6 percent to 10.4 percent among 8th graders (a 58 percent increase), 13.1 percent to 21.7 percent among 10th graders (a 66 percent increase), and 16.6 percent to 26.7 percent among 12th

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[23] Jamal, A., A. Gentzke, S.S. Hu, et al., "Tobacco Use Among Middle and High School Students—United States, 2011-2016," Morbidity and Mortality Weekly Report, 66:597-603, 2017, available at: https://www.cdc.gov/mmwr/volumes/66/wr/mm6623a1.htm.

[24] *Id.*

[25] Wang, T.W., A. Gentzke, S. Sharapova, et al., "Tobacco Product Use Among Middle and High School Students —United States, 2011-2017," Morbidity and Mortality Weekly Report, 67:629-633, 2018, available at: http://dx.doi.org/10.15585/mmwr.mm6722a3.

[26] Miech R, L. Johnston, P.M. O'Malley, et al., "Trends in adolescent vaping, 2017-2019," New England Journal of Medicine, 381:1490-1491, 2019; DOI:10.1056/NEJMc1910739.

graders (a 61 percent increase).[27] This trend continued in the 2019 MTF data. The number of students who had used ENDS products during the previous 12 months and those who had ever used ENDS products significantly increased in 8th, 10th, and 12th grade from 2018 to 2019.[28] Data from the NYTS for the same time period show that, between 2017 and 2018, current e-cigarette use among high school students increased from 11.7 percent to 20.8 percent (a 78 percent increase, $p<0.001$).[29] Current e-cigarette use among middle school students also increased from 3.3 percent to 4.9 percent over the same time period (a 48 percent increase, $p=0.001$), which we calculated as an increase of an estimated 180,000 middle school students reporting past 30-day e-cigarette use in one year.[30] The data from 2019 NYTS have also documented that this is the second year in a row where current (past 30-day) e-cigarette

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[27] Miech, R. A., Johnston, L. D., O'Malley, P. M., et al., "Monitoring the Future national survey results on drug use, 1975-2018: Volume I, Secondary school students," Ann Arbor: Institute for Social Research, The University of Michigan (2019), available at http://monitoringthefuture.org/pubs html#monographs. For each age group, the increase from 2017 to 2018 was statistically significant ($p<.001$).

[28] Miech R, L. Johnston, P.M. O'Malley, et al., "Trends in adolescent vaping, 2017–2019," New England Journal of Medicine; 381:1490-1491, 2019; DOI:10.1056/NEJMc1910739.

[29] Cullen, K.A., B.K. Ambrose, A.S. Gentzke, et al., "Notes from the Field: Increase in e-cigarette use and any tobacco product use among middle and high school students—United States, 2011-2018," Morbidity and Mortality Weekly Report, 67(45);1276-1277, 2018. The NYTS defines e-cigarettes as "battery-powered devices that provide nicotine and other additives to the user in the form of an aerosol."

[30] *Id.*

use reached new highs among youth.[31] The prevalence of current e-cigarette use among high school students was 27.5 percent and middle school students was 10.5 percent.[32] Among high school students, 4.11 million reported having used an e-cigarette in the past month in 2019 with 1.24 million middle school students reporting the same. For the first time ever, the total number of middle and high school students reporting current use of e-cigarettes surpassed 5 million in 2019.[33]

Disturbingly, these data also indicate that a growing percentage of America's youth who use e-cigarettes have become frequent e-cigarette users (defined as reporting use on 20 days or more of the prior 30-day period). An increasing number of youth are thus at greater risk of nicotine addiction at a time when the developing brain is particularly susceptible to permanent

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[31] Cullen, K.A., A.S. Gentzke, M.D. Sawdey, "E-cigarette use among youth in the United States, 2019," JAMA, 322(21);2095-2103, 2019. Several improvements were made to the NYTS in 2019, including switching from paper-and-pencil to electronic survey administration, adding skip patterns and example product images, and updating brand examples to reflect the current tobacco marketplace (*e.g.*, adding JUUL), which may affect the comparability of tobacco product use behaviors, including e-cigarette use behaviors, with previous years. Although trend analyses, which use more data points and are not solely dependent on changes during a single year, may be conducted without major shifts in patterns or findings, the exact magnitude of the effect of these survey improvements in 2019 cannot be fully quantified. Thus, direct statistical comparisons between estimates of tobacco product use between 2018 and 2019 were not conducted.

[32] Cullen, K.A., A.S. Gentzke, M.D. Sawdey, "E-cigarette use among youth in the United States, 2019," JAMA, 322(21);2095-2103, 2019.

[33] *Id.*

changes from nicotine use and when almost all nicotine addiction is established.[34] Data from the 2019 NYTS have documented continued frequent youth ENDS use.[35] The proportion of current high school e-cigarette users who reported use on 20 days or more (of the prior 30-day period), and thus were frequent users, was 34.2 percent in 2019.[36] The proportion of current middle school e-cigarette users who reported use on 20 days or more (of the prior 30-day period) was 18.0 percent in 2019.

This builds upon an increase in frequent ENDS use among youth who report using ENDS products observed in 2018. For example, data from the 2018 NYTS showed that the proportion of current high school e-cigarette users who reported use on 20 days or more (of the prior 30-day period) increased by 38.5 percent, from 20.0 percent in 2017 to 27.7 percent in 2018.[37] In a study that collected data from February to May 2018 and focused specifically on 15-to-17-year-old current users of JUUL products (the most commonly used brand, including among youth), 55.8 percent reported using such ENDS products on 3 or more of the previous 30 days,

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[34] Miech R., Johnston L, O'Malley PM, et al., "Adolescent vaping and nicotine use in 2017-2018—U.S. National Estimates," New England Journal of Medicine; 380:192-3, 2019.

[35] Cullen, K.A., A.S. Gentzke, M.D. Sawdey, "E-cigarette use among youth in the United States, 2019," JAMA, 322(21);2095-2103, 2019.

[36] *Id.*

[37] Cullen, K.A., B.K. Ambrose, A.S. Gentzke, et al., "Notes from the Field: Increase in e-cigarette use and any tobacco product use among middle and high school students—United States, 2011-2018," Morbidity and Mortality Weekly Report, 67(45);1276-1277, 2018.

and over a quarter (25.3 percent) reported use on 10 to 30 days of the prior month.[38]

The concerns caused by the sharp increase in the number of youth using ENDS products are compounded by evidence indicating that youth whose first tobacco product is an ENDS product are at an increased risk of becoming cigarette smokers as compared to non-ENDS users. A 2018 report by the National Academy of Sciences, Engineering, and Medicine entitled "Public Health Consequences of E-Cigarettes," which took into account multiple lines of evidence across different studies and study designs, concluded that "there is substantial evidence that e-cigarette use increases risk of ever using combustible tobacco cigarettes among youth and young adults."[39]

FDA is also concerned about the extraordinary popularity of flavored ENDS products with youth. Research has long shown that flavors increase youth appeal of tobacco products, including ENDS.[40] Evidence continues

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[38] Vallone, D.M., M. Bennett, H. Xiao, et al., "Prevalence and correlates of JUUL use among a national sample of youth and young adults," Tobacco Control,0:1-7, 2017, doi: 10.1136/tobaccocontrol-2018-05463.

[39] National Academies of Sciences, Engineering, and Medicine, "Public health consequences of e-cigarette,". Washington, DC: The National Academies Press, 2018, doi: https://doi.org/10.17226/24952.

[40] *E.g.,* Carpenter, C.M., et al., "New Cigarette Brands with Flavors that Appeal to Youth: Tobacco Marketing Strategies," Health Affairs, 24(6):1601-1610, 2005; Pepper, J. K., K.M. Ribisl, N.T. Brewer, "Adolescents' interest in trying flavoured e-cigarettes," Tobacco Control, 25:ii62-ii66, 2016; Camenga, D. R., M. Morean, G. Kong, et al., "Appeal and use of customizable e-cigarette product features in adolescents," Tobacco Regulatory Science, 4(2):51-

to accumulate, further confirming that youth are particularly attracted to flavored ENDS products. Data from the 2018 NYTS showed that past 30-day use of any flavored e-cigarette increased from 2017 among high school students who reported current e-cigarette use (60.9 percent to 67.8 percent, $p<0.05$).[41] In the 2016-2017 (Wave 4)[42] Population Assessment of Tobacco and Health (PATH) Study,[43] among youth age 12 to 17 who reported using an ENDS product, 93.2 percent reported that their first ENDS use was with a flavored ENDS product.[44] Data from Wave 4 also showed that

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60, 2018; Harrell, M.B., S.R. Weaver, A. Loukas, et al., "Flavored e-cigarette use: characterizing youth, young adult, and adult users," Preventive Medicine Reports, 5:33-40, 2017.

[41] Cullen, K.A., B.K. Ambrose, A.S. Gentzke, et al., "Notes from the Field: Increase in e-cigarette use and any tobacco product use among middle and high school students—United States, 2011-2018," Morbidity and Mortality Weekly Report, 67(45);1276-1277, 2018.

[42] Population Assessment of Tobacco and Health (PATH) Study [United States] Restricted Use Files (ICPSR 36231), available at: https://www.icpsr.umich.edu/icpsrweb/NAHDAP/studies/36231.

[43] The PATH study is a research study that assesses within-person changes and between-person differences in a large national cohort of participants aged 12 years and older over time. Each wave is a follow-up where the PATH study can examine its objectives, iteratively and cumulatively, to generate a broad body of knowledge about tobacco product use in the USA. Data collection for each wave occurred during the following timeframes: Wave 1 (September 2013-December 2014), Wave 2 (October 2014-2015), Wave 3 (October 2015-2016), and Wave 4 (2016-2017).

[44] Rostron B et al. "Prevalence and Reasons for Use of Flavored Cigars and ENDS among US Youth and Adults: Estimates from Wave 4 of the PATH Study, 2016-2017," American Journal of Health Behavior, 44(1);76-81, 2020.

71 percent of current youth ENDS users said they used ENDS products "because they come in flavors I like."[45]

The NYTS survey instrument groups mint- and menthol-flavored products together, so it is not possible to differentiate youth use of mint and menthol flavors separately based on the NYTS data. The 2018 NYTS data indicate that, among high school students whose only tobacco product use is e-cigarettes, known as exclusive e-cigarette users, the proportion who reported fruit-flavored ENDS use was 75.5 percent in 2018[46] and the proportion who reported mint-and menthol-flavored ENDS use was 38.1 percent.[47] In 2019, in the same population, fruit-flavored ENDS use was 66.1 percent and mint- and menthol-flavored ENDS use was 57.3 percent.[48] Among middle school exclusive e-cigarette users, the 2018 NYTS data indicate that use of fruit-flavored ENDS use was 58.1 percent and mint-and menthol-flavored ENDS use was 20.6 percent.[49] In 2019, in the same population, fruit-flavored ENDS use was 67.7 percent and mint- and menthol-flavored ENDS

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[45] *Id.*

[46] Cullen, K.A., A.S. Gentzke, M.D. Sawdey, et al., "E-cigarette use among youth in the United States, 2019," JAMA, 322(21);2095-2103, 2019.

[47] Cullen, K.A., B.K. Ambrose, A.S. Gentzke, et al., "Notes from the Field: Increase in e-cigarette use and any tobacco product use among middle and high school students—United States, 2011-2018," Morbidity and Mortality Weekly Report, 67(45);1276-1277, 2018.

[48] Cullen, K.A., A.S. Gentzke, M.D. Sawdey, "E-cigarette use among youth in the United States, 2019," JAMA, 322(21);2095-2103, 2019.

[49] *Id.*

use was 31.1 percent.[50] Between 2016 and 2019, high school exclusive e-cigarette users who reported mint- and menthol-flavored ENDS use increased from 16.0 percent to 57.3 percent, $p<0.05$.[51] Data for middle school e-cigarette users was inconclusive on this point due to a limited number of middle-school students in the NYTS sample who not only used e-cigarettes within the past 30 days, but whose exclusive tobacco product use in the past 30 days was e-cigarettes.[52] In 2019, the data indicate that more than one million middle and high school exclusive e-cigarette users used mint- or menthol-flavored ENDS in the past 30 days.[53]

However, data from the MTF survey examine mint and menthol JUUL use separately and indicate that youth use of menthol-flavored products is not as high as that for mint- and fruit-flavored products. Specifically, a randomly-selected third of 2019 MTF respondents were asked about their flavored JUUL use.[54] The analytic sample included past 30-day JUUL users who answered the question, "Which JUUL flavor do you use most often?" with response options of Classic Tobacco, Crème, Cucumber, Fruit, Mango, Menthol, Mint, Virginia Tobacco, and Other. Among past 30-day JUUL users in each grade studied (8th, 10th, and 12th), use of mango and mint ranked highest, followed by fruit. Reported use of menthol and tobacco flavors were among the lowest ranked options. Specifically, a number of 8th grade

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[50] *Id.*

[51] *Id.*

[52] *Id.*

[53] *Id.*

[54] Leventhal A., et al., "Flavors of e-Cigarettes Used by Youths in the United States," JAMA, 322(21):2132-2134, 2019.

past 30-day JUUL users reported use of mango (33.5 percent), while the others reported use of mint (29.3 percent), fruit (16.0 percent), and other (14.8 percent).[55] A large percentage of 10th grade past 30-day JUUL users reported use of mint (43.5 percent), while the others reported use of mango (27.3 percent), fruit (10.8 percent), and other (8.4 percent).[56] Close to half of 12th grade past 30-day JUUL users reported use of mint (47.1 percent), while the others reported use of mango (23.8 percent), fruit (8.6 percent), other (6.0 percent), menthol (5.9 percent), and cucumber (4.4 percent).[57]

Data from the 2019 NYTS also indicate that youth overwhelmingly prefer cartridge-based ENDS products,[58] and we have found that these products are easy to conceal, can be used discreetly, may have a high nicotine content, and are manufactured on a large scale. The 2019 survey instrument included a measure for the "usual brand" of e-cigarette used in the past 30 days.

Most youth who were current e-cigarette users reported a cartridge-based e-cigarette as their usual brand.[59] In fact, the leading brand is a cartridge-based

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[55] The remaining flavors, including tobacco and menthol flavors, each had estimates of ≤ 2.3%.

[56] The remaining flavors, including tobacco and menthol flavors, each had estimates of ≤ 3.0%.

[57] The remaining flavors, including tobacco, each had estimates of ≤ 1.5%.

[58] Cullen, K.A., A.S. Gentzke, M.D. Sawdey, "E-cigarette use among youth in the United States, 2019," JAMA, 322(21);2095-2103, 2019.

[59] *Id.* Unpublished data from the 2019 survey list other brands that are used by youth, some of which are available in both cartridge-based and non-cartridge-based forms.

product that commands approximately 70 percent of the market.[60]

Of particular concern are the design features that appear to make the cartridge-based products so popular with young people. Attributes typically present in cartridge-based products include a relatively small size that allows for easy concealability, and intuitive and convenient features that facilitate ease of use, including draw activation, prefilled cartridges or pods, and USB rechargeability.

Small products may allow youth to use the product in circumstances where use of tobacco products is prohibited, such as a school.[61] Small size may also allow the user to quickly conceal the product in the palm of one's hand or in a pocket.[62] Small size may allow for product use in a social setting without others' awareness,[63] par-

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[60] Nielsen Total US xAOC/Convenience Database & Wells Fargo Securities, LLC, in Wells Fargo Securities, Nielsen: Tobacco All Channel Data Thru 10/4—Cig Vol Declines Moderate, October 15, 2019.

[61] *See, e.g.*, Schillo B., et al., "JUUL in School: Teacher and Administrator Awareness and Policies of E-Cigarettes and JUUL in U.S. Middle and High Schools," Health Promot Pract., 21(1):20-24, 2020; "Why 'juuling' has become a nightmare for school administrators," Kaiser Health News (March 26, 2018), available at: https://www.nbcnews.com/health/kids-health/why-juuling-has-become-nightmare-school-administrators-n860106/; "Juul Is Sued by School Districts That Say Vaping Is a Dangerous Drain on Their Resources," The New York Times (October 7, 2019), available at: https://www.nytimes.com/2019/10/07/us/juul-vaping-schools.html.

[62] http://pittsburgh.cbslocal.com/2017/12/13/new-ecigarette-popular-among-kids-easy-to-conceal-from-parents/

[63] https://www.npr.org/sections/health-shots/2017/12/04/568273801/teenagers-embrace-juul-saying-its-discreetenough-to-vape-in-class

ticularly in conjunction with vaping techniques that may be used to prevent or hide the vapor cloud. Additionally, depending on the size and shape of the product, it may also blend in with other equipment that is expected in that setting (*e.g.*, if the ENDS is shaped like a flash drive, for example, next to a computer, where an actual flash drive would be used), or it may otherwise go undetected because parents, teachers, or coaches do not recognize the product as an ENDS.[64]

Products ready for use immediately after purchase have characteristics that facilitate ease of use among young people. With cartridge-based products, there are no settings to change and very little assembly is required. Research on other tobacco products suggests that ease of use is associated with susceptibility to tobacco product uptake among youth.[65] Additional research among youth suggests that younger adolescents are more likely to use more basic ENDS products than older adolescents.[66] Thus, particularly easy-to-use products, such as cartridge-based products, may have lower barriers to initiation.

Other product features that facilitate ease of use include pre-filled cartridges, which are convenient because they do not require filling prior to use and are

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[64] "New vaping devices may go undetected by parents," The Excelsior Springs Standard, April 16, 2018, available at: http://excelsior225 rssing.com/chan-47020297/all_p70.html#item1400.

[65] Chaffee B.W., J. Urata, E.T. Couch, S. Gansky, "Perceived flavored smokeless tobacco ease-of-use and youth susceptibility," Tobacco Regulatory Science, 3(3):367-373, 2017.

[66] Pepper J.K., A.J. MacMonegle, J.M. Nonnemaker, "Adolescents' use of basic, intermediate, and advanced device types for vaping," Nicotine & Tobacco Research, 21(1):55–62, 2019.

easy to dispose of and replace; a draw-activated battery that makes the devices much easier to use than other devices; and rechargeability, an important characteristic for use among youth who recharge via a USB port when connected to a computer or charging adapter from other electronic devices, such as a cellphone.

In the notice of proposed rulemaking for the Deeming Rule, FDA noted that the overall public-health impact of ENDS products would depend crucially upon "who uses the products and how they are used. If such products result in minimal initiation by children and adolescents while significant numbers of smokers quit, then there is a potential for the net public health impact at the population level to be positive. If, on the other hand, there is significant initiation by youth, minimal quitting, or significant dual use of combust[ed] and noncombust[ed] products, then the public health impact could be negative."[67] The data discussed above demonstrate substantial and increasing initiation of ENDS products by youth, particularly certain flavored, cartridge-based products.

C. Additional Relevant Considerations

In issuing the March 2019 Draft Guidance, FDA solicited public comment generally on the proposed approach and specifically sought information that could help inform its decision-making for each key issue. In developing this Final Guidance, FDA considered information provided in the public comments submitted on the March 2019 Draft Guidance. Overall, out of the over 15,000 public comments FDA received in response to the Draft Guidance, many were related to form letter

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[67] 79 Fed. Reg. 23141, 23147 (2016).

campaigns, while approximately 294 public comments provided unique and substantive information. In addition to the comments that provided unique and substantive information, FDA received thousands of general comments expressing support or opposition to the guidance and separate provisions within the guidance. These comments express broad policy views and do not address specific points related to the March 2019 Draft Guidance. Additional information regarding significant comments received in response to the March 2019 Draft Guidance and FDA's responses is described in Appendix A.[68]

FDA also remains concerned about health and safety issues connected to ENDS products—*e.g.*, cases of lung injuries associated with use of vaping products[69]

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[68] FDA generally does not respond to comments in guidance documents and, as noted in the preamble to the deeming rule, generally "[a]gency compliance/enforcement policies are not subject to the requirements that govern notice-and-comment rulemaking." 81 Fed. Reg. at 28,977, 29,010 (citing *Prof'ls & Patients for Customized Care v. Shalala*, 56 F.3d 592 (5th Cir. 1995) (a compliance policy guide is not a substantive rule and not subject to APA's notice-and-comment rulemaking); *Takhar v. Kessler*, 76 F.3d 995, 1002 (9th Cir. 1996) (FDA compliance policy guides were not required to go through notice-and-comment procedures)). Although FDA is addressing comments here, it does so voluntarily and given the circumstances. By responding to comments here, FDA in no way establishes a policy, practice, or precedent requiring the Agency to do so with respect to future iterations of this document or any other guidance document.

[69] *See, e.g.*, Centers for Disease Control and Prevention, "Outbreak of Lung Injury Associated with E-cigarette Use, or Vaping," available at: https://www.cdc.gov/tobacco/basic_information/e-cigarettes/severe-lungdisease/html#latest-outbreak-information; Layden, J. E., I. Ghinai, I. Pray, et al., "Pulmonary Illness Related to E-Cigarette Use in Illinois and Wisconsin—Preliminary Re-

as well as battery explosions with ENDS products[70]—particularly given that these products have been marketed without premarket evaluation. These current public health issues affirm the importance of the premarket review process, as contemplated by the Tobacco Control Act, to scientifically evaluate products based on a public health standard. For example, FDA review of premarket tobacco product applications considers the risks and benefits of the product to the population as a whole, including tobacco product users and non-users. In reviewing premarket tobacco product applications, FDA will consider, among other things: the product's components, ingredients, additives, and properties; manufacturing practices; and any studies or investigations into the health risks of the tobacco product.

D. Enforcement Priorities for ENDS Products

In the discussion that follows, we describe our current intent regarding prioritizing our enforcement resources with respect to certain illegally marketed ENDS products.

FDA will prioritize enforcement of flavored, cartridge-based ENDS products (other than tobacco- and menthol-flavored products), which are produced primarily by large manufacturers. This policy should have minimal impact on small manufacturers (*e.g.*, vape shops) that primarily sell non-cartridge-based ENDS products, un-

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port," New England Journal of Medicine, Sept. 2019; DOI: 10.1056/NEJMoa1911614.

[70] *See, e.g.*, Rossheim, M.E., M.D. Livingston, E.K. Soule, et al., "Electronic Cigarette Explosion and Burn Injuries, US Emergency Departments 2015-2017," Tobacco Control, 2019; 28:472-474, available at: http://dx.doi.org/10.1136/tobaccocontrol-2018-054518.

less they market to youth or fail to take adequate measures to prevent youth access. Specifically, FDA intends to prioritize enforcement regarding the lack of marketing authorization against:

- Any flavored, cartridge-based ENDS product (other than a tobacco- or menthol-flavored ENDS product);
- All other ENDS products for which the manufacturer has failed to take (or is failing to take) adequate measures to prevent minors' access; and
- Any ENDS product that is targeted to minors or whose marketing is likely to promote use of ENDS by minors.

FDA intends to prioritize enforcement beginning February 6, 2020.

Further, FDA intends to prioritize enforcement of any ENDS product that is offered for sale after September 9, 2020, and for which the manufacturer has not submitted a premarket application (or after a negative action by FDA on a timely submitted application).

In addition to violations related to lack of marketing authorization, FDA will continue to take legal action regarding sales of tobacco products to minors and other violations and will closely monitor all sales of ENDS products.

1. Any flavored, cartridge-based ENDS product (other than a tobacco- or menthol-flavored product)

FDA intends to prioritize enforcement for lack of marketing authorization against any flavored, cartridge-based ENDS product (other than a tobacco- or menthol-

flavored ENDS product) that is offered for sale in the United States without regard to whether or when premarket application for such product has been submitted.

In its balancing of the different public health considerations regarding ENDS products, the March 2019 Draft Guidance did not include tobacco-, mint- and menthol-flavored ENDS products in its proposed enforcement priorities, based on the data at that time indicating that these flavors were preferred more by adults than youth. The intent was, to the extent possible consistent with protecting population health, to avoid foreclosing one potential means by which some adult smokers might seek to transition completely away from combusted tobacco products to potentially less harmful tobacco products. Moreover, the March 2019 draft did not distinguish between cartridge-based products and other products, and instead focused on how products are sold rather than product characteristics.

As discussed above, evidence shows that youth are particularly attracted to flavored, cartridge-based ENDS products. Data show that, among youth who reported ever using an ENDS product, a large majority reported their first ENDS use was with a flavored ENDS product.[71] Data also show that among current youth ENDS users, a majority of youth respondents stated that they used ENDS products "because they come in flavors I like."[72] In addition, recent data indicate that flavors

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[71] Rostron B et al. "Prevalence and Reasons for Use of Flavored Cigars and ENDS among US Youth and Adults: Estimates from Wave 4 of the PATH Study, 2016-2017," American Journal of Health Behavior, 44(1);76-81, 2020.

[72] *Id.*

preferred by youth include mint. Data from the 2019 MTF survey indicate that youth use of mint- and fruit-flavored JUUL products is higher than that of menthol- and tobacco-flavored JUUL products.[73] Finally, data from the 2019 NYTS indicate that youth overwhelmingly prefer cartridge-based ENDS products.[74] These products are easy to conceal, can be used discreetly, may have a high nicotine content, and are manufactured on a large scale.

FDA received a number of comments that focused on the popularity of mint- and menthol-flavored ENDS among youth and adult populations. Some commenters suggested that such products would become even more popular if others became less available. They argued that not prioritizing enforcement against mint- and menthol-flavored ENDS products would risk the shift of youth from one flavor of ENDS products to another based on a potential but indeterminate impact on adult consumers. Several comments argued that data suggest that even if youth currently prefer "fruit" and "sweets" to mint and menthol, this does not mean that youth do not still find mint and menthol to be appealing flavors. FDA also received public comments claiming that mint- and menthol-flavored ENDS products help smoking cessation. For example, some commenters focused on the potential role that mint- and menthol-flavored ENDS products could play in helping some adults cease the use of combusted tobacco products.

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[73] Leventhal A., et al., "Flavors of e-Cigarettes Used by Youths in the United States," JAMA, 322(21):2132-2134, 2019.

[74] Cullen, K.A., A.S. Gentzke, M.D. Sawdey, "E-cigarette use among youth in the United States, 2019," JAMA, 322(21);2095-2103, 2019.

It is possible that prioritizing enforcement against mint-flavored ENDS products could at least in the short term make fewer products available for some addicted adult smokers seeking to use ENDS products to transition completely away from cigarettes. However, the comments, as well as the recent surge in youth use of ENDS products, and especially the preferences indicated in the 2019 NYTS and 2019 MTF data, have led FDA to reconsider its approach with regard to prioritizing enforcement of mint-flavored ENDS products.

FDA also received multiple comments urging the Agency to further refine its enforcement priorities in consideration of how the design features of certain ENDS products may make them so popular among youth. Some commenters focused on the features of cartridge-based systems, particularly that they may contain high nicotine content and that they are easy to conceal. Similarly, some commenters focused on the potential impact of nicotine salts, which are used in some brands of cartridge-based ENDS products. In contrast, FDA received a comment arguing that the rise of youth use should not be attributed to all cartridge-based products but rather to a single, uniquely prevalent cartridge-based product, and that FDA's regulatory actions should be tailored accordingly.

As discussed above, data show that flavors are a strong driver for youth use, and that youth overwhelmingly use cartridge-based ENDS products. Moreover, preliminary research indicates that certain effects of nicotine salts in ENDS products (*e.g.*, higher nicotine exposure and faster rate of absorption) may increase the abuse liability of ENDS with nicotine salts, which raises concerns of addiction in youth, particularly due to the vulnerability of the developing adolescent brain. However,

for many individual addicted cigarette smokers, the potential for ENDS to act as a substitute for cigarettes, thereby encouraging smokers to seek to switch completely away from combustible cigarettes, may be dependent, in part, upon the product having acceptability and abuse liability more comparable to a cigarette.

FDA has refined its enforcement priorities in the Final Guidance to focus on flavored, cartridge- based ENDS products (other than tobacco- and menthol-flavored). This approach strikes an appropriate balance between restricting youth access to such products, while maintaining availability of potentially less harmful options for current and former adult smokers who have transitioned or wish to transition completely away from combusted tobacco products. FDA will, however, continue to evaluate new information and adjust these enforcement priorities, as warranted, in light of the best available data about these products.

We also note that the March 2019 Draft Guidance proposed to prioritize enforcement for flavored ENDS products that are offered for sale in ways that pose a greater risk for minors to access such products. Several comments discussed the wide availability of these products and the means by which youth gain access. These included comments that expressed concern regarding the availability of flavored ENDS products on the Internet and in vape shops. Other commenters focused on how the enforcement priorities were unclear and difficult for retailers to understand, and how that may negatively affect "potentially compliant" retail locations that attempt to prevent minor access. Others expressed concern that the enforcement priorities were altogether impractical and costly for retailers. While the March 2019 Draft Guidance proposed to focus its enforcement

priorities of flavored ENDS products on how the product was sold, after considering the comments, the public health threats, and the new evidence described above, FDA determined that focusing on how the product was sold would not appropriately address youth use of the products that are the most popular among youth—*i.e.*, flavored, cartridge-based products. The reality is that youth have continued access to these products in the face of legal prohibitions and even after voluntary actions by some manufacturers. Moreover, as discussed above, the data show that youth overwhelmingly prefer certain flavors of cartridge-based ENDS products.[75] These products are produced on a large scale, are easy to conceal, can be used discreetly, and are not the products typically produced in vape shops that mix nicotine with e-liquid flavors. Given the urgent need to address the dramatic rise in youth use, this Final Guidance prioritizes enforcement with respect to any flavored, cartridge-based ENDS products (other than a tobacco- and menthol-flavored ENDS product) without regard to the location or method of sale. FDA believes that focusing enforcement on these products is important in addressing the increasing rates of youth use of these flavored, cartridge-based products because this is a primary driver in youth experimentation with, and continued use of, ENDS products.

Accordingly, FDA has recalibrated its balancing of public health considerations in light of the public health threats and the significant new evidence described above. This policy reflects FDA's balancing of concerns

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[75] Cullen, K.A., A.S. Gentzke, M.D. Sawdey, "E-cigarette use among youth in the United States, 2019," JAMA, 322(21);2095-2103, 2019.

regarding the appeal of certain flavored, cartridge-based ENDS products to youth; the potential public health benefit of noncombusted options by which some adult smokers might seek to transition completely away from combusted tobacco products; and the potential risks created by extended availability of these new tobacco products without scientific review and evaluation under the applicable public health standard.

2. All other ENDS products without adequate measures to prevent minors' access

FDA intends to prioritize enforcement for lack of a marketing authorization for any other ENDS products (*i.e.*, any tobacco-, menthol-, or non-flavored ENDS products and any non-cartridge- based, flavored ENDS products) when the manufacturer has not taken or is not taking adequate measures to prevent minors' access to these products, without regard to whether or not, or when, a premarket application for such product has been submitted.

In assessing whether a manufacturer is taking (or has taken) adequate measures to prevent minors' access to these ENDS products, factors the Agency intends to consider include, but are not limited to:

- Whether the manufacturer has implemented adequate programs to monitor retailer compliance with age-verification and sales restrictions. Such programs might include, for instance: screening retailers, in advance of establishing or renewing distribution agreements, based on the strength of the retailers' age verification policies; establishing and publicizing a hotline for anonymous reporting of noncompliant sales; implementing a mystery shopper program; requiring use of tech-

nology that tracks age-verification practices; or other mechanisms.

- Whether the manufacturer has established and enforces penalties against retailers that fail to comply with age-verification and sales restrictions. For instance, in response to the September 12th letters, respondent manufacturers stated that they had mechanisms, such as through distribution agreements, to enforce financial penalties and stop sales to retailers in response to noncompliance. In addition to such mechanisms, FDA may consider whether a manufacturer has implemented a policy of notifying FDA of retailer violations.
- If the manufacturer is also a retailer, factors to adequately prevent underage access might include: whether the manufacturer/retailer has implemented programs to ensure compliance with age-verification and sales restrictions; establishing and publicizing a hotline for anonymous reporting of noncompliant sales; checking identification at the door; or other mechanisms.
- If the manufacturer is also a retailer, whether the manufacturer uses adequate age- verification technology (or requires that retailers who sell its products use such technology) to prevent underage access to its website and to prevent underage sales through the Internet. For instance, adequate age-verification could include use of an independent, third-party age- and identity-verification service that compares customer information against third-party data sources, such as public records; and

- Whether the manufacturer limits (or requires that retailers who sell its products to limit) the quantity of ENDS products that a customer may purchase within a given period of time.

FDA's decision to exercise its enforcement authorities with respect to particular products will be fact-specific and determined on a case-by-case basis.

This prioritization takes into account information that was provided by manufacturers in response to the Agency's September 2018 letters, including measures to address youth use that manufacturers can or have already taken to address youth access to ENDS products, as well as information provided in comments to the March 2019 Draft Guidance.

As noted, FDA considered comments about the practical concerns of implementing an enforcement policy based on how products are sold. The factors above reflect information FDA received from industry, including information manufacturers shared during meetings with FDA leadership, in response to the September 2018 letters, and public comments submitted in response to the March 2019 Draft Guidance. From this information, FDA understands that manufacturers have the means to monitor and/or control how their products are sold at retail by, for example, including or requiring terms, conditions, or controls in their contracts with downstream distributors (wholesalers, distributors, importers, and/or retailers) to prevent youth access.

The March 2019 Draft Guidance did not propose to prioritize enforcement for tobacco- or menthol-flavored ENDS products and did not propose to distinguish between cartridge-based and other ENDS products. The

continued significant increase in youth use of ENDS, as demonstrated in the 2019 NYTS and MTF data, as well as the data showing that youth overwhelmingly use flavored, cartridge-based ENDS products, support a reconsideration of the Agency's approach. As noted in the draft guidance, FDA is continuously evaluating new information and adjusting its enforcement priorities in light of the best available data, and it will continue to do so with respect to these unauthorized ENDS products.

As noted above, FDA received a number of comments arguing that the popularity of menthol- flavored ENDS (as well as mint-flavored ENDS, which are discussed above) had increased among youth and adult populations, and suggesting that such products would become even more popular if other flavored ENDS products became less available. They argued that excluding menthol-flavored ENDS products from prioritization would risk the shift of youth from one flavor of ENDS products to another based on a potential but indeterminate impact on adult consumers. FDA also received comments stating that it should immediately begin enforcing premarket review of all ENDS products, including tobacco-flavored ENDS products.

Other commenters emphasized a need for ENDS products to remain available for former smokers who have transitioned or current smokers who want to transition completely away from combustible products. Menthol is unique compared to other available ENDS product flavors as it is the only characterizing flavor available in cigarettes, and it may reduce the irritation and harshness of smoking.[76] Menthol cigarettes are also used by

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[76] *See, e.g.,* Harris, B., "Menthol: A review of its thermoreceptor interactions and their therapeutic applications," International

a substantial portion of the U.S. population, who are addicted to nicotine and may be looking for an alternative product to seek to transition completely away from combusted products.[77] FDA is compelled to act by data that show youth overwhelmingly prefer certain flavors of cartridge-based ENDS products such as fruit, mint, and candy.[78] At the same time, FDA is aware that approximately 9 million adults currently use e-cigarettes.[79] Studies have shown that the majority of adult e-cigarette users use flavored e-cigarettes and there is some evidence to suggest that flavored e-cigarettes may im-

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Journal of Aromatherapy, 16(3-4):117-131, 2006; Galeotti, N., L.D. Mannelli, G. Mazzanti, et al., "Menthol: a natural analgesic compound," Neuroscience Letters, 322(3):145-148, 2002; Nishino, T., Y. Tagaito, Y. Sakurai, "Nasal inhalation of l-menthol reduces respiratory discomfort associated with loaded breathing," American Journal of Respiratory and Critical Care Medicine, 156(1):309-313, 1997; Lawrence, D., B. Cadman, A.C. Hoffman, "Sensory properties of menthol and smoking topography," Tobacco Induced Diseases, 9 Suppl 1(Suppl 1):S3, 2011; Garten, S. & R.V. Falkner, "Continual smoking of mentholated cigarettes may mask the early warning symptoms of respiratory disease," Preventive Medicine, 37(4):291-296, 2003.

[77] *See, e.g.,* United States Department of Health and Human Services. Substance Abuse and Mental Health Services Administration (SAMHSA). Center for Behavioral Health Statistics and Quality. National Survey on Drug Use and Health, 2016. Analysis run on October 12, 2018. SAMHSA's public online data analysis system (PDAS). (Original Data Source: NSDUH 2016)

[78] Cullen, K.A., A.S. Gentzke, M.D. Sawdey, "E-cigarette use among youth in the United States, 2019," JAMA, 322(21);2095-2103, 2019.

[79] Creamer, M.R., "Tobacco Product Use and Cessation Indicators Among Adults- United States 2018," Morbidity and Mortality Weekly Report, 68:1013-1019, 2019, available at: https://www.cdc.gov/mmwr/volumes/68/wr/pdfs/mm6845a2-H.pdf.

prove switching from cigarette smoking to using e-cigarettes, compared to non-flavored e- cigarettes.[80]

FDA seeks both (1) to avoid foreclosing, even if temporarily, one potential means by which some adult smokers might seek to transition completely away from combusted tobacco products to potentially less harmful tobacco products; and (2) to prevent minors' access to ENDS products. FDA believes that this policy strikes an appropriate balance between restricting youth access to ENDS products and maintaining availability of potentially less harmful options for current and former adult smokers who have transitioned or wish to transition completely away from combusted tobacco products.[81]

Moreover, the prioritization of flavored, cartridge-based products articulated in Section D.1 above, and the prioritization of all other flavored ENDS product sold without adequate measures to prevent youth access, should have minimal impact on those vape shops that

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[80] Russell, C. et al. "Changing Patterns of First E-Cigarette Flavor Used and Current Flavors Used by 20,836 Adult Frequent E-Cigarette Users in the USA," Harm Reduction Journal, 15(1):33-47, 2018; Bonhomme, M.G. et al. "Flavoured Non-Cigarette Tobacco Product Use Among US Adults: 2013–2014," Tobacco Control, 25(Suppl 2):4– 13, 2016.

[81] FDA notes that no ENDS product has been approved by FDA as a drug for smoking cessation. However, the premarket review process for ENDS products will provide an opportunity for FDA to further examine the potential of an ENDS product to meet the tobacco product premarket authorization standard of "appropriate for the protection of public health," including adult decisions to completely transition away from use of combustible products to potentially less harmful ENDS products or other non-combustible forms of nicotine delivery.

primarily sell non- cartridge-based ENDS products and that ensure purchasers are of the requisite age and not purchasing for resale (*e.g.*, are not purchasing in large quantities). Should evidence indicate to the contrary, the Agency will take appropriate action.

3. Any ENDS product that is targeted to minors or whose marketing is likely to promote use of ENDS by minors

Many ENDS products have been and continue to be marketed to minors through a wide variety of media and technology, and their labels and labeling, print advertising, and/or online advertising are appealing to minors. Unlike combusted cigarettes and smokeless tobacco products, for which advertising through television and radio (and any other medium of electronic communication subject to regulation by the Federal Communications Commission) has been prohibited since 1971 and 1986 respectively,[82] ENDS products are advertised through television, radio, and online.[83] Social media accounts are frequently used to electronically share tobacco-product-related content with other minors.[84] Sales of such products to minors are prohibited, and FDA is concerned with actions likely to promote unlawful sales and maintain or increase youth use. FDA

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[82] 15 U.S.C. § 1335 ("It shall be unlawful to advertise cigarettes or little cigars on any medium of electronic communication subject to the jurisdiction of the Federal Communications Commission"); 15 U.S.C. § 4402(c) (same, for smokeless tobacco).

[83] U.S. Department of Health and Human Services, "E-Cigarette Use Among Youth and Young Adults. A Report of the Surgeon General," 2016.

[84] *See* Chu, K.-H., J.B. Colditz, B.A. Primack, et al., "JUUL: Spreading Online and Offline," Journal of Adolescent Health, 63(5), 582-586, 2018.

has issued joint warning letters with the FTC to four firms that manufacture, advertise and offer for sale or distribution several flavored e-liquid products for violations related to online posts by social media influencers on each company's behalf.[85] This type of marketing is especially concerning because longitudinal data from Waves 1 (2013-2014) and 2 (2014-2015) of the PATH Study show that engagement with online tobacco marketing is a risk factor for adolescent tobacco use, as adolescents who engaged with online tobacco marketing had greater incidences of initiating tobacco use, increased frequency of use and progression to poly-product use, and lower incidences of cessation compared to those who do not engage.[86]

Researchers have found that certain marketing strategies can increase youth appeal, both in general and with respect to tobacco products in particular. FDA has previously issued warning letters for products that resemble kid-friendly foods and drinks or that resemble other non-ENDS products that are often consumed by youth.[87] This includes labeling and/or advertising that

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[85] FDA News Release, "FDA, FTC take action to protect kids by citing four firms that make, sell flavored e-liquids for violations related to online posts by social media influencers on their behalf," June 7, 2019, available at: https://www.fda.gov/news-events/press-announcements/fda-ftc-take-action-protect-kids-citing-four-firms-make-sell-flavored-e-liquids-violations-related.

[86] Soneji, S., J. Yang, K.E. Knutzen, et al., "Online Tobacco Marketing and Subsequent Tobacco Use," Pediatrics, 141(2):e 20172927, 2018; doi:10.1542/peds.2017-2927.

[87] *E.g.*, "E-Liquids Misleadingly Labeled or Advertised as Food Products," available at: https://www.fda.gov/tobaccoproducts/newsevents/ucm605729.htm; "FDA In Brief: FDA warns companies to stop making, selling or distributing e-liquids marketed to resemble prescription cough syrups," available at: https://www.

results in the product resembling juice boxes, candy, or kid-friendly cereal. Actions by manufacturers to present their ENDS products in this way are likely to promote youth use, and also present a risk of confusion that could be harmful to children, including the risk of accidental poisoning.[88] Other marketing conduct likely to promote youth use includes the use of cartoons as part of e-cigarette manufacturers' and retailers' logos, marketing materials, promotions,[89] Instagram posts,[90] and video advertisements.[91] Cartoon figures are frequently used on product packaging and in television advertising

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fda.gov/news-events/fda-brief/fda-brief-fda-warns-companies-stop-making-selling-or-distributing-e- liquids-marketed-resemble.

[88] *See, e.g.,* Kamboj, A., H.A. Spiller, M.J. Casavant, et al., "Pediatric Exposure to E-Cigarettes, Nicotine, and Tobacco Products in the United States," Pediatrics, 2016;137(6):e2016004.

[89] Allem, J.-P., T. B. Cruz, J.B. Unger, et al., "Return of cartoon to market e-cigarette-related products," Tobacco Control, 0, 1-3, 2018; doi:10.1136/tobaccocontrol-2018-054437 (2018); Jackler, R. K., & Ramamurthi, D., "Unicorns cartoons: marketing sweet and creamy e-juice to youth," Tobacco Control, 26(4), 471-475, 2017; doi:10.1136/tobaccocontrol-2016-053206; Kirkpatrick, M. G., T.B. Cruz, N.L. Goldenson, et al., "Electronic cigarette retailers use Pokémon Go to market products," Tobacco Control, 26(e2), e145, 2017; doi:10.1136/tobaccocontrol-2016-053369 (2017); Padon, A. A., E.K. Maloney & J.N. Cappella, "Youth-targeted e- cigarette marketing in the US," Tobacco Regulatory Science, 3(1), 95-101, 2017; doi:10.18001/TRS.3.1.9.

[90] Allem, J.-P., T.B. Cruz, J.B. Unger, et al., "Return of cartoon to market e-cigarette-related products," Tobacco Control, 0, 1-3, 2018; doi:10.1136/tobaccocontrol-2018-054437.

[91] Padon, A. A., Maloney, E. K., & Cappella, J. N., "Youth-targeted e-cigarette marketing in the US," Tobacco Regulatory Science, 3(1):95-101, 2017; doi:10.18001/TRS.3.1.9.

to promote youth consumption of consumer goods.[92] A common theme discussed in food and beverage industry publications has been using cartoons in marketing and packaging consumer products to target children and teenagers.[93] Another marketing strategy that has been recently employed by manufacturers is labeling, advertising, and/or product design that results in the ENDS product resembling ordinary items that may not draw the attention of adults.[94] Similar marketing conduct likely to promote youth use includes labeling and/or advertising highlighting how the product is 'stealth' or 'se-

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[92] Ethan, D., C.H. Basch, L. Samuel, et al., "An examination of product packaging marketing strategies used to promote pediatric multivitamins," Journal of Community Health, 40(3), 564-568, 2015; doi:10.1007/s10900-014- 9972-1; Kraak, V. I., & Story, M., "Influence of food companies' brand mascots and entertainment companies' cartoon media characters on children's diet and health: a systematic review and research needs," Obesity Reviews, 16(2), 107-126, 2015.

[93] Barrey, S., M. Baudrin, & F. Cochoy, "From fun foods to fun stores," Young Consumers, 11(2);138-147, 2010; Cioletti, J., "Cereal thrillers," Supermarket Business Magazine, 56(10):30, 2001; Cioletti, J., "Future of . . . youth marketing," Beverage World, 122(8), 10 (2003); Cvetan, D., "Active market for active cultures," Dairy Field, 183(4):18, 2000; Fry, J., "Moo kids on the block say they've got more than the white stuff," Beverage World, 114(1596):1, 1995; Landi, H., "High Tea," Beverage World, 130(7):18-22, 2011; Steinriede, K., "The year's best packaging," Beverage Industry, 91(12): 34, 2000; White, L., "A license for profits," Professional Candy Buyer, 19(6):19-21, 2011.

[94] *See, e.g.,* Ramamurthi, D., C. Chau,, R.K. Jackler, "JUUL and Other Stealth Vaporisers: Hiding the Habit From Parents and Teachers," Tobacco Control, Sept. 2018, doi: 10.1136/tobacco control-2018-054455.

cret' and in the form of ordinary objects that may not be readily recognized by parents or teachers.[95]

Any efforts to entice minors to use tobacco products are of concern to FDA. FDA intends to prioritize its enforcement to focus on products that are targeted to minors or likely to promote use of ENDS by minors. Some examples of such products include:

- Products marketed with labeling and/or advertising that resemble kid-friendly foods and drinks or resemble other non-ENDS products that are often marketed and/or appealing to youth. This includes, for example, labeling and/or advertising that results in the product resembling juice boxes, candy, or kid-friendly cereal; and/or
- Products marketed directly to minors by promoting ease of concealing the product or the nature of the product as a tobacco product from parents, teachers, or other adults; and/or
- Products marketed with youth-appealing cartoon or animated characters, such as those that depict or resemble popular children's characters; and/or
- Products marketed, including through paid social media influencers, with popular children's characters and titles (*e.g.*, popular children's YouTube channels, television shows, or characters). This includes, for example, the use of minors or people who portray minors on such shows and their associated show titles.

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[95] *Id.*

4. Any ENDS product that is offered for sale in the United States after September 9, 2020.

The U.S. District Court for the District of Maryland has ordered that premarket applications for all deemed new tobacco products on the market as of August 8, 2016, be submitted by September 9, 2020. Even in the absence of this court order, FDA would prioritize enforcement of any ENDS product that lacks a premarket application after September 9, 2020, for the reasons described in this guidance. For ENDS products other than those described in D.1 - D.3 above, if premarket applications are submitted by September 9, 2020, FDA intends to continue to exercise enforcement discretion for up to one year pending FDA review, unless there is a negative action by FDA on such application. A negative action would consist of the issuance of a Refuse to Accept (RTA), Refuse to File (RTF), and/or No Marketing Order (NMO); or of a letter administratively closing the application, or cancelling the application if FDA finds that it mistakenly accepted the application or that the application was submitted in error. In addition, the other enforcement priorities discussed in this guidance would apply to such products, regardless of whether or not a premarket application has been submitted for the product.

We note that the March 2019 Draft Guidance had included August 8, 2021, as the date for which FDA would prioritize enforcement for flavored ENDS products that had not submitted premarket applications. A number of comments expressed concern about the impact of the August 2021 date on businesses. For example, several commenters argued that any restriction on the sale or distribution of ENDS products could result in companies going out of business. On the other hand, FDA

received many comments suggesting that in light of the problem of increasing youth access and use of ENDS products, FDA should begin enforcing the premarket authorities as applied to deemed new tobacco products earlier than August 8, 2021. Several comments remarked that FDA should have begun enforcing the premarket review requirements against ENDS products already, that FDA's previous premarket review compliance date extensions enabled some companies to "delay or circumvent areas of regulatory compliance," and that further delays were contrary to public health.

Although FDA considered the potential impact of the draft compliance policy on businesses large and small, we note that, pursuant to the Tobacco Control Act, as of the effective date of the final deeming rule, ENDS products were required to have premarket authorization prior to marketing. While some deemed new tobacco products remained on the market in light of FDA's deferred enforcement policy, such policies are subject to change. Manufacturers cannot have settled expectations to market unlawful products, especially in the face of evolving public health concerns. Therefore, FDA believes that manufacturers should have begun contemplating and/or preparing premarket applications no later than the time of the final deeming rule. As discussed in Section II.B of this Final Guidance, FDA has repeatedly publicly discussed the fact that enforcement discretion timelines for deemed tobacco products were under reconsideration and solicited views from stakeholders. Manufacturers may obtain information about the application process from the statutory criteria, as well as published guidances, webinars, and marketing

orders and their accompanying documentation provided by FDA.[96]

Under the circumstances, FDA believes that earlier enforcement of the premarket review provisions is appropriate for ENDS products. This policy should result in earlier submission of applications and allow FDA to better evaluate whether these products meet the applicable premarket standard, such as whether the products are appropriate for the protection of the public health, considering the risks and benefits to the population as a whole, including users and nonusers of the tobacco product. Because of FDA's concerns regarding youth use of ENDS products, as well as other ongoing health concerns regarding vaping more generally, all described at length above, FDA is prioritizing enforcement of premarket review requirements for ENDS products, as described in this section, and is doing so independently of the court order.

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[96] For more information on premarket tobacco product applications please see Premarket Tobacco Product Applications for [ENDS], Guidance for Industry (June 2019), available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/premarket-tobacco-product-applications-electronic-nicotine-delivery-systems-ends; Applications for Premarket Review of New Tobacco Products (updated June 2019) available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/applications-premarket-review-new-tobacco-products. For more information on CTP's other published regulations and guidances, please see https://www.fda.gov/tobacco-products/products-guidance-regulations/rules-regulations-and-guidance; for more information on FDA CTP webinars, please see https://www fda.gov/tobacco-products/compliance-enforcement-training/fda-tobacco-compliance-webinars; for information on marketing orders and accompanying documentation, please see https://www.fda.gov/tobacco-products/compliance-enforcement-training.

This will ensure that FDA has the necessary information to exercise adequate, timely oversight over these relatively novel and potentially harmful products. Enforcing premarket authorization requirements will, consistent with the process set forth in the Tobacco Control Act, ensure that the burden falls on manufacturers of ENDS products to demonstrate that the manufacture and sale of their products is appropriate for the protection of the public health.

E. Avoiding a "Black Market"

FDA is aware of concerns that, given the rise in popularity of ENDS, removal of some of the most popular products from the market may be accompanied by an increase in black market versions of these products that may pose additional health and safety risks to consumers beyond those of the authentic products. Although all newly deemed products currently on the market without premarket authorization are being sold in violation of the Tobacco Control Act, in this section, we use the term "black market" to refer to, for example, products intended to look like another ENDS products that is currently being marketed, products intended to take the place of an ENDS product that a manufacturer has stopped distributing because the product lacks premarket authorization, and ENDS products intended for another country's market but diverted to the U.S. market. Additional risks posed by these products include the potential that they contain harmful chemicals or constituents that are not present in other products, that they are manufactured using comparatively poor quality controls, and that they are designed in ways that facilitate modifications by distributors or users—all of

which increase the risk of adverse events.[97] Moreover, to the extent that such products are sold through non-traditional retail channels, such as social sources or online commercial marketplaces that do not include age- verification requirements, they pose an increased risk of being accessed by minors.

FDA has regulatory tools and enforcement authorities to address ENDS and other tobacco products that are marketed without authorization, that are counterfeit, and/or that are otherwise involved in illicit trade.[98] FDA has previously issued letters to companies suspected of marketing counterfeit or otherwise unauthorized products.[99] Additional potential actions against adulterated or misbranded illicit tobacco could include: (1) issuing a Warning Letter; (2) issuing an import alert and refusing admission of tobacco products imported or offered for import into the United States; and (3) initiating seizure or injunction court actions. Persons en-

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[97] *E.g.*, "Amid Vaping Deaths, California Targets Counterfeit Products," The New York Times (Sept. 17, 2019), available at https://www.nytimes.com/2019/09/16/us/california-vaping.html; "'Juul-alikes' Are Filling Shelves With Sweet, Teen-Friendly Nicotine Flavors" The New York Times (Aug. 13, 2019), available at https://www.nytimes.com/2019/08/13/health/juul-flavors-nicotine.html; Omaiye, E.E., I. Cordova, B. Davis, et. al., "Counterfeit Electronic Cigarette Products with Mislabeled Nicotine Concentrations," Tobacco Regulatory Science, 3(3): 347-357, 2017.

[98] *See, e.g.*, sections 301, 902, 903, 905, 910, and 920 of the FD&C Act.

[99] *E.g.*, "Statement from FDA Commissioner Scott Gottlieb, M.D., on forceful new actions focused on retailers, manufacturers to combat youth access to e-cigarettes as part of FDA's Youth Tobacco Prevention Plan," available at: https://www fda.gov/news-events/press-announcements/statement-fda-commissioner-scott-gottlieb-md-forceful-new-actions-focused-retailers-manufacturers.

gaging in illicit trade in tobacco products may also be criminally prosecuted under the law.

As a result of this policy, FDA will be better situated to combat black market products, including those that are particularly troubling from a public health or safety perspective, such as counterfeit pods entering the country at the border or being sold through illicit, online channels. By prioritizing our focus as outlined in Section IV.D, the Agency can target our supply chain surveillance and investigation resources on the types of ENDS products that are likely to be subject to counterfeiting and/or sale on the black market. As a result, we will be able to more efficiently and effectively deploy our enforcement tools to get counterfeit and black market products off the market. Moreover, FDA believes that there are significant public health benefits of the policy set forth in this guidance, which is aimed at curbing the dramatic rise in youth use of ENDS products and will help address safety issues connected to ENDS products that are not fully understood—*e.g.*, the development of acute or chronic lung injuries associated with use of vaping products as well as battery explosions with ENDS products—particularly given that these products have been marketed without premarket evaluation. These current public health issues affirm the importance of the premarket review process, as contemplated by the Tobacco Control Act, to scientifically evaluate products based on a public health standard.

V. PREMARKET REVIEW FOR OTHER DEEMED NEW TOBACCO PRODUCTS

FDA remains concerned with minors' access to and use of all tobacco products, particularly flavored tobacco products, which appeal to minors and promote initia-

tion.[100] In addition to the tobacco products covered earlier in this guidance document, FDA has considered revising its enforcement priorities with respect to premarket authorization for other deemed new tobacco products. We note that several comments on the March 2019 Draft Guidance suggested that FDA begin immediately enforcing the premarket requirements for flavored deemed tobacco products such as cigars and other deemed tobacco products.

FDA received numerous comments relating to the proposed policy for flavored cigars in the March 2019 Draft Guidance. Some of the comments were supportive of that proposed policy, although some wanted the Agency to take even more aggressive action. Other comments opposed inclusion of flavored cigars as an enforcement priority and disagreed with the bases for the proposed policy. For example, some commenters argued that flavored cigars are used most commonly by adult users and that the inclusion of flavored cigars as an enforcement priority limits adults' freedom to choose their preferred product. Other commenters argued that FDA did not have the data necessary to support the need for "a drastic and unprecedented change in enforcement priorities." Some commenters also stated that the evidence cited by FDA discussing initiation of youth usage of flavored cigars was inconsistent and inconclusive. After consideration of the data regarding youth use of cigars generally and comments received on this issue, we

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[100] U.S. Department of Health and Human Services, "E-cigarette Use Among Youth and Young Adults: A Report of the Surgeon General," 2016; Villanti, A.C., A.L. Johnson, B.K. Ambrose, et al., "Flavored Tobacco Product Use in Youth and Adults: Findings From the First Wave of the PATH Study (2013-2014)," American Journal of Preventive Medicine, 53(2); 139-151, 2017.

have decided to not prioritize enforcement of flavored cigars before September 9, 2020. While there is no public health benefit associated with flavored cigars and FDA remains concerned with youth use of flavored cigars, current data indicate that youth are using flavored cigars at a lower rate than they are using flavored ENDS products.

Comments regarding deemed tobacco products other than ENDS products and cigars, such as waterpipe tobacco (hookah) products, also provided data showing the use of such tobacco products among high school students and stating that evidence reflects that flavors for these tobacco products entice youth. However, such data do not appear to raise comparably urgent public health concerns, as the lower prevalence of youth use of these products suggests that they do not appear to be as appealing to youth at this time.

Accordingly, at this time, FDA has decided to prioritize use of its limited enforcement resources to address the sudden and dramatic increase in youth use of ENDS products, as well as to focus on health and safety concerns connected to ENDS products such as vaping-associated lung injuries. While acknowledging that all new tobacco products on the market without the required authorization are marketed unlawfully and are potentially subject to enforcement action, at any time, in FDA's discretion, FDA's primary focus will be to address the sudden and dramatic increase in youth use of ENDS products, and the products covered by this section of the guidance will therefore be a lower priority.

We have decided not to prioritize enforcement of the tobacco products covered by this section before September 9, 2020. Manufacturers of flavored cigars, however,

just like manufacturers of all other deemed new tobacco products, will be required to submit marketing applications for those products by September 9, 2020, consistent with the U.S. District Court for the District of Maryland's order directing FDA to require that applications be submitted to the Agency by September 9, 2020, for deemed new tobacco products on the market as of August 8, 2016, or be subject to FDA enforcement actions, in FDA's discretion. As part of the premarket review process, FDA may evaluate, among other things, the product's constituents, ingredients, additives, and properties; manufacturing practices; and any studies or investigations into the health risks of the tobacco product. FDA also has stated its intention to issue a regulation that would ban the use of characterizing flavors in cigars, and FDA is actively working towards that proposed rule.

After September 9, 2020, FDA will make enforcement decisions on a case-by-case basis, recognizing that it is unable, as a practical matter, to take enforcement action against every illegally marketed tobacco product, and that it needs to make the best use of Agency resources. FDA intends to prioritize enforcement based on the likelihood of youth use or initiation to make the most efficient use of its resources. In assessing this, factors the Agency intends to consider include, but are not limited to:

- What FDA understands about the number of youth currently using the product or category of product;
- The trends in those numbers, particularly since 2016;
- Whether the product contains added flavors;

- What FDA understands about how the product or category of product is typically sold and how that is likely to impact access and use by minors; and
- What FDA understands about the frequency and other demographics of use by minors.

To illustrate, based on these factors, FDA's lowest priority among these products will include relatively expensive, large hand-rolled cigars that do not have flavors (*e.g.*, fruit, candy, or mint), given what FDA understands to be their comparatively lower youth usage rates.

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FDA is continuously evaluating new information and adjusting its enforcement priorities in light of the best available data, and it will continue to do so with respect to these products. FDA will take appropriate action regarding tobacco products that are marketed without premarket authorization, including as warranted based on changed circumstances, new information, or to better address minors' use of those products.

VI. DOCUMENT HISTORY

January 2020—First edition of guidance issued.

April 2020—Guidance is revised to reflect the court's order in *American Academy of Pediatrics, et al. v. Food and Drug Administration, et al.,* Case No. 8:18-cv-883 (PWG), (D. Md. Apr. 22, 2020), Dkt. No. 182, granting a motion for a 120-day extension (until September 9, 2020) in light of the global outbreak of respiratory illness caused by a new coronavirus. Specific revisions include the following:

- Section II.A—Added reference to order granting 120-day extension.
- Section IV.A (and throughout)—Changed language stating that FDA's new enforcement priorities would begin "30 days after issuance of this Final Guidance" to "February 6, 2020," which is 30 days after the Notice of Availability announcing the Final Guidance was published.
- Section IV.A (and throughout document)—Changed "May 12, 2020" to "September 9, 2020."

APPENDIX A—SIGNIFICANT COMMENTS RECEIVED IN RESPONSE TO MARCH 2019 DRAFT GUIDANCE AND FDA RESPONSES

Legal and statutory framework issues	
Comment	Response
FDA should engage in legislative rulemaking process • The draft guidance constituted a major rule and FDA has not followed procedures established by the Administrative Procedure Act (APA) governing the promulgation of rules • The Regulatory Flexibility Act requires an analysis of a proposed rule's impact on small business and FDA has not conducted such an analysis • FDA is bypassing the requirement to conduct a cost benefit analysis by issuing a guidance	The Final Guidance is a statement of policy that discusses the enforcement of premarket authorities already existing in the statute. It does not establish any rights for any person, is not binding on FDA or the public, and is not subject to requirements of the Regulatory Flexibility Act or the notice-and-comment provisions of the APA. Historically, FDA has not analyzed the economic effects of enforcement guidance, including for reasons such as difficulty in predicting such effects. Alternatives such as issuing warning letters and other enforcement techniques have been considered and used by the Agency. Despite this, as shown by the data high-

instead of formal rule • FDA has not considered regulatory alternatives to the approach outlined in the draft guidance • This action would impose costs and adverse effects on industry which constitutes a major rule which should be subject to the requirements under the Congressional Review Act • Though guidance documents are non-binding, the way the guidance is written, retail outlets would need to comply with standards suggested by the draft guidance as though they were law • Engaging in rulemaking would offer more substantial opportunity for	lighted in the Final Guidance, the rate of youth use of tobacco products (particularly fruit- and candy-flavored and mint-flavored ENDS products) has dramatically increased. FDA retains discretion to enforce premarket authorities. The relevant substantive requirements are those governing premarket authorization as set forth in Section 910. The Final Guidance does not impose new restrictions, for retailers or manufacturers, but rather discusses FDA's enforcement priorities for existing statutory requirements. In Section 910, Congress placed the onus on manufacturers to demonstrate that the marketing of a tobacco product is appropriate for the protection of the public health, taking into account, among other things, the likelihood that those who do not use tobacco products will start using them.

stakeholders to provide public comments and would provide clarity on what stakeholders (through the supply and retail chain), needed to do to come into compliance	FDA provided for a 45-day period for comment on the draft guidance, and interested parties may continue to submit comments after publication of the final guidance, providing a substantial opportunity for public input.
FDA is bypassing statutory restrictions on its discretionary enforcement authority and obligations related to rulemaking, by threatening selective enforcement of its premarket authorization authority.	FDA has discretion to decide how when to enforce its premarket authorization authorities under the FD&C Act. *See Heckler v. Chaney*, 470 U.S. 821, 835 (1985). The Final Guidance is a statement of policy that outlines FDA's enforcement priorities with respect to such requirements.
Guidance should conform to Section 907. • Actions in this guidance should conform to Section 907, which obligates FDA to consider factors not addressed by the guidance, including	Section 907 refers to tobacco product standards. This Final Guidance is not setting tobacco product standards, such as a tobacco product standard restricting or eliminating the use of flavors in ENDS. Instead, it is explaining FDA's enforcement priorities for pre-

technical achievability and countervailing effects. • FDA should not adopt modifications to compliance policy but should instead follow through with a rule that considers the comments from FDA's ANPRM on Flavors in Tobacco Products.	market review requirements already included in the Tobacco Control Act. A flavored product could be marketed consistent with this guidance if it meets the statutory standards for authorization. For example, in April 2019, FDA authorized the marketing of a menthol-flavored IQOS heat-not-burn cigarette product through the PMTA pathway.[101]
FDA is supposed to be an advisory agency, not a regulatory agency, and its actions are an overreach.	The Tobacco Control Act provides FDA with regulatory authority over tobacco products.
FDA's proposed actions are arbitrary and capricious because it has failed to provide adequate reasoning/scientific reasoning/used incomplete or incorrect data.	The enforcement priorities explained in the Final Guidance are based upon and supported by, among other things, multiple high-quality scientific data sources (*e.g.*, NYTS, PATH, MTF).

[101] For more information please see https://www.fda.gov/news-events/press-announcements/fda-permits-sale-iqos-tobacco-heating-system-through-premarket-tobacco-product-application-pathway.

FDA has failed to connect the proposed policy to an official finding that the actions were "appropriate for the protection of public health."	The Final Guidance discusses the enforcement of premarket authorities already existing in statute. Section 910 places the onus on manufacturers to show that the marketing of a tobacco product would be appropriate for the protection of the public health, not on the FDA to show otherwise. The Tobacco Control Act uses the term "appropriate for the protection of the public health," in section 910 and several other provisions. The considerations identified in the statute typically include analysis of whether the action would increase or decrease the likelihood that existing users of tobacco products would stop using such products, and whether it would increase or decrease the likelihood that those who do not use tobacco products will start using the products. The Guidance reflects these considerations.

FDA has been unresponsive/lack of clarity. • Manufacturers have been relying on guidance and information since the deeming rule; this is a drastic departure from deeming and guidances issued since deeming. • Difficult to keep track of FDA's policies and compliance requirements.	FDA has communicated its concerns regarding the increase in youth access in public statements, the March 2019 draft guidance, and requests for information to manufacturers. FDA has consistently informed industry that its compliance policies will be responsive to changed circumstances. There could be no reasonable reliance on a deferred enforcement policy subject to change at any time. The guidance explains why the changed circumstances warrant this prioritization; *i.e.*, the substantial increase in youth use of ENDS in addition to other health and safety considerations. FDA has always stated (and the Tobacco Control Act itself is clear) that deemed new tobacco products are required to obtain premarket authorization and that such products that remain on the market without marketing au-

	thorization are marketed unlawfully.
FDA has stated it will provide further guidance and issue rules to make the product review process more transparent and predictable but has not done so.	FDA has provided guidance and information to industry on the premarket pathways through publishing guidances and marketing orders, as well as posting information via webinars and public workshops.[102] The statute also informs the public of the information needed in a premarket tobacco product application. Industry members have successfully obtained marketing authorization orders with

[102] For more information on premarket tobacco product applications please see Premarket Tobacco Product Applications for [ENDS], Guidance for Industry (June 2019), available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/premarket-tobacco-product-applications-electronic-nicotine-delivery-systems-ends; Applications for Premarket Review of New Tobacco Products (updated June 2019) available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/applications-premarket-review-new-tobacco-products. For more information on CTP's other published regulations and guidances, please see https://www.fda.gov/tobacco-products/products-guidance-regulations/rules-regulations-and-guidance; for more information on FDA CTP webinars, please see https://www fda.gov/tobacco-products/compliance-enforcement-training/fda-tobacco-compliance-webinars; for information on marketing orders and accompanying documentation, please see https://www fda.gov/tobacco-products/compliance-enforcement-training.

	information currently available.
Draft guidance would have unjustifiable retroactive effects on industry actors who were "in compliance" with FDA's previous policy.	This Final Guidance would only affect those products that are illegally on the market; none of the products affected by the guidance were ever in compliance with the premarket authorization requirements of the law. FDA has consistently informed industry that its compliance policies will be responsive to changed circumstances. As discussed in the guidance, FDA stated in the notice of proposed rulemaking for the Deeming Rule, that the overall public health impact of ENDS products would depend crucially upon "who uses the products and how they are used. If such products result in minimal initiation by children and adolescents while significant numbers of smokers quit, then there is a potential for the net impact at the population level to be positive. If, on

	the other hand, there is significant initiation by youth, minimal quitting, or significant dual use of combust[ed] and non-combust[ed] products, then the public health impact could be negative." As such policies are subject to change, manufacturers cannot have settled expectations to market unlawful products, especially in the face of evolving public health concerns. Therefore, FDA believes that manufacturers should have begun contemplating and/or preparing premarket applications at no later than the time of the final deeming rule.
Draft guidance will kill innovation and force industry out of work.	FDA disagrees that the Final Guidance will cause these results. The Final Guidance explains FDA's enforcement priorities for certain deemed new products that are being marketed without required premarket tobacco product authorization. The Final Guidance

	would only affect those products that are illegally on the market; none of the products affected by the guidance were ever in compliance with the premarket authorization requirements of the law. In any event, FDA believes that the use of premarket pathways will incentivize development of innovative tobacco products that meet the applicable statutory standards.
Draft guidance policy on marketing practices would violate the First Amendment as it represents an impermissibly broad commercial speech restriction.	FDA disagrees that the Final Guidance violates the First Amendment. Speech regarding an illegal activity—including distribution of a product that requires premarket review under the FDCA—is not protected under the First Amendment. *See United States v. Caputo,* 517 F,3d 935 941 (7th Cir. 2008) (unapproved device); *United States v. LeBeau,* 654 Fed. App'x 826, 831 (7th Cir. 2016) (unapproved drng); *United States v. Cole,* 84 F. Supp. 3d 1159

	11-66-67 (D. Or. 2015) (unapproved drug). Even if the First Amendment were applicable, the government has a substantial interest in protecting youth from tobacco products, and prioritizing enforcement actions with respect to ENDS products targeted to, or likely to promote use by, minors is a reasonable measure to directly advance that interest. *See, e.g., Discount Tobacco City & Lottery, Inc. v. United States,* 674 F.3d 509 536 (6th Cir. 2012). We have provided additional examples for clarity in the Final Guidance.
Modifications to ENOS Compliance Policy—Flavored ENDS except Tobacco, Mint, Menthol	
Comment	Response
There is no evidence/ limited evidence to connect liquid nicotine use with harmful health effects in youth.	As discussed in the Final Guidance the studies of the effects of nicotine exposure in the naïve adolescent brain find that the adolescent brain is uniquely vulnerable to

	nicotine compared to the adult brain. Repeated exposure to nicotine during adolescence induces long-lasting structural and functional changes in brain regions involved in addiction, attention, learning, and memory.[103] Studies further suggest that nicotine-induced changes in the adolescent brain can lead to long-lasting effects on cognitive function, such as cognitive deficits following nicotine abstinence, and may contribute to the risk for mood and anxiety disorders. Nicotine is the primary addictive substance in tobacco products, including e-cigarettes and

[103] McDonald, C.G., A.K. Eppolito, J.M. Brielmaier, et. al., "Evidence for elevated nicotine-induced structural plasticity in nucleus accumbens of adolescent rats," Brain Research, 1151, 211-218, 2007; doi: 10.1016/j.brainres.2007.03.019; Bergstrom, H.C., R.F. Smith,, N.S. Mollinedo, et al., "Chronic nicotine exposure produces lateralized, age-dependent dendritic remodeling in the rodent basolateral amygdala," Synapse, 64(10), 754- 764, 2010; doi:10.1002/syn.20783; England, L.J., K. Aagaard, M. Bloch, et al., "Developmental toxicity of nicotine: a transdisciplinary synthesis and implications for emerging tobacco products," Neuroscience and Biobehavioral Reviews, 72:176-189, 2017.

	combustible cigarettes. The rate and extent of nicotine delivery significantly impact product abuse liability. Higher nicotine content and faster rates of nicotine delivery increase products' abuse liability due to the rapid absorption of nicotine into the brain. Some e-cigarettes are capable of achieving similar or greater nicotine delivery as cigarettes.[104]

[104] Hiler, M., A. Breland, T. Spindle, et al., "Electronic cigarette user plasma nicotine concentration, puff topography, heart rate, and subjective effects: Influence of liquid nicotine concentration and user experience," Experimental and Clinical Pharmacology, 25(5), 380-392, 2017; doi:10.1037/pha0000140; Lopez, A.A., M.M. Hiler, E.K. Soule, et al., "Effects of Electronic Cigarette Liquid Nicotine Concentration on Plasma Nicotine and Puff Topography in Tobacco Cigarette Smokers: A Preliminary Report," Nicotine & Tobacco Research, 18(5):720-723, 2016; doi:10.1093/ntr/ntv182; Maloney, S. F., A. Breland, E.K. Soule, et al. "Abuse liability assessment of an electronic cigarette in combustible cigarette smokers," Experimental and Clinical Psychopharmacology, 27(5):443-454, 2019; doi:10.1037/pha0000261; O'Connell, G., J.D. Pritchard, C. Prue, et al, "A randomised, open-label, cross- over clinical study to evaluate the pharmacokinetic profiles of cigarettes and e-cigarettes with nicotine salt formulations in US adult smokers," Internal and Emergency Medicine, 14(6):853-861, 2019; doi:10.1007/s11739- 019-02025-3; Ramoa, C. P., M.M. Hiler, T.R. Spindle, et al. "Electronic cigarette nicotine delivery can exceed that of combustible cigarettes: a preliminary report," Tobacco Control, 25(e1): e6-9, 2016; doi:10.1136/tobaccocontrol-2015-052447; Yan, X. S., & C. D'Ruiz,

"Banning" flavors outside of tobacco, mint, and menthol would deter cigarette smokers from quitting or force smokers to restart smoking if they have already quit. • Smokers trying to quit smoking avoid tobacco-, mint-, and menthol-flavored products because they are too similar to flavors of a traditional cigarette. • Stricter policies for ENDS products for youth should not come at expense of adult users.	The Final Guidance does not ban any products but rather identifies FDA's priorities in connection with the enforcement of the statutory premarket review requirements. Moreover, the policy announced in the Final Guidance does not prioritize any menthol-flavored, tobacco-flavored, or non-flavored ENDS products or any non-cartridge-based flavored ENDS products for enforcement where the manufacturer is taking adequate measures to prevent minors' access to these products. Additionally, consumers will be able to access ENDS products (including flavored ENDS products) that receive market authorization. Nicotine replacement therapy products also remain available

"Effects of using electronic cigarettes on nicotine delivery and cardiovascular function in comparison with regular cigarettes," Regulatory Toxicology and Pharmacology, 71(1):24-34, 2015; doi:10.1016/j.yrtph.2014.11.004.

	for tobacco product users who may need assistance with withdrawal symptoms and are also available in several flavors. Available research does not support the argument that smokers trying to quit smoking and transition to ENDS products avoid tobacco and menthol-flavored ENDS products because they are too similar to traditional cigarette flavors. FDA has repeatedly emphasized that the availability of non-combustible options should not come at the expense of addicting a generation of children to nicotine through these same delivery vehicles. FDA believes that this policy strikes an appropriate balance between preventing youth access to ENDS products and maintaining availability of potentially less harmful options for current adult smokers who have transitioned or wish to transition completely

	away from combusted tobacco products.
No basis for prioritizing flavored ENDS products. • The policy will not be successful at keeping kids from using these products; kids use anything that is taboo and illegal. • Youth are more attracted to these products due to peer use than flavors. • Youth use ENDS products for nicotine delivery not for flavors. • Only a correlative, not causal, relationship between youth preference for flavors and increased ENDS usage.	As discussed in the Final Guidance, data from 2018 NYTS as well as from 2019 Monitoring the Future study and 2019 NYTS show a significant increase in youth use of these products. Data also clearly show that flavors are a primary driver in youth experimentation with, and continued use of, ENDS products, and that the flavored ENDS products overwhelmingly used by youth are cartridge-based products. The policy outlined in the Final Guidance prioritizes enforcement of ENDS products that are targeted to minors or likely to promote use of ENDS by minors. FDA expects that this policy and others stated in the guidance will make fewer products available and more difficult for youth to obtain.

No basis for excluding tobacco, mint, and menthol from prioritization. • General increasing popularity of mint and menthol ENDS products amongst youth populations. • Mint- and menthol-flavored products drive youth ENDS usage. • Flavors clearly increase appeal of ENDS products and some flavors have toxic effects and documented respiratory toxicity.	The Final Guidance explains that FDA intends to prioritize mint-flavored, cartridge-based ENDS products (and any other flavored, cartridge-based ENDS product, other than tobacco- or menthol-flavored ENDS products) for enforcement for lack of a marketing authorization. The guidance also explains that FDA intends to prioritize enforcement for lack of a marketing authorization for any tobacco- or menthol-flavored ENDS products and non-cartridge-based flavored ENDS products when the manufacturer is not taking adequate measures to prevent minors' access to these products. Data shows that tobacco- and menthol-flavored ENDS products are not as appealing to minors as other flavored ENDS products. While the NYTS groups mint- and menthol-flavored products together, a

	randomly-selected third of respondents to the Monitoring the Future (MTF) study were asked specifically about their preferred flavors of JUUL and reported use of menthol- and tobacco-flavored products were among the lowest ranked options. Based on the available data and FDA's interest in balancing between preventing youth usage and preserving options for adults trying to transition away from combustible products, FDA is not prioritizing enforcement against tobacco-, menthol-, and non-flavored ENDS products or non-cartridge-based flavored ENDS products except when the manufacturer is not taking adequate measures to prevent minors' access to these products.
Prioritizing flavors for enforcement will create a significant black market for "banned" flavors out-	By black market flavored products, we assume this could refer to, for example, flavored ENDS products, including e-liquids,

side those that are exempted.	put on the market after the guidance, flavored ENDS products diverted from another country's market to the U.S market, and/or flavored ENDS products made to look like another ENDS product that is currently being marketed. FDA has regulatory tools and enforcement authorities to address deemed tobacco products that are marketed without authorization, counterfeit, and/or otherwise involved in illicit trade. *See, e.g.*, sections 301, 902, 903, 905, 910, and 920 of the FD&C Act. This Final Guidance describes the Agency's enforcement priorities for products that are on the market without the required premarket authorization—it does not ban any tobacco product—and illicit ENDS products are necessarily subject to the enforcement priorities identified in the guidance as they do not

	have premarket authorization. Thus, FDA believes that this policy will not significantly increase illicit practices or create new illicit markets, and it could help FDA better address such practices. Once products receive premarket authorization, they can legally enter the market. FDA believes that there are significant public health benefits of the policy set forth in the guidance, which is aimed at curbing the dramatic rise in youth use of ENDS products and will help address safety issues connected to ENDS products that are not fully understood—*e.g.*, lung injuries associated with use of vaping products as well as battery explosions with ENDS products—particularly given that these products have been marketed without premarket evaluation. These current public health issues affirm the impor-

	tance of the premarket review process, as contemplated by the Tobacco Control Act, to scientifically evaluate products based on a public health standard. FDA believes that by pursuing this policy the Agency will be better able to monitor and identify illicit cartridge-based products that are threats to public health and safety. As flavored, cartridge-based products exit the market until they are able to demonstrate that they meet the applicable public health standard and receive authorization, the number of potential flavored, cartridge-based products that could cause these threats will shrink to a more manageable number for FDA to monitor. Thus, FDA expects that to the extent any illicit markets were to develop with respect to cartridge-based products in an attempt to evade premarket review requirements, this guid-

	ance will help FDA better address the public health threats caused by such markets and the overall public health benefits that will likely accrue as a result of the guidance will be greater than any negative effects of increased illicit markets. Moreover, FDA does not believe that the Agency should refrain from enforcing existing statutory authorities merely because regulated entities could find other ways to violate such authorities. The Agency can, and will, continue to monitor the marketing and use of ENDS and other tobacco products, and adjust its policies and approaches as warranted.
Many other harmful products (*e.g.*, alcohol) are available in various flavors attractive to youth; it is inconsistent to only prioritize for enforcement flavored ENDS products.	The policy expressed in this Final Guidance is limited solely to tobacco products over which FDA has statutory authority. The focus of this guidance and the Agency's enforcement priorities is tobacco products, specifically certain ENDS products.

	Moreover, this comment is about flavored alcohol products that are lawfully on the market, whereas this guidance concerns products being sold in violation of the requirement to have premarket authorization, where the product's ingredients and additives are among the considerations in the premarket review.
FDA should focus its enforcement priorities on products that contain nicotine salts and/or should specify differences between nicotine and nicotine salts.	FDA believes that ENDS products containing nicotine salts will be adequately addressed by the enforcement priorities set in this Final Guidance. Research is ongoing to better understand the abuse liability associated with nicotine-salt based e-liquids and new cartridge-style ENDS products, the potential for initiation in youth and nonusers, and the potential for switching from combusted cigarettes in current smokers from use of these products. Pre-

	liminary research indicates that nicotine salts in ENDS products can drive nicotine exposures in users higher than ENDS containing freebase nicotine; these exposures can also be comparable to or potentially higher than cigarettes.[105] In addition to greater nicotine exposures, ENDS with nicotine salts can have faster absorption[106] and potentially faster elimination from the blood.[107] These

[105] Goniewicz, M. L., R. Boykan, C.R. Messina, et al., "High exposure to nicotine among adolescents who use Juul and other vape pod systems ('pods')," Tobacco Control, 28(6), 2019; doi:10.1136/tobaccocontrol-2018-054565; Talih, S., R. Salman, R. El-Hage, et al, "Characteristics and toxicant emissions of JUUL electronic cigarettes," Tobacco Control, 28(6):678-680, 2019; doi:10.1136/tobaccocontrol-2018-054616; Teichert, A., P. Brossard, L.F. Medlin, et al, "Evaluation of Nicotine Pharmacokinetics and Subjective Effects following Use of a Novel Nicotine Delivery System," Nicotine Tobacco Research, 20(4):458-465, 458-465; doi:10.1093/ntr/ntx093.

[106] O'Connell, G., J.D. Pritchard, C. Prue, et al., "A randomised, open-label, cross-over clinical study to evaluate the pharmacokinetic profiles of cigarettes and e-cigarettes with nicotine salt formulations in US adult smokers," Internal and Emergency Medicine, 14:853-861, 2019; doi:10.1007/s11739-019-02025-3.

[107] Bowen, A., & C. Xing, "Nicotine Salt Formulations for Aerosol Devices and Methods Thereof," United States Patent, Pub. No. US 2015/0020824, 2015, https://patentimages.storage.googleapis.com/57/f8/7e/2db69f396801d5/US20150020824A1.pdf (visited Oct 8 2019).

	factors can increase the abuse liability of ENDS with nicotine salts compared to freebase nicotine, and potentially cigarettes. The higher abuse liability of ENDS with nicotine salts compared to freebase nicotine raises concerns of addiction in youth, particularly due to the vulnerability of the developing adolescent brain. However, for many individual addicted cigarette smokers, the potential for ENDS to act as a substitute for cigarettes, thereby encouraging smokers to seek to switch completely away from combustible cigarettes, may be dependent, in part, upon the product having acceptability and abuse liability more comparable to a cigarette. The Final Guidance focuses FDA's priorities on flavored, cartridge-based ENDS products because data show that flavors

	are a strong driver for youth use, and that youth overwhelmingly prefer cartridge-based ENDS products. However, FDA is continuously evaluating new information and adjusting its enforcement priorities in light of the best available data, including any data on ENDS products containing nicotine salts, and it will continue to do so with respect to to these products.
FDA should focus its enforcement priorities on cartridge-based ENDS products.	FDA is concerned about the rising youth appeal and use of ENDS products. The data show that flavors are a strong driver for youth use, and that youth overwhelmingly use cartridge-based ENDS products. Accordingly, such products are a key focus of the Final Guidance. FDA will, however, take appropriate action regarding ENDS that are marketed without premarket authorization, including as warranted based on changed

	circumstances, new information, or to better address minors' use of those products.
Modifications to ENDS Compliance Policy—Offered for sale in ways that pose a greater risk for minors to access such products	
Comment	Response
The Tobacco Control Act prohibits FDA from restricting tobacco sales to a specific category of retail outlets.	FDA is not restricting or even prioritizing enforcement against ENDS products sold in a specific category of retail outlets. Although the March 2019 Draft Guidance proposed to focus its enforcement priorities for flavored ENDS products on how the product was sold (regardless of the type of retail establishment), after considering the comments, the public health threats, and new evidence, FDA determined that focusing on how the product was sold would not be sufficient to address youth use of these products. Given the urgent need to address the dramatic rise in youth

	use, this Final Guidance prioritizes enforcement with respect to any flavored, cartridge-based ENDS products (other than a tobacco- and menthol-flavored ENDS product) without regard to the location or method of sale. With respect to tobacco-, menthol-, and non-flavored ENDS products as well as flavored cartridge-based ENDS products, the Final Guidance states that FDA does not intend to prioritize enforcement where manufacturers have taken adequate measures to prevent youth access. These types of measures generally are among those that manufacturers have informed FDA that they are capable of implementing for ENDS products and none involve a specific category of retail outlet.
Lack of clarity for retail locations	FDA has provided additional details regarding

• Should retail locations have age verification at their door or a separate room for the sale of any ENDS products? • Can retail locations employ less burdensome alternatives? • Concern that the policy could make traditional cigarette products more easily accessible than ENDS products. • Need clarity on how manufacturers or wholesalers can document adequate measures to prevent youth access. • How are retail outlets supposed to balance space constraints with youth access concerns? • FDA should give existing enforce-	factors that it intends to consider in assessing whether a manufacturer is taking adequate measures to prevent youth access. For example, the Final Guidance lists several different types of programs to monitor compliance with age-verification and sales restrictions, all of which are programs that some manufacturers have stated they are capable of implementing for ENDS products. Unlike the Draft Guidance, it does not include, as a factor for prioritization, whether the product is sold by retailers in a location where minors are able to enter at any time. The March 2019 Draft Guidance proposed to focus its enforcement priorities of flavored ENDS products on how the product was sold (regardless of the type of retail establishment). After considering the comments, the public health threats, and new evi-

ment mechanisms the chance to succeed or focus on enforcing existing mechanisms before instituting new policy.	dence, FDA determined that, to address youth use of these products, this Final Guidance should prioritize enforcement with respect to any flavored, cartridge-based ENDS products (other than a tobacco- and menthol-flavored ENDS product) without regard to the location or method of sale. The alarming data on the increase in youth use of ENDS products shows that the FDA's enforcement efforts to date did not adequately address this problem.
Enforcement priorities would effectively ban many retailers from selling ENDS products while allowing sales from vape shops and online retailers. • Concerns that many retailers will be forced to close. • Concerns that this will just cause retailers to shift unauthorized prod-	This Final Guidance prioritizes enforcement with respect to any flavored, cartridge-based ENDS products (other than a tobacco- and menthol-flavored product) without regard to the location or method of sale. In addition, the Final Guidance explains that FDA intends to prioritize enforcement for lack of a marketing authorization

ucts to vape shops and other stores. • Concerns about the rise in youth use of open tank systems and sourcing of e-vapor products at vape shops, as indicated by an analysis of Wave 2 (2014-2015) to Wave 3 (2015-2016) of results from the PATH study.	for tobacco-, menthol-, and non-flavored ENDS products and for non-cartridge- based flavored ENDS products where the manufacturer is not taking adequate measures to prevent youth access to ENDS products. For example, the Final Guidance lists several different types of programs to foster compliance with age-verification and sales restrictions, all of which are programs that some manufacturers have stated they are capable of implementing for ENDS products. Finally, FDA notes that there has been a dramatic rise in youth use of cartridge-based ENDS products since Wave 3 of the PATH study was completed in 2016, as demonstrated by results from the NYTS in 2018 and 2019. These recent data inform FDA's serious public health concerns regarding the sale of certain flavored, cartridge-

	based products without premarket authorization. Moreover, although this Final Guidance should have minimal impact on those vape shops that primarily sell non-cartridge ENDS products and ensure that purchasers are of the requisite age and are not purchasing for resale (*e.g.*, are not purchasing in large quantities), should evidence indicate to the contrary, the Agency will take appropriate action.
Stricter enforcement of current age verifications rules would be an effective enforcement strategy. • Lax enforcement is a primary driver of youth ENDS use. • FDA should increase penalties to retailers who violate current regulations and sell to minors.	As described in the Final Guidance, FDA vigorously enforces the age verification requirements in its compliance check program. FDA has been focusing enforcement efforts on age verification as a strategy to address youth use of tobacco products, and FDA continues to enforce age restrictions. However, FDA believes that age verification alone is not sufficient to address this issue, given the most re-

• Age verification should be as strong as it is for alcohol. • There is a need for stricter age verification for online sales of ENDS products.	cent data that youth use of ENDS products continues to increase. FDA determined that focusing on how the product was sold would not be sufficient to address youth use of these products given the many sources of products available for youth access. The reality is that youth have continued access to ENDS products in the face of legal prohibitions and even after voluntary actions by some manufacturers. FDA believes that the policy expressed in the Final Guidance is a more appropriate means to combat youth use of, and access to, these products.
Many companies already comply with age verification requirements. • Policies that encourage additional measures would harm law-abiding retailers.	The Final Guidance does not require additional age verification measures. Instead, it states that FDA intends to prioritize enforcement for lack of a marketing authorization for tobacco-, menthol-, and non-flavored ENDS products as well as non-cartridge-based flavored

	ENDS products where the manufacturer is not taking adequate measures to prevent youth access to ENDS products.
Online sales of ENDS products should be banned.	This suggested sales restriction is outside of the scope of this guidance, which concerns enforcement of the premarket authorization requirements. At this time, FDA is finalizing this Guidance to address its concerns regarding youth use of ENDS products. The guidance prioritizes enforcement with respect to flavored, cartridge-based ENDS products because data shows that flavors are the primary driver in youth experimentation with, and continued use of, ENDS products, and that youth overwhelmingly use cartridge-based ENDS products. These priorities apply whether the products are sold online or in brick-and-

	mortar stores. However, the Agency will continue to monitor this issue.
Lack of clarity on what quantity limits for online sales would entail.	Given the data that many youth obtain their ENDS products from friends or sources in their social networks, FDA believes that quantity limits are one measure that a manufacturer could adopt to prevent individuals from purchasing large quantities of ENDS products to then distribute to minors on a secondary market. FDA's enforcement decisions will be made on a case-by-case basis and depend on many factors, but FDA intends to consider whether a manufacturer limits the quantity of ENDS products that a customer may purchase within a given period of time as a factor in assessing whether a manufacturer is taking adequate measures to prevent youth access. There is wide variation in these types of ENDS products and, based on some of the

	comments FDA received and the responses to the Agency's September 12, 2018 letters, FDA believes individual manufacturers are best positioned to know how to set purchase limits for their specific products. Therefore, FDA does not believe that further detail is warranted regarding this issue.
Age to purchase ENDS products should be increased to 21.	On December 20, 2019, the President signed into law legislation that raised the federal minimum age of sale of tobacco products from 18 to 21 years. FDA views this as a major step in protecting the next generation of youth from becoming addicted to ENDS and other tobacco products. FDA believes, however, that this change alone is not sufficient to address the epidemic use of ENDS by youth, especially use of flavored, cartridge-based products (except for tobacco- or menthol-flavored products) that

	are easily concealed, produced on a large scale, and (in some cases) sold in bulk quantities that has helped enable resale through social or black market sources. As part of the premarket review process for these products, FDA intends to consider measures taken by manufacturers to control youth access to these products.
Purchasing from other adolescents is a major factor driving ENDS usage in youth populations. • FDA should increase penalties for individuals who provide products to youth. • This type of behavior should be the responsibility of parents, not the government. • Only specialty vape stores should be permitted to sell ENDS.	FDA agrees that social sources remain a concern for ENDS and other tobacco products. Given the popularity of social sources, FDA believes that quantity limits could be effective in preventing individuals from purchasing large quantities of ENDS products to then distribute to minors on a secondary market. Accordingly, FDA intends to consider whether a manufacturer limits the quantity of ENDS products that a customer may purchase within a given

• Data from CDC's 2017 Youth Risk Behavior Surveillance System (YRBSS) found that 86.4% of youth who used ENDS did not purchase them at a retail store. • Youth will find ways to purchase restricted flavored products and increased regulations will be ineffective.	period of time as a factor in assessing whether a manufacturer is taking adequate measures to prevent youth access.
Limits on retail or online sales would remove two of the top purchase options for adult ENDS product users.	The priorities in the Final Guidance are addressed to particular products, not retailers. FDA believes that the Final Guidance strikes an appropriate balance between preventing youth access to ENDS products and maintaining availability of potentially less harmful options for current adult smokers who have transitioned or wish to transition completely away from combusted to-

	bacco products. FDA would consider measures taken by manufacturers to control youth access, not adult access, when determining whether to enforce the premarket authorities with respect to these products.
Does not provide adequate reasoning or specificity for manufacturers to understand what marketing actions would prompt enforcement actions.	FDA's decision to exercise its enforcement authorities with respect to particular products will be determined on a case-by-case basis, informed by the enforcement priorities described in this Final Guidance and any other relevant factors. The Final Guidance provides a number of examples of measures manufactures can take to help prevent youth access to their tobacco products. Such examples reflect information provided by manufacturers in response to the Agency's September 12, 2018 letters, including measures to address youth use that manufacturers can or have already taken to ad-

	dress youth access to ENDS products, as well as information provided in comments to the March 2019 Draft Guidance.
Modifications to ENDS Compliance Policy—flavored ENDS offered for sale after August 8, 2021, without the manufacturer submitting (and FDA receiving) a premarket application	
Comment	Response
Moving up the compliance review date would be harmful. • Has the potential to impact adults using ENDS products for smoking cessation purposes. • Will harm businesses that have already planned for the initial date. • Will exacerbate an already burdensome premarket review process. • Will be difficult for small businesses to	The Tobacco Control Act provides that new tobacco products may not be legally marketed without premarket authorization. Accordingly, all deemed new tobacco products on the market without authorization are illegally marketed products. As discussed in the Final Guidance, industry had notice that FDA would revisi1t its compliance policy if necessary. The Final Guidance announces that FDA intends to prioritize for enforcement ENDS products for which a premarket application has

submit complete applications by August 8, 2021.	not been submitted by September 9, 2020. FDA understands the concerns expressed by these commenters but believes that it is appropriate for ENDS products to undergo premarket review on a shorter timeframe given the rise in youth use, in addition to other new and continuing public health and safety concerns, such as the outbreak of pulmonary injuries and battery hazards.
Leaving products on the market for this long is problematic. • Date is still too far away and will allow harmful products to remain on the market. • Deadline means longer time for products on the market to continue to make unsubstantiated claims without scientific review.	FDA agrees with these commenters that the proposed August 8, 2021, date would allow products that may be harmful to remain on the market too long, would allow products to market unsubstantiated claims without scientific review, and that the data before the agency does not justify later premarket review. The Final Guidance discusses the date for premarket application submission and the importance of earlier sub-

• Leaving products on the market is problematic due to lack of evidence justifying later premarket review.	mission of applications to allow for FDA to better evaluate whether these products meet applicable premarket standards, such as whether the products are appropriate for the protection of the public health, considering the risks and benefits to the population as a whole, including users and nonusers of the tobacco product.
Lack of clarity around date for submission of premarket review applications • FDA should articulate the status of submitted premarket applications and provide manufacturers opportunity to amend applications in light of changing deadlines. • Still unclear what information must be included in a	The Final Guidance discusses dates for submission of applications for premarket review and provides links to application submission information, including where to view marketing orders and accompanying documentation, available at FDA.gov. FDA has provided guidance and information to industry on the premarket pathways through publishing guidances and marketing orders, as well as posting

PMTA and/ or SE report	information via webinars and public workshops.[108]
Modifications to ENDS Compliance Policy—targeted to minors or likely to promote use of ENDS product by minors	
Comment	Response
FDA should use its authority to require ENDS manufacturers to stop running ads with unsubstantiated claims about smoking cessation and modified risk claims.	This is outside of the scope of the Final ENDS guidance, which addresses premarket review requirements for ENDS products. FDA closely monitors retailer, manufacturer, importer, and distributor compliance with Federal to-

[108] For more information on premarket tobacco product applications please see Premarket Tobacco Product Applications for [ENDS], Guidance for Industry (June 2019) available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/premarket-tobacco-product-applications-electronic-nicotine-delivery-systems-ends. Applications for Premarket Review of New Tobacco Products (updated June 2019) available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/applications-premarket-review-new- tobacco-products. For more information on CTP's other published regulations and guidances, please see https://www.fda.gov/tobacco-products/products-guidance-regulations/rules-regulations-and-guidance; for more information on FDA CTP webinars, please see https://www.fda.gov/tobacco-products/compliance-enforcement-training/fda-tobacco-compliance-webinars; for information on marketing orders and accompanying documentation, please see https://fwww.fda.gov/tobacco-products/compliance-enforcement-training.

	bacco laws and regulations and takes corrective action when violations occur. When enforcing FDA's tobacco product authorities, the Agency generally issues a warning letter the first time a compliance check reveals a violation of federal tobacco laws and regulations, including when a manufacturer sells or distributes a product as a modified risk tobacco product without an FDA order in effect. Failure to promptly and adequately correct all violations and ensure compliance with all applicable laws and regulations may lead to enforcement actions, including civil money penalties, seizure, and/or injunction. To the extent that manufacturers are marketing their products for therapeutic purposes, they are subject to FDA's medical product authorities.
Lack of clarity—it is unclear what ENDS prod-	FDA believes the level of detail and examples in

ucts manufacturers (and other parties that engage in ENDS marketing activities) and retailers can do to avoid concerning marketing activities. • Would like to know what specific steps they can take to ensure their marketing reaches adults rather than minors. • Need clarity on what the agency considers targeting or promoting to minors.	the Final Guidance provide sufficient clarity.
FDA should ensure social media platforms are not used as advertising platforms for ENDS products, including monitoring videos that promote ENDS products and limiting the reach of social media influencers who promote products.	To the extent this comment is about the advertising of ENDS products generally, it is outside the scope of the policy. To the extent this comment is about advertising of ENDS products that are targeted to minors or likely to promote use of ENDS by minors, FDA believes the Final Guidance addresses this by indicating that such prod-

	ucts will be an enforcement priority.
A number of ENDS products are designed to be small and discreet, thus promoting ENDS use in minors.	The Final Guidance discusses the Agency's intent to prioritize its enforcement for products that are targeted to minors or likely to promote use of ENDS by minors. One example of such products includes products marketed directly to minors by promoting ease of concealment.
FDA should support stakeholder partnerships to develop common approach and standards in preventing youth access.	FDA CTP's Office of Stakeholder Relations regularly connects with stakeholders. Stakeholders also have access to the ombudsman as well.
Flavored Cigars	
Comment	Response
Enforcing the premarket requirements against flavored cigars would limit adults' freedom to choose their preferred products.	The Final Guidance does not include a policy to prioritize flavored cigars for enforcement. Instead, as described in the Final Guidance, flavored cigars are treated like all other deemed products that are

	not ENDS. Flavored cigars may seek premarket authorization from FDA. Manufacturers of flavored cigars, and of other deemed new tobacco products, will be required to submit marketing applications for those products by September 9, 2020, consistent with the U.S. District Court for the District of Maryland's order, as described in the Guidance.
Eliminating flavored cigars would result in the creation of a black market.	The Final Guidance does not include a policy to prioritize flavored cigars for enforcement. In addition, we do not think development of a black market is likely given that there are a number of "grandfathered" flavored cigars that are lawfully marketed and would remain available to consumers regardless of FDA's enforcement of premarket authorities.

FDA's assertion of product migration of youth is an unfounded hypothesis. • Concerns that FDA mischaracterizes research and does not cite contrary government findings (citing to CDC reports and PATH data) • FDA's data on this topic limited to two studies that only recently became available and has not been vetted • There are limitations to the Wave 1-3 PATH data that FDA cites in support • FDA relies on 2018 NYTS data and incorrectly speculates that youth could migrate to flavored cigars • CDC MMWR data and PATH data contradict suggestions that youth us-	The Final Guidance does not include a policy to prioritize flavored cigars for enforcement.

age of cigars is on the rise • Data show decreasing importance of flavors to first time cigar users	
Only allowing 30 days after guidance is finalized would result in a de facto ban on flavored cigars. • Not enough time for manufacturers to submit SE reports. • May not be enough time for retailers to sell off inventory/FDA should include an additional sell off period of time to the compliance guidance. • Should be able to remain on the market until FDA has reviewed and made a determination on the premarket review application.	The Final Guidance does not include a policy to prioritize flavored cigars for enforcement. In addition, we note that there are a number of "grandfathered" flavored cigars that are lawfully marketed that would remain available to consumers regardless of FDA's enforcement of premarket authorities.

Guidance should address grandfathered flavored cigar products as well.	The Draft and Final Guidance are about enforcement against products that lack required premarket authorization. Grandfathered tobacco products, which do not require premarket authorization, are outside the scope of the policy.
Lack of clarity • Lack of a definition of flavored cigars will lead to confusion and leave retailers misinformed about what constitutes a flavored cigar. • Lack of definition of characterizing flavor.	The Final Guidance no longer discusses prioritizing enforcement for flavored cigars.
FDA should pursue the flavored cigar enforcement policy addressed in the Draft Guidance.	At this time, FDA has decided to focus this Final Guidance on ENDS products, given the recent surge in youth use and additional considerations such as battery explosions and vaping-related illnesses. Nevertheless, FDA is continuously eval-

	uating new information and adjusting its enforcement priorities in light of the best available data. FDA will take appropriate action regarding tobacco products that are marketed without premarket authorization, including cigars, in accordance with the court's order in *American Academy of Pediatrics.* FDA also has stated its intention to issue a flavored cigar rule.
Compliance Policy for Other Deemed Products	
Comment	Response
FDA should modify compliance policy for other deemed products. • Data on waterpipe tobacco use demonstrates increase in youth use.	As discussed in the Final Guidance, consistent with the U.S. District Court: for the District of Maryland's order, FDA intends to enforce premarket requirements for these products after September 9, 2020.
FDA should not modify compliance policy for other deemed products.	As discussed in the Final Guidance, consistent with the U.S. District Court for the District of Mary-

	land's order, FDA intends to enforce premarket requirements for these products after September 9, 2020.
FDA should focus its efforts on menthol cigarettes.	The Final Guidance describes FDA's policy on enforcing premarket requirements for products subject to the deeming rule. Menthol cigarettes are outside the scope of this policy.

U.S. FOOD & DRUG ADMINISTRATION

Memorandum

To:	File
From:	Anne Radway, M.S. Associate Director For Rosanna Beltre -S Digitally signed by Rosanna Beltre -S Date: 2021.07.09 11:28:49 -04'00' Division of Regulatory Project Management Office of Science
Through:	Matthew Holman, Ph.D. Director Office of Science Digitally signed by Matthew R. Holman -S Date: 2021.07.09 11:33:09 -04'00'
Subject:	ENDS Containing Non-Tobacco Flavored E-Liquid: Approach to PMTAs[1] not in Substantive Scientific Review (Phase III)

[1] Premarket Tobacco Product Application

Background

As of September 9, 2020, FDA commenced review of premarket applications for electronic nicotine delivery systems (ENDS) products on the market as of August 8, 2016; applicants were required by a court order to submit applications to FDA by this date. The majority of these applications are for non-tobacco flavored ENDS products.[2] To date, OS has implemented its plan to review a subset of these applications in this first year: the PMTAs selected for review were identified using a plan described in the Premarket Application Review Prioritization Plan memorandum[3], signed August 31, 2020. Office of Science has been tasked with developing a new plan to effectively manage the remaining non-tobacco flavored ENDS PMTAs not in Phase III, substantive scientific review. This task has been assigned by the Acting Commissioner given the likely impact on the marketplace on September 10, 2021 (the end of the enforcement discretion period for deemed tobacco products) and in order to take final action on as many applications as possible by September 10, 2021. The objective is to address these applications by applying a standard for evidence necessary to demonstrate an incremental benefit to adult smokers of non-tobacco flavored ENDS products.

Discussion

As described in Section 910 of the FD&C Act, to receive marketing authorization under the PMTA pathway, FDA must conclude that the marketing of the product

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[2] Refers to open e-liquids, closed e-liquids, and closed e-cigarettes containing non-tobacco flavored e-liquid

[3] See addendums dated September 24, 2020 and May 11, 2021

is appropriate for the protection of public health (APPH), including both tobacco users and nonusers. Based on the information available to date, FDA has determined this evaluation requires evidence that can demonstrate whether an applicant's new non-tobacco flavored product(s) will provide an incremental benefit to adult smokers relative to the applicant's tobacco-flavored product(s). In particular, the evidence necessary for this evaluation would be provided by either a randomized controlled trial (RCT) or a longitudinal cohort study. The absence of these types of studies is considered a fatal flaw, meaning any application lacking this evidence will likely receive a marketing denial order (MDO).

Considering the large number of applications that remain to be reviewed by the September 9, 2021 deadline, OS will conduct a Fatal Flaw review of PMTAs not in Phase III for non-tobacco flavored ENDS products. The Fatal Flaw review is a simple review in which the reviewer examines the submission to identify whether or not it contains the necessary type of studies. The Fatal Flaw review will be limited to determining presence or absence of such studies; it will not evaluate the merits of the studies. To decrease the number of PMTAs without final action by September 9, 2021, OS used a database query to identify the top twelve[4] manufacturers with the largest number of pending PMTAs not in Phase III[5] for non-tobacco flavored e-liquid products. These applications were pulled out of their respective place in the PMTA priority list, and Phase II Filing was

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[4] These applications represent 85% of all pending PMTA applications.

[5] These will be the same manufacturers/PMTAs as identified for prioritized Filing Reviews in the June 30, 2021, memorandum.

initiated (see Appendix A). Following completion of filing those applications that are filed will immediately initiate Fatal Flaw review.

For the remaining PMTAs not in Phase III for non-tobacco flavored e-liquid products, FDA will send an General Correspondence letter requesting the applicant to confirm if their PMTA contains such evidence and, if so, to direct FDA to the location in the application where the studies can be found. Manufacturers eligible for this process, OS is identifying open PMTAs submitted from April 1, 2020 to September 9, 2020 that have been Received, Accepted and/or Filed and have not entered Phase III. Additionally, PMTAs were filtered based on product characterizing flavor (non-tobacco flavors), product type (i.e., open or closed e-liquid or closed e-cigarette), and category/subcategory (i.e., Other/Other). General Correspondence letters will be issued to companies listed in Appendix B. If later FDA discovers a manufacturer was not issued a General Correspondence letter when they should have been, the applications will be evaluated on a case-by-case basis.

U.S. FOOD & DRUG ADMINISTRATION

Memorandum

To:	File
From:	Benjamin Apelberg, PhD Deputy Director Office of Science Digitally signed by Benjamin Apelberg -S Date: 2021.08.17 14:04:15 -04'00'
Through:	Matthew R. Holman, PhD Director Office of Science Digitally signed by Matthew R. Holman -S Date: 2021.08.17 16:06:36 -04'00'
Subject:	PMTA[i] Review: Evidence to Demonstrate Benefit of Flavored[ii] ENDS[iii] to Adult Smokers

[i] Premarket Tobacco Product Application

[ii] Throughout this memo, and solely as a matter of shorthand to aid in the drafting of this document, the term *flavored ENDS* refers to any ENDS other than tobacco-flavored and menthol flavored ENDS.

[iii] Electronic Nicotine Delivery System

Purpose

The purpose of this memo is to describe our findings with respect to the type of evidence that may support a finding that the marketing of a flavored ENDS[iv] is appropriate for the protection of the public health (APPH), in light of the significant concerns that flavored ENDS present with respect to youth appeal, uptake, and use.[v] Specifically, FDA has determined that the known and substantial risk to youth posed by flavored ENDS establishes a high burden for applicants seeking to demonstrate a potential benefit to adult smokers[vi] that could justify that risk. Based on existing

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[iv] For the purpose of this memo, we do not include menthol in the category of *flavored ENDS*. When it comes to evaluating the risks and benefits of a marketing authorization, the assessment for menthol ENDS, as compared to other non-tobacco-flavored ENDS, raises unique considerations. As a result, menthol ENDS PMTAs are not included in the scope of this memorandum, although the statute similarly imposes a high burden to demonstrate a benefit to existing users given the known youth use of menthol ENDS products.

[v] This memo applies to all sub-categories of ENDS, including unflavored "base" e-liquids that are designed to have flavors added to them. This includes e-liquids made for use with open systems as well as closed system ENDS (e.g., cartridges or disposable ENDS) containing e-liquids. Devices determined to include technology to lock the device or otherwise effectively limit access to adult users of legal age are outside the scope of this memo.

[vi] The standard described in Section 910 requires an accounting of the risks and benefits to the population as a whole, balancing the potential impacts to both current tobacco users and non-users. Because the focus of this memo is on ENDS, and further, the potential benefit of ENDS to the population health, we focus our discussion of current users on adult smokers, as they are the group through which the potential benefit to public health is most substantial and could overcome the known risk to youth.

scientific evidence and our experiences in conducting premarket review employing the APPH standard over the last several years, FDA has determined that, to effectively demonstrate this benefit in terms of product use behavior, the strongest types of evidence should be submitted—most likely product specific evidence from a (1) randomized controlled trial (RCT)[vii] or (2) longitudinal cohort study.[viii,ix] Moreover, tobacco-flavored ENDS may offer the same type of public health benefit as fla-

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[vii] A randomized controlled trial is a clinical investigation or a clinical study in which human subject(s) are prospectively, and randomly assigned to one or more interventions (or no intervention) to evaluate the effect(s) of the intervention(s) on behavioral, biomedical, or health-related outcomes. *Control or controlled* means, with respect to a clinical trial, that data collected on human subjects in the clinical trial will be compared to concurrently collected data or to non-concurrently collected data (*e.g.,* historical controls, including a human subject's own baseline data), as reflected in the pre-specified primary or secondary outcome measures.

[viii] A longitudinal cohort study is an observational study in which human subjects from a defined population are examined prospectively over a period of time to assess an outcome or set of outcomes among study groups defined by a common characteristic (e.g., smoking cessation among users of flavored ENDS compared with users of tobacco-flavored ENDS).

[ix] We would also consider evidence from another study design, provided that it could reliably and robustly assess behavior change (product switching or cigarette reduction) over time, comparing users of flavored products with those of tobacco-flavored products. In our review of PMTAs for flavored ENDS so far, we have learned that, in the absence of strong evidence generated by directly observing the behavioral impacts of using a flavored product vs. a tobacco-flavored product over time, we are unable to reach a conclusion that the benefit outweighs the clear risks to youth. Further discussion on types of evidence can be found in this memo (see "Behavioral evidence appropriate to demonstrate the potential benefit to smokers").

vored ENDS, i.e., increased switching and/or significant reduction in smoking, but do not pose the same degree of risk of youth uptake. Therefore, to meet the high burden to demonstrate the potential benefit to current users, a PMTA for flavored ENDS should include a demonstration with acceptably strong evidence that the flavored products have an added benefit relative to that of tobacco-flavored ENDS in facilitating smokers completely switching away from or significantly reducing their smoking.

We intend to conduct a streamlined scientific review of PMTAs for flavored ENDS to determine whether the applications contain evidence of this type. For those that do, we will refer them for further in-depth scientific evaluation as to whether the evidence satisfies that statutory standard for authorization. In the absence of this evidence, we generally intend to issue a marketing denial order. In this memo, we describe the background for this approach, document the scientific evidence related to youth risk, and describe the rationale that informs our determination of the types of evidence that should be submitted to overcome this risk and potentially support a determination that the new product's marketing would be considered APPH.

Background

The Federal Food, Drug, and Cosmetic Act (FD&C Act or Act) requires that "new tobacco products" receive marketing authorization from FDA under one of the pathways specified by the Act in order to be legally marketed in the United States. Under one pathway, the applicant submits a premarket tobacco product application (PMTA) to FDA. Section 910 of the FD&C Act requires that, for a product to receive PMTA marketing

authorization, FDA must conclude, among other things, that the marketing of the product is APPH. The statute specifies that, in assessing APPH, FDA consider the risks and benefits to the population as a whole including both tobacco users and nonusers, taking into account the increased or decreased likelihood that existing users of tobacco products will stop using such products and the increased or decreased likelihood that those who do not use tobacco products will start using such products.

FDA had previously set an extended compliance deadline for the submissions of PMTAs. That extension was challenged in court, which reset the deadline.[x] Consistent with that court order, premarket applications for many new tobacco products, including ENDS currently on the market, were due to FDA by September 9, 2020.

The vast majority of these applications are for flavored ENDS. It is well recognized that ENDS, and particularly flavored ENDS, pose a significant risk to nonusers, especially youth.[1,2] After observing a dramatic increase in the prevalence of ENDS use among U.S. youth in 2018, FDA's Commissioner characterized the problem as a youth vaping epidemic. FDA has initiated a series of actions to address the risk and reduce youth use. Since August 2016, FDA has issued more than 10,000 warning letters and more than 1,400 civil money penalty complaints to retailers for the sale of ENDS products to minors. FDA has also issued a guidance

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[x] *American Academy of Pediatrics. v. FDA*, 379 F. Supp. 3d 461 (D. Md. 2019) (vacating guidance); *American Academy of Pediatrics v. FDA,* No. 8:18-cv-883, Dkt. No. 182 (D. Md. Apr. 22, 2020) (resetting deadline).

that described a policy of prioritizing enforcement of non-tobacco/non-menthol flavored ENDS, "Enforcement Priorities for Electronic Nicotine Delivery Systems (ENDS) and Other Deemed Products on the Market without Premarket Authorization." In this guidance, FDA described evidence that shows flavors (other than tobacco and menthol) were a key driver of the surge in ENDS use among youth and thus prioritized enforcement against certain flavored ENDS products, with the goal of protecting youth from these products.[xi]

After FDA implemented this enforcement policy prioritizing enforcement against a subset of ENDS products known to appeal to youth, there was a meaningful reduction in youth use prevalence. Youth ENDS use peaked in 2019 when these products were widely available. Although several other policy changes and interventions were occurring during this same time period,[xii] it is reasonable to infer that prioritizing enforcement against many flavored products resulting in their removal from the market contributed to the decline in use in 2020. Despite this decline, ENDS remained the most widely used tobacco product among youth, with youth

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[xi] Due to the overwhelming amount of evidence showing a substantial increase in youth use of flavored ENDS products, as well as their demonstrated popularity among youth, in January 2020, FDA finalized a guidance prioritizing enforcement against flavored (other than tobacco or menthol) prefilled pod or cartridge-based e-cigarettes, as well as other categories of unauthorized products.

[xii] The change in ENDS product availability coincided with other events such as the enactment of legislation raising the federal minimum age for sale of tobacco products from 18 to 21 years (Tobacco 21), the outbreak of e-cigarette, or vaping, product-use associated lung injury (EVALI), and public education campaigns which also may have contributed to the decline in ENDS use.

use at levels comparable to what originally led FDA to declare a youth vaping epidemic. Moreover, despite the overall reduction in ENDS youth use observed in 2020, there was simultaneously a substantial rise in youth use of disposable ENDS, products that were largely excluded from the enforcement priorities set forth in the enforcement policy because at that time they were the least commonly used device type among high school ENDS users and therefore remained on the market as a flavored option.[3,4]

Section 910(c)(2)(A) of the FD&C Act requires that FDA deny a PMTA where it finds "there is a lack of a showing that permitting such tobacco product to be marketed would be [APPH]." Through the PMTA review process, FDA conducts a science-based evaluation to determine whether marketing of a new tobacco product is APPH. Section 910(c)(4) requires FDA, in making the APPH determination, to consider the risks and benefits to the population as a whole, including users and nonusers of tobacco, and take into account, among other things, the likelihood that those who do not use tobacco products will start using them. FDA's scientific review is not limited to considering only information in a PMTA, but also extends to any other information before the Agency, including the relevant existing scientific literature (See Section 910(c)(2)). As described in greater detail below, in reviewing PMTAs for flavored ENDS, FDA evaluates, among other things, the potential benefit to adult smokers who may transition away from combustible cigarettes to the ENDS product, weighed against the known risks of flavored ENDS to youth.

The Risk to Youth of Flavored ENDS Products

As noted, the APPH determination includes an assessment of the risks and benefits to the population as a whole, and for ENDS (as well as many other tobacco products) the application of that standard requires assessing the potential impact of the marketing of a new product on youth use. As a group, youth are considered a vulnerable population for various reasons, including that the majority of tobacco use begins before adulthood[5] and thus youth are at particular risk of tobacco initiation. In fact, use of tobacco products, no matter what type, is almost always started and established during adolescence when the developing brain is most vulnerable to nicotine addiction. Indeed, almost 90 percent of adult daily smokers started smoking by the age of 18.[6] Adolescent tobacco users who initiated tobacco use at earlier ages were more likely than those initiating at older ages to report symptoms of tobacco dependence, putting them at greater risk for maintaining tobacco product use into adulthood.[7] On the other hand, youth and young adults who reach the age of 26 without ever starting to use cigarettes will most likely never become a daily smoker.[6] Because of the lifelong implications of nicotine dependence that can be established in youth, preventing tobacco use initiation in young people is a central priority for protecting population health.

Youth use of flavored ENDS

ENDS are now the most commonly used type of tobacco product among youth. In 2020, approximately 19.6% of U.S. high school students and 4.7% of middle school students were current users of ENDS, corresponding to 3.6 million youth and making ENDS the most widely used tobacco product among youth by far.[8] As noted

above, this was a decline from 2019, when 27.5% of high school and 10.5% of middle school students reported ENDS use,[9] which necessitated the FDA enforcement policy described above.

FDA has concluded that the availability of a broad range of flavors is one of the primary reasons for the popularity of ENDS among youth. The majority of youth who use ENDS report using a flavored ENDS product, and the use of flavored ENDS has increased over time. In the 2014 National Youth Tobacco Survey (NYTS), 65.1% of high school and 55.1% of middle school e-cigarette[xiii] users reported using a flavored e-cigarette.[10] By the 2020 NYTS, the proportion of e-cigarette users reporting using a flavored product[xiv] increased to 84.7% of high school users and 73.9% of middle school users.[3] Among high school e-cigarette users, the most common flavors used in 2020 were fruit (73.1%); mint (55.8%); menthol (37.0%); and candy, dessert, or other sweets (36.4%).[3] Among middle school e-cigarette users, the most common flavors used in 2020 were fruit (75.6%); candy, desserts, or other sweets (47.2%); mint (46.5%); and menthol (23.5%).[3]

Youth ENDS users are also more likely to use flavored ENDS compared to adult ENDS users. In PATH Wave 5.5 from 2020, 66.8% of youth ENDS users aged 13 to 17 reported using fruit, followed by 53.8% for mint/

[xiii] We use "e-cigarette" here to be consistent with the survey, but we interpret it to have the same meaning as ENDS.

[xiv] Flavored product use in these studies means use of flavors other than tobacco.

menthol[xv], 23.5% for candy/dessert/other sweets, and 13.3% for tobacco flavor (internal analysis). In the 2020 PATH Adult Telephone Survey, 51.5% of adult ENDS users 25 and older used fruit, 30.4% used mint/menthol, 23.8% used candy/dessert/other sweets, and 22.3% used tobacco flavor (internal analysis). Youth current ENDS users were also more likely than adult current ENDS users to use more than one flavor and to use combinations that did not include tobacco flavors.[11]

Studies show that flavors influence youth initiation of ENDS use. In particular, data show that flavors are associated with product initiation, with the majority of users reporting that their first experience with ENDS was with a flavored product. For instance, in Wave 1 of the PATH Study from 2013-2014, over 80% of youth aged 12-17, 75% of young adults 18-24, and 58% of adults 25 and older reported that the first e-cigarette that they used was flavored.[12] In another PATH study, more youth, young adults and adults who initiated e-cigarette use between Wave 1 and Wave 2 reported use of a flavored product than a non-flavored product.[13] Finally, in PATH Wave 4 from 2016-2017, 93.2% of youth and 83.7% of young adult ever ENDS users reported that their first ENDS product was flavored compared to 52.9% among adult ever users 25 and older.[14]

In addition, nationally representative studies find that when asked to indicate their reasons for using ENDS, youth users consistently select flavors as a top reason.[15,16] In fact, among Wave 4 youth current ENDS us-

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[xv] The PATH Study Questionnaire from Wave 5.5 did not assess mint and menthol separately. However, subsequent data collections (ATS and Wave 6) have separated the two flavors.

ers, 71% reported using ENDS "because they come in flavors I like."[14]

One explanation for this high prevalence and increase in frequency of use is that flavors can influence the rewarding and reinforcing effects of e-liquids, thereby facilitating ENDS use and increasing abuse liability. Research shows that flavored ENDS are rated as more satisfying than non-flavored ENDS, and participants will work harder for and take more puffs of flavored ENDS compared to non-flavored ENDS.[17] Research also shows that flavors can increase nicotine exposure by potentially influencing the rate of nicotine absorption through pH effects and by promoting the reward of ENDS use.[18] Together, this evidence suggests flavored ENDS may pose greater addiction risk relative to tobacco-flavored ENDS, which increases concerns of addiction in youth, particularly due to the vulnerability of the developing adolescent brain, which is discussed further below.

Finally, existing literature on flavored tobacco product use suggests that flavors not only facilitate initiation, but also promote established regular ENDS use. In particular, the flavoring in tobacco products (including ENDS) make them more palatable for novice youth and young adults, which can lead to initiation, more frequent and repeated use, and eventually established regular use. For example, regional studies have found that the use of flavored e-cigarettes was associated with a greater frequency of e-cigarettes used per day among a sample of adolescents in Connecticut in 2014[19] and continuation of e-cigarette use in a sample of adolescents in California from 2014-2017.[20] Use of non-traditional flavors (vs. tobacco, mint/menthol, flavorless) was associated with increased likelihood of continued use and tak-

ing more puffs per episode.[20] Data from a regional survey in Philadelphia, PA found initial use of a flavored (vs. unflavored or tobacco flavored) ENDS was associated with progression to current ENDS use as well as escalation in the number of days ENDS were used across 18 months.[21] Finally, similar effects have been found in the nationally representative PATH study among young adults (18-24 years), where "ever use" of flavored e-cigarettes at Wave 1 was also associated with increased odds of current regular ENDS use a year later at Wave 2.[22] In sum, flavored ENDS facilitate both experimentation and progression to regular use, which could lead to a lifetime of nicotine dependence.

The appeal of flavors across ENDS devices

The appeal of flavors applies across the entire class of ENDS on the market. Indeed, the role of flavors in increasing the appeal of tobacco products to youth—across tobacco product categories—is well-established in the literature.[23-26]

National surveillance data suggest that, within the ENDS category, there is variability in the popularity of device types among youth, suggesting there may be differential appeal of certain product styles. Still, across these different device types, the role of flavor is consistent. As described above, the majority of youth ENDS use involves flavored products: in 2020, the majority of high school and middle school current e-cigarette users reported use of non-tobacco-flavored products (82.9%)[3] and flavored use was favored among both users of closed (87%) and open (76%) ENDS (internal analysis). In particular, across device types, including prefilled pods/cartridges, disposables, tanks, and mod systems, fruit was the most commonly used fla-

vor type among youth, with 66.0% for prefilled pods/cartridges, 82.7% for disposables, 81.7% for tanks, and 78.9% for mod systems among youth reporting using a fruit flavor.[3]

It is also worth noting that the preference for device types and popularity of certain styles is likely fluid and affected by the marketplace, that is, the options, especially flavors, that are available for consumers to choose from. Some evidence for this was observed in the trends both leading up to, and coinciding with, the shifting marketplace following the 2020 enforcement priorities guidance. In particular, the enormous rise in youth ENDS use from 2017-2019 coincided with the ascendance of JUUL (and copy-cat devices) in the marketplace, suggesting a relationship between the availability of JUUL as an option, and the sudden popularity of pod-based devices.[xvi] Then, as noted earlier, when FDA changed its enforcement policy to prioritize pod-based flavored ENDS, which were most appealing to youth at the time, we subsequently observed a substantial rise in use of disposable flavored ENDS[xvii]—a ten-fold increase (from 2.4% to 26.5%) among high school current e-cigarette users.[4] This trend illustrates that the removal of one flavored product option prompted youth to migrate to another ENDS type that offered the desired

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[xvi] This is borne out by the data from 2019 NYTS, in which 59.1% of high school ENDS users reported use of this one brand. Cullen KA, Gentzke AS, Sawdey MD, et al. e-Cigarette Use Among Youth in the United States, 2019. Jama. 2019;322(21):2095-2103.

[xvii] In July 2020, FDA issued Warning letters to three companies for illegally marketing disposable e-cigarettes and for marketing unauthorized modified risk tobacco products.

flavor options, underscoring the fundamental role of flavor in driving appeal.

The harms of youth ENDS use: The adolescent brain and risk for addiction

In addition to the high prevalence of youth ENDS use, the data also suggest this use is leading to increases in nicotine dependence.[10] Indeed, responding to concerns related to youth ENDS dependence, at the end of 2018, FDA held a public hearing to discuss the potential role of drug therapies to support e-cigarette cessation.[xviii]

In 2019, an estimated 30.4% of middle and high school student ENDS users reported frequent use (i.e., use on ≥20 of the past 30 days).[9] By school type, 34.2% (95% CI, 31.2%-37.3%) of high school student ENDS users and 18.0% (95% CI, 15.2%-21.2%) of middle school student ENDS users reported frequent use.[27] Among current ENDS users, 21.4% of high school users and 8.8% of middle school users reported daily ENDS use.[27] Additionally, in a study that examined changes in ENDS use in youth ages 13-18 over a 12-month period, nicotine dependence (measured using the Penn State Electronic Cigarette Dependence Index (PS-ECDI)[28,29] and salivary cotinine concentrations increased, indicating continued ENDS use and greater nicotine exposure over time.[30]

Youth and young adult brains are more vulnerable to nicotine's effects than the adult brain due to ongoing neural development.[31,32] Adolescence is a developmental period consisting of major neurobiological and psy-

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[xviii] On December 5, 2018, FDA hosted a public hearing on "Eliminating Youth Electronic Cigarette and Other Product Use: The Role of Drug Therapies."

chosocial changes and is characterized by increased reward-seeking and risk-taking behaviors (e.g., experimentation with drugs), coupled with heightened sensitivity to both natural and drug rewards and an immature self-regulatory system that is less able to modulate reward-seeking impulses (e.g., diminished harm avoidance, cognitive control, self-regulation).[33-37] Furthermore, evidence from animal studies suggests that nicotine exposure during adolescence enhances the rewarding and reinforcing effects of nicotine in adulthood[38-41]; and can induce short and long-term deficits in attention, learning, and memory.[42-45]

Risk of progression from ENDS to other tobacco products of different health risk

Among youth who use ENDS, there is a risk of progression to other tobacco products of greater health risk. A 2017 systematic review and meta-analysis that summarized nine prospective cohort studies found significantly higher odds of smoking initiation (OR = 3.50, 95% CI: 2.38, 5.16) and past 30-day combusted cigarette use (OR = 4.28, 95% CI: 2.52, 7.27) among youth who had used ENDS at compared to youth who had not used ENDS.46 Similar associations have been observed in longitudinal studies that have been published since the Soneji et al. review.[42,47-56] The 2018 NASEM report concluded that there is substantial evidence that ENDS use increases risk of ever using combusted tobacco cigarettes among youth and young adults.[57] The transition from non-cigarette product use to combusted cigarette use has been observed for other non-cigarette products, such as cigars, as well.[58] Although it is challenging to empirically separate causality from shared risk factors among youth combusted cigarette and ENDS users, some studies have found an association between ENDS

and subsequent combusted cigarette use while controlling for similar risk profiles.[54]

The precise relationship between youth ENDS use and youth smoking remains undetermined. On the one hand, the prevalence of combusted cigarette smoking in youth has continued to decline,[9,59,60] suggesting that youth use of ENDS has not significantly slowed or impeded that positive public health trajectory. On the other hand, there is a growing body of evidence showing a link between ENDS use and subsequent smoking among youth that raises significant concerns. This evidence also increases concern that over time—and particularly if youth ENDS use were to return to the rates seen in 2019 or worsen—the trend of declining cigarette smoking could slow or even reverse.

Other health risks associated with ENDS use

In addition to the risk of tobacco initiation and progression among youth, there is epidemiologic evidence from the cross-sectional[xix] Behavioral Risk Factor Survey system (BRFSS) suggesting positive associations between ENDS use among those who never smoked and some health outcomes. Two studies found associations between ENDS use and self-reported history of asthma, chronic bronchitis, emphysema, or chronic obstructive pulmonary disease with increased ENDS use (i.e., daily use) relating to increased odds of disease.[61,62] Another found an association between ENDS use and respiratory symptoms in younger adults (ages 18-34) but not in older adults.[63] ENDS use has also resulted in acute harm to individuals through battery explosion-related

[xix] Cross-sectional surveys examine these relationships at a single point in time, and as a result, do not establish causality.

burns and e-liquid nicotine poisoning.[64-66] Ultimately, as this is still a relatively novel product category, much remains unknown about other potential long-term health risks.

Conclusion

The exponential growth in youth ENDS use observed from 2017 to 2019, and the enduring prevalence of youth ENDS use in the U.S. is alarming. Despite a reduction in youth use of ENDS from 2019 to 2020, there were still 3.6 million youth ENDS users in 2020 and the majority used a flavored ENDS product. Youth users are more likely to use flavored ENDS than adult ENDS users. Flavors are associated with ENDS initiation and progression among youth. The full extent of the harms of ENDS use are not yet known, but evidence to date suggests they include permanent effects of nicotine on the developing adolescent brain and the risk of nicotine addiction. Studies indicate an additive effect of e-liquid flavorings on the rewarding and reinforcing effects of nicotine containing e-liquids. Studies also demonstrate that e-liquid flavors affect nicotine exposure. Among youth who use ENDS, there is a risk of progression to other tobacco products with greater health risks including combustible cigarettes. Finally, though long-term health risks are not fully understood, studies suggest an association between never-smoking ENDS users and respiratory and cardiovascular health effects. This evidence strongly supports the finding that flavored ENDS pose a significant risk to youth. Moreover, because the appeal of flavor is consistent across ENDS device types, and the harms to youth posed by flavored ENDS use, including nicotine dependence, are not moderated by device type, we find that this conclusion applies to all types of flavored ENDS.

Balancing Known Risks to Youth with a Potential Benefit to Adults

Determining whether marketing a new product is APPH includes evaluating the risks and benefits to the population as a whole. This requires FDA to balance, among other things, the negative public health impact for nonusers against the potential positive public health impact for current tobacco users. Accordingly, for marketing of a new product to be found to be APPH, any risks posed by a new product to youth would need to be overcome by a sufficient benefit to adult users, and as the known risks increase, so too does the burden of demonstrating a substantial enough benefit. In the case of a new flavored ENDS product, the risk of youth initiation and use is substantial, given the clearly documented evidence described above. In order for marketing of a new flavored ENDS product to be found APPH, an applicant would have to show that the significant risk to youth could be overcome by likely benefits substantial enough such that the net impact to public health would be positive, taking into account all relevant evidence and circumstances, including whether there are effective limitations on youth access.

Potential benefit of new flavored ENDS

Current scientific literature demonstrates that ENDS are generally likely to have fewer and lower concentrations of harmful and potentially harmful constituents (HPHCs) than combustible cigarettes, and biomarker studies demonstrate significantly lower exposure to HPHCs among current exclusive ENDS users than current smokers.[57] However, whether this is true for any particular new ENDS product, and the implications for health risks from a particular product, are considered

on a case-by-case basis during the course of FDA's scientific review of a PMTA.

FDA also considers the potential that current cigarette smokers may experience a reduction in health risks if they switch completely to an ENDS, or if they use both products but substantially reduce their cigarette smoking. For a flavored ENDS product, assuming that the evaluation of the product shows the likelihood for lower HPHC exposure, then to demonstrate the likely individual and population benefit, applicants must demonstrate that current smokers are likely to start using the new ENDS product exclusively or predominantly (e.g., dual use with a significant smoking reduction).[64]

Behavioral evidence appropriate to demonstrate the potential benefit to smokers

FDA's PMTA review includes an evaluation of any potential benefits of the product for the likely users, such as a possible reduction in health risks. In general, as FDA stated in its guidance for PMTAs for ENDS,[xx] an assessment of how a new product may be used by current smokers can be derived from a variety of sources. FDA may consider direct behavioral evidence on the specific products under review or indirect evidence derived from studies of behavioral intentions; pharmacological studies of nicotine delivery, abuse liability, and/or use topography; and bridging from studies based on comparable products. Further, in the case of a flavored ENDS product, to demonstrate that the marketing of the new product is APPH, the magnitude of the likely

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[xx] Premarket Tobacco Product Applications for Electronic Nicotine Delivery Systems: Guidance for Industry (p.47); October 2020 Public Meeting on Deemed Tobacco Product Applications

benefit would have to be substantial enough to overcome the significant risk of youth uptake and use posed by the flavored ENDS product.

Section 910(c)(5) of the FD&C Act provides that determining whether marketing of a new tobacco product is APPH shall, when appropriate, be based on "well-controlled investigations, which may include one or more clinical investigations by experts qualified by training and experience to evaluate the tobacco product." FDA believes well-controlled investigations are "appropriate" for demonstrating that permitting the marketing of specific flavored ENDS would be APPH in the face of the significant risks to youth of flavored ENDS. One type of well-controlled investigation that could effectively demonstrate a potential benefit of a flavored ENDS product would be an RCT. In addition, as CTP has previously described,[xxi] another well-controlled investigation that could serve as an alternative to conducting an RCT to demonstrate adequate benefit is a longitudinal cohort study.

For flavored ENDS, the known and substantial risk to youth in particular is high. Therefore, to overcome the risk to youth and show a net population health benefit, the applicant must demonstrate potential benefits to smokers from marketing such products using particularly strong evidence—including both robust study design and methods and the strength of the study results. In other words, because the potential benefit to adults is gained through its impact on smoking behavior, such evidence should be provided to demonstrate that a ben-

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[xxi] Premarket Tobacco Product Applications for Electronic Nicotine Delivery Systems: Guidance for Industry (p.47); October 2020 Public Meeting on Deemed Tobacco Product Applications

efit of a new product is significant enough to overcome the risk to youth. In particular, such evidence should permit FDA to assess whether there is any added or incremental benefit to a flavored ENDS product over a tobacco flavored variety in facilitating smokers completely switching or significantly reducing their smoking. If there is no evidence of such an incremental benefit, then there would be no justification to authorize such products, given the significant increase in risk of youth initiation associated with flavored ENDS compared to tobacco-flavored ENDS. Note, whereas this evidence should be submitted for such a product to be found APPH, it may not be sufficient: having established the benefit to adults, applications containing this evidence would still be evaluated to determine that the totality of the evidence supports a marketing authorization. As it relates to the risk to youth, for example, this assessment includes evaluating the appropriateness of the proposed marketing plan.[xxii]

We have been using the APPH standard for several years in reviewing previous PMTAs for non-ENDS

[xxii] Limiting youth access and exposure to marketing is a critical aspect of product regulation. It is theoretically possible that significant mitigation efforts could adequately reduce youth access and appeal such that the risk for youth initiation would be reduced. However, to date, none of the ENDS PMTAs that FDA has evaluated have proposed advertising and promotion restrictions that would decrease appeal to youth to a degree significant enough to address and counter-balance the substantial concerns, and supporting evidence, discussed above regarding youth use. Similarly, we are not aware of access restrictions that, to date, have been successful in sufficiently decreasing the ability of youth to obtain and use ENDS. Accordingly, for the sake of efficiency, the evaluation of the marketing plans in applications will not occur at this stage of review.

products. Our substantive review of PMTAs for ENDS and our completion of numerous scientific reviews over the last 10 months have deepened our understanding of the APPH evaluation with respect to behavior. These reviews have clarified the position that the expectations for scientific evidence related to potential adult benefit can vary based on demonstrated risk to youth. Although indirect evidence or bridged data from the literature may still be appropriate for many new products, including tobacco-flavored ENDS, robust and direct evidence demonstrating potential benefit has been needed when the known risks are high as with all flavored ENDS products. At the same time, we have learned from experience that, in the absence of strong direct evidence, we are unable to reach a conclusion that the benefit outweighs the clear risks to youth. For instance, applicants who do not conduct their own behavioral studies must rely on, and bridge to, the general ENDS category literature to inform an evaluation of the potential benefit to adult users. To date, that approach has not been sufficient in our evaluation of flavored ENDS PMTAs because, in contrast to the evidence related to youth initiation—which shows clear and consistent patterns of real-world use that support strong conclusions—the evidence regarding the role of flavors in promoting switching among adult smokers is far from conclusive. In fact, the findings are quite mixed and as a result the literature does not establish that flavors differentially promote switching amongst ENDS users in general. Aside from differences in study design/methods, the heterogeneity of the existing literature is likely due, at least in part, to differences in the products studied. Therefore, given the state of the science on flavored ENDS, and the known risks to youth, direct product-specific evidence should be submitted.

In order to adequately assess whether such an added benefit has been demonstrated, FDA has determined that product-specific[xxiii] evidence should be submitted to enable a comparison between the applicant's new flavored products and an appropriate comparator tobacco-flavored product (both ENDS) in terms of their impact on tobacco use behavior among adult smokers. Consistent with section 910(c)(5), this evidence could be generated using either an RCT design or longitudinal cohort study design.

Although CTP will consider other types of evidence, we currently believe other types of evidence, including the types mentioned below, would not likely be sufficiently robust or direct in providing evidence as to the impact of the new ENDS on adult switching or cigarette reduction. Uptake and transition to ENDS use is a behavioral pattern that requires assessment at more than one time point. In addition, the transition from smoking to exclusive ENDS use typically involves a period of dual use. Therefore, evaluating the behavioral outcomes needed to show any benefit of the product requires observing the actual behavior of users over time. With both RCT and cohort study designs, enrolled participants are followed over a period of time, with periodic and repeated measurement of relevant outcomes.

[xxiii] By product-specific, we mean the data are based on studies using the specific new products that are the subject of the application(s). If the applicant has a large number of product variants (e.g., nicotine concentration and/or flavor options), it may be justifiable to bridge data from a study including a subset of their products to one or more of their other products (not included in the study). In contrast, because of the need for product-specific information, bridging from a different set of products (not the subject of the application) would not be appropriate here.

In contrast, cross-sectional surveys entail a one-time assessment of self-reported outcomes: although participants can be asked to retrospect on their past behavior, the single data collection does not enable reliable evaluation of behavior change over time. Consumer perception studies (surveys or experiments) typically assess outcomes believed to be precursors to behavior, such as preferences or intentions related to the new products, but are not designed to directly assess actual product use behavior. Moreover, the general scientific literature, though informative for evaluation of some types of products, is not adequate to address this assessment because it does not provide product-specific information. This is because the effectiveness of a product in promoting switching among smokers arises from a combination of its product features—including labeled characteristics like flavor and nicotine concentration—as well as the sensory and subjective experience of use (taste, throat hit, nicotine delivery), and can also be influenced by how the device itself looks and feels to the use.

While RCTs and cohort studies both enable direct assessment of behavioral outcomes associated with actual product use over time, there are pros and cons to each type of design. While RCTs afford greater control and internal validity; cohort studies enable stronger generalizability because conditions are closer to real-world. We are aware of these as trade-offs and generally do not favor one type over the other for addressing this question.

To be informative, a study using one of these two designs would measure the impact of use of the new or appropriate comparator product tobacco-flavored ENDS and flavored products on adult smokers' tobacco use be-

havior over time[xxiv]; include outcomes related to ENDS use and smoking behavior to assess switching and/or cigarette reduction; and enable comparisons of these outcomes based on flavor type. In some cases, evidence on each individual flavor option may not be feasible; bridging data from one of the applicant's flavors to other flavors of the applicant's in the same flavor category (e.g., "fruit") may be appropriate. Furthermore, consistent with previous FDA guidance, we would expect the applicant to provide justification to support this bridging.[xxv] Likewise, if a flavor is tested with one nicotine concentration, it may be feasible for the applicant to bridge the study results to other nicotine concentrations, under certain circumstances, and with the appropriate justification for bridging.

Data from one of these studies could support a benefit to adult users if the findings showed that, compared to the new tobacco-flavored product, use of (each) new flavored product is associated with greater likelihood of either of these behavioral outcomes for adult smokers: (1) complete switching from cigarettes to exclusive new

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[xxiv] This could include studies that are long-term (i.e., six months or longer). In FDA's (2019) Guidance to Industry, "Premarket Tobacco Product Applications for Electronic Nicotine Delivery Systems", FDA has previously stated that it did not expect that applicants would need to conduct long-term studies to support an application for ENDS. Because the behavior change of interest (switching or cigarette reduction) occurs over a period of time, it is possible that to observe these outcomes, investigators designing these studies may decide to follow participants over a period of six months or longer.

[xxv] Bridging is discussed in FDA's 2019 Guidance to Industry cited above (fn xxiv).

product use or (2) significant reduction in cigarettes per day (CPD).

Conclusion

The known and substantial risk to youth posed by flavored ENDS means that applicants will need a particularly reliable and robust evidence demonstrate a potential for benefit to adult smokers that could justify that risk. Based on our current understanding, a demonstration with sufficiently reliable and robust evidence that the flavored ENDS have an added benefit relative to tobacco-flavored ENDS in facilitating smokers completely switching or reducing their smoking could demonstrate the potential benefit to current users that would outweigh the risk to youth posed by flavored ENDS. That would depend on both the type of evidence presented—whether the evidence is sufficiently reliable and robust—and the findings from the evidence. However, if an application does not contain sufficiently reliable and robust evidence, as discussed in this memo, FDA will be more likely to conclude that the application has not demonstrated the potential benefit.

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U.S. FOOD & DRUG ADMINISTRATION

Memorandum

To:	File
From:	Benjamin Apelberg, PhD Deputy Director Office of Science Digitally signed by Benjamin Apelberg -S Date: 2021.08.25 12:28:45 -04'00'
Through:	Matthew R. Holman, PhD Director Office of Science Digitally signed by Matthew R. Holman -S Date: 2021.08.25 13:57:58 -04'00'
Subject:	Rescission of August 17, 2021, Memorandum re PMTA[i] Review: Evidence to Demonstrate Benefit of Flavored[ii] ENDS[iii] to Adult Smokers

[i] Premarket Tobacco Product Application

[ii] *Flavored ENDS* refers to any ENDS other than tobacco-flavored and menthol-flavored ENDS.

[iii] Electronic Nicotine Delivery System

This memorandum rescinds the August 17, 2021, Memorandum re: PMTA Review: Evidence to Demonstrate Benefit of Flavored ENDS to Adult Smokers. The Agency has reconsidered the process for FDA's PMTA flavored ENDS reviews and has determined that it will not consider or rely on the August 17, 2021, memo as a supporting document in that process. Therefore, the August 17, 2021, memo is no longer needed.

BOILER MAKER

Wages & White Lion Investments LLC DBA Triton Distribution

Premarket Tobacco Product Application (PMTA) for

ENDS Open-System E-Liquid:

Boiler Maker Anvil E-Liquid

In Nicotine Levels—0, 3, 6, 12,18 mg/mL

In Bottle Sizes: 30 mL and 100 mL

Submission Date: September 9, 2020

Table of Contents

ACRONYMS

MODULE 1: ADMINISTRATIVE

GENERAL INFORMATION (21 C.F.R. § 1114.7(C))

1.1 SUBMISSION FORM

Table 1.1-1 e-submitter Information

Contact: Company Identification	
Type of Company:	LLC
Contact	
Title (e.g., Mr., Ms.):	Mr
First/Given Name:	Jon
Middle Name:	
Last Name:	Rose
Suffix (e.g., Sr, Jr, III)	
Degree(s) (e.g., PhD, JD)	
Position Title:	General Manager
Email Address:	jrose@tritondistribution.com
Address	

Company Name:	Wages & White Lion Investments LLC DBA Triton Distribution
Country:	United States
Address Line 1:	789 N. Grove Rd
Address Line 2:	Suite 111
City:	Richardson
State	Texas
Zip Code	75081
Telephone number:	214-880-6440
Fax number:	N/A
Company Headquarters FDA-assigned Facility Establishment Identifier (FEI) Number	3012508792
Company Headquarters D&B D-U-N-S Number	77400931

Table 1.1-2 Submission Information

Submission Info	
Application Type	PMTA
Submission Type	Initial PMTA Submission/ Original Application
Submission Description	Premarket Tobacco Product Application for Boiler Maker Anvil E-liquid

Date of Submission	September 9, 2020

Table 1.1-3 Product Index

Products Included in Submission	Product Identification Number
Anvil 30m 0mg/ml	TP#: TPBD6046X SKU#: BM Anvil 0mg 30ml
Anvil 30m 3mg/ml	TP#: TPBD6046Y SKU#: BM Anvil 3mg 30ml
Anvil 30ml 6mg/ml	TP#: TPBD6046Y SKU#: BM Anvil 6mg 30ml
Anvil 30ml 12mg/ml	TP#: TPBD6046Z SKU#: BM Anvil 12mg 30ml
Anvil 30ml 18mg/ml	TP#: TPBD60471 SKU#: BM Anvil 18mg 30ml
Anvil 100ml 0mg/ml	TP#: TPBD6046T SKU#: BM Anvil 0mg 100ml
Anvil 100ml 3mg/ml	TP#: TPBD6046V SKU#: BM Anvil 3mg 100ml
Anvil 100ml 6mg/ml	TP#: TPBD6046W SKU#: BM Anvil 6mg 100ml

Anvil 100ml 12mg/ml	TP#: TPBD6046W SKU#: BM Anvil 12mg 100ml

Table 1.1-4 Product Identification Information

Unique Identification (SKU)	BM Anvil 0mg 30ml
Product Name	**Anvil 30ml 0mg/ml**
Nicotine Concentration	00mg/ml
PG/VG Ratio	70/30
Package Volume	30ml
Product Category	ENDS Component or Part
Product Sub-Category	E-Liquid
Package Type	Plastic Bottle
Package Quantity	One Bottle
E-Liquid Volume	30ml
Characterizing Flavor	Tobacco
TP Number	TPBD6046X
Unique Identification (SKU)	BM Anvil 3mg 30ml
Product Name	**Anvil 30m 3mg/ml**
Nicotine Concentration	03mg/ml
PG/VG Ratio	70/30
Package Volume	30ml

Product Category	ENDS Component or Part
Product Sub-Category	E-Liquid
Package Type	Plastic Bottle
Package Quantity	One Bottle
E-Liquid Volume	30ml
Characterizing Flavor	Tobacco
TP Number	TPBD6046Y
Unique Identification (SKU)	BM Anvil 6mg 30ml
Product Name	**Anvil 30ml 6mg/ml**
Nicotine Concentration	06mg/ml
PG/VG Ratio	70/30
Package Volume	30ml
Product Category	ENDS Component or Part
Product Sub-Category	E-Liquid
Package Type	Plastic Bottle
Package Quantity	One Bottle
E-Liquid Volume	30ml
Nicotine Concentration	00mg/ml
PG/VG Ratio	70/30
Package Volume	100ml
Product Category	ENDS Component or Part
Product Sub-Category	E-Liquid

Package Type	Plastic Bottle
Package Quantity	One Bottle
E-Liquid Volume	100ml
Characterizing Flavor	Tobacco
TP Number	TPBD6046T
Unique Identification (SKU)	BM Anvil 3mg 100ml
Product Name	**Anvil 100ml 3mg/ml**
Nicotine Concentration	03mg/ml
PG/VG Ratio	70/30
Package Volume	100ml
Product Category	ENDS Component or Part
Product Sub-Category	E-Liquid
Package Type	Plastic Bottle
Package Quantity	One Bottle
E-Liquid Volume	100ml
Characterizing Flavor	Tobacco
TP Number	TPBD6046v
Unique Identification (SKU)	BM Anvil 6mg 100ml
Product Name	**Anvil 100ml 6mg/ml**
Nicotine Concentration	06mg/ml
PG/VG Ratio	70/30
Package Volume	100ml

Product Category	ENDS Component or Part
Product Sub-Category	E-Liquid
Package Type	Plastic Bottle
Package Quantity	One Bottle
E-Liquid Volume	100ml
Characterizing Flavor	Tobacco
TP Number	TPBD6046W
Unique Identification (SKU)	BM Anvil 3mg 30ml
Product Name	**Anvil 100ml 12mg/ml**
Nicotine Concentration	12mg/ml
PG/VG Ratio	70/30
Package Volume	100ml
Product Category	ENDS Component or Part
Product Sub-Category	E-Liquid
Package Type	Plastic Bottle
Package Quantity	One Bottle
E-Liquid Volume	100ml
Characterizing Flavor	Tobacco
TP Number	TPBD6046v

1.2 COVER LETTER AND CERTIFICATION STATEMENT

See Module 1.

1.3 ADMINISTRATIVE INFORMATION

Primary Contact	
Contact Type:	Manufacturer
Title (e.g., Mr., Ms.):	Mr.
First/Given Name:	Jon
Middle Name:	
Last Name:	Rose
Position Title:	General Manager
Email Address:	jrose@tritondistribution.com

Primary Contact	
Company Name:	Triton Distribution
Street	789 N. Grove Rd.
City	Richardson
State	Texas
Zip Code	75081
Country	United States
Telephone Number:	214-880-6440

Manufacturer Information	
Contact Type:	Manufacturer

Company Name:	Triton Distribution
FDA FEI Number:	3012508792
Street	789 N. Grove Rd.
City	Richardson
State	Texas
Zip Code	75081
Country:	United States
Telephone Number:	214-880-6440

1.4 INDUSTRY TO FDA CORRESPONDENCE REGARDING APPLICATION STATUS

This section is not applicable to Boiler Maker Anvil E-Liquid's PMTA based on Triton Distribution current knowledge and information.

1.5 INDUSTRY TO FDA CORRESPONDENCE—OTHER

This section is not applicable to Boiler Maker Anvil E-Liquid's PMTA based on Triton Distribution current knowledge and information.

1.6 MEETINGS WITH INDUSTRY

This section is not applicable to Boiler Maker Anvil E-Liquid's PMTA based on Triton Distribution current knowledge and information.

1.7 DISPUTE RESOLUTION

This section is not applicable to Boiler Maker Anvil E-Liquid's PMTA based on Triton Distribution current knowledge and information.

1.8 INDUSTRY PERIODIC REPORT

See below summary of required FDA periodic reporting.

Table 1.8-1 Industry Periodic Report

Date	Title	PMTA Location
	FURLS Listing	Module 1

1.9 PRODUCT LABELS AND LABELING

Table 1.9-1 Labels and Labeling

Type of Labeling Material	Title	Filename Located in Module 1
Bottle Label	Boiler Maker Anvil 30mL 0mg/ml	**BM Anvil 0mg.jpg**
Bottle Label	Boiler Maker Anvil 30mLmg/ml	**BM Anvil Nic 30mL.jpg**
Bottle Label	Boiler Maker Anvil 30mL 3mg/ml	**BM Anvil Nic 30mL.jpg**
Bottle Label	Boiler Maker Anvil 30mL 6mg/ml	**BM Anvil Nic 30mL.jpg**
Bottle Label	Boiler Maker Anvil 30mL 12mg/ml	**BM Anvil Nic 30mL.jpg**
Bottle Label	Boiler Maker Anvil 30mL 18mg/ml	**BM Anvil Nic 30mL.jpg**

Bottle Label	Boiler Maker Anvil 100ml 0mg/ml	**BM Anvil 0mg.jpg**
Bottle Label	Boiler Maker Anvil 100mlmg/ml	**BM Anvil Nic 100ml.jpg**
Bottle Label	Boiler Maker Anvil 100ml 3mg/ml	**BM Anvil Nic 100ml.jpg**
Bottle Label	Boiler Maker Anvil 100ml 6mg/ml	**BM Anvil Nic 100ml.jpg**
Bottle Label	Boiler Maker Anvil 100ml 12mg/ml	**BM Anvil Nic 100ml.jpg**

1.10 PRODUCT PROMOTIONAL MATERIAL

Triton Distribution stopped exhibiting at industry trade expos in 2017. Since 2015, Triton Distribution severely limited promotional material, relying on our primary marketing method of age-restricted specialty vape shop product referrals to their customers for Triton Distribution products. Current promotional material is the website: www.tritondistribution.com.

Table 1.10-1 Product Promotional Material

Type of Promotional Material	Title	Filename Located in Module 1
POS	*Poster (Discontinued 2018)*	Boilmaker_POSTER(1).pdf

POS	Facebook Post 2016 (Discontinued 2018)	Boilermaker line 6-19-16.png
POS	Facebook Post 2016 (Discontinued 2018)	Boilermaker line 7-20-16.png
POS	Facebook Post 2016 (Discontinued 2018)	Boilermaker line 8-2-16.png
POS	Facebook Post 2016 (Discontinued 2018)	Boilermaker-Anvil 6-22-16.png
Email	Email blast graphic introducing the new bottle format to showcase design changes that reflect no food or character design.	
Website	www.Boiler Maker.com	N/A

1.11 GRANDFATHER EVIDENCE

Not Applicable. Although Boiler Maker Anvil E-Liquid s are currently marketed in the United States (U.S.) as of August 8, 2016, Boiler Maker Anvil E-Liquid is a "new tobacco product" in accordance with Section 910(a)(1) of the FD&C Act in that it was not commercially marketed in the U.S. as of February 15, 2007. See Table 1.11-1 for evidence establishing the August 8, 2016 status of the Boiler Maker Anvil E-Liquid.

Table 1.11-1 Pre 8/8/16 Product Sales

Description	Date	PMTA Location
Sales invoice from Triton Distribution to wholesale customer (retail vape store)	8/4/16	**Module 1**
Sales invoice from Triton Distribution to wholesale customer (retail vape store)	8/4/16	**Module 1**
Sales invoice from Triton Distribution to wholesale customer (retail vape store)	8/4/16	**Module 1**

1.12 FDA TO INDUSTRY CORRESPONDENCE

This section is not applicable to Boiler Maker Anvil E-Liquid's PMTA based on Triton Distribution current knowledge and information.

1.13 MASTERFILE AUTHORIZATION

Table 1.13-1 Tobacco Product Master File Authorizations

TPMF	Description	PMTA Location
MF0000403	Cardno ChemRisk Comprehensive	Module 1

	Literature Review on ENDS and E-Liquids	
MF0000401	Capella confidential formulation information	Module 1
MF0000397	Flavor West confidential formulation information	Module 1
MF0000262	FlavourArt confidential formulation information	Module 1
MF0000068	Nicotine River confidential formulation information	Module 1
MF0000384	Chubby Gorilla confidential information	Module 1
MF0000363	Alternative Ingredients confidential formulation information	Module 1

1.14 HEALTH DOCUMENTS

Table 1.14-1 Health Documents Index

Date	Title	PMTA Location
09/03/2020	FDA Form 3473	Module 1

1.15 REQUESTED DOCUMENTS

Table 1.15-1 Requested Documents Index

Date	Title	PMTA Location
	Ingredient Listing Report —Paper submission to FDA	Module 1

MODULE 2: SUMMARY

2.1 INDEX OF ALL STUDIES

To save time and reduce overall application costs, Triton Distribution is participating in a Coalition with other, similarly situated e-liquid companies in order to pool resources to fund the development of certain, required non-product specific data including a comprehensive review of the scientific literature. The peer-reviewed literature included and summarized in TPMF No. MF0000403 and the Cardno ChemRisk: ENDS & E-Liquid—State of the Science; January 13, 2020 (henceforth "State of the Science") report covers the areas directly applicable to establishing the population effect of the Boiler Maker Anvil E-Liquid, including the published studies and articles, as well as subject matter databases, related to the topic areas identified in FDA's PMTA Guidance: *in vivo* and *in vitro* toxicology (*e.g.*, carcinogenesis, genotoxicity, mutagenicity, reactive oxygen species, inflammation, cytotoxicity, respiratory health, cardiovascular disease, and reproductive and developmental toxicity), clinical health, abuse liability and pharmacokinetics, trends in usage and factors that influence ENDS usage (*e.g.*, susceptibility, consumer perception, initiation, cessation, transition), topography, human factors, biomarkers of harm and exposure,

and population health (*e.g.*, FDA's Population Assessment of Tobacco and Health (PATH)).

Table 2.1-1 Subject Matter Database Index

Key Area of Investigation	Database	PMTA Location
Health Risks of the Tobacco Product	Cardiovascular Disease	2.6.1.1
	Respiratory	2.6.1.2
	In Vitro Toxicology	2.6.1.1.1, 2.6.1.2.1, 2.6.1.3.1, 2.6.1.4.1
	In Vivo Toxicology	2.6.1.1.2, 2.6.1.2.2, 2.6.1.3.2, 2.6.1.4.2
Effect on Tobacco Use Behavior among Current Users	Abuse Liability	2.6.3.2
	Topography	2.6.3.3.1
	Usage	2.6.3.3.4
	Cessation	2.6.3.3.10
	Adverse Events	5.5
	Explosions	5.5
Effect on Tobacco Use Initiation among Non-Users	Initiation	2.6.3.3.9
Effect of Marketing on Con-	Perception	2.6.3.1

sumer Understanding and Perceptions		
Effect on the Population as a Whole	Indoor Air Quality and Secondhand Exposures	6.6
	Biomarkers	2.6.1.5
	Transition	2.6.3.3.8

Along with developing the literature review, product-specific analyses were done for HPHCs, User Surveys and Environmental Assessments see Table 2.1-2 for more information.

Table 2.1-2 Index of All Studies and Analyses

Key Area of Investigation	Study name	Performing Organization	PMTA Location
Health Risks of the Tobacco Product	Vapor HPHC Analysis	Adact Medical Ltd.	4.2
Effect on Tobacco Use Behavior among Current Users	Electronic Product Use Survey	Cardno ChemRisk 235 Pine St 23rd Floor San Francisco, CA 94104	5.3

Effect on the Environment	Environmental Assessments	Triton Distribution Template prepared by: Azim Chowdhury, JD, Partner Keller & Heckman LLP 1001 G Street Suite 500W Washington, DC 20001	Module 7

2.2 INTEGRATED SUMMARY

2.2.1 INTRODUCTION

Triton Distribution ("Triton Distribution"), the e-liquid manufacturer and distributor, hereby submits this Premarket Tobacco Product Application (PMTA) on behalf of the brand owner, Boiler Maker LLC, pursuant to Section 910 of the Federal Food, Drug, and Cosmetic Act (FD&C Act), as amended by the Family Smoking Prevention and Tobacco Control Act (TCA). This PMTA requests marketing authorization for the Boiler Maker Anvil E-Liquid line of open-system e-liquid products.[1] Boiler Maker Anvil E-Liquid is currently available in the following nicotine concentration levels: 0, 3, 6, 12, & 18mg/mL and in 30 ml or 120 mL plastic

[1] *See* Federal Food, Drug, and Cosmetic Act (FD&C Act) § 910(c)(1)(A)(i), 21 U.S.C. § 301 (2012).

bottle sizes. Although Boiler Maker Anvil E-Liquid open-system e-liquid products are currently marketed in the U.S. as of August 8, 2016, Boiler Maker Anvil E-Liquid is a "new tobacco product" in accordance with Section 910(a)(1) of the FD&C Act in that it was not commercially marketed in the U.S. as of February 15, 2007. Triton Distribution understands that the Food and Drug Administration (FDA or Agency) may not authorize a PMTA unless it meets the statutory requirements of the TCA, including scientific data demonstrating the "tobacco product to be marketed would be appropriate for the protection of the public health." Triton Distribution believes that this submission demonstrates that its Boiler Maker Anvil E-Liquid product is appropriate for the protection of the public health (APPH) in a robust and scientifically valid manner based on product testing and extensive literature review. This submission meets the regulatory requirements of an application based on Section 910 of the FD&C Act and the criteria set forth in 21 C.F.R. § 1105.10, as well as FDA's final rule on refuse-to-accept procedures for PMTAs.[2] Triton Distribution remains committed to working with FDA and demonstrating that the marketing of its open-system e-liquid products to adult tobacco users is APPH.

2.2.2 STATEMENT OF COMPLIANCE

This application meets the content requirements of section 910(b)(1) and should receive a substantive scientific review (see Module 2 Section 2.2.2.1).

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[2] *See* U.S. Food & Drug Admin., *Direct Final Rule*, 81 Fed. Reg. 52329 (Aug. 8, 2016), https://www.federalregister.gov/documents/2016/08/08/2016-18534/refuse-to-accept-procedures-for-premarket-tobacco-product-submissions.

2.2.2.1 REQUIRED ELEMENTS FOR PMTAS

This application contains all of the statutorily required elements for PMTAs set forth in Section 910(b)(1) of the Tobacco Control Act, specifically:

Table 2.2-1 Required Elements for PMTAs

§ 910(b)(1) Requirement	PMTA Location
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	TPMF No. MF0000403, the Cardno ChemRisk: ENDS & E-Liquid—State of the Science; January 13, 2020 report, subject matter databases and the summary of recent published literature found in Module 2 Section 2.9. See also Module 3, 4, 5, 6
A full statement of the components, ingredients, additives, and properties, and of the principle or principles of operation, of such tobacco product	Module 3
A full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and, when relevant, packing	Module 2 Section 2.3 Module 3

and installation of, such tobacco product	
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	Not Applicable; See Module 2 Section 2.2.2.2
Such samples of such tobacco product and of components thereof as the Secretary may reasonably require	Product samples will be available upon request.
Specimens of the labeling proposed to be used for such tobacco product	Module 1 Section 1.9

2.2.2.2 STATEMENT OF COMPLIANCE WITH APPLICABLE TOBACCO STANDARD

Triton Distribution hereby states that it has taken action to comply with the requirements under Section 907 of the Act that apply to Boiler Maker Anvil E-Liquid. Currently, there are no tobacco product standards applicable to Boiler Maker Anvil E-Liquid.

2.2.3 BACKGROUND AND MOTIVATION

Triton Distribution was founded in 2014. Triton Distribution was started by an industry veteran looking to create a superior vape experience. Our brand seeks to help current adult smokers find an alternative to traditional cigarettes. Triton Distribution strives to lead vaping forward with our quality, affordability, service, transparency, advocacy, and responsible marketing standards.

2.2.4 PMTA COALITION APPROACH TO GENERATING COMPREHENSIVE LITERATURE REVIEW TO SUPPORT BOILER MAKER ANVIL E-LIQUID PMTA AND FDA'S REQUIREMENTS FOR FILING ACCEPTANCE

Due to the accelerated September 9, 2020 court-mandated PMTA submission deadline for newly deemed products on the market as of August 8, 2016,[3] Triton Distribution and Boiler Maker have joined with other, similarly situated members of industry to form a Coalition in an effort to make the current PMTA process more efficient while reducing the burden on government and individual manufacturer's resources. As the Agency's June 2019 Final Guidance on PMTAs for Electronic Nicotine Delivery Systems (ENDS) (the "PMTA

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[3] *See* American Acad. of Pediatrics, et al. v. FDA, Case No. 8:18-cv-00883 (2019). As the Court made clear in its Memorandum Opinion, "New products for which applications have not been filed within this period shall be subject to FDA enforcement actions ***in the FDA's discretion***." *Id.* (emphasis added). The Court further stated that "FDA shall have the ability to exempt [n]ew [p]roducts from [the] filing requirements for good ***cause on a case-by-case basis***." *Id.* (emphasis added).

Guidance") clarifies, these applications require a significant amount of both product-specific and non-product specific data, and are expected to require countless hours and cost millions of dollars—making it virtually impossible for the small organizations that make up the majority of businesses, such as Triton Distribution, in the industry to submit complete applications on their own, particularly in light of the accelerated deadline.

To save time and reduce overall application costs, Triton Distribution is participating in a Coalition with other, similarly situated e-liquid companies in order to pool resources to fund the development of certain, required non-product specific data (e.g., comprehensive review of the scientific literature). Otherwise, pursuing such efforts on an individual basis would be time- and cost-prohibitive for companies like ours who are focused on marketing reduced-harm nicotine products to adult combustible cigarette smokers and tobacco users. Our Coalition approach to developing the literature review, along with product-specific analysis, marketing restrictions, etc. described herein, is also intended to be consistent with the Trump Administration's current thinking as recently communicated by Secretary Alex Azar—namely, that the U.S. Department of Health and Human Services (HHS) and FDA are working "to create pathways that would streamline approval for open-tank, small vape shop-based products."[4]

Triton Distribution is also relying on shared tobacco product master files (TPMFs) covering common component materials such as flavor ingredients and container

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[4] *HHS Secretary Alex Azar*, The Scott Sands Show (Jan. 21, 2020), https://www.iheart.com/podcast/139-the-scottshow-27091419/episode/hhs-secretary-alex-azar-56131042/.

closures systems (bottles). Not only will reliance on TPMFs help Triton Distribution distribute costs, this approach should also help FDA by preventing unnecessary duplication in review efforts, since supporting data for common product elements will be consistent across multiple applications.

2.2.5 PRODUCT DESCRIPTION

Boiler Maker Anvil E-Liquid is an open-system e-liquid product that, based on the HPHC results and published literature, is a potentially less harmful substitute for combustible tobacco products, including cigarettes. Manufacturing, marketing, and labeling are focused on current adult smokers with the intent that Boiler Maker Anvil E-Liquid will not reach unintended users. Manufacturing, controls, and labeling are all focused on maximizing the safety and quality of the product.

Boiler Maker Anvil E-Liquid is available in 30 mL and 100 mL bottle sizes, and in the following nicotine concentration levels: 0, 3, 6, 12 & 18mg/mL (Table 2.2-2 Product Identification Information). Complete formulations are provided for Boiler Maker Anvil 0, 3, 6, 12 & 18 mg 30 mL and 100 mL in Module 3 Section 3.2

Table 2.2-2 Product Identification Information

Unique Identification (SKU)	BM Anvil 0mg 30ml
Product Name	**Anvil 30ml 0mg/ml**
Nicotine Concentration	00mg/ml
PG/VG Ratio	70/30
Package Volume	30ml

Product Category	ENDS Component or Part
Product Sub-Category	E-Liquid
Package Type	Plastic Bottle
Package Quantity	One Bottle
E-Liquid Volume	30ml
Characterizing Flavor	Tobacco
TP Number	TPBD6046X
PG/VG Ratio	70/30
Package Volume	100ml
Product Category	ENDS Component or Part
Product Sub-Category	E-Liquid
Package Type	Plastic Bottle
Package Quantity	One Bottle
E-Liquid Volume	100ml
Characterizing Flavor	Tobacco
TP Number	TPBD6046V

The PMTA submission is Bundled/Grouped Submission covering all nicotine levels and bottle sizes for the Boiler Maker Anvil E-Liquid. We have included the Form FDA 4057b, Unique Identifying Information for New Tobacco Products in a Group Submission of PMTAs form (Module 1).

2.2.6 THE MARKETING OF BOILER MAKER ANVIL E-LIQUID IS APPROPRIATE FOR THE PROTECTION OF THE PUBLIC HEALTH BECAUSE BOILER MAKER ANVIL E-LIQUID IS USED BY ADULT SMOKERS AND TOBACCO USERS.

Under the FD&C Act, marketing authorization is warranted upon a showing that the marketing of the new tobacco product "is APPH".[5] This determination is made based on a number of factors, including youth access and appeal, and an evaluation of "the risks and benefits to the population as a whole, including both the users of tobacco products and persons who do not currently use tobacco products." The APPH standard also takes into consideration "the increased or decreased likelihood that existing users of tobacco products will stop using such products" and "the increased or decreased likelihood that those who do not use tobacco products will start using such products."[6] Accordingly, it is clear that one of the objectives of the FDA premarket review process is to provide existing adult combustible cigarette users with tobacco product alternatives to decrease morbidity and mortality associated with such tobacco use (while recognizing that no tobacco product is risk-free), and to prevent more harmful or addictive products from entering the market. Indeed, the TCA specifically contemplates adults' continued access to tobacco products (which would include Boiler Maker Anvil E-liquid), and requires FDA to regulate in a manner that would allow adults to access tobacco

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[5] *See* FD&C Act § 910(c), 21 U.S.C. § 301 (2012).

[6] *See* FD&C Act § 910(c)(4), 21 U.S.C. § 301 (2012).

products that are lower risk than conventional, combustible cigarettes. Specifically, the TCA is designed "to provide new and flexible enforcement authority to ensure that there is effective oversight of the tobacco industry's efforts to develop, introduce, and promote less harmful tobacco products."[7] At the same time, it is clear that the public health standard under Section 910 of the FD&C Act does *not* require the applicant to prove that the product significantly reduces harm and the risk of tobacco-related disease to individual tobacco users, as this is the standard for a modified risk order under Section 911 of the FD&C Act.

As further detailed in this application, we demonstrate that the marketing of the Boiler Maker Anvil E-Liquid as an alternative source of nicotine for existing adult tobacco product users is APPH.

2.2.6.1 MARKETING TO CURRENT ADULT USERS

Triton Distribution is committed to marketing the Boiler Maker Anvil E-Liquid product as described in this application (Module 2 Section 2.4) to existing adult users, including current adult smokers. As the Director of Health Improvement at Public Health England recently noted, "there is widespread academic and clinical consensus that while not without risk, vaping is far less harmful than smoking," and that "there is no situation where it would be better for your health to continue smoking rather than switching completely to vaping." (Tait, 2019). Indeed, switching from traditional cigarettes to Boiler Maker Anvil E-liquid could prevent between 1.6 million and 6.6 million premature deaths over

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[7] Tobacco Control Act of 2009, Pub. L. No. 111-31, § 3(4), 123 Stat. 1776, 1782 (2009).

ten years in the U.S. (Levy, Borland, Lindblom, & et al, 2018). This is supported by the findings of the National Academies of Science, Engineering and Medicine (NASEM) which completed a comprehensive analysis of the published literature and concluded, in pertinent part, that "Laboratory tests of e-cigarette ingredients, *in vitro* toxicological tests, and short-term human studies suggest that e-cigarettes are likely to be far less harmful than combustible tobacco cigarettes" (National Academies of Sciences, 2018). Indeed, an even more recent review of the relevant science published in the *Expert Review of Respiratory Medicine Journal* contends that there is growing evidence showing that e-cigarette emission aerosols are relatively safe compared to tobacco smoke (Polosa, O'Leary, Tashkin, Emma, & Caruso, 2019).

Accordingly, as detailed in this application, based on product testing, manufacturing quality controls, comparisons to other available tobacco products, evidence of adult-only sales and a restricted, adult-oriented marketing plan and age-gating measures, as well as a comprehensive review of the scientific literature, we demonstrate that the marketing of Boiler Maker Anvil E-Liquid as an alternative source of nicotine for current adult combustible tobacco users is APPH.

2.2.6.2 SALES LIMITATION AND MARKETING PLAN

See the Sales Limitation and Marketing Plan set forth in Module 2 Section 2.4.2, which describes how Boiler Maker Anvil E-Liquid will continue to be strictly marketed and sold to adults in adult-only retailers and through age-verified online websites. As described in Module 2 Section 2.4 among other things, Boiler Maker Anvil E-Liquid will not be promoted by Triton Distri-

bution, partners, sponsors, influencers, bloggers, or brand ambassadors on social media, radio or television.

Boiler Maker LLC provides distributors, wholesalers, and retailers responsible marketing material from website banner ads to physical promotional items to help support growth. We do this through our media and promotional request forms on our website.

Since its inception, Boiler Maker has been committed to complying with all legal and regulatory requirements, including age restrictions for the online sale of electronic nicotine delivery systems (ENDS). Boiler Maker opposes all illegal underage tobacco use and shares FDA's concerns regarding the recent increases in teenage vaping. Boiler Maker's mission has always been focused on providing strict access to ENDS products. These restrictions assist in ensuring that products sold on Boiler Maker's website are available to adults seeking potentially less risky alternatives to combustible cigarettes. The Company has implemented robust age-verification software, as described below.

Specifically, in addition to a pop-up "age gate" prior to entering the website (see below), the Company has implemented AgeCheckner.Net (https://agechecker.net/), which provides state-of-the-art age verification services to online stores that sell age restricted products such as vaporizers and tobacco related products. To verify that the age of a potential customer is 21 or older, the system uses intelligent matching technology to match the name, address and date of birth provided by the customer to information contained in an extensive database of trusted records from various data sources. Upon checkout, the AgeChecker.Net system verifies that the billing address on the personal check or credit card of-

fered for payment by the purchaser matches the address listed in its database.

TRITON
DISTRIBUTION

ARE YOU OF LEGAL SMOKING AGE?

THE PRODUCTS AND SERIVCES ON THIS WEBSITE ARE INTENDED FOR ADULT USE ONLY, BY ENTERING THIS WEBSITE, YOU CERTIFY THAT YOU ARE OVER THE AGE OF 21.

I AM OVER THE AGE OF 21	I AM NOT OVER THE AGE OF 21

2.2.7 THE PUBLIC HEALTH BENEFIT OF FLAVORS: MARKETING OF BOILER MAKER ANVIL E-LIQUID WOULD HELP ADULTS TRANSITION AWAY FROM SMOKING CIGARETTES, DOES NOT INCREASE YOUTH INITIATION OF NICOTINE OR TOBACCO PRODUCTS, AND DOES NOT INCREASE THE RISK OF HARM TO THE USER.

The PMTA Guidance highlights a number of surveys, including the National Youth Tobacco Survey (NYTS) and PATH study results, to emphasize that minors are increasingly using flavored ENDS and prefer non-tobacco and non-menthol flavors. But it is undeniable that flavors appeal to adults as well. There is a growing body of scientific evidence supporting that flavors are crucial to getting adult smokers to make the switch and stay away from combustible cigarettes.

Indeed, numerous published studies support the important role of flavored ENDS for harm reduction. Recently, for example, the *Harm Reduction Journal* published the results of an extensive online survey which assessed the first and current vapor product flavors

used by a non-probabilistic sample of 20,836 adult frequent vapers in the U.S (Russell, McKeganey, Hamilton-Barclay, & Nides, 2018). That survey found that cigarette smokers who switch to Boiler Maker Anvil E-liquid are doing so increasingly with a variety of fruit and other non-tobacco flavors.

Another recent survey of more than 69,000 adult vapers found that just 16% identified tobacco, menthol, or mint as flavors they used most often; the vast majority preferred fruit and sweet flavors (Farsalinos, 2018).

The overall survey results from all participating Coalition members further supports that the marketing of Boiler Maker Anvil E-Liquid is APPH (the "Coalition Survey"). Nearly 10,000 participants provided responses in the combined analysis. In that Mint/Menthol, Dessert, and Tobacco were among the top four flavor choices by 33.57%, 28.18%, and 26.6% of all respondents, respectively. "Fruity" flavor was the number one flavor preference by 49.98% of all respondents. Only about 3% of all respondents stated that they preferred no flavor, confirming that flavors appeal to adults and could serve an important role in transitioning existing adult users away from more harmful, combustible cigarette products.

These findings are consistent with the Consumer Advocates for Smoke-Free Alternatives Association (CASAA) consumer survey results. CASAA surveys its membership from time to time to assess use patterns, consumer behaviors, and various demographic and other information, the most comprehensive survey to date being conducted in late 2015 (CASAA's Survey) (Phillips, 2016). The purpose of the survey was to elicit information from CASAA members to present to the Office

of Information and Regulatory Affairs (OIRA) in January 2016 to help inform decisions in connection with FDA's proposed deeming of Boiler Maker Anvil E-liquid as tobacco products. The study population included nearly 20,000 CASAA members and their smoking/quitting history. Nearly a third of the CASAA Survey respondents stated they started out using tobacco or menthol flavors but now always or almost always use other flavors. This change in flavor preference away from tobacco or menthol flavors has powerful implications for not only the role of flavors in helping smokers' transition from smoking to vaping, but also in connection with helping vapers maintain smoking abstinence and preventing relapse to smoking.[8]

As FDA is aware, non-tobacco and non-menthol flavors in and of themselves do not constitute marketing to teenagers. Moreover, while teenagers may illegally use flavored vaping products, analysis of data from the 2019 NYTS released on December 6, 2019 by the Centers for Disease Control and Prevention (CDC) indicates that flavors are not the main reason why teenagers vape (Cullen, Gentzke, Sawdey, & et al., 2019). The number one reason (56.1%) why teenagers try Boiler Maker Anvil E-liquid is simple curiosity.

If teens are attracted to flavors, the abundance of evidence shows that youth are particularly attracted to fla-

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[8] There is a tendency to view the case of a person who quits smoking before starting to use vapor products as a negative, but this ignores the reality that smokers are at a high risk of relapse. Thus, the fact that a former smoker chooses to use low-risk vapor products rather than begin smoking again is clearly a positive development. An example of one such story can be found at CASAA's collection of testimonials http://www.casaa.org/testimonials/glointhedark/.

vored, *cartridge-based* ENDS products, as FDA itself acknowledges in its recent Enforcement Priorities for Electronic Nicotine Delivery Systems (ENDS) Guidance (hereafter, "Enforcement Priorities Guidance"),. This has led FDA to take the position that it will prioritize enforcement against any flavored, cartridge-based ENDS product lacking marketing authorization. FDA also states in the Enforcement Priorities Guidance that the majority of adult e-cigarette users use flavored e-cigarettes, and that there is some evidence to suggest that flavored e-cigarettes may improve switching from combustible cigarette smoking to using e-cigarettes. In addition, data from the 2019 NYTS indicate that youth overwhelmingly prefer cartridge-based ENDS products because these products are easy to conceal, can be used discreetly, can have high nicotine content, and are manufactured on a large scale.

Open-system e-liquid products, however, are not subject to these same risks, perhaps explaining why FDA chose not to effectively "ban" flavors in these products by eliminating the premarket review compliance period. In short, FDA concludes that flavored pod/cartridge-based systems are the main culprit and source of underage use. Boiler Maker Anvil E-Liquid, because it is an open-system e-liquid, would not be subject to these same risks leading to underage use. Moreover, as described herein, Boiler Maker has enacted strict marketing guidelines and age-verification procedures, among other things, to further ensure Boiler Maker Anvil E-Liquid is not inadvertently marketed or sold to minors.

In addition, based on ingredient and testing data, Triton Distribution found no significant differences among all of its flavored e-liquid products The hazardous and

potentially hazardous constituents (HPHC) is consistent among all flavors (full reports can be found in Module 4 Section 4.2).

Furthermore, there is no evidence that Boiler Maker Anvil E-Liquid's product flavor variants present issues of youth access or appeal. As described herein, Boiler Maker has responsibly marketed and sold its products only to adults. Boiler Maker employs robust age-verification technology, only allows website sales to consumers who are at least 21 years of age and does not offer products in packaging that is targeted to minors or likely to promote use of ENDS by minors. Boiler Maker LLC voluntarily implemented 21+ age sales restriction on 4/1/2019. Between the beginning of the reporting period on 12/8/18 until 4/1/2019 when 21+ age restriction was implemented, Boiler Maker LLC had only one sale to an individual under the age of 21 (20 years of age at the time of purchase).

Further, in light of the heightened regulatory scrutiny and the fast-approaching PMTA deadline, Triton Distribution has begun implementing certain supply chain and distribution network controls to further ensure product quality and safety and to further prevent youth access. See Module 2 Section 2.4 for more information.

In sum, throughout this PMTA submission, we support that Boiler Maker Anvil E-Liquid is APPH because the availability of this flavored e-liquid product would help adults transition away from smoking combustible cigarettes, would not increase youth initiation of nicotine or tobacco products, and would not increase the risk of harm to the user.

2.2.8 NONCLINICAL STUDIES

When compared to smoke-chemistry analysis of combustible cigarettes, as well as recently authorized reduced-risk products such as IQOS, Boiler Maker Anvil E-Liquid demonstrates substantially lower potential exposures to numerous HPHCs and other constituents when used as intended, on par with other ENDS products on the market, based on publicly available information.

Triton Distribution utilized a third-party lab, Adact, to assess the levels of certain HPHCs in the vapor produced using Boiler Maker Anvil E-Liquid. The results were used to calculate a worst-case potential exposure to consumers. The exposure model data was then utilized to compare relative exposure to HPHCs from Boiler Maker's e-liquids to HPHC results from traditional tobacco products (e.g., cigarettes) and recently authorized heated tobacco products (i.e., IQOS), a modified risk tobacco product, obtained from direct testing as well as published literature. Finally, we conducted toxicological evaluations of those compounds expected to have higher exposures resulting from e-liquid use than from traditional tobacco use. In sum, for the reasons set forth below, the HPHC results support that the marketing of these products is appropriate for the protection of the public health when used by adult smokers and tobacco users. The full HPHC reports and data, as well as the analysis of same, is included in the memorandum in Module 4. In sum, the HPHC results for the Boiler Maker Anvil e-liquid support that the marketing of the product is APPH when used by adult smokers and tobacco users.

2.2.9 SYSTEMATIC LITERATURE REVIEW

As required by Proposed Rule § 1114.7((k)(2)) this application contains full reports of all information, including the substantive information required by section 1114.27(b)(1)(ii), all favorable and unfavorable studies; published or known to Triton Distribution, or which should reasonably be known, concerning investigations, including nonclinical and human subject studies. The PMTA Coalition's comprehensive review of the scientific literature covering the areas directly applicable to establishing the population effect of the Boiler Maker Anvil E-Liquid , including the published studies and articles, as well as detailed subject matter databases, related to the topic areas identified in FDA's PMTA Guidance: *in vivo* and *in vitro* toxicology (*e.g.*, carcinogenesis, genotoxicity, mutagenicity, reactive oxygen species, inflammation, cytotoxicity, respiratory health, cardiovascular disease, and reproductive and developmental toxicity), clinical health, abuse liability and pharmacokinetics, trends in usage and factors that influence ENDS usage (*e.g.*, susceptibility, consumer perception, initiation, cessation, transition), topography, human factors, biomarkers of harm and exposure, and population health (*e.g.*, FDA's PATH study). The peer-reviewed literature included and summarized in TPMF No. MF0000403, the State of the Science report and the subject matter databases offer important insight into the impact of ENDS like Boiler Maker Anvil E-Liquid on public health.[9] As part of this review, hundreds of

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[9] In the PMTA Guidance for Industry (FDA, 2019), the US Food and Drug Administration (FDA) recommends that applicants demonstrate a comprehensive understanding of the currently available

published literature including, but not limited to consumer perceptions and intentions, initiation and cessation, product use patterns, human factors, abuse liability, biomarkers of potential harm (BOPH), biomarkers of exposure (BOE), and toxicological and clinical evaluations of health outcomes. The purpose of the literature review is to evaluate the current state of the science on ENDS and their impact on public health for the US population, including both users and non-users of these products. The methods and findings from the National Academy of Sciences, Engineering, and Medicine (NASEM) report "Public Health Consequences of E-Cigarettes" (NASEM, 2018) were used as the foundation of the current literature review.

As described in Appendix B of the NASEM report, the committee performed numerous literature searches across six databases: PubMed, Scopus, Web of Science, PsycINFO (ProQuest), MEDLINE (Ovid), and Embase (Ovid). There was no limit to the start date of the search and the last search was completed August 31, 2017. Topics of interest included health effects of e-cigarettes; e-cigarettes and transitions to and from combustible tobacco cigarette smoking; e-cigarettes and dependence; e-cigarettes and combustible tobacco cigarette smoking initiation; and e-cigarette and combustible tobacco cigarette smoking cessation. The searches included the following key words and phrases: e-cigarette, e-cigarettes, "electronic cigarette," "electronic cigarettes," "electronic nicotine delivery," "electronic nicotine device," vape, vaping, e-liquid, dependence, withdrawal, craving, appeal, addition, "abuse liability," "subjective effects," "smoking urge," "urge to smoke," "smoking desire," "desire to smoke," "smoking initiation," "initiation," "smoking cessation," "cessation," "quit," "abstinence," "smoking reduction," and "harm reduction." The committee excluded the term "e-liquid" from searches in Scopus and Web of Science, due to produced results related to geothermal energy. Additionally, searches in PubMed and MEDLINE used the Medical Subject Headings (MeSH) terms "electronic cigarettes," "tobacco use disorder," "substance withdrawal syndrome," "craving," and "smoking cessation."

In addition to reviewing the findings of the NASEM, updated literature searches were conducted using the above-described methodology. Additional search terms included "nicotine salt" and "nic salts" to ensure capture of publications describing the latest pod

published articles have evaluated some aspect of ENDS on public health.

Health effects have been evaluated at the cellular level, in animal models and in human subjects. The ability to draw strong conclusions regarding associations between ENDS and chronic health conditions are limited due to the latency required between initiation of use and disease development. These conditions are also difficult to assess because of the confounding factors associated with prior or concurrent use of combustible tobacco products.

Common themes have been observed with regards to behavioral health. Individuals who perceive ENDS as more harmful or as harmful as combustible cigarettes are less likely to initiate use of these products. Perception of the products and likelihood of initiation are influenced by family, friends, and marketing techniques. Concerns that flavored ENDS products cause youth to initiate use are not supported by high quality research.

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vaping technology. The current literature review submitted with the full PMTA will include literature published from August 2017 through the end of June 2019. This text reflects a brief review of the literature published since the release of the NASEM report. As part of future PMTA submissions, a comprehensive evaluation of all literature published since the release of the NASEM report will be provided. In the interest of time, given the rapidly approaching May 12, 2020 deadline, we have relied on the NASEM report to cover studies published through August 2017. Additionally, given the publicity that e-cigarettes were given following the end date of our literature review, novel studies that were published after June 30, 2019 were considered for inclusion. In the current report, studies identified in the updated literature search were evaluated and the findings were synthesized, with the purpose of providing a comprehensive state-of-the-science evaluation of the literature published since the release of the NASEM report.

Conversely, flavored ENDS products aid in the cessation of combustible tobacco products. The majority of clinical studies published are based on first- and second-generation ENDS products which may not be as efficient at nicotine delivery as newer products. However, as new literature is published, consistent use of ENDS is associated with increased likelihood of cessation of combustible products and if not cessation, the reduction in overall consumption of cigarettes per day. There is strong population and randomized control trial (RCT) evidence suggesting that ENDS are effective for cessation of combustible cigarettes.

A more recent study assessed abuse liability and addiction using PATH data (Shiffman & Sembower, Dependence on E-Cigarettes and Cigarettes in a Cross-Sectional Study of US Adults, 2020). The study assessed dependence among current and former adult e-cigarette users on combustible cigarettes and e-cigarettes, compared with dependence on combustible cigarettes. The researchers found that use of e-cigarettes appears to be consistently associated with lower nicotine dependence than cigarette smoking. The recent study compared dependence on combustible cigarettes and dependence on e-cigarettes across a variety of populations, varying by current and historical product use. ***In every comparison, e-cigarette use was associated with significantly less dependence than cigarette smoking***. While few e-cigarette users scored as highly dependent on e-cigarettes, most smokers were highly dependent on combustible cigarettes. Most striking was the consistency of the findings across multiple subpopulations of users, whether stratified by daily vs. non-daily use, or by current or former usage, and whether analyzed within-persons or between persons. ***In every***

case, dependence was significantly lower on e-cigarettes than on combustible cigarettes, usually meaningfully so.

The topography and pharmacokinetics of e-cigarettes are dependent upon several factors: experience of the user, nicotine concentration in the e-liquid, type of nicotine (*e.g.*, freebase or nicotine salt), and "humectant"[10] composition. Device characteristics also affect topography: power, resistance, airflow, and generation. Some studies have shown that the pharmacokinetics of ENDS may approach or in some cases exceed that of a combustible cigarette. These same factors impact the abuse liability of ENDS. More efficient ENDS may lead to increased dependency on these products. Nevertheless, current studies indicate that dependency associated with ENDS is less than that associated with combustible cigarettes. However, due to the likelihood of polytobacco use in evaluated populations, it is hard to distinguish between dependency due to combustible tobacco use and dependency due to ENDS use.

Biomarkers of potential harm (BOPH) and biomarkers of exposure (BOE) have been evaluated in several user populations. As noted by the FDA, biomarkers of harm have limited interpretability because there are no BOPH that are ENDS specific. Many BOPH could be measured in response to illness, comorbid conditions, and other lifestyle factors. BOE are much more specific to ENDS exposure and several studies have been conducted that show comparisons between BOE due to ENDS use and BOE levels associated with combustible cigarettes. BOEs for volatile organic compounds, alde-

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[10] PG and VG are humectants when their intended function is retention of moisture. In e-liquid, they function primarily as solvents, however.

hydes, and polycyclic aromatic hydrocarbons are consistently measured at lower concentrations due to ENDS use in comparison to combustible cigarettes. Findings for heavy metal exposure are mixed and have been measured at concentrations comparable to combustible cigarettes.

All of the above components deal with the impact of ENDS on the individual. However, a critical component of the PMTA is to understand the overall impact of ENDS on population health. This evaluation includes all user types: non-users, current smokers, current ENDS users, dual users, former smokers, etc. An adult smoker who switches to ENDS is exposed to fewer chemicals and would likely observe an overall benefit from switching away from combustible cigarettes to ENDS use. If youth who never would have initiated cigarettes initiate ENDS, they may slightly increase their individual risk of harm relative to life-long abstinence from any nicotine or tobacco products. However, concerns that initiation of ENDS by youth who would not have initiated combustible will result in harm to the population as a whole are not supported by the weight of evidence. Several well-designed modelling studies estimating the effects of ENDS on population health predict the technologies to have an overall benefit to the population compared to combustible cigarettes.

2.2.10 CONCLUSION

It is clear from the body of evidence available to date Boiler Maker Anvil E-Liquid is a safer alternative source of nicotine compared to combustible cigarettes for current adult smokers. As detailed herein, the HPHC results for Boiler Maker Anvil E-Liquid clearly represent large reductions in exposure when compared

to the available HPHC data from traditional combustible cigarette products, as well as the FDA-authorized IQOS, which was recently granted authorization to make certain reduced-exposure claims.[11] The vast majority of tested HPHCs were not detected. Even when exposures were calculated using our extremely conservative model assumptions, exposures for the HPHCs that were detected were far lower than those expected from traditional tobacco products for formaldehyde. Finally, for those compounds for which the exposure model indicated higher exposure than what would be expected from traditional combustible tobacco products, the available toxicological information indicates that these compounds would not be expected to cause any concerns when considered against the overall large concentrations of HPHCs from using combustible cigarettes or IQOS.

In addition, common themes have been observed across health effect studies and behavioral health outcome studies. Topography and pharmacokinetic findings are influenced by many factors. Nevertheless, studies to

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[11] Specifically, FDA has authorized the following reduced-exposure claims for the IQOS:

- The IQOS system heats tobacco but does not burn it.
- This significantly reduces the production of harmful and potentially harmful chemicals.
- Scientific studies have shown that switching completely from conventional cigarettes to the IQOS system significantly reduces your body's exposure to harmful or potentially harmful chemicals.

See *FDA Authorizes Marketing of IQOS Tobacco Heating System with 'Reduced Exposure' Information* https://www.fda.gov/news-events/press-announcements/fda-authorizes-marketing-iqos-tobacco-heating-system-reduced-exposure-information.

date show that nicotine delivery from ENDS may be comparable to combustible tobacco but the dependency to these products is generally found to be less than that of combustible cigarettes. Overall, the literature to date shows an overall public health benefit of switching to ENDS use for adult smokers.

Specifically, Triton Distribution believes it has shown that the continued marketing of Boiler Maker Anvil E-Liquid is APPH, based on the following:

- Chemistry, manufacturing, and control of the Boiler Maker Anvil E-Liquid products.
- A systematic review of the scientific literature reflecting publicly available information on ENDS and complementing the product-specific scientific studies and information on Boiler Maker Anvil E-Liquid.
- Product-specific analyses, including HPHC vapor analysis.
- Boiler Maker's non-youth oriented/mature marketing, labeling, and packaging.
- Strict age-restrictions and retailer and distribution requirements intended to prevent illegal youth access.

The information presented herein demonstrates that Boiler Maker Anvil E-Liquid substantially mitigates the known hazards of combustible tobacco products and exhibits safety and performance comparable to other open-system e-liquid products currently marketed in the United States. Boiler Maker Anvil E-Liquid presents benefits to the population as a whole, such that current tobacco users who choose to continue using nicotine-containing products will have additional op-

tions for less toxic products, thereby potentially decreasing the negative health impact relative to combustible cigarette tobacco use.

Neither Triton Distribution nor Boiler Maker found any concrete evidence that never users or former users of tobacco products were more likely to initiate or reinitiate tobacco use based on exposure to Boiler Maker Anvil E-Liquid. The risks of secondary exposure to Boiler Maker Anvil E-Liquid are substantially mitigated compared to combustible tobacco products. Nor is there any evidence that Boiler Maker Anvil E-Liquid is likely to discourage cessation of tobacco use in current smokers.

In addition to the results of a customer survey (Module 5) using validated questions make clear that Boiler Maker has historically marketed and sold its products, including Boiler Maker Anvil E-Liquid , to legacy adult smokers. The survey results further confirm that neither Triton Distribution nor Boiler Maker (including the Boiler Maker Anvil E-Liquid) has contributed to the recent surge in underage e-cigarette use identified by several national youth tobacco surveys. This application further details an adult-focused labeling and marketing plan to ensure that Boiler Maker Anvil E-Liquid will continue to only be marketed to the target population, and not to non-tobacco users or youth, once authorized by FDA.

For the aforementioned reasons, as well as those discussed in greater detail in this PMTA, Triton Distribution believes that the continued marketing of Boiler Maker Anvil E-Liquid is APPH. Boiler Maker Anvil E-Liquid offers a potentially less risky alternative to combustible tobacco products. The availability of this prod-

uct's flavored variants would help adults to transition away from smoking combustible cigarettes, would not lead to increased youth initiation of nicotine or tobacco products, and would not increase the risk of harm to the individual user.

In sum, the data and information provided in this application and TPMF No. MF0000403, the State of the Science report and the subject matter databases meet FDA's threshold for PMTA authorization and establishes that the marketing of Boiler Maker Anvil E-Liquid to current adult tobacco users is appropriate for the protection of the public health.

2.3 PRODUCT DESCRIPTION AND MANUFACTURING SUMMARY

MANUFACTURING (SECTION 1114.7(J))

Manufacturing, controls, and labeling are all focused on maximizing the safety and quality of the product. The manufacturing processes are developed to consistently manufacture e-liquid products of the required quality that comply with their specifications. Triton Distribution applies rigorous processes and practices to ensure that e-liquid is consistently produced and controlled according to the ISO 9000 quality management system.

Each bottle is packaged in a secondary package to protect against light exposure and physical damage (the entire bottling and packaging is completed in the U.S.). The manufacturing process detailed in Module 3 meets food preparation standards to include non-porous sanitized preparation work surfaces and a ceiling constructed of non-porous material.

The Boiler Maker Anvil E-Liquid is made up of the following ingredients:

- Vegetable glycerin (single chemical substance)
- Propylene glycol (single chemical substance)
- Nicotine (single chemical substance)
- Menthol (single chemical substance)
- Proprietary flavor blends from (complex purchased ingredients)

The PG/VG ratio is 70/30 for the Boiler Maker Anvil E-Liquid. The 100% complete chemical compositions of each of the products is provided in Module 3 Section 3.2 (CONFIDENTIAL).

Product stability and shelf-life (Module 3) are supported by the quality of these ingredients, and by Triton Distribution's use of secondary packaging that serves to protect the liquid from light and degradation under recommended storage conditions (*i.e.*, away from heat and light).

2.4 TARGET MARKET FOR TOBACCO PRODUCT

LABELING & MARKETING PLANS (21 C.F.R. § 1114.7(F))

Manufacturing, marketing, and labeling have historically been—and continue to be—focused on current adult smokers with the objective that the product will not reach unintended users.

Triton Distribution is committed to marketing Boiler Maker Anvil E-Liquid as described in this application to existing adult users, including current adult smokers. Triton Distribution employs mature product packaging directed to experienced, adult tobacco consumers, and opposes the use of imagery of food items, or other imagery that may appeal to youth.

Boiler Maker Anvil E-Liquid has been marketed and promoted through three primary sales channels: retailers, distributors, and trade shows as described further in this submission. Triton Distribution relies on retail partners in adult-targeted sales channels to introduce their customers to Boiler Maker Anvil E-Liquid. Traditionally this takes place primarily in specialty, adult-oriented vape shops where employees recommend Triton Distribution's Boiler Maker Anvil E-Liquid as a premium product for their customers.

Boiler Maker has developed a marketing strategy that identifies the target market of current adult tobacco and nicotine users, understands users' needs and behaviors, builds brand credibility, and offers consistent and quality e-liquid products that meet the highest quality standards. Significantly, Triton Distribution has established measures to limit youth exposure to our products and advertising. Boiler Maker's Sales Limitations and Marketing Plan and Guidelines included in Module 2 Section 2.4 represents Triton Distribution thinking and approach in sales, marketing, and distribution of its product in the market with emphasis in growing direct and indirect sales to vape and smoke shops nationwide, while minimizing exposure to non-users, particularly youth.

2.4.1 LABELING

As required under section 910(b)(1)(F) of the FD&C Act, this PMTA includes specimens of proposed labeling for the new tobacco product. Labeling specimens for Boiler Maker Anvil E-Liquid are included in Module 1 Section 1.9 and comply with all federal and state re-

quirements for labeling.[12] Specifically, with respect to the nicotine addiction warning codified in 21 C.F.R. Part 1143, the nicotine-containing Boiler Maker Anvil E-Liquid labels state "WARNING: This product contains nicotine. Nicotine is an addictive chemical." The warning meets all of the parameters set forth in 21 C.F.R. § 1143.3(a)(1) with respect to font, text, size, placement, and formatting of the warning statement on the package labels. All labels on Boiler Maker Anvil E-Liquid bottles are fully compliant with FD&C Act and state law requirements, were designed with a mature adult audience in mind, and include additional warning language described below.

Boiler Maker Anvil E-Liquid labels have always included age restrictions and numerous warnings (including California Proposition 65 warnings), as well as lot numbers, and date of production. Importantly, Triton Distribution introduced all these product safety standards before they were required by law, further exemplifying Triton Distribution's commitment to socially responsible business practices.

Labeling specimens for Boiler Maker Anvil E-Liquid products are included in Module 1 Section 1.9 and complies with all federal and state requirements for labeling.[13] Specifically, with respect to the nicotine addiction

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[12] These requirements include the required nicotine addiction warning for covered tobacco products, consistent with 21 CFR 1143; the name and place of business for the manufacturer, importer, or distributor, consistent with 21 USC § 387c; a net quantity of contents, consistent with 21 USC § 387c; and that statement "Sale only allowed in the United States, consistent with 21 USC § 387t.

[13] These requirements include the required nicotine addiction warning for covered tobacco products, consistent with 21 CFR

warning codified in 21 C.F.R. Part 1143, the nicotine-containing product labels state "WARNING: This product contains nicotine. Nicotine is an addictive chemical." The warning need meets all of the parameters set forth in 21 C.F.R. § 1143.3(a)(1) with respect to font, text, size, placement, and formatting of the warning statement on the package labels and secondary packaging. Indeed, the regulation requires that the required warning statement "appear directly on the package" and "be clearly visible underneath any cellophane or other clear wrapping as follows":

- Be located in a conspicuous and prominent place on the two "principal display panels" of the package; (e.g. in the case of a cylindrical e-liquid bottle, the warning is placed as close to 180° opposite side of the cylinder)
- Comprise at least 30 percent of each of the principal display panels;
- Be printed in at least 12-point font size and must occupy the greatest possible proportion of the warning label area set aside for the required text;
- Be printed in conspicuous and legible Helvetica bold or Arial bold type or other similar sans serif fonts and in black text on a white background or white text on a black background in a manner that contrasts by typography, layout, or color, with all other printed material on the package;

1143; the name and place of business for the manufacturer, importer, or distributor, consistent with 21 USC § 387c; a net quantity of contents, consistent with 21 USC § 387c; and that statement "Sale only allowed in the United States, consistent with 21 USC § 387t.

- Be capitalized and punctuated as indicated in 21 CFR § 1143.3(a)(1); and
- Be centered in the warning area in which the text is required to be printed and positioned such that the text of the required warning statement and the other information on the principal display panels have the same orientation.

Boiler Maker Anvil E-Liquid's labeling also includes other required elements, including:

- the name and place of business of the tobacco product manufacturer, packer, or distributor;
- an accurate statement of the quantity of the contents in terms of weight, measure, or numerical count; and
- the statement "Sale only allowed in the United States" on labels, packaging, and shipping containers pursuant to Section 920(a) of the Federal Food, Drug, and Cosmetic Act (FD&C Act).

In addition to the required nicotine addiction warning, the labeling and secondary packaging includes additional warning language depending the 30mL or 100ml bottle size due to availability of space. These warnings include:

On 30mL bottle labels:

- **California Proposition 65:** ⚠ WARNING: THIS PRODUCT CAN EXPOSE YOU TO CHEMICALS INCLUDING FORMALDEHYDE, WHICH IS KNOWN TO THE STATE OF CALIFORNIA TO CAUSE CANCER, AND NICOTINE, WHICH IS KNOWN TO THE STATE OF CALIFORNIA TO CAUSE BIRTH DE-

FECTS OR OTHER REPRODUCTIVE HARM. FOR MORE INFORMATION, GO TO WWW.P65WARNINGS.CA.GOV.

- WARNING: THIS IS NOT A FOOD. KEEP AWAY FROM CHILDREN AND PETS. DO NOT DRINK OR INGEST. AVOID SKIN CONTACT. IF ACCIDENTAL INGESTION OCCURS, CONTACT POISON CONTROL: 1-800-222-1222

On 100ml bottle labels:

- **California Proposition 65:** ⚠ WARNING: THIS PRODUCT CAN EXPOSE YOU TO CHEMICALS INCLUDING FORMALDEHYDE, WHICH IS KNOWN TO THE STATE OF CALIFORNIA TO CAUSE CANCER, AND NICOTINE, WHICH IS KNOWN TO THE STATE OF CALIFORNIA TO CAUSE BIRTH DEFECTS OR OTHER REPRODUCTIVE HARM. FOR MORE INFORMATION, GO TO WWW.P65WARNINGS.CA.GOV.
- **WARNING:** THIS IS NOT A FOOD. KEEP AWAY FROM CHILDREN AND PETS. DO NOT DRINK OR INGEST. AVOID SKIN CONTACT. IF ACCIDENTAL INGESTION OCCURS, CONTACT POISON CONTROL: 1-800-222-1222

In addition, to ensure that Boiler Maker Anvil E-Liquid is not potentially attractive to non-users and minors in particular, all labels, labeling, and other packaging will be limited to three colors; white, black, and blue to indicate the flavor collection is "Fruits" to assist adults who may be visually impaired. Except any warning required

to be contrasted (i.e., the nicotine addiction warning). Such warnings will be in both black text on a white background and white text on black background depending on the panel. Also, labels, labeling, and packaging will not include any graphical elements aside from gradient background dots on non-warning areas, borders, hairlines, and other similar means of demarcating different pieces of text. Other colors and/or graphical elements will only be used in the context of a warning (e.g., a warning regarding the accidental ingestion of nicotine) and when used in icons required for, or permitted by, government entities (e.g., the exclamation point in triangle icon required for a California Proposition 65 warning).

2.4.2 SALES LIMITATION AND MARKETING PLAN

As demonstrated by consumer use survey data (See Module 5) and age-verification measures, it is clear that Boiler Maker Anvil E-Liquid is used by adult consumers as an alternate to traditional tobacco products (e.g., cigarettes). Based on the scientific evidence, product testing, survey data, Triton Distribution believes that their e-liquid products are appropriate for the protection of the public health when used by adult smokers and tobacco users.

The focus of this sales limitation and marketing plan is to ensure that the Boiler Maker Anvil e-liquid is used by adults and not intentionally marketed to, sold to, or used by those who have not attained the age of 21 years ("Minors"). Marketing directed toward Minors is strictly prohibited.

Triton Distribution is committed to fully complying with all applicable laws and regulations governing e-liquids, including the Federal Food Drug & Cosmetic Act (21

USC Ch. 9 et seq.) as modified by the Family Smoking Prevention and Tobacco Control Act and 21 CFR Parts 1100, 1140 and 1143 (Deeming Tobacco Products To Be Subject to the Federal Food, Drug and Cosmetic Act, May 10, 2016) (the "Tobacco Control Act"); the Child Nicotine Poisoning Prevention Act of 2015, 15 U.S.C. §§ 1471, et seq. and its implementing regulations; and the Federal Trade Commission Act, 15 U.S.C. §§ 41-58, as amended, and its implementing regulations ("FTC Act").

Boiler Maker believes that the marketing materials produced by e-liquid manufacturers and vape retailers creates a visual representation of our industry to the general public. Irresponsible marketing of e-liquid and vaping technology is leading to increased tensions between anti-vaping activist groups, legislators, and advocacy groups which in turn can lead to consumer litigation, state attorney general actions, and FDA/FTC action; creating more unwanted negative media. Negative media attention regarding the vapor industry is not just bad for the public image of the industry, but also a distraction from the true reason for vaping technology—to reduce harm to smokers. It is our responsibility as e-liquid manufacturers and vape retailers to ensure we engage in highly disciplined marketing practices by adhering to the principles set out in this Marketing Plan. Significantly, Triton Distribution has taken swift, concrete measures to limit youth exposure to our products and advertising. Specifically, Boiler Maker and Triton Distribution have established retailer and distributor agreements, and policies in place to prevent marketing to youth.

The Boiler Maker Anvil E-liquid is only be sold to, and used by, adults 21 years and older. Online sales are re-

stricted to adults following age verification through independent, third-party agencies using public records databases. Currently, Boiler Maker uses the third-party age verification software Age Checker.net. As described below, Boiler Maker's packaging and advertising materials must maintain all nicotine and other warning requirements as directed by state and federal authorities.

Triton Distribution and Boiler Maker prohibit marketing material that could reasonably be perceived to be targeting individuals below the legal vaping age. Such marketing material includes childish images, cartoons, characters, mascots or childish or juvenile designs that might appeal to youth. Boiler Maker's marketing of its Boiler Maker Anvil E-liquid should not be directed at Minors and no channel of marketing should be used if more than 15% of its audience is Minors. This restriction includes, but is not necessarily limited to, TV, Internet, print and radio advertising (see below), as well as event marketing or sponsorships. For regional (local, city or state) advertising, content must be directed to persons who meet or exceed the specific region's age of majority. Boiler Maker's Boiler Maker Anvil E-liquid will not utilize names, imagery or designs that intentionally mimic, play upon, invoke or otherwise infringe upon existing trademarks, trade names or trade dress, particularly if they are associated with products that are, or were, primarily marketed to Minors. Boiler Maker's Boiler Maker Anvil E-liquid will not be portrayed as any sort of smoking cessation device or as a product which may be used to help quit smoking. Boiler Maker's Boiler Maker Anvil E-liquid will not be marketed as providing a therapeutic value, as being safe or healthy for consumers, or as products which do not pro-

duce secondhand health effects. Boiler Maker's Boiler Maker Anvil E-liquid should not be marketed or sold using modified risk descriptors or claims (*e.g.*, "light," "low," and/ or "mild"). By way of example only, Boiler Maker Anvil E-liquid is not marketed as (a) having no ash or smoke, (b) having no tar, (c) being less harmful, (d) posing lower risk of disease or (e) as containing reduced or zero levels of harmful ingredients Triton Distribution will not use health professionals to market or otherwise endorse their Boiler Maker Anvil E-liquid, directly or indirectly.

Marketing Strategy Focus:

- No Appeal to Minors. Triton Distribution and Boiler Maker prohibit marketing material that could reasonably be perceived to be targeting individuals below the legal vaping age. Such marketing material includes childish images, cartoons, characters, mascots or childish or juvenile designs that might appeal to youth.
- Intended Audience for Marketing. Triton Distribution and Boiler Maker's marketing should not be directed at Minors and no channel of marketing should be used if more than 15% of its audience is Minors. This restriction includes, but is not necessarily limited to, TV, Internet, print and radio advertising (see below), as well as event marketing or sponsorships. For regional (local, city or state) advertising, content must be directed to persons who meet or exceed the specific region's age of majority.
- No Improper Use of Trademarks or Trade Dress. Triton Distribution and Boiler Maker's Products will not utilize names, imagery or designs that in-

tentionally mimic, play upon, invoke or otherwise infringe upon existing trademarks, trade names or trade dress, particularly if they are associated with products that are, or were, primarily marketed to Minors. Triton Distribution and Boiler Maker fully support all local, state and federal age restrictions applicable to its products.

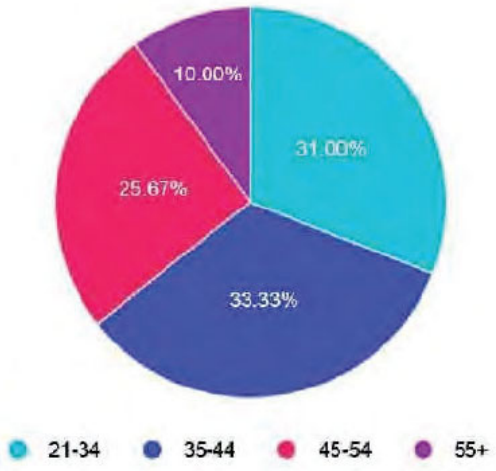
- Age-Gating to 21. Boiler Maker's website age-gates to prevent visitors under the age of 21 from gaining access.
- Minimum Age. Company shall ensure that all models used in advertising and social media for Company products are, and appear to be, at least 35 years old.
- Online sales are restricted to adults following age verification through independent, third-party agencies using public records databases. Currently, Boiler Maker uses the third-party age verification software AgeChecker.net.
- Triton Distribution and Boiler Maker requires all U.S. retailers of its products, including online retailers, to comply with FDA's requirements and guidance for retailers, as applicable. Specifically, all U.S. retailers of Company products should:

    1. Implement strict age verification policies requiring that their employees verify photo IDs of anyone who is 27 years of age or younger before such persons enter the establishment. Minors should not be permitted into any retail establishment that sells Triton Distribution and Boiler Maker's Products.

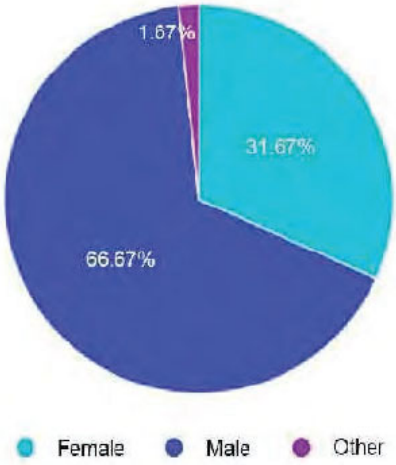
2. Immediately respond to and implement remedies to address any FDA or other government authority warning letters or enforcement actions.
3. Display signage indicating that (a) "Minors Are Not Allowed on Premises" and (b) "Products are Not for Sale to Minors" or (c) "Underage Sale Prohibited."
4. Comply with FDA's guidance documents for retailers, including Tobacco Retailer Training Programs and FDA Retailer Training and Enforcement.
5. Restrict sales of Products to adults through either direct verification of government issued photo ID upon delivery of product or through the use of online age verification technologies provided by independent third-party agencies using public records databases.

Consumer Demographics

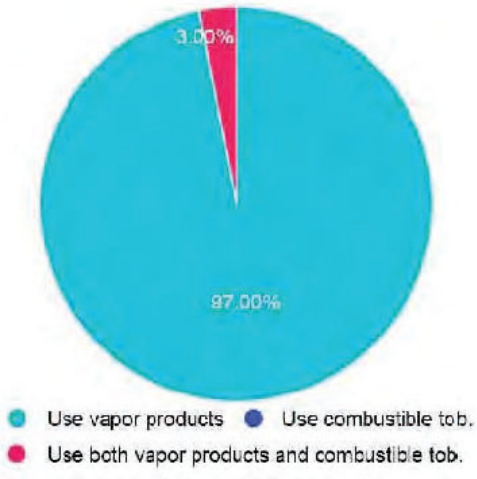
- Demographic Characteristics of Boiler Maker LLC
  - Age - 21-34 31% | 35-44 33.33% | 45-54 25.67% | 55+ 10%



- Gender—Female 31.67% | Male 66.67% | Other 1.67%

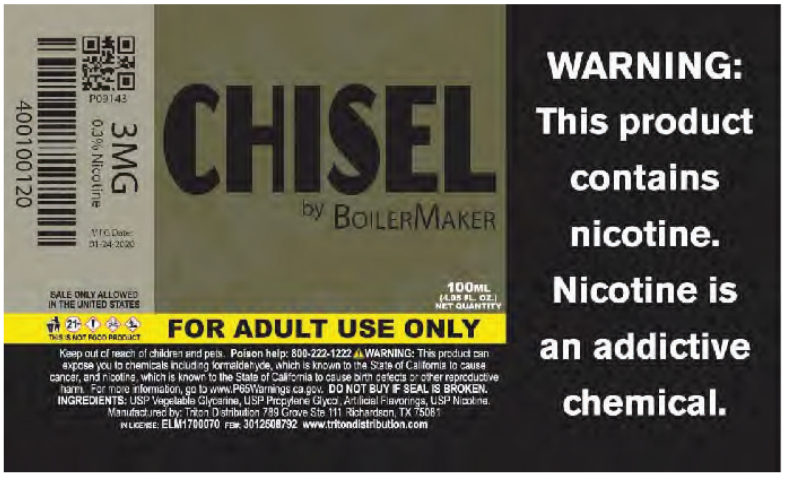


- Tobacco use status—Use only Boiler Maker Anvil E-liquid 97% | Use both Boiler Maker Anvil E-liquid and combustible tobacco products 3% | Use only combustible tobacco products 0%



Labeling—See Module 1

Sample:



Boiler Maker does not use cartoon characters in its advertisements or marketing or any other particularly youth-attractive packages. Boiler Maker will not design the packaging of it's vape products in a manner

that could be confused by children as a food or drink. Boiler Maker will not use other's intellectual property (including, but not limited to, mascots, animals, characters, or commercially recognizable toys or candy) to market our products.

- Triton Distribution will use child resistant packaging and appropriate flow restrictors in compliance with the Child Nicotine Poisoning Prevention Act of 2015.
- Triton Distribution will not make smoking cessation claims (i.e. Quit smoking now). Triton Distribution will not make health-related claims (i.e. Healthier than smoking, Less risk of disease/cancer, No Secondhand Effects).
- Triton Distribution will not make modified risk claims (i.e. Less harmful than tobacco, No Smoke, Diacetyl Free).

2.4.3 DISTRIBUTOR AND RETAILER GUIDELINES

Distributor and retailers must contractually agree with Triton Distribution's Distributor and Retailer Sales Limitations and Requirements in 2.4 Target Market for Tobacco Product folder.

Triton Distribution enters into written agreements with its distributors and retailers to do business, which include indemnification provisions. An example of the Distributor and Retailer Agreement can be found in 2.4 Target Market for Tobacco Product folder. Triton Distribution requires down-stream distributors and retailers to comply with these requirements and establishes and enforces contractual penalties for such contracted parties. All Triton Distribution distributors and retailers are obligated to maintain compliance with all appli-

cable Federal, State and Local laws and regulations, as applicable, including:

- The Federal Food, Drug and Cosmetic Act (FD&C Act), as amended by the Family Smoking Prevention and Tobacco Control Act (TCA)
- State and Local Health Codes
- State and Local Licensing and Tax Programs
- State and Local Laws and Regulations Applicable to Distribution of Triton Distribution and Boiler Maker's Products, including state laws regarding state minimum purchase age for Boiler Maker Anvil E-liquid and delivery sales requirements, California's Stop Tobacco Access to Kids Enforcement Act (STAKE Act), and California Safe Drinking Water and Toxic Enforcement Act of 1986 (Proposition 65)

Specifically, Triton Distribution requires its downstream distributors and retailers to sell only to people who are old enough (at least 21 years old throughout the U.S.), confirmed using valid ID for any face-to-face transactions with consumers. If sales are made online, distributors and retailers must use adequate age-verification technology to prevent underage access to the website and to prevent underage sales through the Internet. Triton Distribution's policy requires it to screen retailers in advance of establishing or renewing distribution agreements based on the strength of the retailers' age verification policies. As part of its continuous compliance monitoring efforts, Triton Distribution requires retailers to develop an internal compliance check program, such as a mystery shopper program.

Boiler Maker Anvil E-Liquid is not advertised via any channels (including print, television, social media, earned media, or similar) except on Triton Distribution's website and in adult-only brick-and-mortar facilities. Advertisement on Triton Distribution's website will be restricted to consumers who have registered to gain access. Advertising in brick-and-mortar facilities will be limited only to those areas of the facility that cannot be seen from outside the facility.

2.4.4 QUANTITY LIMITS FOR ONLINE SALES

As a measure to prevent youth access, Triton Distribution has measures in place to monitor for any "bulk" purchases, and to limit transactions to the quantity a reasonable consumer would be expected to purchase during a single transaction. This includes limiting orders to ten (10) 30mL bottles or ten (10) 100ml bottles per transaction. Downstream distributors or retailers are required to follow Triton Distribution's transaction limit. Furthermore, downstream distributors and retailers should implement a process to flag repeated transactions within a seven (7) day period and investigate those transactions for suspicious activity.

2.4.5 PREVENTING YOUTH ACCESS TO COMPANY PRODUCTS

Triton Distribution product sales comply with Tobacco 21 across the country.

Triton Distribution product sales must comply with all county, city, and state age restriction laws for e-vapor product purchase. Boiler Maker Anvil E-Liquid online product sales are restricted to adults age verified by independent third-party companies using public records

databases. For all sales made in person to individuals under the age of 27 years old, age verify by means of government issued photographic identification containing the bearer's date of birth. Compliance with California's Stop Tobacco Access to Kids Enforcement Act ("STAKE Act") for sales in California. California law prohibits the sale of tobacco products to anyone under the age of 21 (Cal. Bus. & Prof. Code § 22958(a)) and the STAKE Act imposes mandatory steps that online distributors and sellers of tobacco products are required to follow to verify that a purchaser of these items is 21 years of age or older. The steps required under the STAKE ACT are:

- Attempt to match the name, address and date of birth provided by the customer to information contained in records in a database of individuals whose age has been verified to be 21 years or older by reference to an appropriate database of government records kept by the distributor, a direct marketing firm, or any other entity.
- Verify that the billing address on the check or credit card offered for payment by the purchaser matches the address listed in the database.
- If unable to verify that the purchaser is 21 years of age through the above, require the customer or recipient to submit an age-verification kit consisting of an attestation signed by the customer that he or she is 21 years of age or older and a copy of a valid form of government identification.
- Verify that the billing address on the check or credit card provided by the consumer matches the address listed in the form of government identification.

- For credit card transactions, submit information to each credit card company so that the words "tobacco product" may be printed in the purchaser's credit card statement.
- Regardless of the form of payment, prior to shipping the tobacco product to a California customer, make a telephone call after 5 p.m. to the purchaser or recipient confirming the order. The call may be a recorded message left on voicemail.
- Deliver only to the purchaser or recipient's verified billing address on the check or credit card used for payment. Delivery to a post office box address is prohibited.

While FDA has not yet provided specific requirements on how companies should verify the age of those purchasing such products over the internet, Triton Distribution and Boiler Maker is fully compliant with the most stringent state laws in this regard, using third-party age verification service Age-Checker.net, including California's Stop Tobacco Access to Kids Enforcement Act (STAKE Act). California law prohibits the sale of tobacco products to anyone under the age of 21 (Cal. Bus. & Prof. Code § 22958(a)) and the STAKE Act imposes mandatory steps that online distributors and sellers of tobacco products are required to follow to verify that a purchaser of these items is 21 years of age or older.

2.4.6 SOCIAL MEDIA

Triton Distribution does not endorse or permit use of youthful-looking models or any advertising of our product that conveys the appearance of marketing to underage consumers. Boiler Maker does not currently utilize

social media influencers. The current online marketing strategy is restricted to product photos and other forms of responsible marketing. In addition, Boiler Maker Anvil E-Liquid labels have always warned against underage use.

2.5 NONCLINICAL OVERVIEW

2.5.1 HARMFUL AND POTENTIALLY HARMFUL CONSTITUENTS

Triton Distribution utilized a third-party lab, Adact, to assess the levels of certain HPHCs in the vapor produced using Boiler Maker Anvil E-Liquid. The results were used to calculate a worst-case potential exposure to consumers. The exposure model data was then utilized to compare relative exposure to HPHCs from Boiler Maker's e-liquids to HPHC results from traditional tobacco products (e.g., cigarettes) and recently authorized heated tobacco products (i.e., IQOS), a modified risk tobacco product, obtained from direct testing as well as published literature. Finally, we conducted toxicological evaluations of those compounds expected to have higher exposures resulting from e-liquid use than from traditional tobacco use. In sum, for the reasons set forth below, the HPHC results support that the marketing of these products is appropriate for the protection of the public health when used by adult smokers and tobacco users. The full HPHC reports and data, as well as the analysis of same, is included in the memorandum in Module 4. In sum, the HPHC results for the Boiler Maker Anvil e-liquid support that the marketing of the product is APPH when used by adult smokers and tobacco users. See Module 4, Section 4.2.

For full reports of all information, including the substantive information required by section 1114.27(b)(1)(ii), all

favorable and unfavorable studies; published or known to Triton Distribution, or which should reasonably be known, concerning investigations, including * * *

* * * * *

2.6.3.3.4 REASONS FOR USE

Similar to youth and young adults, adult prevalence of ENDS use is dependent upon how usage is defined. Adults report using ENDS to aid with cessation of combustible cigarettes, because they are available in appealing flavors, and because they do not smell like combustible cigarettes.

2.6.3.3.5 USE OF FLAVORS

Boiler Maker Anvil E-Liquid is included in this submission include the following flavors: Boiler Maker Anvil. In the case of ENDS e-liquid, all products are flavored. The primary ingredients in e-liquid, propylene glycol and glycerin, are completely flavorless, and the concentration of nicotine used in the products imparts no flavor.

Flavored e-liquids are an essential part of the ENDS category, and the existence of a market for these products is proof that they are valued by consumers. When it comes to evaluating the role of flavors in facilitating or constraining positive population health outcomes from e-cigarettes, relevant questions include the impact of flavors on adult smokers who transition (or not) to e-cigarettes, as well as their role in preventing relapse in former smokers who vape. Negative population health outcomes are likely if flavors play a specific causal role in youth vaping initiation *and* subsequently cause these youth to progress to smoking. Importantly, there is no evidentiary basis to popular concerns that flavors are

solely intended to attract or appeal to youth. To date, there is no evidence that flavors cause youth smoking.

NASEM did not specifically evaluate e-liquid flavorings in their 2018 report, but noted that "most e-cigarette products are available in desirable flavors and have other characteristics that generate aerosols with a unique profile of pleasurable sensory stimuli due to the taste, sights, smells, and airway sensations, that (like combustible tobacco cigarettes) could have synergistic effects with nicotine on dependence risk" (NASEM, 2018, p. 257).

The complexities around flavored e-cigarette use are likely not well captured by the PATH study. In particular, the survey is ill-equipped to answer the question of whether specific flavors exert a specific effect on youth use of e-cigarettes, as the survey groups non-tobacco flavors into a limited number of very broad categories.

Numerous published studies also highlight the important role of flavored ENDS for harm reduction. Recently, for example, the *Harm Reduction Journal* published the results of an extensive online survey which assessed the first and current vapor product flavors used by a non-probabilistic sample of 20,836 adult frequent vapers in the U.S. (Russell, McKeganey, Dickson, & Nides, 2018). That survey found that cigarette smokers who switch to Boiler Maker Anvil E-liquid are doing so increasingly with a variety of fruit and other non-tobacco flavors. Another recent survey of more than 69,000 adult vapers found that just 16% identified tobacco, menthol, or mint as flavors they used most often; the vast majority preferred fruit and dessert flavors (Farsalinos, 2018).

In addition, a large sample on-line survey by Landry et al (2019) found that among adults 18 and over, non-tobacco flavors were preferred by most current e-cigarette users and that flavors were a common reason for adult e-cigarette initiation (Landry, et al., 2019).

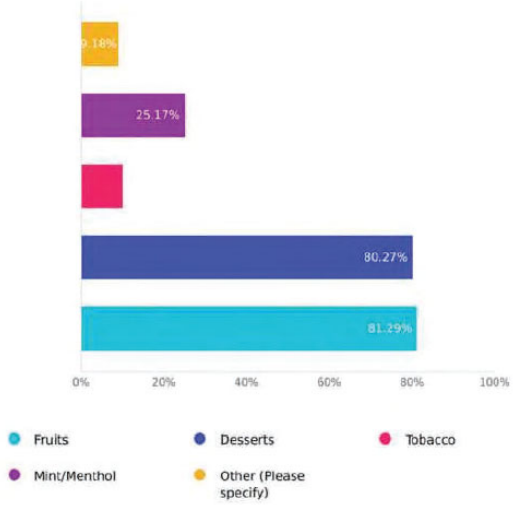
Research addressing the specific role of flavors in vaping effectiveness is in its infancy, however, a recent study by Voos et al offers some important insight (Voos, et al., 2020). This study examined changes in nicotine delivery, puff topography, and satisfaction associated with different flavors among regular smokers who were non-regular e-cigarette users. This is the first study to do so among daily cigarette smokers, allowing the researchers to explore the complex interaction between flavors and study outcomes. The study suggested that there was enhanced nicotine delivery from cherry and menthol flavors. The study also demonstrated that different flavors can result in varying nicotine delivery when used by daily cigarette smokers. When examining puff topography during the controlled puffing session, puff duration was significantly longer with use of an e-cigarette compared to a combustible cigarette for all flavors, which is consistent with previous research (Hua et al. 2013; Hammond et al. 2005). In general, participants rated all flavors as less harmful to their health than a combustible cigarette, and participants did not view flavors as differing in perceived risk. Interestingly, there was a significant difference in perceived harm of flavors between participants who smoke mentholated versus non-mentholated combustible cigarettes. Participants who smoke mentholated cigarettes viewed flavors as significantly less harmful to their health compared with participants who used non-mentholated cigarettes.

But a new analysis of data from the 2019 NYTS, released in December 2019 by the CDC and the FDA, shows that flavors are definitely not the main reason kids vape (Wang T.W., Gentzke A.S., M.R., & et, 2019). The number one reason was curiosity. Among the teens who were surveyed, 56.1% listed curiosity as a reason they tried e-cigarettes. That was more than double the next most popular reason, "friend or family member used them" (23.9%). "They are available in flavors, such as mint, candy, fruit, or chocolate" came in third at 22.3%. The teens could choose multiple answers, which makes flavors' weak showing even more apparent.

With respect to Boiler Maker Anvil E-Liquid survey results (Module 5) demonstrate that it is and will continue to be used by existing adult users. With respect to flavors, the consumer survey results demonstrated only 19% of respondents chose Tobacco when asked "What type of electronic nicotine product flavors do you tend to prefer and use? Select all that apply:" with answer choices of "I prefer to use unflavored electronic nicotine products", "Mint or Menthol", "Tobacco", "Coffee-based", "Fruity", "Dessert", "Candy", "Other", or "Not applicable, I do not use electronic nicotine products". Results are shown in Figure 2.6-1.

Figure 2.6-1 Representation to question "What type of electronic nicotine product flavors do you tend to prefer and use? Select all that apply:" (Question 30)

Fig 2.61



2.6.3.3.6 NATIONAL YOUTH TOBACCO SURVEY AND THE YOUTH "EPIDEMIC"

NYTS, MTF (Monitoring the Future Survey), YRBS (Youth Risk Behavior Survey), and PATH, surveys collect data from which estimates of e-cigarette use prevalence among youth in the U.S. can be drawn. Recently, there has been a great deal of concern regarding point-prevalence increases in past 30-day use in cross-sectional data from NYTS and MTF surveys. These increases have been characterized as an "epidemic" with preliminary analyses of 2018 MTF and NYTS data speculating the point prevalence increase can be explained by "new" vaping devices such as JUUL (Miech et al 2018, Cullen et al 2018).

Tobacco control experts have questioned the appropriateness of this label (West, et al) (Fairchild, Healton, Curran, Abrams, & Bayer, 2019). Indeed, two recent detailed analyses of NYTS data do not support claims

that the point prevalence increase between 2017 and 2018 constitutes an epidemic of youth nicotine addiction (West et al, Glasser et al). West et al (2019) sought to examine evidence from the NYTS being used to support new regulatory initiatives, and found a "gaping chasm between the vision of an epidemic of e-cigarette use threatening to engulf a new generation in nicotine addiction and the reality of the evidence contained in the NYTS." Specifically, their analysis found that "[i]n bringing forward proposals for regulatory action, the FDA did not place e- cigarette use in the context of use of other tobacco products." Their analysis of NYTS data from 2018 and earlier years shows a strong association between lifetime history of use of tobacco products and use of e-cigarettes: in 2018, high school students who had smoked more than 100 cigarettes in their lifetime were some 27 times more likely to have used e-cigarettes in the past 30 days than students who had never tried any tobacco product. Use of e-cigarettes on 20 or more days in the past month was seen in only 1.0% of those who had never tried any tobacco product in 2018. West, et al. also concluded that the NYTS fails to give evidence at the population level that e-cigarettes are acting as a gateway to smoking in American adolescents. Importantly, the study by West et al sought to measure whether youth were becoming addicted to nicotine through vaping and found little evidence of substantial nicotine addiction attributable to the use of e-cigarettes.

A later peer reviewed study by Glasser et al of the 2018 NYTS data supported the conclusions in the West et all study (Glasser, Johnson, Johnson, & Niaura, 2020). Although vaping increased among U.S. youth in 2018 over 2017, the increases are characterized by patterns

of low p30d vaping frequency and high poly-product use, and a low prevalence of vaping among more frequent but tobacco naïve vapers. These results underscore the importance of including the full context of use patterns. The majority of vapers (60.0% - 88.9% by use frequency) were concurrent p30d or ever tobacco users. About 4% of students were tobacco naïve and vaped in the p30d, but few (0.4%) vaped regularly on 20 or more days. The authors emphasized that reporting youth vaping data with frequency and tobacco product co-use will give public health decision makers the best possible information to protect public health.

FDA announced in mid-2018 that early NYTS data revealed a sudden shift in past 30-day e-cigarette use among high schoolers, which had jumped to 20.8% (Cullen, et al., 2018). Prior to that, the percentage of high schoolers who used an e-cigarette at least once in the past 30 days had started to decease, falling from 15.8% in 2016 to 11.0% in 2017, before surging in 2018 (Jamal, Gentzke, Hu, & et al., 2017).

Analysis of Federal survey data reveals that while underage vaping increased in 2018, it does not confirm an epidemic. Nearly 70% of the students who vape—but do not smoke—used ENDS five days or less during that 30-day period. This pattern corresponds with "party" or "weekend" social vaping. While this is not an activity that we encourage by any means, it is much different from regular, daily consumption. What is more, the majority of current vapers surveyed were *not* "never smokers" before they started vaping. In the underage nonsmoking group, 57% of frequent vapers had previously smoked. The percentages were even higher among legal-age and current smokers (Rodu, 2019). While illegal underage vaping should always be discouraged, the

fact that so many of the young people experimenting with ENDS had already smoked cigarettes challenges FDA's assertion that ENDS use threatens to hook an entire generation of kids into a lifetime of addiction.

More recent analysis of the 2018 NYTS demonstrate that the survey does not support claims of a new epidemic of nicotine addiction stemming from use of e-cigarettes, nor concerns that declines in youth tobacco addiction stand to be reversed after years of progress. Rather, among current e-cigarette users who had never tried tobacco products, responses consistently pointed to minimal dependence (West & Brown, 2019).

Meanwhile, it must be noted that while vaping has become more common, the cigarette smoking rate continues to fall to all-time lows among all age groups, including teenagers. According to the CDC, in 2017, 7.6% of high school students reported smoking cigarettes in the past 30 days—a decrease from 15.8% in 2011.[21] Among young adults aged 18-24, 10.4% smoked cigarettes in 2017—21% decline since 2016, when the young adult smoking rate was 13.1%, and a 45% decrease since 2011, when 18.9% young adults smoked.[22] Among adults (older than 24), only 14% reported smoking "every day" or "someday"—the lowest level ever recorded, down from 15.5% in 2016, and a 67% decrease since 1965 (Wang & et al., 2018).

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[21] *Youth and Tobacco Use*, CENTER FOR DISEASE CONTROL AND PREVENTION (Feb. 28, 2019), https://www.cdc.gov/tobacco/data_statistics/fact_sheets/youth_data/tobacco_use/index.htm.

[22] *Young adult smoking rate drops to 10%*, TRUTH INITIATIVE INSPIRING TOBACCO-FREE LIVES (Sept. 5, 2018), https://truthinitiative.org/news/young-adult-smoking-rate-drops-10.

In addition, a recent study has found that youngsters who use e-cigarettes are less likely to use cigarettes in the future compared to those who use other tobacco products (Shahab, Beard, & Brown, 2020). The researchers called this the "gateway effect" (moving on the full-fledged smoking) and determined that it is small among those who begin tobacco product use with e-cigarettes. Data come from 78 265 adolescents in the NYTS (2014-2017), of whom 38,630 provided information about the first tobacco product they had used in 2014/15. Ever, past 30-day, and established (30 day use and 100+ lifetime cigarette) cigarette smoking was compared in adolescents who first used an e-cigarette (exposure group), a non-cigarette combustible (CT) or other non-combustible tobacco (NT) product (behavioral controls), and propensity score matched adolescents without initial e-cigarette use (synthetic controls). The study found that, relative to behavioral controls, adolescents who tried e-cigarettes first were less likely to have ever smoked cigarettes, to be past 30-day, or NT initiators, or be established cigarette smokers, or NT initiators. E-cigarette initiators were also less likely than synthetic controls (without initial e-cigarette use) to have ever smoked cigarettes, be past 30 day, or be established cigarette smokers. In sum, the study found that less than 1% of U.S. adolescents who use e-cigarettes first were established cigarette smokers. They were less likely to be smokers than adolescents who tried other combustible or non-combustible tobacco products first and propensity score matched adolescents without initial e-cigarette use.

2.6.3.3.7 CONSUMER PERCEPTION

Research that evaluates consumer perceptions of e-cigarettes, including the perceived risks and benefits,

can provide valuable insight into understanding why consumers initiate and use these products. Perceived benefits of e-cigarettes can include, but are not limited to, expected and actual positive experiences (*e.g.*, taste), social acceptance, avoidance of smoking restrictions, a cool and/or IEB novel product, an effective smoking cessation aid, and safety for bystander. Perceived risks can include, but are not limited to, addictiveness and negative health risks associated with tobacco product use and can be measured in absolute terms or relative to another tobacco product.

E-cigarettes constitute a broad class of products that vary by device type (*e.g.*, cigalikes, rechargeable, tanks and mods), e-liquid composition (*e.g.*, additives, nicotine), and flavors (*e.g.*, tobacco, menthol, fruit). NASEM (2018) reported that the perceptions of potential risks and benefits of e-cigarette use "vary widely," but the report did not review perceptions of e-cigarettes and the relation to e-cigarette use in detail (NASEM, 2018).

With respect to Boiler Maker Anvil E-Liquid, survey results (Module 5) demonstrate that Boiler Maker Anvil E-Liquid is, and will continue to be, used by existing adult users. For this population, the fact that the Boiler Maker Anvil E-Liquid is less harmful than combustible cigarettes, as demonstrated from the test results and health effects summarized above, the continued availability of Boiler Maker Anvil E-Liquid is APPH. Furthermore, as discussed above, to ensure that Boiler Maker Anvil E-Liquid is not considered appealing to youth or nonsmokers, Triton Distribution has implemented strict labeling and marketing restrictions (Module 2 Section 2.4).

2.6.3.3.8 TRANSITION

There are several factors associated with the use of tobacco products, and an individual's usage state (*e.g.*, non-user, e-cigarette user, dual user, smoker, etc.) may change over time. For youth, transition between states can be highly variable and individual usage states may change often.

Due to the limited time points of observation with the PATH dataset, continued evaluation of the potential for e-cigarettes to lead to combustible cigarette use are needed.

With respect to Boiler Maker Anvil E-Liquid survey results (Module 5 Section 5.3) demonstrate that there is a reasonable degree of certainty that Boiler Maker Anvil E-Liquid is, and will continue to be used, by existing adult users.

2.6.3.3.9 INITIATION

There is currently no conclusive evidence to support concerns that e-cigarettes are a "gateway to smoking." The current evidence suggests that there may be underlying factors that contribute to adolescent initiation of tobacco product use more generally also contribute to initiation of e-cigarettes. Considering that adolescents who were susceptible to e-cigarettes did not have increased likelihood of combustible cigarette use, but that those who were susceptible to combustible cigarettes were more likely to use all products, e-cigarettes may present a lower health risk to those susceptible to e-cigarettes and combustible cigarettes.

Initiation of ENDS use in youth has many contributory factors: use of e-cigarettes by friends, siblings, or parents, perceptions of little to no harm, and the belief that

e-cigarettes were less harmful than tobacco cigarettes, flavors, and as an alternative to combustible cigarettes. Many of these factors are similar to reasons for initiation or experimentation with combustible tobacco, alcohol, or marijuana (Ellickson et al., 2004; Hemovich et al., 2011; Tang and Orwin, 2009; Vega et al., 1993). Data is limited, due to the cross-sectional nature of available studies, to determine if initiation of e-cigarette use leads to continued, long-term use of combustible cigarettes.

With respect to Boiler Maker Anvil E-Liquid survey results (Module 5 Section 5.3) demonstrate that it is and will continue to be used by existing adult users. Triton Distribution does not sell or market to minors and does not have any youth initiation concerns.

2.6.3.3.10 CESSATION

Smoking combustible cigarettes is questionably detrimental to both personal health and public health. As ENDS are a newer product, there is no consensus on their contributions to the health of individuals who vape or to the general public. The most important consideration in deciding whether e-cigarettes produce a public health benefit is determining if using e-cigarettes is an effective cessation method for combustible cigarette use. In fact, the 2018 NASEM report states that the central research question around the possible public health benefit of e-cigarettes is "Do e-cigarettes help smokers quit smoking combustible tobacco cigarettes?" (NASEM, 2018, p. 541). However, the authors also recognize that to determine the scope of possible public health benefits, researchers must not only answer the question of "How effective are e-cigarettes as a cessa-

tion method?", but also "What proportion of smokers use e-cigarettes in their quitting attempt?" as well.

There have been several studies that longitudinally evaluated PATH study data to assess the likelihood of cigarette cessation and/or reduction associated with e-cigarette use among current cigarette smokers, and the likelihood of smokers using e-cigarettes as opposed to another cessation aid to quit smoking (Benmarhnia et al., 2018; Berry et al., 2019; Kalkhoran et al., 2019; Rodu and Plurphanswat, 2017; Verplaetse et al., 2018; Watkins et al., 2018b).

The NASEM (2018) report provided a conceptual framework for smoking cessation transitions and defined smoking cessation as "stopping all combustible tobacco product use" (NASEM, 2018). The committee evaluated whether e-cigarettes help smokers quit smoking combustible tobacco products by investigating the effectiveness of e-cigarettes as a cessation aid compared to no treatment, placebo treatment, or FDA-approved therapies.

NASEM (2018) concluded that based on limited evidence from the RCTs and the overall body of observational evidence, there was limited evidence that e-cigarettes may be an effective smoking cessation aid, and noted that further evaluation through RCTs with more treatment comparisons were necessary. The NASEM (2018) report noted that observational data is limited because it does not account for the specific e-cigarette product, the pattern of use, and user characteristics, including an interest in quitting, which are all factors that may affect how effective an e-cigarette is as a cessation aid. Further, observational data largely reflect dual or intermittent use of e-cigarettes, which the

report noted, "may not contribute to cessation success any more than does poor adherence to FDA-approved cessation medications" (NASEM, 2018).

The most compelling evidence on e-cigarettes and cessation to date is an RCT by Hajek et al., (2019), who evaluated the 1-year efficacy of refillable e-cigarettes as compared with NRT, both combined with behavioral support, in adults seeking to quit smoking. The authors concluded that refillable e-cigarettes had greater efficacy than NRT for smoking cessation (Hajek et al., 2019).

As more data becomes available, the evidence is supporting the benefits of ENDS for cessation of combustible cigarettes. As products improve, e-cigarettes are becoming more satisfying and the most recent research is showing a positive benefit of ENDS on public health with more and more adults using them as an alternative to combustible cigarettes.

With respect to Boiler Maker Anvil E-Liquid, because of financial and time restraints, advertising/marketing and label consumer perception studies will not be completed. However, the survey results (Module 5 Section 5.3), along with the enclosed labeling and marketing plans (Module 2 Section 2.4), demonstrate that Boiler Maker Anvil E-Liquid is and will continue to be used by existing adult users. More specifically, pursuant to the marketing plan, advertising and marketing are strictly limited. The label/labeling will be viewed by experienced ENDS users and current customers, or in a setting where prospective users can easily become educated (*e.g.*, vape shops). In addition to the study by Hajek et al, several high-quality analyses of population

data suggest that regular vaping can aid in smoking cessation.

Kalkorhan PATH analysis (Kalkhoran, Chang, & Rigotti, Electronic Cigarette Use and Cigarette Abstinence Over Two Years among U.S. Smokers in the Population Assessment of Tobacco and Health Study, 2019)

A recent nationally-representative longitudinal cohort study of U.S. adult cigarette smokers study by Kalkhoran et al (2019) found that "daily e-cigarette use, compared to no e-cigarette use, was associated with a 77% increased odds of prolonged cigarette smoking abstinence over the subsequent two years. Non-daily e-cigarette use was not associated with subsequent abstinence." They analyzed data from adult cigarette smokers in Waves 1 to 3 of the PATH study, with an aim of determining the association between e-cigarette use and subsequent smoking cessation in a nationally representative cohort of U.S. smokers followed for two years. They found that "Among Wave 1 cigarette smokers, 3.6% were current daily e-cigarette users, 18% were current non-daily e-cigarette users, and 78% reported no current e-cigarette use. In multivariable adjusted analyses, daily e-cigarette use at Wave 1 was associated with higher odds of prolonged cigarette smoking abstinence at Waves 2 and 3 compared to non-use of e- cigarettes (11% vs 6%, AOR 1.77, 95% CI 1.08-2.89). Non-daily e-cigarette use was not associated with prolonged cigarette smoking abstinence. Among Wave 1 daily e-cigarette users who were abstinent from cigarette smoking at Wave 3, 63% were using e-cigarettes at Wave 3."

The Kalkhoran et al 2019 study is significant as it is the first nationally representative cohort study presenting

showing an association between e-cigarette use and sustained combustible cigarette abstinence rates over two years. Their results are consistent with the hypothesis that regular use of e-cigarettes (as opposed to infrequent use) can help smokers to stop smoking combustible cigarettes. While infrequent use is not associated with prolonged quitting, it is noteworthy that in England, dual use of e-cigarettes has been found to increase quit attempts (Jackson, Shahab, West, & Brown, 2020).

National and multinational survey data from Europe support the findings of Kalkhoran et al. (Farsalinos, et al., 2019). A study of vape shops in Greece (Diamantopoulou et al 2019) found that "[t]he strongest correlate of being a former smoker was daily e-cigarette use." (Diamantopoulou, Barbouni, Merakou, & Lagiou, 2019) The same study found "vapeshops customers in Greece are mainly current and former smokers with the majority of them having quit smoking. E-cigarette use by never smokers is rare and none of them subsequently initiate smoking."

2.6.4 CONCLUSION OF SYSTEMATIC LITERATURE SEARCH

The current literature indicates that ENDS may be a safer alternative source of nicotine compared to combustible cigarettes. Common themes have been observed across health effect studies and behavioral health outcome studies. Topography and pharmacokinetic findings are influenced by many factors. Nevertheless, studies to date show that nicotine delivery from ENDS may be comparable to combustible tobacco but the dependency to these products, especially the earlier generations, is found to be less than that of combustible cigarettes. Overall, the collective body of literature re-

viewed shows an overall benefit of ENDS use on population health in comparison to combustible cigarettes.

2.7 POPULATION HEALTH OVERVIEW

EFFECT ON POPULATION AS A WHOLE (21 C.F.R. § 1114.7(L))

Based on the literature, the presence of ENDS on the market was initiated to provide an alternative source of nicotine to individuals seeking ways to stop smoking. In addition to the intended consequences of adults switching from combustible tobacco to e-cigarettes, an evaluation of the population must also account for the unintended consequences of youth initiating use of these products. A proper assessment will include multiple time points because usage states and transitions states are fluid can change over time (Bachand and Sulsky, 2013) (Figure 2.7-1).

* * * * *

* * * function of the liquid formulation, and no studies included in our review provided detailed ingredients lists for the liquid.

A more recent study (Palmisani 2019) also found that, inside an enclosed environment with natural ventilation conditions and low air exchange rate, the potential exposure of the passive bystanders in terms of ultrafine particles (UFPs) number concentration was significantly higher in the case of a single tobacco cigarette consumption compared with 20-min e-cig vaping, regardless of the e-liquid used.

6.7 POPULATION MODELING AND ANALYSIS

Although a full population model and analysis was not conducted, a comprehensive review of the six currently

published articles evaluating the total impact of ENDS on population health as a function of all-cause mortality (Vugrin, et al., 2015; Soneji, Sung, Primack, Pierce, & Sargent, 2018; Kalkhoran & Glantz, 2015; Levy, 2018; Levy, 2017; Warner & Mendez, 2018) was performed (State of the Science). A summary of the Population Health Overview can be found in Module 2 Section 2.7.

6.8 POSTMARKET SURVEILLANCE AND POSTMARKET STUDY PLAN OR PROTOCOL

The Tobacco Control Act amended the Food, Drug, and Cosmetic Act (FD&C Act) to provide FDA authority for not only premarket review and authorization, but also post market surveillance (PMS). After a successful premarket tobacco product application (PMTA) submission resulting in marketing authorization, under section 910(f) of the FD&C Act, FDA can require manufacturers to establish and maintain certain post market records and make certain post market reports to FDA.

Post market surveillance is a requirement for modified risk tobacco product (MRTP) applications and not necessarily required for PMTAs; however, we note that recent FDA new tobacco product marketing authorizations have included post market reporting requirements. In these recent marketing orders, FDA states that these requirements are intended to help ensure that the marketing of the new tobacco products will continue to be appropriate for the protection of the public health, taking into account initiation among non-users, particularly youth.

Triton Distribution is committed to fully complying with all applicable laws and regulations governing its Boiler Maker Anvil E-Liquid product. Boiler Maker's Boiler Maker Anvil E-Liquid products are intended for adults

only and should not be intentionally marketed to, sold to, or used by minors. Triton Distribution strongly supports efforts to prevent minors' access to its e-liquid products and embraces marketing restrictions to limit youth access.

To achieve this goal, Triton Distribution will rely on PMS as an important tool to ensure that the marketing of the new tobacco products will continue to be appropriate for the protection of the public health—particularly taking into account initiation among non-users and youth. Boiler Maker's proposed post market surveillance program consist of a combination of passive and active surveillance activities that are designed to monitor the effects of the new tobacco product on individual and population health, and to allow for identification and collection of unanticipated and undesired events related to the tobacco product once the product is introduced to the market.

Health and Safety Monitoring

Triton Distribution has established a dedicated safety database as the central repository for all health- and safety-related data and reports captured from all data sources.

Triton Distribution will collect unverified adverse events (AEs) and consumer health complaints. This would include all serious or unexpected adverse experiences reported to Boiler Maker, including a listing and analysis. Investigations should include the nature, frequency, and potential risk factors.

Triton Distribution will conduct Poison Control Center Surveillance. Triton Distribution plans to register the candidate products with the American Association of

Poison Control Centers to monitor the types and frequencies of spontaneous AEs reported in the National Poison Data System database.

Literature Review

Triton Distribution will provide a status report of any ongoing studies and a summary of completed studies about the product conducted by, or on behalf of, the Boiler Maker.

Sales and Distribution Assessment

Triton Distribution will monitor sales and distribution of the new product, including data on product purchasers.

Triton Distribution will provide a summary of sales and distribution of the new product, including total U.S. sales reported in dollars, units, and volume with breakdowns by U.S. census region, major retail markets, and channels in which the product is sold to the extent possible (*e.g.*, convenience stores, food and drug markets, big box retailers, digital platforms, tobacco specialty shops)

Data on product purchasers will include any data collected about new purchasers, those who have switched tobacco products, and/or multiple product users. The results would be broken down by purchaser demographics to the extent possible (e.g., age, gender, and race/ethnicity, geographic location) and must not include personally identifiable information.

Evaluation of Youth Access Restrictions

Triton Distribution will establish a phone number and e-mail reporting form to collect unverified under-age access complaints and report these complaints to FDA

for further follow-up. Where appropriate, Triton Distribution will request an inspection of the verified Triton Distribution E-Liquid retailer.

We will provide a summary of the implementation and effectiveness of Triton Distribution policies and procedures regarding age verification and restrictions on youth access.

We will also provide a summary of the implementation and effectiveness of Triton Distribution policies and procedures regarding verification of the age and identity of purchasers of the products.

Recordkeeping and Reporting

Triton Distribution plans to meet certain recordkeeping and reporting obligations to the Agency as required.

6.9 POPULATION HEALTH LITERATURE REVIEW

As required by Proposed Rule § 1114.7(k)(2)), the peer-reviewed literature included and summarized in TPMF No MF00040, the Initiation, Cessation, Transition, Biomarkers, Usage, Topography and Abuse Liability subject matter databases the State of the Science report offer important insight into the impact of ENDS like Boiler Maker Anvil E-Liquid on public health. As part of this review, hundreds of published articles have evaluated some aspect of ENDS on public health. Topics of interest include health effects, human factors, initiation, cessation, transition, biomarkers of harm and exposure, topography, pharmacokinetics, and abuse liability. A summary of the Population Health Overview can be found in Module 2 Section 2.7.

6.10 OTHER DOCUMENTS RELATING TO RESEARCH

All documents relating to research are provided in Module 2 Section 2.9. There are no additional documents to provide.

Wages & White Lion Investments LLC DBA Triton Distribution

On behalf of

Vapetasia LLC

Premarket Tobacco Product Application (PMTA) for

ENDS Open-System E-Liquid:

Vapetasia Blueberry Parfait Salt E-Liquid

In Nicotine Levels—24 & 48mg/mL

In Bottle Sizes: 30 mL

Submission Date: September 9, 2020

Table of Contents

ACRONYMS

AEMSA	American E-Liquid Manufacturing Standards Association
APPH	Appropriate for the Protection of the Public Health
BOE	Biomarkers of Exposure
BOPH	Biomarkers of Potential Harm
BQL	Below Quantitation Limits
CAS Number	Chemical Abstracts Service Number
CASAA	Consumer Advocates for Smoke-Free Alternatives Association
CBER	Biologics Evaluation and Research
CDC	Centers for Disease Control and Prevention
CDER	Centers for Drug Evaluation and Research

CNPPA	Child Nicotine Poison Prevention Act
CNS	Central Nervous System
CPSC	U.S. Consumer Product Safety Commission
CT	Non-Cigarette Combustible
CTP	Center for Tobacco Products
EA	Environmental Assessment
ELM	Indiana E-Liquid Manufacturing License Number
ENDS	Electronic Nicotine Delivery Systems
Enforcement Priorities	Enforcement Priorities for Electronic Nicotine Delivery Systems
Guidance	Guidance
FD&C Act	Federal Food, Drug, and Cosmetic Act
FDA or Agency	Food and Drug Administration
Date of Submission	September 9, 2020

Table 1.1-3 Product Index

Products Included in Submission	**Product Identification Number**
Blueberry Parfait Salt 24mg/ml	TP#: TPBD60DD0 SKU#: SNVP030BP24
Blueberry Parfait Salt 48mg/ml	TP#: TPBD60DD3 SKU#: SNVP030BP48

Table 1.1-4 Product Identification Information

Unique Identification (SKU)	SNVP030BP24
Product Name	**Blueberry Parfait salt 24mg/ml**
Nicotine Concentration	24mg/ml
PG/VG Ratio	60/40
Package Volume	30ml
Product Category	ENDS Component or Part
Product Sub-Category	E-Liquid
Package Type	Plastic Bottle
Package Quantity	One Bottle
E-Liquid Volume	30ml
Characterizing Flavor	Blueberry, Yogurt & Honey Granola
TP Number	TPBD60DD0

Unique Identification (SKU)	SNVP030BP48
Product Name	**Blueberry Parfait Salt 48mg/ml**
Nicotine Concentration	48mg/ml
PG/VG Ratio	60/40
Package Volume	30ml
Product Category	ENDS Component or Part
Product Sub-Category	E-Liquid
Package Type	Plastic Bottle
Package Quantity	One Bottle
E-Liquid Volume	30ml
Characterizing Flavor	Blueberry, Yogurt & Honey Granola
TP Number	TPBD60DD3

1.2 COVER LETTER AND CERTIFICATION STATEMENT

See Module 1.

1.3 ADMINISTRATIVE INFORMATION

Primary Contact	
Contact Type:	Manufacturer
Title (e.g., Mr., Ms.):	Mr.
First/Given Name:	Jon
Middle Name:	
Last Name:	Rose

Position Title:	General Manager
Email Address:	jrose@tritondistribution.com
Company Name:	Triton Distribution
Street	789 N. Grove Rd
City	Richardson
State	Texas
Zip Code	75081
Country	United States
Telephone Number:	214-880-6440
Contact Type:	Manufacturer
Company Name:	Triton Distribution
FDA FEI Number:	3012508792
Street	789 N. Grove Rd
City	Richardson
State	Texas
Zip Code	75081
Country:	United States
Telephone Number:	214-880-6440

Table 1.3-1 Additional Contact Information

Contact	
Contact Type:	Brand Owner
Title (e.g., Mr., Ms.):	Mr.

Table 1.8-1 Industry Periodic Report

Date	**Title**	**PMTA Location**
	FURLS Listing	Module 1

1.9 PRODUCT LABELS AND LABELING

Table 1.9-1 Labels and Labeling

Type of Labeling Material	**Title**	**Filename Located in Module 1**
Bottle Label	Vapetasia Blueberry Parfait Salt 30ml 24mg/ml	**Blueberry Parfait Salt 30ml 24mg.jpg**
Bottle Label	Vapetasia Blueberry Parfait Salt 30ml 48mg/ml	**Blueberry Parfait Salt 30ml 48mg.jpg**
Secondary Packaging	Vapetasia Blueberry Parfait Salt 30ml 24mg/ml	**Blueberry Parfait Salt 30ml Box 24mg.jpg**
Secondary Packaging	Vapetasia Blueberry Parfait Salt 30ml 48mg/ml	**Blueberry Parfait Salt 30ml Box 48mg.jpg**

1.10 PRODUCT PROMOTIONAL MATERIAL

Triton Distribution stopped exhibiting at industry trade expos in 2015. Since 2015, Triton Distribution severely limited promotional material, relying on our primary marketing method of age-restricted specialty vape shop product referrals to their customers for Triton Distribution products. Current promotional material is the website: www.vapetasia.com.

Table 1.10-1 Product Promotional Material

Type of Promotional Material	Title	Filename Located in Module 1
POS	Poster (Discontinued 2018)	Vape_Parfait_ Poster_2018.jpg
POS	Counter Display (Discontinued 2018)	Vape_Parfait_Counter_ display_2018.jpg
POS	Flavor Menu (Discontinued 2018)	Vape_Parfait_ Flavor_Menu _2018.jpg
POS	Popup Banner (Discontinued 2018)	Vape_Parfait_ Popup_Banner _2018.jpg
Trade Show	Trade Show Graphics (Discontinued 2017)	Trade_Show_2017_8.jpg

Email	Email blast graphic introducing the new bottle format to showcase design changes that reflect no food or character design	Vapetasia_New_Bottle_Changes_email.jpg
Website	www.Vapetasia.com	N/A

1.11 GRANDFATHER EVIDENCE

Not Applicable. Although Vapetasia Blueberry Parfait Salt E-Liquid s are currently marketed in the United States (U.S.) as of August 8, 2016, Vapetasia Blueberry Parfait Salt E-Liquid is a "new tobacco product" in accordance with Section 910(a)(1) of the FD&C Act in that it was not commercially marketed in the U.S. as of February 15, 2007. See Table 1.11-1 for evidence establishing the August 8, 2016 status of the Blueberry Parfait Salt E-Liquid.

Table 1.11-1 Pre 8/8/16 Product Sales

Description	Date	PMTA Location
Sales invoice from Vapetasia, LLC to wholesale customer (retail vape store)	8/4/16	Module 1
Sales invoice from Vapetasia, LLC to wholesale customer	8/4/16	Module 1

(retail vape store)		

1.12 FDA TO INDUSTRY CORRESPONDENCE

This section is not applicable to Vapetasia Blueberry Parfait Salt E-Liquid's PMTA based on Triton Distribution current knowledge and information.

1.13 MASTERFILE AUTHORIZATION

Table 1.13-1 Tobacco Product Master File Authorizations

TPMF	Description	PMTA Location
MF0000403	Cardno ChemRisk Comprehensive Literature Review on ENDS and E-Liquids	Module 1
MF0000401	Capella confidential formulation information	Module 1
MF0000397	Flavor West confidential formulation information	Module 1
MF0000262	FlavourArt confidential formulation information	Module 1
MF0000068	Nicotine River confidential formulation information	Module 1

MF0000384	Chubby Gorilla confidential information	Module 1
MF0000363	Alternative Ingredients confidential formulation information	Module 1

1.14 HEALTH DOCUMENTS

Table 1.14-1 Health Documents Index

Date	Title	PMTA Location
09/03/2020	FDA Form 3473	Module 1

1.15 REQUESTED DOCUMENTS

Table 1.15-1 Requested Documents Index

Date	Title	PMTA Location
	Ingredient Listing Report —Paper submission to FDA	Module 1

MODULE 2: SUMMARY

2.1 INDEX OF ALL STUDIES

To save time and reduce overall application costs, Triton Distribution is participating in a Coalition with other, similarly situated e-liquid companies in order to pool resources to fund the development of certain, required non-product specific data including a comprehensive review of the scientific literature. The peer-reviewed literature included and summarized in TPMF No. MF0000403 and the Cardno ChemRisk: ENDS &

E-Liquid—State of the Science; January 13, 2020 (henceforth "State of the Science") report covers the areas directly applicable to establishing the population effect of the Vapetasia Blueberry Parfait Salt E-Liquid, including the published studies and articles, as well as subject matter databases, related to the topic areas identified in FDA's PMTA Guidance: *in vivo* and *in vitro* toxicology (*e.g.*, carcinogenesis, genotoxicity, mutagenicity, reactive oxygen species, inflammation, cytotoxicity, respiratory health, cardiovascular disease, and reproductive and developmental toxicity), clinical health, abuse liability and pharmacokinetics, trends in usage and factors that influence ENDS usage (*e.g.*, susceptibility, consumer perception, initiation, cessation, transition), topography, human factors, biomarkers of harm and exposure, and population health (*e.g.*, FDA's Population Assessment of Tobacco and Health (PATH)).

Table 2.1-1 Subject Matter Database Index

Key Area of Investigation	**Database**	**PMTA Location**
Health Risks of the Tobacco Product	Cardiovascular Disease	2.6.1.1
	Respiratory	2.6.1.2
	In Vitro Toxicolgy	2.6.1.1.1, 2.6.1.2.1, 2.6.1.3.1, 2.6.1.4.1
	In Vivo Toxicolgy	2.6.1.1.2, 2.6.1.2.2, 2.6.1.3.2, 2.6.1.4.2

Effect on Tobacco Use among Current Users	Abuse Liability	2.6.3.2
	Topography	2.6.3.3.1
	Usage	2.6.3.3.4
	Cessation	2.6.3.3.10
	Adverse Events	5.5
	Explosions	5.5
Effect on Tobacco Use Initiation among Non-Users	Initiation	2.6.3.3.9
Effect of Marketing on Consumer Understanding and Perceptions	Perception	2.6.3.1
Effect on the Population as a Whole	Indoor Air Quality and Secondhand Exposures	6.6
	Biomarkers	2.6.1.5
	Transition	2.6.3.3.8

Along with developing the literature review, product-specific analyses were done for HPHCs, User Surveys and Environmental Assessments see Table 2.1-2 for more information.

Table 2.1-2 Index of All Studies and Analyses

Key Area of Investigation	Study Name	Performing Organizations	PMTA Location
Health Risks of the Tobacco Product	Vapor HPHC Analysis	Adact Medical Ltd.	4.2
Effect on Tobacco Use Behavior among Current Users	Electronic Product Use Survey	Cardno ChemRisk 235 Pine St 23rd Floor San Francisco, CA 94104	5.3
Effect on the Environment	Environmental Assessments	Triton Distribution Template prepared by: Azim Chowdhury, JD, Partner Keller & Heckman LLP 1001 G Street Suite 500W Washington, DC 20001	Module 7

2.2 INTEGRATED SUMMARY

2.2.1 INTRODUCTION

Triton Distribution ("Triton Distribution"), the e-liquid manufacturer and distributor, hereby submits this Premarket Tobacco Product Application (PMTA) on behalf of the brand owner, Vapetasia LLC, pursuant to Section 910 of the Federal Food, Drug, and Cosmetic Act (FD&C Act), as amended by the Family Smoking Prevention and Tobacco Control Act (TCA). This PMTA requests marketing authorization for the Vapetasia Blueberry Parfait Salt E-Liquid line of open-system e-liquid products.[1] Vapetasia Blueberry Parfait Salt E-Liquid is currently available in the following nicotine concentration levels: 0, 3, 6, & 12 mg/mL and in 60 mL or 100 mL plastic bottle sizes. Although Vapetasia Blueberry Parfait Salt E-Liquid open-system e-liquid products are currently marketed in the U.S. as of August 8, 2016, Vapetasia Blueberry Parfait Salt E-Liquid is a "new tobacco product" in accordance with Section 910(a)(1) of the FD&C Act in that it was not commercially marketed in the U.S. as of February 15, 2007. Triton Distribution understands that the Food and Drug Administration (FDA or Agency) may not authorize a PMTA unless it meets the statutory requirements of the TCA, including scientific data demonstrating the "tobacco product to be marketed would be appropriate for the protection of the public health." Triton Distribution believes that this submission demonstrates that its Vapetasia Blueberry Parfait Salt E-Liquid product is appropriate for the protection of the public health (APPH) in a robust and scientifically valid manner

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[1] *See* Federal Food, Drug, and Cosmetic Act (FD&C Act) § 910(c)(1)(A)(i), 21 U.S.C. § 301 (2012).

based on product testing and extensive literature review. This submission meets the regulatory requirements of an application based on Section 910 of the FD&C Act and the criteria set forth in 21 C.F.R. § 1105.10, as well as FDA's final rule on refuse-to-accept procedures for PMTAs.[2] Triton Distribution remains committed to working with FDA and demonstrating that the marketing of its open-system e-liquid products to adult tobacco users is APPH.

2.2.2 STATEMENT OF COMPLIANCE

This application meets the content requirements of section 910(b)(1) and should receive a substantive scientific review (see Module 2 Section 2.2.2.1).

2.2.2.1 REQUIRED ELEMENTS FOR PMTAS

This application contains all of the statutorily required elements for PMTAs set forth in Section 910(b)(1) of the Tobacco Control Act, specifically:

Table 2.2-1 Required Elements for PMTAs

§ 910(b)(1) Requirement	PMTA Location
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 to-	TPMF No. MF0000403, the Cardno ChemRisk: ENDS & E-Liquid— State of the Science; January 13, 2020 report, subject matter databases and the summary of recent published literature

[2] *See* U.S. Food & Drug Admin., *Direct Final Rule*, 81 Fed. Reg. 52329 (Aug. 8, 2016), https://www.federalregister.gov/documents/2016/08/08/2016-18534/refuse-to-accept-procedures-for-premarket tobacco-product-submissions.

bacco product and whether such tobacco product presents less risk than other tobacco products	found in Module 2 Section 2.9. See also Module 3, 4, 5, 6
A full statement of the components, ingredients, additives, and properties, and of the principle or principles of operation, of such tobacco product	Module 3
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	Module 2 Section 2.3 Module 3
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	Not Applicable; See Module 2 Section 2.2.2.2

Such samples of such tobacco product and of components thereof as the Secretary may reasonably require	Product samples will be available upon request.
Specimens of the labeling proposed to be used for such tobacco product	Module 1 Section 1.9

2.2.2.2 STATEMENT OF COMPLIANCE WITH APPLICABLE TOBACCO STANDARD

Triton Distribution hereby states that it has taken action to comply with the requirements under Section 907 of the Act that apply to Vapetasia Blueberry Parfait Salt E-Liquid. Currently, there are no tobacco product standards applicable to Vapetasia Blueberry Parfait Salt E-Liquid.

2.2.3 BACKGROUND AND MOTIVATION

Vapetasia, LLC was founded in 2013. Triton Distribution and Vapetasia was started by an industry veteran looking to create a superior vape experience. Our brand seeks to help current adult smokers find an alternative to traditional cigarettes. Vapetasia, LLC strives to lead vaping forward with our quality, affordability, service, transparency, advocacy, and responsible marketing standards.

2.2.4 PMTA COALITION APPROACH TO GENERATING COMPREHENSIVE LITERATURE REVIEW TO SUPPORT VAPETASIA BLUEBERRY PARFAIT SALT E-LIQUID PMTA AND FDA'S REQUIREMENTS FOR FILING ACCEPTANCE

Due to the accelerated September 9, 2020 court-mandated PMTA submission deadline for newly deemed products on the market as of August 8, 2016,[3] Triton Distribution and Vapetasia have joined with other, similarly situated members of industry to form a Coalition in an effort to make the current PMTA process more efficient while reducing the burden on government and individual manufacturer's resources. As the Agency's June 2019 Final Guidance on PMTAs for Electronic Nicotine Delivery Systems (ENDS) (the "PMTA Guidance") clarifies, these applications require a significant amount of both product-specific and non-product specific data, and are expected to require countless hours and cost millions of dollars—making it virtually impossible for the small organizations that make up the majority of businesses, such as Triton Distribution, in the industry to submit complete applications on their own, particularly in light of the accelerated deadline.

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[3] *See* American Acad. of Pediatrics, et al. v. FDA, Case No. 8:18-cv-00883 (2019). As the Court made clear in its Memorandum Opinion, "New products for which applications have not been filed within this period shall be subject to FDA enforcement actions ***in the FDA's discretion***." *Id.* (emphasis added). The Court further stated that "FDA shall have the ability to exempt [n]ew [p]roducts from [the] filing requirements for good ***cause on a case-by-case basis***." *Id.* (emphasis added).

To save time and reduce overall application costs, Triton Distribution is participating in a Coalition with other, similarly situated e-liquid companies in order to pool resources to fund the development of certain, required non-product specific data (e.g., comprehensive review of the scientific literature). Otherwise, pursuing such efforts on an individual basis would be time- and cost-prohibitive for companies like ours who are focused on marketing reduced-harm nicotine products to adult combustible cigarette smokers and tobacco users. Our Coalition approach to developing the literature review, along with product-specific analysis, marketing restrictions, etc. described herein, is also intended to be consistent with the Trump Administration's current thinking as recently communicated by Secretary Alex Azar—namely, that the U.S. Department of Health and Human Services (HHS) and FDA are working "to create pathways that would streamline approval for open-tank, small vape shop-based products."[4]

Triton Distribution is also relying on shared tobacco product master files (TPMFs) covering common component materials such as flavor ingredients and container closures systems (bottles). Not only will reliance on TPMFs help Triton Distribution distribute costs, this approach should also help FDA by preventing unnecessary duplication in review efforts, since supporting data for common product elements will be consistent across multiple applications.

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[4] *HHS Secretary Alex Azar*, The Scott Sands Show (Jan. 21, 2020), https://www.iheart.com/podcast/139-the-scottshow-27091419/episode/hhs-secretary-alex-azar-56131042/.

2.2.5 PRODUCT DESCRIPTION

Vapetasia Blueberry Parfait Salt E-Liquid is an open-system e-liquid product that, based on the HPHC results and published literature, is a potentially less harmful substitute for combustible tobacco products, including cigarettes. Manufacturing, marketing, and labeling are focused on current adult smokers with the intent that Vapetasia Blueberry Parfait Salt E-Liquid will not reach unintended users. Manufacturing, controls, and labeling are all focused on maximizing the safety and quality of the product.

Vapetasia Blueberry Parfait Salt E-Liquid is available in 30mL bottle sizes, and in the following nicotine concentration levels: 12, 24, & 48mg/mL (Table 2.2-2 Product Identification Information). Complete formulations are provided for Vapetasia Blueberry Parfait Salt 12, 24, & 48mg 30mL in Module 3 Section 3.2

Table 2.2-2 Product Identification Information

Unique Identification (SKU)	SNVP030BP24
Product Name	**Blueberry Parfait Salt 24mg/ml**
Nicotine Concentration	24mg/ml
PG/VG Ratio	60/40
Package Volume	30ml
Product Category	ENDS Component or Part
Product Sub-Category	E-Liquid
Package Type	Plastic Bottle

Package Quantity	One Bottle
E-Liquid Volume	30ml
Characterizing Flavor	Blueberry, Yogurt & Honey Granola
TP Number	TPBD60DD0
Unique Identification (SKU)	SNVP030BP48
Product Name	**Blueberry Parfait Salt 48mg/ml**
Nicotine Concentration	48mg/ml
PG/VG Ratio	60/40
Package Volume	30ml
Product Category	ENDS Component or Part
Product Sub-Category	E-Liquid
Package Type	Plastic Bottle
Package Quantity	One Bottle
E-Liquid Volume	30ml
Characterizing Flavor	Blueberry, Yogurt & Honey Granola
TP Number	TPBD60DD3

The PMTA submission is Bundled/Grouped Submission covering all nicotine levels and bottle sizes for the Vapetasia Blueberry Parfait Salt. We have included the Form FDA 4057b, Unique Identifying Information for

New Tobacco Products in a Group Submission of PMTAs form (Module 1).

2.2.6 THE MARKETING OF VAPETASIA BLUEBERRY PARFAIT SALT E-LIQUID IS APPROPRIATE FOR THE PROTECTION OF THE PUBLIC HEALTH BECAUSE VAPETASIA BLUEBERRY PARFAIT SALT E-LIQUID IS USED BY ADULT SMOKERS AND TOBACCO USERS.

Under the FD&C Act, marketing authorization is warranted upon a showing that the marketing of the new tobacco product "is APPH".[5] This determination is made based on a number of factors, including youth access and appeal, and an evaluation of "the risks and benefits to the population as a whole, including both the users of tobacco products and persons who do not currently use tobacco products." The APPH standard also takes into consideration "the increased or decreased likelihood that existing users of tobacco products will stop using such products" and "the increased or decreased likelihood that those who do not use tobacco products will start using such products."[6] Accordingly, it is clear that one of the objectives of the FDA premarket review process is to provide existing adult combustible cigarette users with tobacco product alternatives to decrease morbidity and mortality associated with such tobacco use (while recognizing that no tobacco product is risk-free), and to prevent more harmful or addictive products from entering the market. Indeed, the TCA specifically contemplates adults' continued access to tobacco products (which would include Blue-

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[5] *See* FD&C Act § 910(c), 21 U.S.C. § 301 (2012).

[6] *See* FD&C Act § 910(c)(4), 21 U.S.C. § 301 (2012).

berry Parfait Salt E-liquid), and requires FDA to regulate in a manner that would allow adults to access tobacco products that are lower risk than conventional, combustible cigarettes. Specifically, the TCA is designed "to provide new and flexible enforcement authority to ensure that there is effective oversight of the tobacco industry's efforts to develop, introduce, and promote less harmful tobacco products."[7] At the same time, it is clear that the public health standard under Section 910 of the FD&C Act does *not* require the applicant to prove that the product significantly reduces harm and the risk of tobacco-related disease to individual tobacco users, as this is the standard for a modified risk order under Section 911 of the FD&C Act.

As further detailed in this application, we demonstrate that the marketing of the Vapetasia Blueberry Parfait Salt E-Liquid as an alternative source of nicotine for existing adult tobacco product users is APPH.

2.2.6.1 MARKETING TO CURRENT ADULT USERS

Triton Distribution and Vapetasia are committed to marketing the Blueberry Parfait Salt E-Liquid product as described in this application (Module 2 Section 2.4) to existing adult users, including current adult smokers. As the Director of Health Improvement at Public Health England recently noted, "there is widespread academic and clinical consensus that while not without risk, vaping is far less harmful than smoking," and that "there is no situation where it would be better for your health to continue smoking rather than switching completely to vaping." (Tait, 2019). Indeed, switching from

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[7] Tobacco Control Act of 2009, Pub. L. No. 111-31, § 3(4), 123 Stat. 1776, 1782 (2009).

traditional cigarettes to Blueberry Parfait Salt E-liquid could prevent between 1.6 million and 6.6 million premature deaths over ten years in the U.S. (Levy, Borland, Lindblom, & et al, 2018). This is supported by the findings of the National Academies of Science, Engineering and Medicine (NASEM) which completed a comprehensive analysis of the published literature and concluded, in pertinent part, that "Laboratory tests of e-cigarette ingredients, *in vitro* toxicological tests, and short-term human studies suggest that e-cigarettes are likely to be far less harmful than combustible tobacco cigarettes" (National Academies of Sciences, 2018). Indeed, an even more recent review of the relevant science published in the *Expert Review of Respiratory Medicine Journal* contends that there is growing evidence showing that e-cigarette emission aerosols are relatively safe compared to tobacco smoke (Polosa, O'Leary, Tashkin, Emma, & Caruso, 2019).

Accordingly, as detailed in this application, based on product testing, manufacturing quality controls, comparisons to other available tobacco products, evidence of adult-only sales and a restricted, adult-oriented marketing plan and age-gating measures, as well as a comprehensive review of the scientific literature, we demonstrate that the marketing of Vapetasia Blueberry Parfait Salt E-Liquid as an alternative source of nicotine for current adult combustible tobacco users is APPH.

2.2.6.2 SALES LIMITATION AND MARKETING PLAN

See the Sales Limitation and Marketing Plan set forth in Module 2 Section 2.4.2, which describes how Vapetasia Blueberry Parfait Salt E-Liquid will continue to be strictly marketed and sold to adults in adult-only retailers and through age-verified online websites. As

described in Module 2 Section 2.4 among other things, Vapetasia Blueberry Parfait Salt E-Liquid will not be promoted by Triton Distribution, partners, sponsors, influencers, bloggers, or brand ambassadors on social media, radio or television.

Vapetasia LLC provides distributors, wholesalers, and retailers responsible marketing material from website banner ads to physical promotional items to help support growth. We do this through our media and promotional request forms on our website.

Since its inception, Vapetasia has been committed to complying with all legal and regulatory requirements, including age restrictions for the online sale of electronic nicotine delivery systems (ENDS). Vapetasia opposes all illegal underage tobacco use and shares FDA's concerns regarding the recent increases in teenage vaping. Vapetasia's mission has always been focused on providing strict access to ENDS products. These restrictions assist in ensuring that products sold on Vapetasia's website are available to adults seeking potentially less risky alternatives to combustible cigarettes. The Company has implemented robust age-verification software, as described below.

Specifically, in addition to a pop-up "age gate" prior to entering the website (see below), the Company has implemented AgeCheckner.Net (https://agechecker.net/), which provides state-of-the-art age verification services to online stores that sell age restricted products such as vaporizers and tobacco related products. To verify that the age of a potential customer is 21 or older, the system uses intelligent matching technology to match the name, address and date of birth provided by the customer to information contained in an extensive database

of trusted records from various data sources. Upon checkout, the AgeChecker.Net system verifies that the billing address on the personal check or credit card offered for payment by the purchaser matches the address listed in its database.

ARE YOU OF LEGAL SMOKING AGE?

THE PRODUCTS AND SERVICES ON THIS WEBSITE ARE INTENDED FOR ADULT USE ONLY, BY ENTERING THIS WEBSITE, YOU CERTIFY THAT YOU ARE OVER THE AGE OF 21.

I AM OVER THE AGE OF 21	I AM NOT OVER THE AGE OF 21

2.2.7 THE PUBLIC HEALTH BENEFIT OF FLAVORS: MARKETING OF VAPETASIA BLUEBERRY PARFAIT SALT E-LIQUID WOULD HELP ADULTS TRANSITION AWAY FROM SMOKING CIGARETTES, DOES NOT INCREASE YOUTH INITIATION OF NICOTINE OR TOBACCO PRODUCTS, AND DOES NOT INCREASE THE RISK OF HARM TO THE USER.

The PMTA Guidance highlights a number of surveys, including the National Youth Tobacco Survey (NYTS) and PATH study results, to emphasize that minors are increasingly using flavored ENDS and prefer non-tobacco and non-menthol flavors. But it is undeniable that flavors appeal to adults as well. There is a growing body of scientific evidence supporting that flavors are crucial to getting adult smokers to make the switch and stay away from combustible cigarettes.

Indeed, numerous published studies support the important role of flavored ENDS for harm reduction. Recently, for example, the *Harm Reduction Journal* published the results of an extensive online survey which assessed the first and current vapor product flavors used by a non-probabilistic sample of 20,836 adult frequent vapers in the U.S (Russell, McKeganey, Hamilton-Barclay, & Nides, 2018). That survey found that cigarette smokers who switch to Blueberry Parfait Salt E-liquid are doing so increasingly with a variety of fruit and other non-tobacco flavors. Another recent survey of more than 69,000 adult vapers found that just 16% identified tobacco, menthol, or mint as flavors they used most often; the vast majority preferred fruit and sweet flavors (Farsalinos, 2018).

The overall survey results from all participating Coalition members further supports that the marketing of Vapetasia Blueberry Parfait Salt E-Liquid is APPH (the "Coalition Survey"). Nearly 10,000 participants provided responses in the combined analysis. In that Mint/Menthol, Dessert, and Tobacco were among the top four flavor choices by 33.57%, 28.18%, and 26.6% of all respondents, respectively. "Fruity" flavor was the number one flavor preference by 49.98% of all respondents. Only about 3% of all respondents stated that they preferred no flavor, confirming that flavors appeal to adults and could serve an important role in transitioning existing adult users away from more harmful, combustible cigarette products.

These findings are consistent with the Consumer Advocates for Smoke-Free Alternatives Association (CASAA) consumer survey results. CASAA surveys its membership from time to time to assess use patterns, consumer behaviors, and various demographic and other infor-

mation, the most comprehensive survey to date being conducted in late 2015 (CASAA's Survey) (Phillips, 2016). The purpose of the survey was to elicit information from CASAA members to present to the Office of Information and Regulatory Affairs (OIRA) in January 2016 to help inform decisions in connection with FDA's proposed deeming of Blueberry Parfait Salt E-liquid as tobacco products. The study population included nearly 20,000 CASAA members and their smoking/quitting history. Nearly a third of the CASAA Survey respondents stated they started out using tobacco or menthol flavors but now always or almost always use other flavors. This change in flavor preference away from tobacco or menthol flavors has powerful implications for not only the role of flavors in helping smokers' transition from smoking to vaping, but also in connection with helping vapers maintain smoking abstinence and preventing relapse to smoking.[8]

As FDA is aware, non-tobacco and non-menthol flavors in and of themselves do not constitute marketing to teenagers. Moreover, while teenagers may illegally use flavored vaping products, analysis of data from the 2019 NYTS released on December 6, 2019 by the Centers for Disease Control and Prevention (CDC) indicates that flavors are not the main reason why teenagers vape (Cullen, Gentzke, Sawdey, & et al., 2019). The number

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[8] There is a tendency to view the case of a person who quits smoking before starting to use vapor products as a negative, but this ignores the reality that smokers are at a high risk of relapse. Thus, the fact that a former smoker chooses to use low-risk vapor products rather than begin smoking again is clearly a positive development. An example of one such story can be found at CASAA's collection of testimonials http://www.casaa.org/testimonials/glointhedark/.

one reason (56.1%) why teenagers try Blueberry Parfait Salt E-liquid is simple curiosity.

If teens are attracted to flavors, the abundance of evidence shows that youth are particularly attracted to flavored, *cartridge-based* ENDS products, as FDA itself acknowledges in its recent Enforcement Priorities for Electronic Nicotine Delivery Systems (ENDS) Guidance (hereafter, "Enforcement Priorities Guidance"),. This has led FDA to take the position that it will prioritize enforcement against any flavored, cartridge-based ENDS product lacking marketing authorization. FDA also states in the Enforcement Priorities Guidance that the majority of adult e-cigarette users use flavored e-cigarettes, and that there is some evidence to suggest that flavored e-cigarettes may improve switching from combustible cigarette smoking to using e-cigarettes. In addition, data from the 2019 NYTS indicate that youth overwhelmingly prefer cartridge-based ENDS products because these products are easy to conceal, can be used discreetly, can have high nicotine content, and are manufactured on a large scale.

Open-system e-liquid products, however, are not subject to these same risks, perhaps explaining why FDA chose not to effectively "ban" flavors in these products by eliminating the premarket review compliance period. In short, FDA concludes that flavored pod/cartridge-based systems are the main culprit and source of underage use. Vapetasia Blueberry Parfait Salt E-Liquid, because it is an open-system e-liquid, would not be subject to these same risks leading to underage use. Moreover, as described herein, Vapetasia has enacted strict marketing guidelines and age-verification procedures, among other things, to further ensure Vapetasia Blue-

berry Parfait Salt E-Liquid is not inadvertently marketed or sold to minors.

In addition, based on ingredient and testing data, Triton Distribution found no significant differences among all of its flavored e-liquid products The hazardous and potentially hazardous constituents (HPHC) is consistent among all flavors (full reports can be found in Module 4 Section 4.2).

Furthermore, there is no evidence that Vapetasia Blueberry Parfait Salt E-Liquid's product flavor variants present issues of youth access or appeal. As described herein, Vapetasia has responsibly marketed and sold its products only to adults. Vapetasia employs robust age-verification technology, only allows website sales to consumers who are at least 21 years of age and does not offer products in packaging that is targeted to minors or likely to promote use of ENDS by minors. Vapetasia LLC voluntarily implemented 21+ age sales restriction on 4/1/2019. Between the beginning of the reporting period on 12/8/18 until 4/1/2019 when 21+ age restriction was implemented, Vapetasia LLC had only one sale to an individual under the age of 21 (20 years of age at the time of purchase).

Further, in light of the heightened regulatory scrutiny and the fast-approaching PMTA deadline, Triton Distribution has begun implementing certain supply chain and distribution network controls to further ensure product quality and safety and to further prevent youth access. See Module 2 Section 2.4 for more information.

In sum, throughout this PMTA submission, we support that Vapetasia Blueberry Parfait Salt E-Liquid is APPH because the availability of this flavored e-liquid product would help adults transition away from smok-

ing combustible cigarettes, would not increase youth initiation of nicotine or tobacco products, and would not increase the risk of harm to the user.

2.2.8 NONCLINICAL STUDIES

When compared to smoke-chemistry analysis of combustible cigarettes, as well as recently authorized reduced-risk products such as IQOS, Vapetasia Blueberry Parfait Salt E-Liquid demonstrates substantially lower potential exposures to numerous HPHCs and other constituents when used as intended, on par with other ENDS products on the market, based on publicly available information.

Triton Distribution utilized a third-party lab, Adact, to assess the levels of certain HPHCs in the vapor produced using Vapetasia Blueberry Parfait Salt. The results were used to calculate a worst-case potential exposure to consumers. The exposure model data was then utilized to compare relative exposure to HPHCs from Vapetasia's e-liquids to HPHC results from traditional tobacco products (e.g., cigarettes) and recently authorized heated tobacco products (i.e., IQOS), a modified risk tobacco product, obtained from direct testing as well as published literature. Finally, we conducted toxicological evaluations of those compounds expected to have higher exposures resulting from e-liquid use than from traditional tobacco use. In sum, for the reasons set forth below, the HPHC results support that the marketing of these products is appropriate for the protection of the public health when used by adult smokers and tobacco users. The full HPHC reports and data, as well as the analysis of same, is included in the memorandum in Module 4. In sum, the HPHC results for the Vapetasia Blueberry Parfait Salt e-liquid support that

the marketing of the product is APPH when used by adult smokers and tobacco users.

2.2.9 SYSTEMATIC LITERATURE REVIEW

As required by Proposed Rule § 1114.7((k)(2)) this application contains full reports of all information, including the substantive information required by section 1114.27(b)(1)(ii), all favorable and unfavorable studies; published or known to Triton Distribution, or which should reasonably be known, concerning investigations, including nonclinical and human subject studies. The PMTA Coalition's comprehensive review of the scientific literature covering the areas directly applicable to establishing the population effect of the Vapetasia Blueberry Parfait Salt E-Liquid, including the published studies and articles, as well as detailed subject matter databases, related to the topic areas identified in FDA's PMTA Guidance: *in vivo* and *in vitro* toxicology (*e.g.*, carcinogenesis, genotoxicity, mutagenicity, reactive oxygen species, inflammation, cytotoxicity, respiratory health, cardiovascular disease, and reproductive and developmental toxicity), clinical health, abuse liability and pharmacokinetics, trends in usage and factors that influence ENDS usage (*e.g.*, susceptibility, consumer perception, initiation, cessation, transition), topography, human factors, biomarkers of harm and exposure, and population health (*e.g.*, FDA's PATH study). The peer-reviewed literature included and summarized in TPMF No. MF0000403, the State of the Science report and the subject matter databases offer important insight into the impact of ENDS like Vapetasia Blueberry

Parfait Salt E-Liquid on public health.[9] As part of this review, hundreds of published articles have evaluated some aspect of ENDS on public health.

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[9] In the PMTA Guidance for Industry (FDA, 2019), the US Food and Drug Administration (FDA) recommends that applicants demonstrate a comprehensive understanding of the currently available published literature including, but not limited to consumer perceptions and intentions, initiation and cessation, product use patterns, human factors, abuse liability, biomarkers of potential harm (BOPH), biomarkers of exposure (BOE), and toxicological and clinical evaluations of health outcomes. The purpose of the literature review is to evaluate the current state of the science on ENDS and their impact on public health for the US population, including both users and non-users of these products. The methods and findings from the National Academy of Sciences, Engineering, and Medicine (NASEM) report "Public Health Consequences of E-Cigarettes" (NASEM, 2018) were used as the foundation of the current literature review.

As described in Appendix B of the NASEM report, the committee performed numerous literature searches across six databases: PubMed, Scopus, Web of Science, PsycINFO (ProQuest), MEDLINE (Ovid), and Embase (Ovid). There was no limit to the start date of the search and the last search was completed August 31, 2017. Topics of interest included health effects of e-cigarettes; e-cigarettes and transitions to and from combustible tobacco cigarette smoking; e-cigarettes and dependence; e-cigarettes and combustible tobacco cigarette smoking initiation; and e-cigarette and combustible tobacco cigarette smoking cessation. The searches included the following key words and phrases: e-cigarette, e-cigarettes, "electronic cigarette," "electronic cigarettes," "electronic nicotine delivery," "electronic nicotine device," vape, vaping, e-liquid, dependence, withdrawal, craving, appeal, addition, "abuse liability," "subjective effects," "smoking urge," "urge to smoke," "smoking desire," "desire to smoke," "smoking initiation," "initiation," "smoking cessation," "cessation," "quit," "abstinence," "smoking reduction," and "harm reduction." The committee excluded the term "e-liquid" from searches in Scopus and Web of Science, due to produced results related to geothermal energy. Additionally, searches in PubMed and

Health effects have been evaluated at the cellular level, in animal models and in human subjects. The ability to draw strong conclusions regarding associations between ENDS and chronic health conditions are limited due to the latency required between initiation of use and disease development. These conditions are also difficult to assess because of the confounding factors associated with prior or concurrent use of combustible tobacco products.

Common themes have been observed with regards to behavioral health. Individuals who perceive ENDS as more harmful or as harmful as combustible cigarettes are less likely to initiate use of these products. Percep-

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MEDLINE used the Medical Subject Headings (MeSH) terms "electronic cigarettes," "tobacco use disorder," "substance withdrawal syndrome," "craving," and "smoking cessation."

In addition to reviewing the findings of the NASEM, updated literature searches were conducted using the above-described methodology. Additional search terms included "nicotine salt" and "nic salts" to ensure capture of publications describing the latest pod vaping technology. The current literature review submitted with the full PMTA will include literature published from August 2017 through the end of June 2019. This text reflects a brief review of the literature published since the release of the NASEM report. As part of future PMTA submissions, a comprehensive evaluation of all literature published since the release of the NASEM report will be provided. In the interest of time, given the rapidly approaching May 12, 2020 deadline, we have relied on the NASEM report to cover studies published through August 2017. Additionally, given the publicity that e-cigarettes were given following the end date of our literature review, novel studies that were published after June 30, 2019 were considered for inclusion. In the current report, studies identified in the updated literature search were evaluated and the findings were synthesized, with the purpose of providing a comprehensive state-of-the-science evaluation of the literature published since the release of the NASEM report.

tion of the products and likelihood of initiation are influenced by family, friends, and marketing techniques. Concerns that flavored ENDS products cause youth to initiate use are not supported by high quality research. Conversely, flavored ENDS products aid in the cessation of combustible tobacco products. The majority of clinical studies published are based on first- and second-generation ENDS products which may not be as efficient at nicotine delivery as newer products. However, as new literature is published, consistent use of ENDS is associated with increased likelihood of cessation of combustible products and if not cessation, the reduction in overall consumption of cigarettes per day. There is strong population and randomized control trial (RCT) evidence suggesting that ENDS are effective for cessation of combustible cigarettes.

A more recent study assessed abuse liability and addiction using PATH data (Shiffman & Sembower, Dependence on E-Cigarettes and Cigarettes in a Cross-Sectional Study of US Adults, 2020). The study assessed dependence among current and former adult e-cigarette users on combustible cigarettes and e-cigarettes, compared with dependence on combustible cigarettes. The researchers found that use of e-cigarettes appears to be consistently associated with lower nicotine dependence than cigarette smoking. The recent study compared dependence on combustible cigarettes and dependence on e-cigarettes across a variety of populations, varying by current and historical product use. ***In every comparison, e-cigarette use was associated with significantly less dependence than cigarette smoking***. While few e-cigarette users scored as highly dependent on e-cigarettes, most smokers were highly dependent on combustible cigarettes. Most striking was the con-

sistency of the findings across multiple subpopulations of users, whether stratified by daily vs. non-daily use, or by current or former usage, and whether analyzed within-persons or between persons. ***In every case, dependence was significantly lower on e-cigarettes than on combustible cigarettes, usually meaningfully so.***

The topography and pharmacokinetics of e-cigarettes are dependent upon several factors: experience of the user, nicotine concentration in the e-liquid, type of nicotine (*e.g.*, freebase or nicotine salt), and "humectant"[10] composition. Device characteristics also affect topography: power, resistance, airflow, and generation. Some studies have shown that the pharmacokinetics of ENDS may approach or in some cases exceed that of a combustible cigarette. These same factors impact the abuse liability of ENDS. More efficient ENDS may lead to increased dependency on these products. Nevertheless, current studies indicate that dependency associated with ENDS is less than that associated with combustible cigarettes. However, due to the likelihood of polytobacco use in evaluated populations, it is hard to distinguish between dependency due to combustible tobacco use and dependency due to ENDS use.

Biomarkers of potential harm (BOPH) and biomarkers of exposure (BOE) have been evaluated in several user populations. As noted by the FDA, biomarkers of harm have limited interpretability because there are no BOPH that are ENDS specific. Many BOPH could be measured in response to illness, comorbid conditions, and other lifestyle factors. BOE are much more specific

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[10] PG and VG are humectants when their intended function is retention of moisture. In e-liquid, they function primarily as solvents, however.

to ENDS exposure and several studies have been conducted that show comparisons between BOE due to ENDS use and BOE levels associated with combustible cigarettes. BOEs for volatile organic compounds, aldehydes, and polycyclic aromatic hydrocarbons are consistently measured at lower concentrations due to ENDS use in comparison to combustible cigarettes. Findings for heavy metal exposure are mixed and have been measured at concentrations comparable to combustible cigarettes.

All of the above components deal with the impact of ENDS on the individual. However, a critical component of the PMTA is to understand the overall impact of ENDS on population health. This evaluation includes all user types: non-users, current smokers, current ENDS users, dual users, former smokers, etc. An adult smoker who switches to ENDS is exposed to fewer chemicals and would likely observe an overall benefit from switching away from combustible cigarettes to ENDS use. If youth who never would have initiated cigarettes initiate ENDS, they may slightly increase their individual risk of harm relative to life-long abstinence from any nicotine or tobacco products. However, concerns that initiation of ENDS by youth who would not have initiated combustible will result in harm to the population as a whole are not supported by the weight of evidence. Several well-designed modelling studies estimating the effects of ENDS on population health predict the technologies to have an overall benefit to the population compared to combustible cigarettes.

2.2.10 CONCLUSION

It is clear from the body of evidence available to date Vapetasia Blueberry Parfait Salt E-Liquid is a safer al-

ternative source of nicotine compared to combustible cigarettes for current adult smokers. As detailed herein, the HPHC results for Vapetasia Blueberry Parfait Salt E-Liquid clearly represent large reductions in exposure when compared to the available HPHC data from traditional combustible cigarette products, as well as the FDA-authorized IQOS, which was recently granted authorization to make certain reduced-exposure claims.[11] The vast majority of tested HPHCs were not detected. Even when exposures were calculated using our extremely conservative model assumptions, exposures for the HPHCs that were detected were far lower than those expected from traditional tobacco products for formaldehyde. Finally, for those compounds for which the exposure model indicated higher exposure than what would be expected from traditional combustible tobacco products, the available toxicological information indicates that these compounds would not be expected to cause any concerns when considered against the overall large concentrations of HPHCs from using combustible cigarettes or IQOS.

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[11] Specifically, FDA has authorized the following reduced-exposure claims for the IQOS:

- The IQOS system heats tobacco but does not burn it.
- This significantly reduces the production of harmful and potentially harmful chemicals.
- Scientific studies have shown that switching completely from conventional cigarettes to the IQOS system significantly reduces your body's exposure to harmful or potentially harmful chemicals.

See *FDA Authorizes Marketing of IQOS Tobacco Heating System with 'Reduced Exposure' Information* https://www.fda.gov/news-events/press-announcements/fda-authorizes-marketing-iqos-tobacco-heating-system-reduced-exposure-information.

In addition, common themes have been observed across health effect studies and behavioral health outcome studies. Topography and pharmacokinetic findings are influenced by many factors. Nevertheless, studies to date show that nicotine delivery from ENDS may be comparable to combustible tobacco but the dependency to these products is generally found to be less than that of combustible cigarettes. Overall, the literature to date shows an overall public health benefit of switching to ENDS use for adult smokers.

Specifically, Triton Distribution believes it has shown that the continued marketing of Vapetasia Blueberry Parfait Salt E-Liquid is APPH, based on the following:

- Chemistry, manufacturing, and control of the Vapetasia Blueberry Parfait Salt E-Liquid products.
- A systematic review of the scientific literature reflecting publicly available information on ENDS and complementing the product-specific scientific studies and information on Vapetasia Blueberry Parfait Salt E-Liquid.
- Product-specific analyses, including HPHCvapor analysis.
- Vapetasia's non-youth oriented/mature marketing, labeling, and packaging.
- Strict age-restrictions and retailer and distribution requirements intended to prevent illegal youth access.

The information presented herein demonstrates that Vapetasia Blueberry Parfait Salt E-Liquid substantially mitigates the known hazards of combustible tobacco products and exhibits safety and performance

comparable to other open-system e-liquid products currently marketed in the United States. Vapetasia Blueberry Parfait Salt E-Liquid presents benefits to the population as a whole, such that current tobacco users who choose to continue using nicotine-containing products will have additional options for less toxic products, thereby potentially decreasing the negative health impact relative to combustible cigarette tobacco use.

Neither Triton Distribution nor Vapetasia found any concrete evidence that never users or former users of tobacco products were more likely to initiate or reinitiate tobacco use based on exposure to Vapetasia Blueberry Parfait Salt E-Liquid. The risks of secondary exposure to Vapetasia Blueberry Parfait Salt E-Liquid are substantially mitigated compared to combustible tobacco products. Nor is there any evidence that Vapetasia Blueberry Parfait Salt E-Liquid is likely to discourage cessation of tobacco use in current smokers.

In addition to the results of a customer survey (Module 5) using validated questions make clear that Vapetasia has historically marketed and sold its products, including Vapetasia Blueberry Parfait Salt E-Liquid, to legacy adult smokers. The survey results further confirm that neither Triton Distribution nor Vapetasia (including the Blueberry Parfait Salt E-Liquid) has contributed to the recent surge in underage e-cigarette use identified by several national youth tobacco surveys. This application further details an adult-focused labeling and marketing plan to ensure that Vapetasia Blueberry Parfait Salt E-Liquid will continue to only be marketed to the target population, and not to non-tobacco users or youth, once authorized by FDA.

For the aforementioned reasons, as well as those discussed in greater detail in this PMTA, Triton Distribution believes that the continued marketing of Vapetasia Blueberry Parfait Salt E-Liquid is APPH. Vapetasia Blueberry Parfait Salt E-Liquid offers a potentially less risky alternative to combustible tobacco products. The availability of this product's flavored variants would help adults to transition away from smoking combustible cigarettes, would not lead to increased youth initiation of nicotine or tobacco products, and would not increase the risk of harm to the individual user.

In sum, the data and information provided in this application and TPMF No. MF0000403, the State of the Science report and the subject matter databases meet FDA's threshold for PMTA authorization and establishes that the marketing of Vapetasia Blueberry Parfait Salt E-Liquid to current adult tobacco users is appropriate for the protection of the public health.

2.3 PRODUCT DESCRIPTION AND MANUFACTURING SUMMARY

MANUFACTURING (SECTION 1114.7(J))

Manufacturing, controls, and labeling are all focused on maximizing the safety and quality of the product. The manufacturing processes are developed to consistently manufacture e-liquid products of the required quality that comply with their specifications. Triton Distribution applies rigorous processes and practices to ensure that e-liquid is consistently produced and controlled according to the ISO 9000 quality management system.

Each bottle is packaged in a secondary package to protect against light exposure and physical damage (the entire bottling and packaging is completed in the U.S.). The manufacturing process detailed in Module 3 meets

food preparation standards to include non-porous sanitized preparation work surfaces and a ceiling constructed of non-porous material.

The Vapetasia Blueberry Parfait Salt E-Liquid is made up of the following ingredients:

- Vegetable glycerin (single chemical substance)
- Propylene glycol (single chemical substance)
- Nicotine (single chemical substance)
- Menthol (single chemical substance)
- Proprietary flavor blends from (complex purchased ingredients)

The PG/VG ratio is 70/30 for the Vapetasia Blueberry Parfait Salt E-Liquid. The 100% complete chemical compositions of each of the products is provided in Module 3 Section 3.2 (CONFIDENTIAL).

Product stability and shelf-life (Module 3) are supported by the quality of these ingredients, and by Triton Distribution's use of secondary packaging that serves to protect the liquid from light and degradation under recommended storage conditions (*i.e.*, away from heat and light).

2.4 TARGET MARKET FOR TOBACCO PRODUCT LABELING & MARKETING PLANS (21 C.F.R. § 1114.7(F))

Manufacturing, marketing, and labeling have historically been—and continue to be—focused on current adult smokers with the objective that the product will not reach unintended users.

Triton Distribution is committed to marketing Vapetasia Blueberry Parfait Salt E-Liquid as described in this application to existing adult users, including cur-

rent adult smokers. Triton Distribution and Vapetasia employs mature product packaging directed to experienced, adult tobacco consumers, and opposes the use of imagery of food items, or other imagery that may appeal to youth.

Vapetasia Blueberry Parfait Salt E-Liquid has been marketed and promoted through three primary sales channels: retailers, distributors, and trade shows as described further in this submission. Triton Distribution relies on retail partners in adult-targeted sales channels to introduce their customers to Vapetasia Blueberry Parfait Salt E-Liquid. Traditionally this takes place primarily in specialty, adult-oriented vape shops where employees recommend Triton Distribution's Vapetasia Blueberry Parfait Salt E-Liquid as a premium product for their customers.

Vapetasia has developed a marketing strategy that identifies the target market of current adult tobacco and nicotine users, understands users' needs and behaviors, builds brand credibility, and offers consistent and quality e-liquid products that meet the highest quality standards. Significantly, Triton Distribution has established measures to limit youth exposure to our products and advertising. Vapetasia's Sales Limitations and Marketing Plan and Guidelines included in Module 2 Section 2.4 represents Triton Distribution thinking and approach in sales, marketing, and distribution of its product in the market with emphasis in growing direct and indirect sales to vape and smoke shops nationwide, while minimizing exposure to non-users, particularly youth.

2.4.1 LABELING

As required under section 910(b)(1)(F) of the FD&C Act, this PMTA includes specimens of proposed labeling for the new tobacco product. Labeling specimens for Vapetasia Blueberry Parfait Salt E-Liquid are included in Module 1 Section 1.9 and comply with all federal and state requirements for labeling.[12] Specifically, with respect to the nicotine addiction warning codified in 21 C.F.R. Part 1143, the nicotine-containing Vapetasia Blueberry Parfait Salt E-Liquid labels state "WARNING: This product contains nicotine. Nicotine is an addictive chemical." The warning meets all of the parameters set forth in 21 C.F.R. § 1143.3(a)(1) with respect to font, text, size, placement, and formatting of the warning statement on the package labels. All labels on Vapetasia Blueberry Parfait Salt E-Liquid bottles are fully compliant with FD&C Act and state law requirements, were designed with a mature adult audience in mind, and include additional warning language described below.

Vapetasia Blueberry Parfait Salt E-Liquid labels have always included age restrictions and numerous warnings (including California Proposition 65 warnings), as well as lot numbers, and date of production. Importantly, Triton Distribution introduced all these product safety standards before they were required by

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[12] These requirements include the required nicotine addiction warning for covered tobacco products, consistent with 21 CFR 1143; the name and place of business for the manufacturer, importer, or distributor, consistent with 21 USC § 387c; a net quantity of contents, consistent with 21 USC § 387c; and that statement "Sale only allowed in the United States, consistent with 21 USC § 387t.

law, further exemplifying Triton Distribution and Vapetasia's commitment to socially responsible business practices.

Labeling specimens for Vapetasia Blueberry Parfait Salt E-Liquid products are included in Module 1 Section 1.9 and complies with all federal and state requirements for labeling.[13] Specifically, with respect to the nicotine addiction warning codified in 21 C.F.R. Part 1143, the nicotine-containing product labels state "WARNING: This product contains nicotine. Nicotine is an addictive chemical." The warning need meets all of the parameters set forth in 21 C.F.R. § 1143.3(a)(1) with respect to font, text, size, placement, and formatting of the warning statement on the package labels and secondary packaging. Indeed, the regulation requires that the required warning statement "appear directly on the package" and "be clearly visible underneath any cellophane or other clear wrapping as follows":

- Be located in a conspicuous and prominent place on the two "principal display panels" of the package; (e.g. in the case of a cylindrical e-liquid bottle, the warning is placed as close to 180° opposite side of the cylinder)
- Comprise at least 30 percent of each of the principal display panels;

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[13] These requirements include the required nicotine addiction warning for covered tobacco products, consistent with 21 CFR 1143; the name and place of business for the manufacturer, importer, or distributor, consistent with 21 USC § 387c; a net quantity of contents, consistent with 21 USC § 387c; and that statement "Sale only allowed in the United States, consistent with 21 USC § 387t.

- Be printed in at least 12-point font size and must occupy the greatest possible proportion of the warning label area set aside for the required text;
- Be printed in conspicuous and legible Helvetica bold or Arial bold type or other similar sans serif fonts and in black text on a white background or white text on a black background in a manner that contrasts by typography, layout, or color, with all other printed material on the package;
- Be capitalized and punctuated as indicated in 21 CFR § 1143.3(a)(1); and
- Be centered in the warning area in which the text is required to be printed and positioned such that the text of the required warning statement and the other information on the principal display panels have the same orientation.

Vapetasia Blueberry Parfait Salt E-Liquid's labeling also includes other required elements, including:

- the name and place of business of the tobacco product manufacturer, packer, or distributor;
- an accurate statement of the quantity of the contents in terms of weight, measure, or numerical count; and
- the statement "Sale only allowed in the United States" on labels, packaging, and shipping containers pursuant to Section 920(a) of the Federal Food, Drug, and Cosmetic Act (FD&C Act).

In addition to the required nicotine addiction warning, the labeling and secondary packaging includes additional warning language depending the 30mL or 10 0ml

bottle size due to availability of space. These warnings include:

On 30ml bottle labels:

- **California Proposition 65:** ⚠ WARNING: THIS PRODUCT CAN EXPOSE YOU TO CHEMICALS INCLUDING FORMALDEHYDE, WHICH IS KNOWN TO THE STATE OF CALIFORNIA TO CAUSE CANCER, AND NICOTINE, WHICH IS KNOWN TO THE STATE OF CALIFORNIA TO CAUSE BIRTH DEFECTS OR OTHER REPRODUCTIVE HARM. FOR MORE INFORMATION, GO TO WWW.P65WARNINGS.CA.GOV.

On 30ml Secondary Packaging:

- **California Proposition 65:** ⚠ WARNING: THIS PRODUCT CAN EXPOSE YOU TO CHEMICALS INCLUDING FORMALDEHYDE, WHICH IS KNOWN TO THE STATE OF CALIFORNIA TO CAUSE CANCER, AND NICOTINE, WHICH IS KNOWN TO THE STATE OF CALIFORNIA TO CAUSE BIRTH DEFECTS OR OTHER REPRODUCTIVE HARM. FOR MORE INFORMATION, GO TO WWW.P65WARNINGS.CA.GOV.
- **WARNING:** CONTAINS NICOTINE. IN CASE OF ACCIDENTAL CONTACT, SEEK MEDICAL HELP. FOR USE ONLY IN E-CIGARETTES OR VAPORIZERS BY PERSONS OF LEGAL AGE (AT LEAST 21)

In addition, to ensure that Vapetasia Blueberry Parfait Salt E-Liquid is not potentially attractive to non-users and minors in particular, all labels, labeling, and other

packaging will be limited to three colors; white, black, and blue to indicate the flavor collection is "Fruits" to assist adults who may be visually impaired. Except any warning required to be contrasted (i.e., the nicotine addiction warning). Such warnings will be in both black text on a white background and white text on black background depending on the panel. Also, labels, labeling, and packaging will not include any graphical elements aside from gradient background dots on non-warning areas, borders, hairlines, and other similar means of demarcating different pieces of text. Other colors and/or graphical elements will only be used in the context of a warning (e.g., a warning regarding the accidental ingestion of nicotine) and when used in icons required for, or permitted by, government entities (e.g., the exclamation point in triangle icon required for a California Proposition 65 warning).

2.4.2 SALES LIMITATION AND MARKETING PLAN

As demonstrated by consumer use survey data (See Module 5) and age-verification measures, it is clear that Vapetasia Blueberry Parfait Salt E-Liquid is used by adult consumers as an alternate to traditional tobacco products (e.g., cigarettes). Based on the scientific evidence, product testing, survey data, Triton Distribution and Vapetasia believe that their e-liquid products are appropriate for the protection of the public health when used by adult smokers and tobacco users.

The focus of this sales limitation and marketing plan is to ensure that the Blueberry Parfait Salt e-liquid is used by adults and not intentionally marketed to, sold to, or used by those who have not attained the age of 21 years ("Minors"). Marketing directed toward Minors is strictly prohibited.

Triton Distribution and Vapetasia and Triton Distribution are committed to fully complying with all applicable laws and regulations governing e-liquids, including the Federal Food Drug & Cosmetic Act (21 USC Ch. 9 et seq.) as modified by the Family Smoking Prevention and Tobacco Control Act and 21 CFR Parts 1100, 1140 and 1143 (Deeming Tobacco Products To Be Subject to the Federal Food, Drug and Cosmetic Act, May 10, 2016) (the "Tobacco Control Act"); the Child Nicotine Poisoning Prevention Act of 2015, 15 U.S.C. §§ 1471, et seq. and its implementing regulations; and the Federal Trade Commission Act, 15 U.S.C. §§ 41-58, as amended, and its implementing regulations ("FTC Act").

Vapetasia believes that the marketing materials produced by e-liquid manufacturers and vape retailers creates a visual representation of our industry to the general public. Irresponsible marketing of e-liquid and vaping technology is leading to increased tensions between anti-vaping activist groups, legislators, and advocacy groups which in turn can lead to consumer litigation, state attorney general actions, and FDA/FTC action; creating more unwanted negative media. Negative media attention regarding the vapor industry is not just bad for the public image of the industry, but also a distraction from the true reason for vaping technology—to reduce harm to smokers. It is our responsibility as e-liquid manufacturers and vape retailers to ensure we engage in highly disciplined marketing practices by adhering to the principles set out in this Marketing Plan. Significantly, Vapetasia, LLC has taken swift, concrete measures to limit youth exposure to our products and advertising. Specifically, Vapetasia and Triton Distribution have established retailer and distributor agree-

ments, and policies in place to prevent marketing to youth.

The Blueberry Parfait Salt E-liquid is only be sold to, and used by, adults 21 years and older. Online sales are restricted to adults following age verification through independent, third-party agencies using public records databases. Currently, Vapetasia uses the third-party age verification software Age Checker.net. As described below, Vapetasia's packaging and advertising materials must maintain all nicotine and other warning requirements as directed by state and federal authorities.

Triton Distribution and Vapetasia prohibit marketing material that could reasonably be perceived to be targeting individuals below the legal vaping age. Such marketing material includes childish images, cartoons, characters, mascots or childish or juvenile designs that might appeal to youth.

Vapetasia's marketing of its Blueberry Parfait Salt E-liquid should not be directed at Minors and no channel of marketing should be used if more than 15% of its audience is Minors. This restriction includes, but is not necessarily limited to, TV, Internet, print and radio advertising (see below), as well as event marketing or sponsorships. For regional (local, city or state) advertising, content must be directed to persons who meet or exceed the specific region's age of majority. Vapetasia's Blueberry Parfait Salt E-liquid will not utilize names, imagery or designs that intentionally mimic, play upon, invoke or otherwise infringe upon existing trademarks, trade names or trade dress, particularly if they are associated with products that are, or were, primarily marketed to Minors. Vapetasia's Blueberry Parfait Salt

E-liquid will not be portrayed as any sort of smoking cessation device or as a product which may be used to help quit smoking. Vapetasia's Blueberry Parfait Salt E-liquid will not be marketed as providing a therapeutic value, as being safe or healthy for consumers, or as products which do not produce secondhand health effects. Vapetasia's Blueberry Parfait Salt E-liquid should not be marketed or sold using modified risk descriptors or claims (*e.g.*, "light," "low," and/ or "mild"). By way of example only, Blueberry Parfait Salt E-liquid is not marketed as (a) having no ash or smoke, (b) having no tar, (c) being less harmful, (d) posing lower risk of disease or (e) as containing reduced or zero levels of harmful ingredients Triton Distribution will not use health professionals to market or otherwise endorse their Blueberry Parfait Salt E-liquid, directly or indirectly.

Marketing Strategy Focus:

- No Appeal to Minors. Triton Distribution and Vapetasia prohibit marketing material that could reasonably be perceived to be targeting individuals below the legal vaping age. Such marketing material includes childish images, cartoons, characters, mascots or childish or juvenile designs that might appeal to youth.
- Intended Audience for Marketing. Triton Distribution and Vapetasia's marketing should not be directed at Minors and no channel of marketing should be used if more than 15% of its audience is Minors. This restriction includes, but is not necessarily limited to, TV, Internet, print and radio advertising (see below), as well as event marketing or sponsorships. For regional (local, city or

state) advertising, content must be directed to persons who meet or exceed the specific region's age of majority.

- No Improper Use of Trademarks or Trade Dress. Triton Distribution and Vapetasia's Products will not utilize names, imagery or designs that intentionally mimic, play upon, invoke or otherwise infringe upon existing trademarks, trade names or trade dress, particularly if they are associated with products that are, or were, primarily marketed to Minors. Triton Distribution and Vapetasia fully support all local, state and federal age restrictions applicable to its products.
- Age-Gating to 21. Vapetasia's website age-gates to prevent visitors under the age of 21 from gaining access.
- Minimum Age. Company shall ensure that all models used in advertising and social media for Company products are, and appear to be, at least 35 years old.
- Online sales are restricted to adults following age verification through independent, third-party agencies using public records databases. Currently, Vapetasia uses the third-party age verification software AgeChecker.net.
- Triton Distribution and Vapetasia requires all U.S. retailers of its products, including online retailers, to comply with FDA's requirements and guidance for retailers, as applicable. Specifically, all U.S. retailers of Company products should:

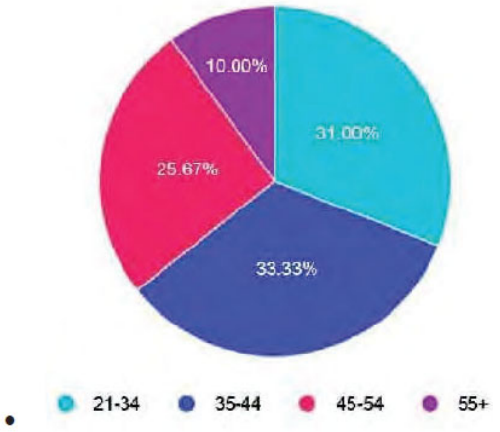
    1. Implement strict age verification policies requiring that their employees verify

photo IDs of anyone who is 27 years of age or younger before such persons enter the establishment. Minors should not be permitted into any retail establishment that sells Triton Distribution and Vapetasia's Products.

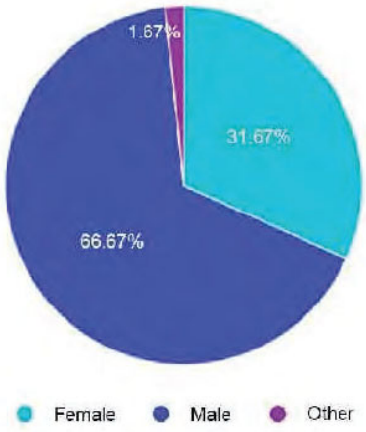
2. Immediately respond to and implement remedies to address any FDA or other government authority warning letters or enforcement actions.
3. Display signage indicating that (a) "Minors Are Not Allowed on Premises" and (b) "Products are Not for Sale to Minors" or (c) "Underage Sale Prohibited."
4. Comply with FDA's guidance documents for retailers, including Tobacco Retailer Training Programs and FDA Retailer Training and Enforcement.
5. Restrict sales of Products to adults through either direct verification of government issued photo ID upon delivery of product or through the use of online age verification technologies provided by independent third-party agencies using public records databases.

Consumer Demographics

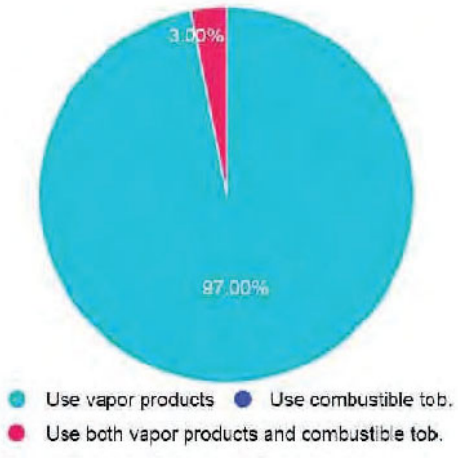
- Demographic Characteristics of Vapetasia LLC
  - Age - 21-34 31% | 35-44 33.33% | 45-54 25.67% | 55+ 10%



- Gender—Female 31.67% | Male 66.67% | Other 1.67%



- Tobacco use status—Use only Blueberry Parfait Salt E-liquid 97% | Use both Blueberry Parfait Salt E-liquid and combustible tobacco products 3% | Use only combustible tobacco products 0%



Labeling—See Module 1

Sample:

Vapetasia does not use cartoon characters in its advertisements or marketing or any other particularly youth-attractive packages. Vapetasia will not design the packaging of it's vape products in a manner that could be confused by children as a food or drink. Vapetasia will not use other's intellectual property (including, but not limited to, mascots, animals, characters, or commercially recognizable toys or candy) to market our products.

- Vapetasia, LLC will use child resistant packaging and appropriate flow restrictors in compliance with the Child Nicotine Poisoning Prevention Act of 2015.
- Vapetasia, LLC will not make smoking cessation claims (i.e. Quit smoking now).
- Vapetasia, LLC will not make health-related claims (i.e. Healthier than smoking, Less risk of disease/cancer, No Secondhand Effects).
- Vapetasia, LLC will not make modified risk claims (i.e. Less harmful than tobacco, No Smoke, Diacetyl Free).

2.4.3 DISTRIBUTOR AND RETAILER GUIDELINES

Distributor and retailers must contractually agree with Triton Distribution's Distributor and Retailer Sales Limitations and Requirements in 2.4 Target Market for Tobacco Product folder.

Triton Distribution enters into written agreements with its distributors and retailers to do business, which include indemnification provisions. An example of the Distributor and Retailer Agreement can be found in 2.4 Target Market for Tobacco Product folder. Triton Distribution requires down-stream distributors and retail-

ers to comply with these requirements and establishes and enforces contractual penalties for such contracted parties. All Triton Distribution distributors and retailers are obligated to maintain compliance with all applicable Federal, State and Local laws and regulations, as applicable, including:

- The Federal Food, Drug and Cosmetic Act (FD&C Act), as amended by the Family Smoking Prevention and Tobacco Control Act (TCA)
- State and Local Health Codes
- State and Local Licensing and Tax Programs
- State and Local Laws and Regulations Applicable to Distribution of Triton Distribution and Vapetasia's Products, including state laws regarding state minimum purchase age for Blueberry Parfait Salt E-liquid and delivery sales requirements, California's Stop Tobacco Access to Kids Enforcement Act (STAKE Act), and California Safe Drinking Water and Toxic Enforcement Act of 1986 (Proposition 65)

Specifically, Triton Distribution requires its downstream distributors and retailers to sell only to people who are old enough (at least 21 years old throughout the U.S.), confirmed using valid ID for any face-to-face transactions with consumers. If sales are made online, distributors and retailers must use adequate age-verification technology to prevent underage access to the website and to prevent underage sales through the Internet. Triton Distribution's policy requires it to screen retailers in advance of establishing or renewing distribution agreements based on the strength of the retailers' age verification policies. As part of its continu-

ous compliance monitoring efforts, Triton Distribution requires retailers to develop an internal compliance check program, such as a mystery shopper program.

Vapetasia Blueberry Parfait Salt E-Liquid is not advertised via any channels (including print, television, social media, earned media, or similar) except on Triton Distribution's website and in adult-only brick-and-mortar facilities. Advertisement on Triton Distribution and Vapetasia's website will be restricted to consumers who have registered to gain access. Advertising in brick-and-mortar facilities will be limited only to those areas of the facility that cannot be seen from outside the facility.

2.4.4 QUANTITY LIMITS FOR ONLINE SALES

As a measure to prevent youth access, Triton Distribution has measures in place to monitor for any "bulk" purchases, and to limit transactions to the quantity a reasonable consumer would be expected to purchase during a single transaction. This includes limiting orders to ten (10) 30ml bottles or ten (10) 100ml bottles per transaction. Downstream distributors or retailers are required to follow Triton Distribution's transaction limit. Furthermore, downstream distributors and retailers should implement a process to flag repeated transactions within a seven (7) day period and investigate those transactions for suspicious activity.

2.4.5 PREVENTING YOUTH ACCESS TO COMPANY PRODUCTS

Triton Distribution product sales comply with Tobacco 21 across the country.

Triton Distribution product sales must comply with all county, city, and state age restriction laws for e-vapor product purchase. Vapetasia Blueberry Parfait Salt E-Liquid online product sales are restricted to adults age verified by independent third-party companies using public records databases. For all sales made in person to individuals under the age of 27 years old, age verify by means of government issued photographic identification containing the bearer's date of birth. Compliance with California's Stop Tobacco Access to Kids Enforcement Act ("STAKE Act") for sales in California. California law prohibits the sale of tobacco products to anyone under the age of 21 (Cal. Bus. & Prof. Code § 22958(a)) and the STAKE Act imposes mandatory steps that online distributors and sellers of tobacco products are required to follow to verify that a purchaser of these items is 21 years of age or older. The steps required under the STAKE ACT are:

- Attempt to match the name, address and date of birth provided by the customer to information contained in records in a database of individuals whose age has been verified to be 21 years or older by reference to an appropriate database of government records kept by the distributor, a direct marketing firm, or any other entity.
- Verify that the billing address on the check or credit card offered for payment by the purchaser matches the address listed in the database.
- If unable to verify that the purchaser is 21 years of age through the above, require the customer or recipient to submit an age-verification kit consisting of an attestation signed by the customer that

he or she is 21 years of age or older and a copy of a valid form of government identification.

- Verify that the billing address on the check or credit card provided by the consumer matches the address listed in the form of government identification.
- For credit card transactions, submit information to each credit card company so that the words "tobacco product" may be printed in the purchaser's credit card statement.
- Regardless of the form of payment, prior to shipping the tobacco product to a California customer, make a telephone call after 5 p.m. to the purchaser or recipient confirming the order. The call may be a recorded message left on voicemail.
- Deliver only to the purchaser or recipient's verified billing address on the check or credit card used for payment. Delivery to a post office box address is prohibited.

While FDA has not yet provided specific requirements on how companies should verify the age of those purchasing such products over the internet, Triton Distribution and Vapetasia is fully compliant with the most stringent state laws in this regard, using third-party age verification service Age-Checker.net, including California's Stop Tobacco Access to Kids Enforcement Act (STAKE Act). California law prohibits the sale of tobacco products to anyone under the age of 21 (Cal. Bus. & Prof. Code § 22958(a)) and the STAKE Act imposes mandatory steps that online distributors and sellers of tobacco products are required to follow to verify that a purchaser of these items is 21 years of age or older.

2.4.6 SOCIAL MEDIA

Neither Triton Distribution nor Vapetasia does not endorse or permit use of youthful-looking models or any advertising of our product that conveys the appearance of marketing to underage consumers. Vapetasia does not currently utilize social media influencers. The current online marketing strategy is restricted to product photos and other forms of responsible marketing. In addition, Vapetasia Blueberry Parfait Salt E-Liquid labels have always warned against underage use.

2.5 NONCLINICAL OVERVIEW

2.5.1 HARMFUL AND POTENTIALLY HARMFUL CONSTITUENTS

Triton Distribution utilized a third-party lab, Adact, to assess the levels of certain HPHCs in the vapor produced using Vapetasia Blueberry Parfait Salt. The results were used to calculate a worst-case potential exposure to consumers. The exposure model data was then utilized to compare relative exposure to HPHCs from Vapetasia's e-liquids to HPHC results from traditional tobacco products (e.g., cigarettes) and recently authorized heated tobacco products (i.e., IQOS), a modified risk tobacco product, obtained from direct testing as well as published literature. Finally, we conducted toxicological evaluations of those compounds expected to have higher exposures resulting from e-liquid use than from traditional tobacco use. In sum, for the reasons set forth below, the HPHC results support that the marketing of these products is appropriate for the protection of the public health when used by adult smokers and tobacco users. The full HPHC reports and data, as well as the analysis of same, is included in the memorandum in Module 4. In sum, the HPHC results for the

Vapetasia Blueberry Parfait Salt e-liquid support that the marketing of the product is APPH when used by adult smokers and tobacco users. See Module 4, Section 4.2.

For full reports of all information, including the substantive information required by section 1114.27(b)(1)(ii), all favorable and unfavorable studies; published or known to Triton Distribution, or which should reasonably be known, concerning investigations, including nonclinical and human subject studies. ***See* TPMF No. MF0000403; *see also* State of the Science Report.**

2.5.2 VAPETASIA BLUEBERRY PARFAIT SALT E-LIQUID TOXICOLOGICAL PROFILE AND HEALTH EFFECTS

FDA's Proposed Rule indicates that while applicants are not required to conduct toxicological analyses, an application should contain substantive information regarding either the health risks of the new tobacco product or a comparison of the health risks compared to other tobacco product categories, in order to be accepted for review (Proposed Rule § 1114.27(b)(1)(ii)). Accordingly, although specific toxicological testing of Vapetasia Blueberry Parfait Salt E-Liquid was not conducted due to time and financial constraints for Triton Distribution, a comprehensive review of the published literature contained in TPMF No. MF0000403, the State of the Science[14] report and the subject matter databases (found in Module 2 Section 2.9) was performed to provide information on the health effects of ENDS

[14] Full citations for references cited in the summaries below can be found in the Cardno ChemRisk: ENDS & E-Liquid—State of the Science; January 13, 2020 report.

similar to Vapetasia Blueberry Parfait Salt E-Liquid. Module 2 Section 2.6 contains a detailed summary of the health effects of ENDS based on published *in vitro*, *in vivo* and human health studies that assessed the impact on cardiovascular disease, respiratory effects, inflammation, cancer, reproductive health, biomarkers, and pharmacokinetics.

2.6 INDIVIDUAL HEALTH OVERVIEW

As required by Proposed Rule § 1114.7((k)(2)) this application contains full reports of all information, including the substantive information required by section 1114.27(b)(1)(ii), all favorable and unfavorable studies; published or known to Triton Distribution, or which should reasonably be known, concerning investigations, including nonclinical and human subject studies. The PMTA Coalition's comprehensive review of the scientific literature covering the areas directly applicable to establishing the population effect of the Vapetasia Blueberry Parfait Salt E-Liquid, including the published studies and articles, as well as detailed subject matter databases, related to the topic areas identified in FDA's PMTA Guidance: *in vivo* and *in vitro* toxicology (*e.g.*, carcinogenesis, genotoxicity, mutagenicity, reactive oxygen species, inflammation, cytotoxicity, respiratory health, cardiovascular disease, and reproductive and developmental toxicity), clinical health, abuse liability and pharmacokinetics, trends in usage and factors that influence ENDS usage (*e.g.*, susceptibility, consumer perception, initiation, cessation, transition), topography, human factors, biomarkers of harm and exposure, and population health (*e.g.*, FDA's PATH study). The peer-reviewed literature included and summarized in TPMF No. MF0000403, the State of the Science report and the subject matter databases offer important in-

sight into the impact of ENDS like Vapetasia Blueberry Parfait Salt E-Liquid on public health.[15] As part of this review, hundreds of published articles have evaluated some aspect of ENDS on public health.

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* * * use and maintaining comparability between cross-sectional studies (Amato et al. 2016; Levy et al., 2019). A 2019 review of nationally representative tobacco surveillance surveys and largescale on-line surveys of adults found that study design, populations surveyed, implementation of the survey and use definitions dramatically influenced the overall findings resulting in

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[15] In the PMTA Guidance for Industry (FDA, 2019), the US Food and Drug Administration (FDA) recommends that applicants demonstrate a comprehensive understanding of the currently available published literature including, but not limited to consumer perceptions and intentions, initiation and cessation, product use patterns, human factors, abuse liability, biomarkers of potential harm (BOPH), biomarkers of exposure (BOE), and toxicological and clinical evaluations of health outcomes. The purpose of the literature review is to evaluate the current state of the science on ENDS and their impact on public health for the US population, including both users and non-users of these products. The methods and findings from the National Academy of Sciences, Engineering, and Medicine (NASEM) report "Public Health Consequences of E-Cigarettes" (NASEM, 2018) were used as the foundation of the current literature review.

As described in Appendix B of the NASEM report, the committee performed numerous literature searches across six databases: PubMed, Scopus, Web of Science, PsycINFO (ProQuest), MEDLINE (Ovid), and Embase (Ovid). There was no limit to the start date of the search and the last search was completed August 31, 2017. Topics of interest included health effects of e-cigarettes; e-cigarettes and transitions to and from combustible tobacco cigarette * * *

variability of prevalence estimates across surveys and over time (Levy et al., 2019).

2.6.3.3.4 REASONS FOR USE

Similar to youth and young adults, adult prevalence of ENDS use is dependent upon how usage is defined. Adults report using ENDS to aid with cessation of combustible cigarettes, because they are available in appealing flavors, and because they do not smell like combustible cigarettes.

2.6.3.3.5 USE OF FLAVORS

Vapetasia Blueberry Parfait Salt E-Liquid s included in this submission include the following flavors: Blueberry Parfait Salt. In the case of ENDS e-liquid, all products are flavored. The primary ingredients in e-liquid, propylene glycol and glycerin, are completely flavorless, and the concentration of nicotine used in the products imparts no flavor.

Flavored e-liquids are an essential part of the ENDS category, and the existence of a market for these products is proof that they are valued by consumers. When it comes to evaluating the role of flavors in facilitating or constraining positive population health outcomes from e-cigarettes, relevant questions include the impact of flavors on adult smokers who transition (or not) to e-cigarettes, as well as their role in preventing relapse in former smokers who vape. Negative population health outcomes are likely if flavors play a specific causal role in youth vaping initiation *and* subsequently cause these youth to progress to smoking. Importantly, there is no evidentiary basis to popular concerns that flavors are solely intended to attract or appeal to youth. To date, there is no evidence that flavors cause youth smoking.

NASEM did not specifically evaluate e-liquid flavorings in their 2018 report, but noted that "[m]ost e-cigarette products are available in desirable flavors and have other characteristics that generate aerosols with a unique profile of pleasurable sensory stimuli due to the taste, sights, smells, and airway sensations, that (like combustible tobacco cigarettes) could have synergistic effects with nicotine on dependence risk" (NASEM, 2018, p. 257).

The complexities around flavored e-cigarette use are likely not well captured by the PATH study. In particular, the survey is ill-equipped to answer the question of whether specific flavors exert a specific effect on youth use of e-cigarettes, as the survey groups non-tobacco flavors into a limited number of very broad categories.

Numerous published studies also highlight the important role of flavored ENDS for harm reduction. Recently, for example, the *Harm Reduction Journal* published the results of an extensive online survey which assessed the first and current vapor product flavors used by a non-probabilistic sample of 20,836 adult frequent vapers in the U.S. (Russell, McKeganey, Dickson, & Nides, 2018). That survey found that cigarette smokers who switch to Blueberry Parfait Salt E-liquid are doing so increasingly with a variety of fruit and other non-tobacco flavors. Another recent survey of more than 69,000 adult vapers found that just 16% identified tobacco, menthol, or mint as flavors they used most often; the vast majority preferred fruit and dessert flavors (Farsalinos, 2018).

In addition, a large sample on-line survey by Landry et al (2019) found that among adults 18 and over, non-

tobacco flavors were preferred by most current e-cigarette users and that flavors were a common reason for adult e-cigarette initiation (Landry, et al., 2019).

Research addressing the specific role of flavors in vaping effectiveness is in its infancy, however, a recent study by Voos et al offers some important insight (Voos, et al., 2020). This study examined changes in nicotine delivery, puff topography, and satisfaction associated with different flavors among regular smokers who were non-regular e-cigarette users. This is the first study to do so among daily cigarette smokers, allowing the researchers to explore the complex interaction between flavors and study outcomes. The study suggested that there was enhanced nicotine delivery from cherry and menthol flavors. The study also demonstrated that different flavors can result in varying nicotine delivery when used by daily cigarette smokers. When examining puff topography during the controlled puffing session, puff duration was significantly longer with use of an e-cigarette compared to a combustible cigarette for all flavors, which is consistent with previous research (Hua et al. 2013; Hammond et al. 2005). In general, participants rated all flavors as less harmful to their health than a combustible cigarette, and participants did not view flavors as differing in perceived risk. Interestingly, there was a significant difference in perceived harm of flavors between participants who smoke mentholated versus non-mentholated combustible cigarettes. Participants who smoke mentholated cigarettes viewed flavors as significantly less harmful to their health compared with participants who used non-mentholated cigarettes.

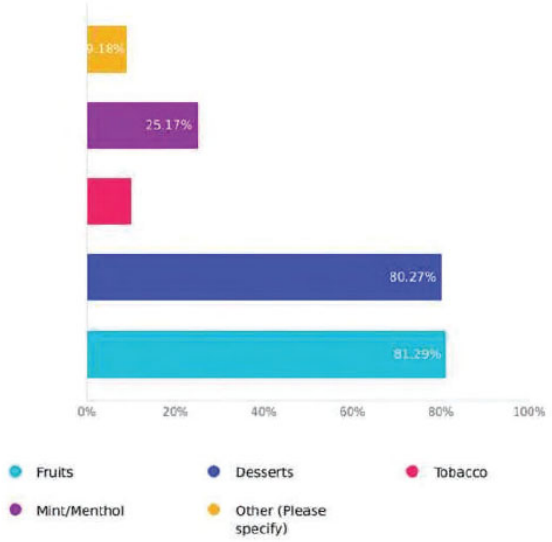
But a new analysis of data from the 2019 NYTS, released in December 2019 by the CDC and the FDA,

shows that flavors are definitely not the main reason kids vape (Wang T.W., Gentzke A.S., M.R., & et, 2019). The number one reason was curiosity. Among the teens who were surveyed, 56.1% listed curiosity as a reason they tried e-cigarettes. That was more than double the next most popular reason, "friend or family member used them" (23.9%). "They are available in flavors, such as mint, candy, fruit, or chocolate" came in third at 22.3%. The teens could choose multiple answers, which makes flavors' weak showing even more apparent.

With respect to Vapetasia Blueberry Parfait Salt E-Liquid survey results (Module 5) demonstrate that it is and will continue to be used by existing adult users. With respect to flavors, the consumer survey results demonstrated only 19% of respondents chose Tobacco when asked "What type of electronic nicotine product flavors do you tend to prefer and use? Select all that apply:" with answer choices of "I prefer to use unflavored electronic nicotine products", "Mint or Menthol", "Tobacco", "Coffee-based", "Fruity", "Dessert", "Candy", "Other", or "Not applicable, I do not use electronic nicotine products". Results are shown in Figure 2.6-1.

Figure 2.6-1 Representation to question "What type of electronic nicotine product flavors do you tend to prefer and use? Select all that apply:" (Question 30)

Fig 2.61



2.6.3.3.6 NATIONAL YOUTH TOBACCO SURVEY AND THE YOUTH "EPIDEMIC"

NYTS, MTF (Monitoring the Future Survey), YRBS (Youth Risk Behavior Survey), and PATH, surveys collect data from which estimates of e-cigarette use prevalence among youth in the U.S. can be drawn. Recently, there has been a great deal of concern regarding point-prevalence increases in past 30-day use in cross-sectional data from NYTS and MTF surveys. These increases have been characterized as an "epidemic" with preliminary analyses of 2018 MTF and NYTS data speculating the point prevalence increase can be explained by "new" vaping devices such as JUUL (Miech et al 2018, Cullen et al 2018).

Tobacco control experts have questioned the appropriateness of this label (West, et al) (Fairchild, Healton, Curran, Abrams, & Bayer, 2019). Indeed, two recent detailed analyses of NYTS data do not support claims that the point prevalence increase between 2017 and 2018 constitutes an epidemic of youth nicotine addiction (West et al, Glasser et al). West et al (2019) sought to examine evidence from the NYTS being used to support new regulatory initiatives, and found a "gaping chasm between the vision of an epidemic of e-cigarette use threatening to engulf a new generation in nicotine addiction and the reality of the evidence contained in the NYTS." Specifically, their analysis found that "[i]n bringing forward proposals for regulatory action, the FDA did not place e- cigarette use in the context of use of other tobacco products." Their analysis of NYTS data from 2018 and earlier years shows a strong association between lifetime history of use of tobacco products and use of e-cigarettes: in 2018, high school students who had smoked more than 100 cigarettes in their lifetime were some 27 times more likely to have used e-cigarettes in the past 30 days than students who had never tried any tobacco product. Use of e-cigarettes on 20 or more days in the past month was seen in only 1.0% of those who had never tried any tobacco product in 2018. West, et al. also concluded that the NYTS fails to give evidence at the population level that e-cigarettes are acting as a gateway to smoking in American adolescents. Importantly, the study by West et al sought to measure whether youth were becoming addicted to nicotine through vaping and found little evidence of substantial nicotine addiction attributable to the use of e-cigarettes.

A later peer reviewed study by Glasser et al of the 2018 NYTS data supported the conclusions in the West et all study (Glasser, Johnson, Johnson, & Niaura, 2020). Although vaping increased among U.S. youth in 2018 over 2017, the increases are characterized by patterns of low p30d vaping frequency and high poly-product use, and a low prevalence of vaping among more frequent but tobacco naïve vapers. These results underscore the importance of including the full context of use patterns. The majority of vapers (60.0% - 88.9% by use frequency) were concurrent p30d or ever tobacco users. About 4% of students were tobacco naïve and vaped in the p30d, but few (0.4%) vaped regularly on 20 or more days. The authors emphasized that reporting youth vaping data with frequency and tobacco product co-use will give public health decision makers the best possible information to protect public health.

FDA announced in mid-2018 that early NYTS data revealed a sudden shift in past 30-day e-cigarette use among high schoolers, which had jumped to 20.8% (Cullen, et al., 2018). Prior to that, the percentage of high schoolers who used an e-cigarette at least once in the past 30 days had started to decease, falling from 15.8% in 2016 to 11.0% in 2017, before surging in 2018 (Jamal, Gentzke, Hu, & et al., 2017).

Analysis of Federal survey data reveals that while underage vaping increased in 2018, it does not confirm an epidemic. Nearly 70% of the students who vape—but do not smoke—used ENDS five days or less during that 30-day period. This pattern corresponds with "party" or "weekend" social vaping. While this is not an activity that we encourage by any means, it is much different from regular, daily consumption. What is more, the majority of current vapers surveyed were *not* "never

smokers" before they started vaping. In the underage nonsmoking group, 57% of frequent vapers had previously smoked. The percentages were even higher among legal-age and current smokers (Rodu, 2019). While illegal underage vaping should always be discouraged, the fact that so many of the young people experimenting with ENDS had already smoked cigarettes challenges FDA's assertion that ENDS use threatens to hook an entire generation of kids into a lifetime of addiction.

More recent analysis of the 2018 NYTS demonstrate that the survey does not support claims of a new epidemic of nicotine addiction stemming from use of e-cigarettes, nor concerns that declines in youth tobacco addiction stand to be reversed after years of progress. Rather, among current e-cigarette users who had never tried tobacco products, responses consistently pointed to minimal dependence (West & Brown, 2019).

Meanwhile, it must be noted that while vaping has become more common, the cigarette smoking rate continues to fall to all-time lows among all age groups, including teenagers. According to the CDC, in 2017, 7.6% of high school students reported smoking cigarettes in the past 30 days—a decrease from 15.8% in 2011.[21] Among young adults aged 18-24, 10.4% smoked cigarettes in 2017—21% decline since 2016, when the young adult smoking rate was 13.1%, and a 45% decrease since 2011,

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[21] *Youth and Tobacco Use*, CENTER FOR DISEASE CONTROL AND PREVENTION (Feb. 28, 2019), https://www.cdc.gov/tobacco/data_statistics/fact_sheets/youth_data/tobacco_use/index.htm.

when 18.9% young adults smoked.[22] Among adults (older than 24), only 14% reported smoking "every day" or "someday"—the lowest level ever recorded, down from 15.5% in 2016, and a 67% decrease since 1965 (Wang & et al., 2018).

In addition, a recent study has found that youngsters who use e-cigarettes are less likely to use cigarettes in the future compared to those who use other tobacco products (Shahab, Beard, & Brown, 2020). The researchers called this the "gateway effect" (moving on the full-fledged smoking) and determined that it is small among those who begin tobacco product use with e-cigarettes. Data come from 78 265 adolescents in the NYTS (2014-2017), of whom 38,630 provided information about the first tobacco product they had used in 2014/15. Ever, past 30-day, and established (30 day use and 100+ lifetime cigarette) cigarette smoking was compared in adolescents who first used an e-cigarette (exposure group), a non-cigarette combustible (CT) or other non-combustible tobacco (NT) product (behavioral controls), and propensity score matched adolescents without initial e-cigarette use (synthetic controls). The study found that, relative to behavioral controls, adolescents who tried e-cigarettes first were less likely to have ever smoked cigarettes, to be past 30-day, or NT initiators, or be established cigarette smokers, or NT initiators. E-cigarette initiators were also less likely than synthetic controls (without initial e-cigarette use) to have ever smoked cigarettes, be past 30 day, or be established cigarette smokers. In sum, the study

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[22] *Young adult smoking rate drops to 10%*, TRUTH INITIATIVE INSPIRING TOBACCO-FREE LIVES (Sept. 5, 2018), https://truthinitiative.org/news/young-adult-smoking-rate-drops-10.

found that less than 1% of U.S. adolescents who use e-cigarettes first were established cigarette smokers. They were less likely to be smokers than adolescents who tried other combustible or non-combustible tobacco products first and propensity score matched adolescents without initial e-cigarette use.

2.6.3.3.7 CONSUMER PERCEPTION

Research that evaluates consumer perceptions of e-cigarettes, including the perceived risks and benefits, can provide valuable insight into understanding why consumers initiate and use these products. Perceived benefits of e-cigarettes can include, but are not limited to, expected and actual positive experiences (*e.g.*, taste), social acceptance, avoidance of smoking restrictions, a cool and/or IEB novel product, an effective smoking cessation aid, and safety for bystanders. Perceived risks can include, but are not limited to, addictiveness and negative health risks associated with tobacco product use and can be measured in absolute terms or relative to another tobacco product.

E-cigarettes constitute a broad class of products that vary by device type (*e.g.*, cigalikes, rechargeable, tanks and mods), e-liquid composition (*e.g.*, additives, nicotine), and flavors (*e.g.*, tobacco, menthol, fruit). NASEM (2018) reported that the perceptions of potential risks and benefits of e-cigarette use "vary widely," but the report did not review perceptions of e-cigarettes and the relation to e-cigarette use in detail (NASEM, 2018).

With respect to Vapetasia Blueberry Parfait Salt E-Liquid, survey results (Module 5) demonstrate that Vapetasia Blueberry Parfait Salt E-Liquid is, and will continue to be, used by existing adult users. For this population, the fact that the Vapetasia Blueberry Par-

fait Salt E-Liquid is less harmful than combustible cigarettes, as demonstrated from the test results and health effects summarized above, the continued availability of Vapetasia Blueberry Parfait Salt E-Liquid is APPH. Furthermore, as discussed above, to ensure that Vapetasia Blueberry Parfait Salt E-Liquid is not considered appealing to youth or non-smokers, Triton Distribution has implemented strict labeling and marketing restrictions (Module 2 Section 2.4).

2.6.3.3.8 TRANSITION

There are several factors associated with the use of tobacco products, and an individual's usage state (*e.g.*, non-user, e-cigarette user, dual user, smoker, etc.) may change over time. For youth, transition between states can be highly variable and individual usage states may change often.

Due to the limited time points of observation with the PATH dataset, continued evaluation of the potential for e-cigarettes to lead to combustible cigarette use are needed.

With respect to Vapetasia Blueberry Parfait Salt E-Liquid survey results (Module 5 Section 5.3) demonstrate that there is a reasonable degree of certainty that Vapetasia Blueberry Parfait Salt E-Liquid is, and will continue to be used, by existing adult users.

2.6.3.3.9 INITIATION

There is currently no conclusive evidence to support concerns that e-cigarettes are a "gateway to smoking." The current evidence suggests that there may be underlying factors that contribute to adolescent initiation of tobacco product use more generally also contribute to initiation of e-cigarettes. Considering that adolescents

who were susceptible to e-cigarettes did not have increased likelihood of combustible cigarette use, but that those who were susceptible to combustible cigarettes were more likely to use all products, e-cigarettes may present a lower health risk to those susceptible to e-cigarettes and combustible cigarettes.

Initiation of ENDS use in youth has many contributory factors: use of e-cigarettes by friends, siblings, or parents, perceptions of little to no harm, and the belief that e-cigarettes were less harmful than tobacco cigarettes, flavors, and as an alternative to combustible cigarettes. Many of these factors are similar to reasons for initiation or experimentation with combustible tobacco, alcohol, or marijuana (Ellickson et al., 2004; Hemovich et al., 2011; Tang and Orwin, 2009; Vega et al., 1993). Data is limited, due to the cross-sectional nature of available studies, to determine if initiation of e-cigarette use leads to continued, long-term use of combustible cigarettes.

With respect to Vapetasia Blueberry Parfait Salt E-Liquid survey results (Module 5 Section 5.3) demonstrate that it is and will continue to be used by existing adult users. Triton Distribution does not sell or market to minors and does not have any youth initiation concerns.

2.6.3.3.10 CESSATION

Smoking combustible cigarettes is questionably detrimental to both personal health and public health. As ENDS are a newer product, there is no consensus on their contributions to the health of individuals who vape or to the general public. The most important consideration in deciding whether e-cigarettes produce a public health benefit is determining if using e-cigarettes is an

effective cessation method for combustible cigarette use. In fact, the 2018 NASEM report states that the central research question around the possible public health benefit of e-cigarettes is "Do e-cigarettes help smokers quit smoking combustible tobacco cigarettes?" (NASEM, 2018, p. 541). However, the authors also recognize that to determine the scope of possible public health benefits, researchers must not only answer the question of "How effective are e-cigarettes as a cessation method?", but also "What proportion of smokers use e-cigarettes in their quitting attempt?" as well.

There have been several studies that longitudinally evaluated PATH study data to assess the likelihood of cigarette cessation and/or reduction associated with e-cigarette use among current cigarette smokers, and the likelihood of smokers using e-cigarettes as opposed to another cessation aid to quit smoking (Benmarhnia et al., 2018; Berry et al., 2019; Kalkhoran et al., 2019; Rodu and Plurphanswat, 2017; Verplaetse et al., 2018; Watkins et al., 2018b).

The NASEM (2018) report provided a conceptual framework for smoking cessation transitions and defined smoking cessation as "stopping all combustible tobacco product use" (NASEM, 2018). The committee evaluated whether e-cigarettes help smokers quit smoking combustible tobacco products by investigating the effectiveness of e-cigarettes as a cessation aid compared to no treatment, placebo treatment, or FDA-approved therapies.

NASEM (2018) concluded that based on limited evidence from the RCTs and the overall body of observational evidence, there was limited evidence that e-cigarettes may be an effective smoking cessation aid, and

noted that further evaluation through RCTs with more treatment comparisons were necessary. The NASEM (2018) report noted that observational data is limited because it does not account for the specific e-cigarette product, the pattern of use, and user characteristics, including an interest in quitting, which are all factors that may affect how effective an e-cigarette is as a cessation aid. Further, observational data largely reflect dual or intermittent use of e-cigarettes, which the report noted, "may not contribute to cessation success any more than does poor adherence to FDA-approved cessation medications" (NASEM, 2018).

The most compelling evidence on e-cigarettes and cessation to date is an RCT by Hajek et al., (2019), who evaluated the 1-year efficacy of refillable e-cigarettes as compared with NRT, both combined with behavioral support, in adults seeking to quit smoking. The authors concluded that refillable e-cigarettes had greater efficacy than NRT for smoking cessation (Hajek et al., 2019).

As more data becomes available, the evidence is supporting the benefits of ENDS for cessation of combustible cigarettes. As products improve, e-cigarettes are becoming more satisfying and the most recent research is showing a positive benefit of ENDS on public health with more and more adults using them as an alternative to combustible cigarettes.

With respect to Vapetasia Blueberry Parfait Salt E-Liquid, because of financial and time restraints, advertising/marketing and label consumer perception studies will not be completed. However, the survey results (Module 5 Section 5.3), along with the enclosed labeling and marketing plans (Module 2 Section 2.4),

demonstrate that Vapetasia Blueberry Parfait Salt E-Liquid is and will continue to be used by existing adult users. More specifically, pursuant to the marketing plan, advertising and marketing are strictly limited. The label/labeling will be viewed by experienced ENDS users and current customers, or in a setting where prospective users can easily become educated (*e.g.*, vape shops). In addition to the study by Hajek et al, several high-quality analyses of population data suggest that regular vaping can aid in smoking cessation.

Kalkorhan PATH analysis (Kalkhoran, Chang, & Rigotti, Electronic Cigarette Use and Cigarette Abstinence Over Two Years among U.S. Smokers in the Population Assessment of Tobacco and Health Study, 2019)

A recent nationally-representative longitudinal cohort study of U.S. adult cigarette smokers study by Kalkhoran et al (2019) found that "daily e-cigarette use, compared to no e-cigarette use, was associated with a 77% increased odds of prolonged cigarette smoking abstinence over the subsequent two years. Non-daily e-cigarette use was not associated with subsequent abstinence." They analyzed data from adult cigarette smokers in Waves 1 to 3 of the PATH study, with an aim of determining the association between e-cigarette use and subsequent smoking cessation in a nationally representative cohort of U.S. smokers followed for two years. They found that "Among Wave 1 cigarette smokers, 3.6% were current daily e-cigarette users, 18% were current non-daily e-cigarette users, and 78% reported no current e-cigarette use. In multivariable adjusted analyses, daily e-cigarette use at Wave 1 was associated with higher odds of prolonged cigarette smoking abstinence at Waves 2 and 3 compared to non-use of e- cigarettes (11% vs 6%, AOR 1.77, 95% CI 1.08-2.89).

Non-daily e-cigarette use was not associated with prolonged cigarette smoking abstinence. Among Wave 1 daily e-cigarette users who were abstinent from cigarette smoking at Wave 3, 63% were using e-cigarettes at Wave 3."

The Kalkhoran et al 2019 study is significant as it is the first nationally representative cohort study presenting showing an association between e-cigarette use and sustained combustible cigarette abstinence rates over two years. Their results are consistent with the hypothesis that regular use of e-cigarettes (as opposed to infrequent use) can help smokers to stop smoking combustible cigarettes. While infrequent use is not associated with prolonged quitting, it is noteworthy that in England, dual use of e-cigarettes has been found to increase quit attempts (Jackson, Shahab, West, & Brown, 2020).

National and multinational survey data from Europe support the findings of Kalkhoran et al. (Farsalinos, et al., 2019). A study of vape shops in Greece (Diamantopoulou et al 2019) found that "[t]he strongest correlate of being a former smoker was daily e-cigarette use." (Diamantopoulou, Barbouni, Merakou, & Lagiou, 2019) The same study found "[v]apeshops customers in Greece are mainly current and former smokers with the majority of them having quit smoking. E-cigarette use by never smokers is rare and none of them subsequently initiate smoking."

2.6.4 CONCLUSION OF SYSTEMATIC LITERATURE SEARCH

The current literature indicates that ENDS may be a safer alternative source of nicotine compared to combustible cigarettes. Common themes have been observed across health effect studies and behavioral

health outcome studies. Topography and pharmacokinetic findings are influenced by many factors. Nevertheless, studies to date show that nicotine delivery from ENDS may be comparable to combustible tobacco but the dependency to these products, especially the earlier generations, is found to be less than that of combustible cigarettes. Overall, the collective body of literature reviewed shows an overall benefit of ENDS use on population health in comparison to combustible cigarettes.

2.7 POPULATION HEALTH OVERVIEW

EFFECT ON POPULATION AS A WHOLE (21 C.F.R. § 1114.7(L))

Based on the literature, the presence of ENDS on the market was initiated to provide an alternative source of nicotine to individuals seeking ways to stop smoking. In addition to the intended consequences of adults switching from combustible tobacco to e-cigarettes, an evaluation of the population must also account for the unintended consequences of youth initiating use of these products. A proper assessment will include multiple time points because usage states and transitions states are fluid can change over time (Bachand and Sulsky, 2013) (Figure 2.7-1).

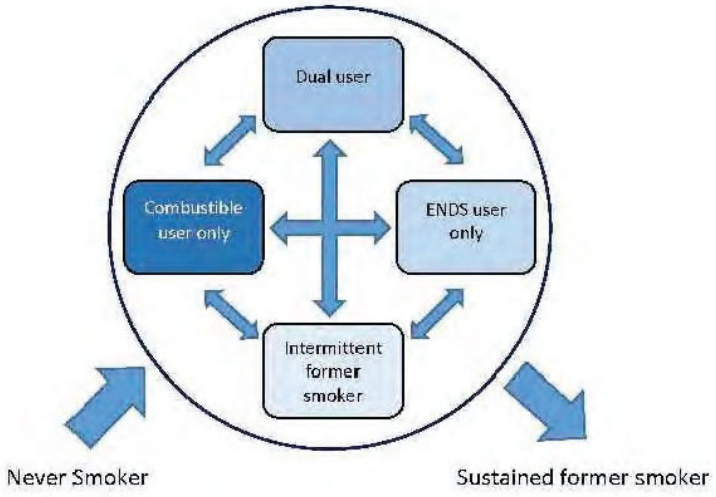

Figure 2.7-1 Usage states and potential transitions states for combustible cigarette smokers and ENDS users

At any point in time, every person in a population is in one of the above "smoking states". An individual's smoking state can transition over the course of their life. A cross-sectional study * * *

* * * * *

6.6 INDOOR AIR QUALITY AND SECONDHAND EXPOSURES

In addition to perceived harm and addictiveness of self-use and exposure to ENDS, several studies have evaluated adults perceived harm of secondhand exposure to ENDS (Nahhas et al., 2019; Nguyen et al., 2017; Tan et al., 2015). Universally, any study that compared combustible cigarettes and e-cigarettes found greatly increased effects on the indoor air quality and bystander concentrations from combustible cigarettes. Individual VOC elevations are likely a strong function of the liquid

formulation, and no studies included in our review provided detailed ingredients lists for the liquid.

A more recent study (Palmisani 2019) also found that, inside an enclosed environment with natural ventilation conditions and low air exchange rate, the potential exposure of the passive bystanders in terms of ultrafine particles (UFPs) number concentration was significantly higher in the case of a single tobacco cigarette consumption compared with 20-min e-cig vaping, regardless of the e-liquid used.

6.7 POPULATION MODELING AND ANALYSIS

Although a full population model and analysis was not conducted, a comprehensive review of the six currently published articles evaluating the total impact of ENDS on population health as a function of all-cause mortality (Vugrin, et al., 2015; Soneji, Sung, Primack, Pierce, & Sargent, 2018; Kalkhoran & Glantz, 2015; Levy, 2018; Levy, 2017; Warner & Mendez, 2018) was performed (State of the Science). A summary of the Population Health Overview can be found in Module 2 Section 2.7.

6.8 POSTMARKET SURVEILLANCE AND POSTMARKET STUDY PLAN OR PROTOCOL

The Tobacco Control Act amended the Food, Drug, and Cosmetic Act (FD&C Act) to provide FDA authority for not only premarket review and authorization, but also post market surveillance (PMS). After a successful premarket tobacco product application (PMTA) submission resulting in marketing authorization, under section 910(f) of the FD&C Act, FDA can require manufacturers to establish and maintain certain post market records and make certain post market reports to FDA.

Post market surveillance is a requirement for modified risk tobacco product (MRTP) applications and not necessarily required for PMTAs; however, we note that recent FDA new tobacco product marketing authorizations have included post market reporting requirements. In these recent marketing orders, FDA states that these requirements are intended to help ensure that the marketing of the new tobacco products will continue to be appropriate for the protection of the public health, taking into account initiation among non-users, particularly youth.

Triton Distribution is committed to fully complying with all applicable laws and regulations governing its Blueberry Parfait Salt E-Liquid product. Vapetasia's Blueberry Parfait Salt E-Liquid products are intended for adults only and should not be intentionally marketed to, sold to, or used by minors. Triton Distribution strongly supports efforts to prevent minors' access to its e-liquid products and embraces marketing restrictions to limit youth access.

To achieve this goal, Triton Distribution will rely on PMS as an important tool to ensure that the marketing of the new tobacco products will continue to be appropriate for the protection of the public health—particularly taking into account initiation among non-users and youth. Vapetasia's proposed post market surveillance program consist of a combination of passive and active surveillance activities that are designed to monitor the effects of the new tobacco product on individual and population health, and to allow for identification and collection of unanticipated and undesired events related to the tobacco product once the product is introduced to the market.

Health and Safety Monitoring

Triton Distribution has established a dedicated safety database as the central repository for all health- and safety-related data and reports captured from all data sources.

Triton Distribution will collect unverified adverse events (AEs) and consumer health complaints. This would include all serious or unexpected adverse experiences reported to Vapetasia, including a listing and analysis. Investigations should include the nature, frequency, and potential risk factors.

Triton Distribution will conduct Poison Control Center Surveillance. Triton Distribution plans to register the candidate products with the American Association of Poison Control Centers to monitor the types and frequencies of spontaneous AEs reported in the National Poison Data System database.

Literature Review

Triton Distribution will provide a status report of any ongoing studies and a summary of completed studies about the product conducted by, or on behalf of, the Vapetasia.

Sales and Distribution Assessment

Triton Distribution will monitor sales and distribution of the new product, including data on product purchasers.

Triton Distribution will provide a summary of sales and distribution of the new product, including total U.S. sales reported in dollars, units, and volume with breakdowns by U.S. census region, major retail markets, and channels in which the product is sold to the extent pos-

sible (*e.g.*, convenience stores, food and drug markets, big box retailers, digital platforms, tobacco specialty shops)

Data on product purchasers will include any data collected about new purchasers, those who have switched tobacco products, and/or multiple product users. The results would be broken down by purchaser demographics to the extent possible (e.g., age, gender, and race/ethnicity, geographic location) and must not include personally identifiable information.

Evaluation of Youth Access Restrictions

Triton Distribution will establish a phone number and e-mail reporting form to collect unverified under-age access complaints and report these complaints to FDA for further follow-up. Where appropriate, Triton Distribution will request an inspection of the verified Triton Distribution E-Liquid retailer.

We will provide a summary of the implementation and effectiveness of Triton Distribution policies and procedures regarding age verification and restrictions on youth access.

We will also provide a summary of the implementation and effectiveness of Triton Distribution policies and procedures regarding verification of the age and identity of purchasers of the products.

Recordkeeping and Reporting

Triton Distribution plans to meet certain recordkeeping and reporting obligations to the Agency as required.

6.9 POPULATION HEALTH LITERATURE REVIEW

As required by Proposed Rule § 1114.7(k)(2)), the peer-reviewed literature included and summarized in TPMF No MF00040, the Initiation, Cessation, Transition, Biomarkers, Usage, Topography and Abuse Liability subject matter databases the State of the Science report offer important insight into the impact of ENDS like Vapetasia Blueberry Parfait Salt E-Liquid on public health. As part of this review, hundreds of published articles have evaluated some aspect of ENDS on public health. Topics of interest include health effects, human factors, initiation, cessation, transition, biomarkers of harm and exposure, topography, pharmacokinetics, and abuse liability. A summary of the Population Health Overview can be found in Module 2 Section 2.7.

6.10 OTHER DOCUMENTS RELATING TO RESEARCH

All documents relating to research are provided in Module 2 Section 2.9. There are no additional documents to provide.

MODULE 7: ENVIRONMENTAL IMPACT

7.1 NATIONAL ENVIRONMENTAL POLICY ACT OF 1969

FDA's regulations implementing the National Environmental Policy Act of 1969 require that "[a]ll applications [. . .] requesting agency action require the submission of an environmental assessment (EA) or a claim of categorical exclusion." *See* 21 C.F.R. § 25.15(a). Currently, there are no categorical exclusions in place for tobacco products.[45] Per 21 C.F.R. § 25.15, the EAs ad-

[45] Per 21 CFR 25.35, the only categorical exclusion that applies to PMTA submissions is an issuance of an order that a new tobacco

dress the relevant environmental issues and contain sufficient information to enable the Agency to determine whether the proposed action may significantly affect the quality of the human environment. The attached EAs evaluate the potential environmental impacts (*e.g.*, greenhouse gas emissions) from the use and disposal of the products and packaging. Accordingly, the marketing of this product (these products) complies with 21 CFR Part 25. For the basis of our conclusion, see the following Environmental Assessments listed in Table 7.1-1:

Table 7.1-1 Environmental Assessment listings included in the PMTA submission.

Product Identification Number	Product Name	PMTA Location
Vapetasia Blueberry Parfait Salt 30ml 24mg	Vapetasia Blueberry Parfait Salt 30ml 24mg/ml	Module 7
Vapetasia Blueberry Parfait Salt 30ml 48mg	Vapetasia Blueberry Parfait Salt 30ml 48mg/ml	Module 7

product may not be introduced or delivered for introduction into interstate commerce (i.e., a denial of a marketing authorization after FDA's review of a PMTA).

2.6.3.2.1 PATH DATA ON ABUSE LIABILITY

The PATH study includes items to capture withdrawal symptoms, which include feeling angry, anxious, depressed, difficulty concentrating, eating more, insomnia and restlessness. Two studies were identified to compare the potential for dependence (Liu et al., 2017) and withdrawal (Hughes and Callas, 2018) between e-cigarettes and combustible cigarette. In general, the findings studies that have evaluated PATH data indicate lower potential for addiction and withdrawal from the use of e-cigarettes when compared to combustible cigarette products.

A more recent study also assessed abuse liability and addiction using PATH data (Shiffman & Sembower (n.d.), Dependence on E-Cigarettes and Cigarettes in a Cross-Sectional Study of US Adults). The study assessed dependence among current and former adult e-cigarette users on cigarettes and e-cigarettes, compared with dependence on cigarettes. Using cross-sectional data from the PATH study from 2013-2016, psychometrically assessed dependence was compared for cigarettes and e-cigarettes among current and former exclusive and dual users of the products, and among e-cigarette users who had and had not recently stopped smoking. The study pulled form a population-based representative sample of U.S. adults and used a 16-item scale assessing tobacco dependence (on a 1-5 scale), previously validated for assessment and comparison of dependence on varied tobacco products, including cigarettes and e-cigarettes. Among current users, dependence on e-cigarettes was significantly lower than dependence on cigarettes, in within-subjects comparisons among dual users of both e-cigarettes and cigarettes, and in separate groups of e-cigarette users and ciga-

rette smokers, and among both daily and non-daily users of each product. Among former users, residual symptoms were significantly lower for e-cigarettes than cigarettes, both among former dual users and among users of one product. In sum, the researchers found that use of e-cigarettes appears to be consistently associated with lower nicotine dependence than cigarette smoking.

This authors further noted that the PATH data for the first time allowed direct comparison of dependence on cigarettes and on e-cigarettes on the same metric in a large representative population sample. The recent study compared dependence on cigarettes and dependence on e-cigarettes across a variety of populations, varying by current and historical product use. ***In every comparison, e-cigarette use was associated with significantly less dependence than cigarette smoking***. While few e-cigarette users scored as highly dependent on e-cigarettes, most smokers were highly dependent on cigarettes. Most striking was the consistency of the findings across multiple subpopulations of users, whether stratified by daily vs. non-daily use, or by current or former usage, and whether analyzed within-persons or between persons. ***In every case, dependence was significantly lower on e-cigarettes than on cigarettes, usually meaningfully so***.

2.6.3.2.2 ABUSE LIABILITY IN THE LITERATURE

The NASEM committee drew three conclusions from the evaluation of the literature regarding ENDS and abuse liability: individuals who use ENDS have symptoms of dependence, the risk and severity of dependence is higher from combustible tobacco cigarette than

for ENDS, and product characteristics influence the risk and severity of ENDS dependence.

January 13, 2020

ENDS & E-Liquid—State of the Science

Prepared for Authorized Companies—Confidential

Date January 13, 2020

Prepared by:

Cardno ChemRisk
20 Stanwix Street
Suite 505
Pittsburgh, PA 15222

* * * * *

CI: 0.99-5.14, respectively). Dai & Hao (Dai and Hao, 2016) investigated the association of e-cigarette flavors and the intention to quit smoking in 1,338 respondents from the 2014 National Youth Tobacco Survey. Smokers who also used flavored e-cigarettes had statistically significantly lower odds of planning to quit smoking (OR = 0.6; 95% CI: 0.4-0.9) compared to smokers who did not use e-cigarettes. This association was not statistically significant for users of non-flavored e-cigarettes (OR = 0.9; 95% CI: 0.6-1.4).

In conclusion, there is not enough evidence from well-designed studies to determine whether e-cigarette flavors aid in smoking cessation. The observational cohort studies had mixed results and the cross-sectional studies that addressed flavor did not do so in a manner to directly answer this secondary research question.

6.3.1.5 Conclusions

There have been many new studies on the relationship between using e-cigarettes and smoking cessation since the NASEM report in 2018. However, the state of the science on the issue has only progressed marginally. The subject is complicated by personal factors (i.e. motivation to quit, patterns of cigarette and ENDS use), product factors (i.e. device type, nicotine strength, flavors), and study design factors (i.e. experimental vs. observational, definition of cessation, follow-up time) that all play a role in the intricacy of this association.

There is additional evidence that e-cigarettes can aid in smoking cessation. This is largely supported by the strongest randomized controlled trial published since the 2018 NASEM report (Hajek et al., 2018).

There is also some evidence from randomized controlled trials that users of e-cigarettes reduce their consumption of combustible cigarettes. The most current available nationally representative data shows that close to 25% of people who attempt to quit smoking use e-cigarettes in their cessation efforts. Their popularity as a cessation method is higher in young smokers and lower in older smokers. However, no conclusions can be made about the association of e-cigarettes flavors and smoking cessation as there have not been enough studies investigating this research question.

U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov

April 12, 2021

ACCEPTANCE

Wages & White Lion Investments LLC DBA Triton Distribution
Attention: Jon Rose, General Manager
789 N. Grove Rd, Suite 111
Richardson, Texas 75081

FDA Submission Tracking Numbers (STNs): PM0003790-PD1 through PM0003790-PD281, see Appendix A

Dear Mr. Rose:

We accept your PMTAs[1] for the tobacco products identified in Appendix A. Note that attributes in Appendix A may display converted values.

Your PMTAs will move forward in the review process. FDA may request to conduct inspections, which may include manufacturing inspections and clinical and nonclinical research inspections, to verify the information submitted in your PMTAs. The results of these inspections may also be used to verify the information submit-

[1] Premarket Tobacco Product Application (PMTA) submitted under section 910 of the Federal Food, Drug, and Cosmetic Act (FD&C Act)

ted in any additional applications that reference the same manufacturing and research information. To ensure that the appropriate records and personnel will be available during the inspections, FDA will notify the point(s) of contact identified prior to the inspection start date.

We will notify you if samples are required for independent testing and verification. If samples are required, you will be notified by letter of the number of samples required and the laboratory address where samples must be received. All requested samples should be received by the laboratory identified in the letter within 14 calendar days of the request.

If you have any questions, please contact Sammrawit Girma, Regulatory Health Project Manager, at (240) 701-9097 or Sammrawit.Girma@fda.hhs.gov.

Sincerely,

Digitally signed by Ryan Nguy -S
Date: 2021.04.12 08:31:40 -04'00'

Ryan Nguy
Team Supervisor, Regulatory Health Project Manager
Division of Regulatory Project Management
Office of Science
Center for Tobacco Products

Enclosures (if provided electronically, the Appendix is not included in physical mail):

Appendix A—New Tobacco Products Subject of This Letter

Appendix A[2,3]
New Tobacco Products Subject of This Letter

Common Attributes	
Submission date	September 09, 2020
Receipt date	September 09, 2020
Applicant	Wages & White Lion Investments LLC dba Triton Distribution
Product manufacturer	Wages & White Lion Investments LLC dba Triton Distribution
Product category	ENDS(VAPES)
Product subcategory	ENDS Component
Attributes	New Tobacco Product
STN	PM0003790
Static Product ID	PD1
Product Name	Boiler Maker Anvil 0mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Anvil
Additional Property	Nicotine: 0mg/mL, PG/VG Ratio: 70/30, E-Liquid

[2] Properties to uniquely identify the new tobacco products were provided by the applicant as of the date of this letter, and not confirmed by FDA. Upon scientific review, the unique identification may be revised.

[3] Brand/sub-brand or other commercial name used in commercial distribution

	Volumes: 30mL, 100mL
STN	PM0003790
Static Product ID	PD2
Product Name	Boiler Maker Anvil 3mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Anvil
Additional Property	Nicotine: 3mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 30mL, 100mL
STN	PM0003790
Static Product ID	PD3
Product Name	Boiler Maker Anvil 6mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Anvil
Additional Property	Nicotine: 6mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 30mL, 100mL
STN	PM0003790
Static Product ID	PD4
Product Name	Boiler Maker Anvil 12mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Anvil

Additional Property	Nicotine: 12mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 30mL, 100mL
STN	PM0003790
Static Product ID	PD5
Product Name	Boiler Maker Anvil 18mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Anvil
Additional Property	Nicotine: 18mg/mL, PG/VG Ratio: 70/30, E-Liquid Volume: 30mL
STN	PM0003790
Static Product ID	PD6
Product Name	Boiler Maker Chisel 0mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Chisel
Additional Property	Nicotine: 0mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 30mL, 100mL
STN	PM0003790
Static Product ID	PD7
Product Name	Boiler Maker Chisel 3mg
Package Type	Bottle
Package Quantity	1 Bottle

Characterizing Flavor	Chisel
Additional Property	Nicotine: 3mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 30mL, 100mL
STN	PM0003790
Static Product ID	PD8
Product Name	Boiler Maker Chisel 6mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Chisel
Additional Property	Nicotine: 6mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 30mL, 100mL
STN	PM0003790
Static Product ID	PD9
Product Name	Boiler Maker Chisel 12mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Chisel
Additional Property	Nicotine: 12mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 30mL, 100mL
STN	PM0003790
Static Product ID	PD10
Product Name	Boiler Maker Chisel 18mg
Package Type	Bottle

Package Quantity	1 Bottle
Characterizing Flavor	Chisel
Additional Property	Nicotine: 18mg/mL, PG/VG Ratio: 70/30, E-Liquid Volume: 30mL
STN	PM0003790
Static Product ID	PD11
Product Name	Boiler Maker Forge 0mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Forge
Additional Property	Nicotine: 0mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 30mL, 100mL
STN	PM0003790
Static Product ID	PD12
Product Name	Boiler Maker Forge 3mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Forge
Additional Property	Nicotine: 3mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 30mL, 100mL
STN	PM0003790
Static Product ID	PD13
Product Name	Boiler Maker Forge 6mg

Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Forge
Additional Property	Nicotine: 6mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 30mL, 100mL
STN	PM0003790
Static Product ID	PD14
Product Name	Boiler Maker Forge 12mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Forge
Additional Property	Nicotine: 12mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 30mL, 100mL
STN	PM0003790
Static Product ID	PD15
Product Name	Boiler Maker Forge 18mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Forge
Additional Property	Nicotine: 18mg/mL, PG/VG Ratio: 70/30, E-Liquid Volume: 30mL
STN	PM0003790
Static Product ID	PD16

Product Name	Boiler Maker Hammer 0mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Hammer
Additional Property	Nicotine: 0mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 30mL, 100mL
STN	PM0003790
Static Product ID	PD17
Product Name	Boiler Maker Hammer 3mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Hammer
Additional Property	Nicotine: 3mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 30mL, 100mL
STN	PM0003790
Static Product ID	PD18
Product Name	Boiler Maker Hammer 6mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Hammer
Additional Property	Nicotine: 6mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 30mL, 100mL
STN	PM0003790

Static Product ID	PD19
Product Name	Boiler Maker Hammer 12mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Hammer
Additional Property	Nicotine: 12mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 30mL, 100mL
STN	PM0003790
Static Product ID	PD20
Product Name	Boiler Maker Hammer 18mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Hammer
Additional Property	Nicotine: 18mg/mL, PG/VG Ratio: 70/30, E-Liquid Volume: 30mL
STN	PM0003790
Static Product ID	PD21
Product Name	Boiler Maker Rivet 0mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Rivet
Additional Property	Nicotine: 0mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 30mL, 100mL

STN	PM0003790
Static Product ID	PD22
Product Name	Boiler Maker Rivet 3mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Rivet
Additional Property	Nicotine: 3mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 30mL, 100mL
STN	PM0003790
Static Product ID	PD23
Product Name	Boiler Maker Rivet 6mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Rivet
Additional Property	Nicotine: 6mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 30mL, 100mL
STN	PM0003790
Static Product ID	PD24
Product Name	Boiler Maker Rivet 12mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Rivet
Additional Property	Nicotine: 12mg/mL, PG/VG Ratio: 70/30, E-Liquid

	Volumes: 30mL, 100mL
STN	PM0003790
Static Product ID	PD25
Product Name	Boiler Maker Rivet 18mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Rivet
Additional Property	Nicotine: 18mg/mL, PG/VG Ratio: 70/30, E-Liquid Volume: 30mL
STN	PM0003790
Static Product ID	PD26
Product Name	Boiler Maker Vise 0mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Vise
Additional Property	Nicotine: 0mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 30mL, 100mL
STN	PM0003790
Static Product ID	PD27
Product Name	Boiler Maker Vise 3mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Vise
Additional Property	Nicotine: 3mg/mL, PG/VG

	Ratio: 70/30, E-Liquid Volumes: 30mL, 100mL
STN	PM0003790
Static Product ID	PD28
Product Name	Boiler Maker Vise 6mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Vise
Additional Property	Nicotine: 6mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 30mL, 100mL
STN	PM0003790
Static Product ID	PD29
Product Name	Boiler Maker Vise 12mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Vise
Additional Property	Nicotine: 12mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 30mL, 100mL
STN	PM0003790
Static Product ID	PD30
Product Name	Boiler Maker Vise 18mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Vise

Additional Property	Nicotine: 18mg/mL, PG/VG Ratio: 70/30, E-Liquid Volume: 30mL
STN	PM0003790
Static Product ID	PD31
Product Name	Chewy Clouds Big Granny 0mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Big Granny
Additional Property	Nicotine: 0mg/mL, PG/VG Ratio: 70/30, E-Liquid Volume: 60mL
STN	PM0003790
Static Product ID	PD32
Product Name	Chewy Clouds Big Granny 3mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Big Granny
Additional Property	Nicotine: 3mg/mL, PG/VG Ratio: 70/30, E-Liquid Volume: 60mL
STN	PM0003790
Static Product ID	PD33
Product Name	Chewy Clouds Big Granny 6mg

Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Big Granny
Additional Property	Nicotine: 6mg/mL, PG/VG Ratio: 70/30, E-Liquid Volume: 60mL
STN	PM0003790
Static Product ID	PD34
Product Name	Chewy Clouds Red Wedge 0mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Red Wedge
Additional Property	Nicotine: 0mg/mL, PG/VG Ratio: 70/30, E-Liquid Volume: 60mL
STN	PM0003790
Static Product ID	PD35
Product Name	Chewy Clouds Red Wedge 3mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Red Wedge
Additional Property	Nicotine: 3mg/mL, PG/VG Ratio: 70/30, E-Liquid Volume: 60mL
STN	PM0003790

Static Product ID	PD36
Product Name	Chewy Clouds Red Wedge 6mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Red Wedge
Additional Property	Nicotine: 6mg/mL, PG/VG Ratio: 70/30, E-Liquid Volume: 60mL
STN	PM0003790
Static Product ID	PD37
Product Name	Chewy Clouds Sour Grape 0mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Sour Grape
Additional Property	Nicotine: 0mg/mL, PG/VG Ratio: 70/30, E-Liquid Volume: 60mL
STN	PM0003790
Static Product ID	PD38
Product Name	Chewy Clouds Sour Grape 3mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Sour Grape
Additional Property	Nicotine: 3mg/mL, PG/VG

	Ratio: 70/30, E-Liquid Volume: 60mL
STN	PM0003790
Static Product ID	PD39
Product Name	Chewy Clouds Sour Grape 6mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Sour Grape
Additional Property	Nicotine: 6mg/mL, PG/VG Ratio: 70/30, E-Liquid Volume: 60mL
STN	PM0003790
Static Product ID	PD40
Product Name	Cloud Company Arise 0mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Arise
Additional Property	Nicotine: 0mg/mL, PG/VG Ratio: 85/15, E-Liquid Volume: 120mL
STN	PM0003790
Static Product ID	PD41
Product Name	Cloud Company Arise 1.5mg
Package Type	Bottle
Package Quantity	1 Bottle

Characterizing Flavor	Arise
Additional Property	Nicotine: 1.5mg/mL, PG/VG Ratio: 85/15, E-Liquid Volume: 120mL
STN	PM0003790
Static Product ID	PD42
Product Name	Cloud Company Arise 3mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Arise
Additional Property	Nicotine: 3mg/mL, PG/VG Ratio: 85/15, E-Liquid Volume: 120mL
STN	PM0003790
Static Product ID	PD43
Product Name	Cloud Company Arise 6mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Arise
Additional Property	Nicotine: 6mg/mL, PG/VG Ratio: 85/15, E-Liquid Volume: 120mL
STN	PM0003790
Static Product ID	PD44
Product Name	Cloud Company Arise 9mg
Package Type	Bottle

Package Quantity	1 Bottle
Characterizing Flavor	Arise
Additional Property	Nicotine: 9mg/mL, PG/VG Ratio: 85/15, E-Liquid Volume: 120mL
STN	PM0003790
Static Product ID	PD45
Product Name	Cloud Company Billow 0mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Billow
Additional Property	Nicotine: 0mg/mL, PG/VG Ratio: 80/20, E-Liquid Volume: 120mL
STN	PM0003790
Static Product ID	PD46
Product Name	Cloud Company Billow 1.5mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Billow
Additional Property	Nicotine: 1.5mg/mL, PG/VG Ratio: 80/20, E-Liquid Volume: 120mL
STN	PM0003790
Static Product ID	PD47
Product Name	Cloud Company Billow 3mg

Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Billow
Additional Property	Nicotine: 3mg/mL, PG/VG Ratio: 80/20, E-Liquid Volume: 120mL
STN	PM0003790
Static Product ID	PD48
Product Name	Cloud Company Billow 6mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Billow
Additional Property	Nicotine: 6mg/mL, PG/VG Ratio: 80/20, E-Liquid Volume: 120mL
STN	PM0003790
Static Product ID	PD49
Product Name	Cloud Company Billow 9mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Billow
Additional Property	Nicotine: 9mg/mL, PG/VG Ratio: 80/20, E-Liquid Volume: 120mL
STN	PM0003790
Static Product ID	PD50

Product Name	Cloud Company Kumo 0mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Kumo
Additional Property	Nicotine: 0mg/mL, PG/VG Ratio: 80/20, E-Liquid Volume: 120mL
STN	PM0003790
Static Product ID	PD51
Product Name	Cloud Company Kumo 1.5mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Kumo
Additional Property	Nicotine: 1.5mg/mL, PG/VG Ratio: 80/20, E-Liquid Volume: 120mL
STN	PM0003790
Static Product ID	PD52
Product Name	Cloud Company Kumo 3mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Kumo
Additional Property	Nicotine: 3mg/mL, PG/VG Ratio: 80/20, E-Liquid Volume: 120mL
STN	PM0003790

Static Product ID	PD53
Product Name	Cloud Company Kumo 6mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Kumo
Additional Property	Nicotine: 6mg/mL, PG/VG Ratio: 80/20, E-Liquid Volume: 120mL
STN	PM0003790
Static Product ID	PD54
Product Name	Cloud Company Kumo 9mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Kumo
Additional Property	Nicotine: 9mg/mL, PG/VG Ratio: 80/20, E-Liquid Volume: 120mL
STN	PM0003790
Static Product ID	PD55
Product Name	Cloud Company Revel 0mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Revel
Additional Property	Nicotine: 0mg/mL, PG/VG Ratio: 80/20, E-Liquid Volume: 120mL

STN	PM0003790
Static Product ID	PD56
Product Name	Cloud Company Revel 1.5mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Revel
Additional Property	Nicotine: 1.5mg/mL, PG/VG Ratio: 80/20, E-Liquid Volume: 120mL
STN	PM0003790
Static Product ID	PD57
Product Name	Cloud Company Revel 3mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Revel
Additional Property	Nicotine: 3mg/mL, PG/VG Ratio: 80/20, E-Liquid Volume: 120mL
STN	PM0003790
Static Product ID	PD58
Product Name	Cloud Company Revel 6mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Revel
Additional Property	Nicotine: 6mg/mL, PG/VG Ratio: 80/20, E-Liquid

	Volume: 120mL
STN	PM0003790
Static Product ID	PD59
Product Name	Cloud Company Revel 9mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Revel
Additional Property	Nicotine: 9mg/mL, PG/VG Ratio: 80/20, E-Liquid Volume: 120mL
STN	PM0003790
Static Product ID	PD60
Product Name	Cloud Company Sky 0mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Sky
Additional Property	Nicotine: 0mg/mL, PG/VG Ratio: 85/15, E-Liquid Volume: 120mL
STN	PM0003790
Static Product ID	PD61
Product Name	Cloud Company Sky 1.5mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Sky
Additional Property	Nicotine: 1.5mg/mL, PG/VG

	Ratio: 85/15, E-Liquid Volume: 120mL
STN	PM0003790
Static Product ID	PD62
Product Name	Cloud Company Sky 3mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Sky
Additional Property	Nicotine: 3mg/mL, PG/VG Ratio: 85/15, E-Liquid Volume: 120mL
STN	PM0003790
Static Product ID	PD63
Product Name	Cloud Company Sky 6mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Sky
Additional Property	Nicotine: 6mg/mL, PG/VG Ratio: 85/15, E-Liquid Volume: 120mL
STN	PM0003790
Static Product ID	PD64
Product Name	Cloud Company Sky 9mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Sky

Additional Property	Nicotine: 9mg/mL, PG/VG Ratio: 85/15, E-Liquid Volume: 120mL
STN	PM0003790
Static Product ID	PD65
Product Name	Cloud Science Alpha 0mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Alpha
Additional Property	Nicotine: 0mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD66
Product Name	Cloud Science Alpha 3mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Alpha
Additional Property	Nicotine: 3mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD67
Product Name	Cloud Science Alpha 6mg
Package Type	Bottle
Package Quantity	1 Bottle

Characterizing Flavor	Alpha
Additional Property	Nicotine: 6mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD68
Product Name	Cloud Science Alpha 12mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Alpha
Additional Property	Nicotine: 12mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD69
Product Name	Cloud Science Delta 0mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Delta
Additional Property	Nicotine: 0mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD70
Product Name	Cloud Science Delta 3mg
Package Type	Bottle

Package Quantity	1 Bottle
Characterizing Flavor	Delta
Additional Property	Nicotine: 3mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD71
Product Name	Cloud Science Delta 6mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Delta
Additional Property	Nicotine: 6mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD72
Product Name	Cloud Science Delta 12mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Delta
Additional Property	Nicotine: 12mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD73
Product Name	Cloud Science Epsilon 0mg

Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Epsilon
Additional Property	Nicotine: 0mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD74
Product Name	Cloud Science Epsilon 3mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Epsilon
Additional Property	Nicotine: 3mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD75
Product Name	Cloud Science Epsilon 6mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Epsilon
Additional Property	Nicotine: 6mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD76

Product Name	Cloud Science Epsilon 12mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Epsilon
Additional Property	Nicotine: 12mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD77
Product Name	Cloud Science Epsilon-m 0mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Epsilon-m
Additional Property	Nicotine: 0mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD78
Product Name	Cloud Science Epsilon-m 3mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Epsilon-m
Additional Property	Nicotine: 3mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL

STN	PM0003790
Static Product ID	PD79
Product Name	Cloud Science Epsilon-m 6mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Epsilon-m
Additional Property	Nicotine: 6mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD80
Product Name	Cloud Science Epsilon-m 12mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Epsilon-m
Additional Property	Nicotine: 12mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD81
Product Name	Cloud Science Gamma 0mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Gamma

Additional Property	Nicotine: 0mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD82
Product Name	Cloud Science Gamma 3mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Gamma
Additional Property	Nicotine: 3mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD83
Product Name	Cloud Science Gamma 6mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Gamma
Additional Property	Nicotine: 6mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD84
Product Name	Cloud Science Gamma 12mg
Package Type	Bottle
Package Quantity	1 Bottle

Characterizing Flavor	Gamma
Additional Property	Nicotine: 12mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD85
Product Name	Cloud Science Gamma-m 0mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Gamma-m
Additional Property	Nicotine: 0mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD86
Product Name	Cloud Science Gamma-m 3mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Gamma-m
Additional Property	Nicotine: 3mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD87
Product Name	Cloud Science Gamma-m

	6mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Gamma-m
Additional Property	Nicotine: 6mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD88
Product Name	Cloud Science Gamma-m 12mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Gamma-m
Additional Property	Nicotine: 12mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD89
Product Name	Cold Fusion Galil 1 0mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Galil 1
Additional Property	Nicotine: 0mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790

Static Product ID	PD90
Product Name	Cold Fusion Galil 2 3mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Galil 2
Additional Property	Nicotine: 3mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD91
Product Name	Cold Fusion Galil 3 6mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Galil 3
Additional Property	Nicotine: 6mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD92
Product Name	Cold Fusion Galil 4 12mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Galil 4
Additional Property	Nicotine: 12mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL

STN	PM0003790
Static Product ID	PD93
Product Name	Cold Fusion Galil 5 18mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Galil 5
Additional Property	Nicotine: 18mg/mL, PG/VG Ratio: 70/30, E-Liquid Volume: 60mL
STN	PM0003790
Static Product ID	PD94
Product Name	Cold Fusion Hiss Tank 1 0mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Hiss Tank 1
Additional Property	Nicotine: 0mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD95
Product Name	Cold Fusion Hiss Tank 2 3mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Hiss Tank 2

Additional Property	Nicotine: 3mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD96
Product Name	Cold Fusion Hiss Tank 3 6mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Hiss Tank 3
Additional Property	Nicotine: 6mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD97
Product Name	Cold Fusion Hiss Tank 4 12mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Hiss Tank 4
Additional Property	Nicotine: 12mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD98
Product Name	Cold Fusion Hiss Tank 5 18mg

Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Hiss Tank 5
Additional Property	Nicotine: 18mg/mL, PG/VG Ratio: 70/30, E-Liquid Volume: 60mL
STN	PM0003790
Static Product ID	PD99
Product Name	Cold Fusion Shock & Awe 1 0mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Shock & Awe 1
Additional Property	Nicotine: 0mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD100
Product Name	Cold Fusion Shock & Awe 2 3mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Shock & Awe 2
Additional Property	Nicotine: 3mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790

Static Product ID	PD101
Product Name	Cold Fusion Shock & Awe 3 6mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Shock & Awe 3
Additional Property	Nicotine: 6mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD102
Product Name	Cold Fusion Shock & Awe 4 12mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Shock & Awe 4
Additional Property	Nicotine: 12mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD103
Product Name	Cold Fusion Shock & Awe 5 18mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Shock & Awe 5
Additional Property	Nicotine: 18mg/mL, PG/VG

	Ratio: 70/30, E-Liquid Volume: 60mL
STN	PM0003790
Static Product ID	PD104
Product Name	Cold Fusion Warning Shot 1 0mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Warning Shot 1
Additional Property	Nicotine: 0mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD105
Product Name	Cold Fusion Warning Shot 3 3mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Warning Shot 3
Additional Property	Nicotine: 3mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD106
Product Name	Cold Fusion Warning Shot 3 6mg
Package Type	Bottle

Package Quantity	1 Bottle
Characterizing Flavor	Warning Shot 3
Additional Property	Nicotine: 6mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD107
Product Name	Cold Fusion Warning Shot 4 12mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Warning Shot 4
Additional Property	Nicotine: 12mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD108
Product Name	Cold Fusion Warning Shot 5 18mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Warning Shot 5
Additional Property	Nicotine: 18mg/mL, PG/VG Ratio: 70/30, E-Liquid Volume: 60mL
STN	PM0003790
Static Product ID	PD109

Product Name	Jimmy The Juice Man Crème Brulee 0mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Crème Brulee
Additional Property	Nicotine: 0mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD110
Product Name	Jimmy The Juice Man Crème Brulee 3mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Crème Brulee
Additional Property	Nicotine: 3mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD111
Product Name	Jimmy The Juice Man Crème Brulee 6mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Crème Brulee
Additional Property	Nicotine: 6mg/mL, PG/VG Ratio: 70/30, E-Liquid

	Volumes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD112
Product Name	Jimmy The Juice Man Crème Brulee 12mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Crème Brulee
Additional Property	Nicotine: 12mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD113
Product Name	Jimmy The Juice Man Crème Brulee 18mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Crème Brulee
Additional Property	Nicotine: 18mg/mL, PG/VG Ratio: 70/30, E-Liquid Volume: 60mL
STN	PM0003790
Static Product ID	PD114
Product Name	Jimmy The Juice Man Peachy Strawberry 0mg
Package Type	Bottle
Package Quantity	1 Bottle

Characterizing Flavor	Peachy Strawberry
Additional Property	Nicotine: 0mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD115
Product Name	Jimmy The Juice Man Peachy Strawberry 1.5mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Peachy Strawberry
Additional Property	Nicotine: 1.5mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD116
Product Name	Jimmy The Juice Man Peachy Strawberry 3mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Peachy Strawberry
Additional Property	Nicotine: 3mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD117
Product Name	Jimmy The Juice Man

	Peachy Strawberry 6mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Peachy Strawberry
Additional Property	Nicotine: 6mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD118
Product Name	Jimmy The Juice Man Peachy Strawberry 12mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Peachy Strawberry
Additional Property	Nicotine: 12mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD119
Product Name	Jimmy The Juice Man Peachy Strawberry 18mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Peachy Strawberry
Additional Property	Nicotine: 18mg/mL, PG/VG Ratio: 70/30, E-Liquid Volume: 60mL

STN	PM0003790
Static Product ID	PD120
Product Name	Jimmy The Juice Man Raspberry French 0mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Raspberry French
Additional Property	Nicotine: 0mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD121
Product Name	Jimmy The Juice Man Raspberry French 3mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Raspberry French
Additional Property	Nicotine: 3mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD122
Product Name	Jimmy The Juice Man Raspberry French 6mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Raspberry French

Additional Property	Nicotine: 6mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD123
Product Name	Jimmy The Juice Man Raspberry French 12mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Raspberry French
Additional Property	Nicotine: 12mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD124
Product Name	Jimmy The Juice Man Raspberry French 18mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Raspberry French
Additional Property	Nicotine: 18mg/mL, PG/VG Ratio: 70/30, E-Liquid Volume: 60mL
STN	PM0003790
Static Product ID	PD125
Product Name	Jimmy The Juice Man Shurb 0mg

Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Shurb
Additional Property	Nicotine: 0mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD126
Product Name	Jimmy The Juice Man Shurb 3mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Shurb
Additional Property	Nicotine: 3mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD127
Product Name	Jimmy The Juice Man Shurb 6mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Shurb
Additional Property	Nicotine: 6mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790

Static Product ID	PD128
Product Name	Jimmy The Juice Man Shurb 12mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Shurb
Additional Property	Nicotine: 12mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD129
Product Name	Jimmy The Juice Man Shurb 18mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Shurb
Additional Property	Nicotine: 18mg/mL, PG/VG Ratio: 70/30, E-Liquid Volume: 60mL
STN	PM0003790
Static Product ID	PD130
Product Name	Jimmy The Juice Man Strawberry Astronaut 0mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Strawberry Astronaut
Additional Property	Nicotine: 0mg/mL, PG/VG

	Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD131
Product Name	Jimmy The Juice Man Strawberry Astronaut 3mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Strawberry Astronaut
Additional Property	Nicotine: 3mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD132
Product Name	Jimmy The Juice Man Strawberry Astronaut 6mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Strawberry Astronaut
Additional Property	Nicotine: 6mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD133
Product Name	Jimmy The Juice Man Strawberry Astronaut 12mg
Package Type	Bottle

Package Quantity	1 Bottle
Characterizing Flavor	Strawberry Astronaut
Additional Property	Nicotine: 12mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD134
Product Name	Jimmy The Juice Man Strawberry Astronaut 18mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Strawberry Astronaut
Additional Property	Nicotine: 18mg/mL, PG/VG Ratio: 70/30, E-Liquid Volume: 60mL
STN	PM0003790
Static Product ID	PD135
Product Name	Kings Crown Bound By The Crown 0mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Bound By The Crown
Additional Property	Nicotine: 0mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD136

Product Name	Kings Crown Bound By The Crown 1.5mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Bound By The Crown
Additional Property	Nicotine: 1.5mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD137
Product Name	Kings Crown Bound By The Crown 3mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Bound By The Crown
Additional Property	Nicotine: 3mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD138
Product Name	Kings Crown Bound By The Crown 6mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Bound By The Crown
Additional Property	Nicotine: 6mg/mL, PG/VG Ratio: 70/30, E-Liquid

	Volumes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD139
Product Name	Kings Crown Bound By The Crown 12mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Bound By The Crown
Additional Property	Nicotine: 12mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD140
Product Name	Kings Crown Bound By The Crown 18mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Bound By The Crown
Additional Property	Nicotine: 18mg/mL, PG/VG Ratio: 70/30, E-Liquid Volume: 60mL
STN	PM0003790
Static Product ID	PD141
Product Name	Kings Crown Claim Your Throne 0mg
Package Type	Bottle
Package Quantity	1 Bottle

Characterizing Flavor	Claim Your Throne
Additional Property	Nicotine: 0mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD142
Product Name	Kings Crown Claim Your Throne 1.5mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Claim Your Throne
Additional Property	Nicotine: 1.5mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD143
Product Name	Kings Crown Claim Your Throne 3mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Claim Your Throne
Additional Property	Nicotine: 3mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD144
Product Name	Kings Crown Claim Your

	Throne 6mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Claim Your Throne
Additional Property	Nicotine: 6mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD145
Product Name	Kings Crown Claim Your Throne 12mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Claim Your Throne
Additional Property	Nicotine: 12mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD146
Product Name	Kings Crown Claim Your Throne 18mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Claim Your Throne
Additional Property	Nicotine: 18mg/mL, PG/VG Ratio: 70/30, E-Liquid Volume: 60mL

STN	PM0003790
Static Product ID	PD147
Product Name	Kings Crown Fight Your Fate 0mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Fight Your Fate
Additional Property	Nicotine: 0mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD148
Product Name	Kings Crown Fight Your Fate 1.5mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Fight Your Fate
Additional Property	Nicotine: 1.5mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD149
Product Name	Kings Crown Fight Your Fate 3mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Fight Your Fate

Additional Property	Nicotine: 1.5mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD150
Product Name	Kings Crown Fight Your Fate 6mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Fight Your Fate
Additional Property	Nicotine: 6mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD151
Product Name	Kings Crown Fight Your Fate 12mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Fight Your Fate
Additional Property	Nicotine: 12mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD152
Product Name	Kings Crown Fight Your Fate 18mg

Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Fight Your Fate
Additional Property	Nicotine: 18mg/mL, PG/VG Ratio: 70/30, E-Liquid Volume: 60mL
STN	PM0003790
Static Product ID	PD153
Product Name	Kings Crown The King 0mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	The King
Additional Property	Nicotine: 0mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD154
Product Name	Kings Crown The King 1.5mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	The King
Additional Property	Nicotine: 1.5mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD155

Product Name	Kings Crown The King 3mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	The King
Additional Property	Nicotine: 3mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD156
Product Name	Kings Crown The King 6mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	The King
Additional Property	Nicotine: 6mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD157
Product Name	Kings Crown The King 12mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	The King
Additional Property	Nicotine: 12mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790

Static Product ID	PD158
Product Name	Kings Crown The King 18mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	The King
Additional Property	Nicotine: 18mg/mL, PG/VG Ratio: 70/30, E-Liquid Volume: 60mL
STN	PM0003790
Static Product ID	PD159
Product Name	Signature Series Coco Bacco 0mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Coco Bacco
Additional Property	Nicotine: 0mg/mL, PG/VG Ratio: 70/30, E-Liquid Volume: 60mL
STN	PM0003790
Static Product ID	PD160
Product Name	Signature Series Coco Bacco 3mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Coco Bacco
Additional Property	Nicotine: 3mg/mL, PG/VG Ratio: 70/30, E-Liquid Vol-

	ume: 60mL
STN	PM0003790
Static Product ID	PD161
Product Name	Signature Series Coco Bacco 6mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Coco Bacco
Additional Property	Nicotine: 6mg/mL, PG/VG Ratio: 70/30, E-Liquid Volume: 60mL
STN	PM0003790
Static Product ID	PD162
Product Name	Signature Series Mom's Pistachio 0mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Mom's Pistachio
Additional Property	Nicotine: 0mg/mL, PG/VG Ratio: 70/30, E-Liquid Volume: 60mL
STN	PM0003790
Static Product ID	PD163
Product Name	Signature Series Mom's Pistachio 3mg
Package Type	Bottle
Package Quantity	1 Bottle

Characterizing Flavor	Mom's Pistachio
Additional Property	Nicotine: 3mg/mL, PG/VG Ratio: 70/30, E-Liquid Volume: 60mL
STN	PM0003790
Static Product ID	PD164
Product Name	Signature Series Mom's Pistachio 6mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Mom's Pistachio
Additional Property	Nicotine: 6mg/mL, PG/VG Ratio: 70/30, E-Liquid Volume: 60mL
STN	PM0003790
Static Product ID	PD165
Product Name	Signature Series Queen's Tea 0mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Queen's Tea
Additional Property	Nicotine: 0mg/mL, PG/VG Ratio: 70/30, E-Liquid Volume: 60mL
STN	PM0003790
Static Product ID	PD166
Product Name	Signature Series Queen's

	Tea 3mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Queen's Tea
Additional Property	Nicotine: 3mg/mL, PG/VG Ratio: 70/30, E-Liquid Volume: 60mL
STN	PM0003790
Static Product ID	PD167
Product Name	Signature Series Queen's Tea 6mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Queen's Tea
Additional Property	Nicotine: 6mg/mL, PG/VG Ratio: 70/30, E-Liquid Volume: 60mL
STN	PM0003790
Static Product ID	PD168
Product Name	Signature Series Toasted Strawberry 0mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Toasted Strawberry
Additional Property	Nicotine: 0mg/mL, PG/VG Ratio: 70/30, E-Liquid Volume: 60mL

STN	PM0003790
Static Product ID	PD169
Product Name	Signature Series Toasted Strawberry 3mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Toasted Strawberry
Additional Property	Nicotine: 3mg/mL, PG/VG Ratio: 70/30, E-Liquid Volume: 60mL
STN	PM0003790
Static Product ID	PD170
Product Name	Signature Series Toasted Strawberry 6mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Toasted Strawberry
Additional Property	Nicotine: 6mg/mL, PG/VG Ratio: 70/30, E-Liquid Volume: 60mL
STN	PM0003790
Static Product ID	PD171
Product Name	Suicide Bunny Bunny Season 0mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Bunny Season

Additional Property	Nicotine: 0mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD172
Product Name	Suicide Bunny Bunny Season 3mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Bunny Season
Additional Property	Nicotine: 3mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD173
Product Name	Suicide Bunny Bunny Season 6mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Bunny Season
Additional Property	Nicotine: 6mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD174
Product Name	Suicide Bunny Derailed 0mg
Package Type	Bottle

Package Quantity	1 Bottle
Characterizing Flavor	Derailed
Additional Property	Nicotine: 0mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD175
Product Name	Suicide Bunny Derailed 1.5mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Derailed
Additional Property	Nicotine: 1.5mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD176
Product Name	Suicide Bunny Derailed 3mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Derailed
Additional Property	Nicotine: 3mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD177
Product Name	Suicide Bunny Derailed 6mg

Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Derailed
Additional Property	Nicotine: 6mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD178
Product Name	Suicide Bunny Derailed 12mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Derailed
Additional Property	Nicotine: 12mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD179
Product Name	Suicide Bunny Derailed 18mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Derailed
Additional Property	Nicotine: 18mg/mL, PG/VG Ratio: 70/30, E-Liquid Volume: 60mL
STN	PM0003790

Static Product ID	PD180
Product Name	Suicide Bunny Madrina 0mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Madrina
Additional Property	Nicotine: 0mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD181
Product Name	Suicide Bunny Madrina 1.5mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Madrina
Additional Property	Nicotine: 1.5mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD182
Product Name	Suicide Bunny Madrina 3mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Madrina
Additional Property	Nicotine: 3mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL

STN	PM0003790
Static Product ID	PD183
Product Name	Suicide Bunny Madrina 6mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Madrina
Additional Property	Nicotine: 6mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD184
Product Name	Suicide Bunny Madrina 12mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Madrina
Additional Property	Nicotine: 12mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD185
Product Name	Suicide Bunny Madrina 18mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Madrina

Additional Property	Nicotine: 18mg/mL, PG/VG Ratio: 70/30, E-Liquid Volume: 60mL
STN	PM0003790
Static Product ID	PD186
Product Name	Suicide Bunny Mother's Milk and Cookies 0mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Mother's Milk and Cookies
Additional Property	Nicotine: 0mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD187
Product Name	Suicide Bunny Mother's Milk and Cookies 3mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Mother's Milk and Cookies
Additional Property	Nicotine: 3mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD188
Product Name	Suicide Bunny Mother's Milk and Cookies 6mg

Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Mother's Milk and Cookies
Additional Property	Nicotine: 6mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD189
Product Name	Suicide Bunny Mother's Milk 0mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Mother's Milk
Additional Property	Nicotine: 0mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD190
Product Name	Suicide Bunny Mother's Milk 1.5mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Mother's Milk
Additional Property	Nicotine: 1.5mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790

Static Product ID	PD191
Product Name	Suicide Bunny Mother's Milk 3mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Mother's Milk
Additional Property	Nicotine: 3mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD192
Product Name	Suicide Bunny Mother's Milk 6mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Mother's Milk
Additional Property	Nicotine: 6mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD193
Product Name	Suicide Bunny Mother's Milk 12mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Mother's Milk

Additional Property	Nicotine: 12mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD194
Product Name	Suicide Bunny Mother's Milk 18mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Mother's Milk
Additional Property	Nicotine: 18mg/mL, PG/VG Ratio: 70/30, E-Liquid Volume: 60mL
STN	PM0003790
Static Product ID	PD195
Product Name	Suicide Bunny Queen Cake 0mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Queen Cake
Additional Property	Nicotine: 0mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD196
Product Name	Suicide Bunny Queen Cake 1.5mg

Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Queen Cake
Additional Property	Nicotine: 1.5mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD197
Product Name	Suicide Bunny Queen Cake 3mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Queen Cake
Additional Property	Nicotine: 3mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD198
Product Name	Suicide Bunny Queen Cake 6mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Queen Cake
Additional Property	Nicotine: 6mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL

STN	PM0003790
Static Product ID	PD199
Product Name	Suicide Bunny Queen Cake 12mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Queen Cake
Additional Property	Nicotine: 12mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD200
Product Name	Suicide Bunny Queen Cake 18mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Queen Cake
Additional Property	Nicotine: 18mg/mL, PG/VG Ratio: 70/30, E-Liquid Volume: 60mL
STN	PM0003790
Static Product ID	PD201
Product Name	Suicide Bunny Sucker Punch 0mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Sucker Punch

Additional Property	Nicotine: 0mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD202
Product Name	Suicide Bunny Sucker Punch 1.5mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Sucker Punch
Additional Property	Nicotine: 1.5mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD203
Product Name	Suicide Bunny Sucker Punch 3mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Sucker Punch
Additional Property	Nicotine: 3mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD204
Product Name	Suicide Bunny Sucker Punch 6mg

Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Sucker Punch
Additional Property	Nicotine: 6mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD205
Product Name	Suicide Bunny Sucker Punch 12mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Sucker Punch
Additional Property	Nicotine: 12mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD206
Product Name	Suicide Bunny Sucker Punch 18mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Sucker Punch
Additional Property	Nicotine: 18mg/mL, PG/VG Ratio: 70/30, E-Liquid Volume: 60mL

STN	PM0003790
Static Product ID	PD207
Product Name	Suicide Bunny The O.B. 0mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	The O.B.
Additional Property	Nicotine: 0mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD208
Product Name	Suicide Bunny The O.B. 1.5mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	The O.B.
Additional Property	Nicotine: 1.5mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD209
Product Name	Suicide Bunny The O.B. 3mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	The O.B.
Additional Property	Nicotine: 3mg/mL, PG/VG Ratio: 70/30, E-Liquid Vol-

	umes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD210
Product Name	Suicide Bunny The O.B. 6mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	The O.B.
Additional Property	Nicotine: 6mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD211
Product Name	Suicide Bunny The O.B. 12mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	The O.B.
Additional Property	Nicotine: 12mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD212
Product Name	Suicide Bunny The O.B. 18mg
Package Type	Bottle
Package Quantity	1 Bottle

Characterizing Flavor	The O.B.
Additional Property	Nicotine: 18mg/mL, PG/VG Ratio: 70/30, E-Liquid Volume: 60mL
STN	PM0003790
Static Product ID	PD213
Product Name	Suicide Bunny Wanderlust 0mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Wanderlust
Additional Property	Nicotine: 0mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD214
Product Name	Suicide Bunny Wanderlust 1.5mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Wanderlust
Additional Property	Nicotine: 1.5mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD215

Product Name	Suicide Bunny Wanderlust 3mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Wanderlust
Additional Property	Nicotine: 3mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD216
Product Name	Suicide Bunny Wanderlust 6mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Wanderlust
Additional Property	Nicotine: 6mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD217
Product Name	Suicide Bunny Wanderlust 12mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Wanderlust
Additional Property	Nicotine: 12mg/mL, PG/VG Ratio: 70/30, E-Liquid Vol-

	umes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD218
Product Name	Suicide Bunny Wanderlust 18mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Wanderlust
Additional Property	Nicotine: 18mg/mL, PG/VG Ratio: 70/30, E-Liquid Volume: 60mL
STN	PM0003790
Static Product ID	PD219
Product Name	Teleos Afterparty 0mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Afterparty
Additional Property	Nicotine: 0mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD220
Product Name	Teleos Afterparty 3mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Afterparty

Additional Property	Nicotine: 3mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD221
Product Name	Teleos Afterparty 6mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Afterparty
Additional Property	Nicotine: 6mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD222
Product Name	Teleos Afterparty 12mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Afterparty
Additional Property	Nicotine: 12mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD223
Product Name	Teleos Bits 0mg
Package Type	Bottle
Package Quantity	1 Bottle

Characterizing Flavor	Bits
Additional Property	Nicotine: 0mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD224
Product Name	Teleos Bits 3mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Bits
Additional Property	Nicotine: 3mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD225
Product Name	Teleos Bits 6mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Bits
Additional Property	Nicotine: 6mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD226
Product Name	Teleos Bits 12mg
Package Type	Bottle

Package Quantity	1 Bottle
Characterizing Flavor	Bits
Additional Property	Nicotine: 12mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD227
Product Name	Teleos Boo 0mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Boo
Additional Property	Nicotine: 0mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD228
Product Name	Teleos Boo 3mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Boo
Additional Property	Nicotine: 3mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD229
Product Name	Teleos Boo 6mg

Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Boo
Additional Property	Nicotine: 6mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD230
Product Name	Teleos Boo 12mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Boo
Additional Property	Nicotine: 12mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD231
Product Name	Telos Crunch 0mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Crunch
Additional Property	Nicotine: 0mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD232

Product Name	Telos Crunch 3mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Crunch
Additional Property	Nicotine: 3mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD233
Product Name	Telos Crunch 6mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Crunch
Additional Property	Nicotine: 6mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD234
Product Name	Telos Crunch 12mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Crunch
Additional Property	Nicotine: 12mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790

Static Product ID	PD235
Product Name	Teleos Eight Bells 0mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Eight Bells
Additional Property	Nicotine: 0mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD236
Product Name	Teleos Eight Bells 3mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Eight Bells
Additional Property	Nicotine: 3mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD237
Product Name	Teleos Eight Bells 6mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Eight Bells
Additional Property	Nicotine: 6mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL

STN	PM0003790
Static Product ID	PD238
Product Name	Teleos Eight Bells 12mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Eight Bells
Additional Property	Nicotine: 12mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD239
Product Name	Teleos Experiment One 0mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Experiment One
Additional Property	Nicotine: 0mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD240
Product Name	Teleos Experiment One 3mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Experiment One
Additional Property	Nicotine: 3mg/mL, PG/VG Ratio: 70/30, E-Liquid Vol-

	umes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD241
Product Name	Teleos Experiment One 6mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Experiment One
Additional Property	Nicotine: 6mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD242
Product Name	Teleos Experiment One 12mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Experiment One
Additional Property	Nicotine: 12mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD243
Product Name	Teleos Experiment Two 0mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Experiment Two

Additional Property	Nicotine: 0mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD244
Product Name	Teleos Experiment Two 3mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Experiment Two
Additional Property	Nicotine: 3mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD245
Product Name	Teleos Experiment Two 6mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Experiment Two
Additional Property	Nicotine: 6mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD246
Product Name	Teleos Experiment Two 12mg
Package Type	Bottle
Package Quantity	1 Bottle

Characterizing Flavor	Experiment Two
Additional Property	Nicotine: 12mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD247
Product Name	Teleos The Milk 0mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	The Milk
Additional Property	Nicotine: 0mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD248
Product Name	Teleos The Milk 3mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	The Milk
Additional Property	Nicotine: 3mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD249
Product Name	Teleos The Milk 6mg
Package Type	Bottle

Package Quantity	1 Bottle
Characterizing Flavor	The Milk
Additional Property	Nicotine: 6mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD250
Product Name	Teleos The Milk 12mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	The Milk
Additional Property	Nicotine: 12mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD251
Product Name	Teleos Remixe Milk 2 0mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Milk 2
Additional Property	Nicotine: 0mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD252
Product Name	Teleos Remixe Milk 2 1.5mg

Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Milk 2
Additional Property	Nicotine: 1.5mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD253
Product Name	Teleos Remixe Milk 2 3mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Milk 2
Additional Property	Nicotine: 3mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD254
Product Name	Teleos Remixe Milk 2 6mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Milk 2
Additional Property	Nicotine: 6mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD255

Product Name	Teleos Remixe Milk 2 12mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Milk 2
Additional Property	Nicotine: 12mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD256
Product Name	Teleos Remixed Chewy 1 0mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Chewy 1
Additional Property	Nicotine: 0mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD257
Product Name	Teleos Remixed Chewy 2 1.5mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Chewy 2
Additional Property	Nicotine: 1.5mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL

STN	PM0003790
Static Product ID	PD258
Product Name	Teleos Remixed Chewy 2 3mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Chewy 2
Additional Property	Nicotine: 3mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD259
Product Name	Teleos Remixed Chewy 2 6mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Chewy 2
Additional Property	Nicotine: 6mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD260
Product Name	Teleos Remixed Chewy 2 12mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Chewy 2

Additional Property	Nicotine: 12mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD261
Product Name	Teleos Remixed Pound Cake 1 0mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Pound Cake 1
Additional Property	Nicotine: 0mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD262
Product Name	Teleos Remixed Pound Cake 2 1.5mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Pound Cake 2
Additional Property	Nicotine: 1.5mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD263
Product Name	Teleos Remixed Pound Cake 1 3mg

Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Pound Cake 1
Additional Property	Nicotine: 3mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD264
Product Name	Teleos Remixed Pound Cake 1 6mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Pound Cake 1
Additional Property	Nicotine: 6mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD265
Product Name	Teleos Remixed Pound Cake 112mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Pound Cake 1
Additional Property	Nicotine: 12mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790

Static Product ID	PD266
Product Name	Teleos The Cookie 0mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	The Cookie
Additional Property	Nicotine: 0mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD267
Product Name	Teleos The Cookie 3mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	The Cookie
Additional Property	Nicotine: 3mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD268
Product Name	Teleos The Cookie 6mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	The Cookie
Additional Property	Nicotine: 6mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL

STN	PM0003790
Static Product ID	PD269
Product Name	Teleos The Cookie 12mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	The Cookie
Additional Property	Nicotine: 12mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 120mL
STN	PM0003790
Static Product ID	PD270
Product Name	Vape Hooligan Dropkick 0mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Dropkick
Additional Property	Nicotine: 0mg/mL, PG/VG Ratio: 70/30, E-Liquid Volume: 60mL
STN	PM0003790
Static Product ID	PD271
Product Name	Vape Hooligan Dropkick 3mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Dropkick

Additional Property	Nicotine: 3mg/mL, PG/VG Ratio: 70/30, E-Liquid Volume: 60mL
STN	PM0003790
Static Product ID	PD272
Product Name	Vape Hooligan Dropkick 6mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Dropkick
Additional Property	Nicotine: 6mg/mL, PG/VG Ratio: 70/30, E-Liquid Volume: 60mL
STN	PM0003790
Static Product ID	PD273
Product Name	Vape Hooligan Dropkick 12mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Dropkick
Additional Property	Nicotine: 12mg/mL, PG/VG Ratio: 70/30, E-Liquid Volume: 60mL
STN	PM0003790
Static Product ID	PD274
Product Name	Vape Hooligan Knuckles 0mg

Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Knuckles
Additional Property	Nicotine: 0mg/mL, PG/VG Ratio: 70/30, E-Liquid Volume: 60mL
STN	PM0003790
Static Product ID	PD275
Product Name	Vape Hooligan Knuckles 3mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Knuckles
Additional Property	Nicotine: 3mg/mL, PG/VG Ratio: 70/30, E-Liquid Volume: 60mL
STN	PM0003790
Static Product ID	PD276
Product Name	Vape Hooligan Knuckles 6mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Knuckles
Additional Property	Nicotine: 6mg/mL, PG/VG Ratio: 70/30, E-Liquid Volume: 60mL

STN	PM0003790
Static Product ID	PD277
Product Name	Vape Hooligan Knuckles 12mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Knuckles
Additional Property	Nicotine: 12mg/mL, PG/VG Ratio: 70/30, E-Liquid Volume: 60mL
STN	PM0003790
Static Product ID	PD278
Product Name	Vape Hooligan Peacemaker 0mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Peacemaker
Additional Property	Nicotine: 0mg/mL, PG/VG Ratio: 70/30, E-Liquid Volume: 60mL
STN	PM0003790
Static Product ID	PD279
Product Name	Vape Hooligan Peacemaker 3mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Peacemaker

Additional Property	Nicotine: 3mg/mL, PG/VG Ratio: 70/30, E-Liquid Volume: 60mL
STN	PM0003790
Static Product ID	PD280
Product Name	Vape Hooligan Peacemaker 6mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Peacemaker
Additional Property	Nicotine: 6mg/mL, PG/VG Ratio: 70/30, E-Liquid Volume: 60mL
STN	PM0003790
Static Product ID	PD281
Product Name	Vape Hooligan Peacemaker 12mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Peacemaker
Additional Property	Nicotine: 12mg/mL, PG/VG Ratio: 70/30, E-Liquid Volume: 60mL

U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov

April 12, 2021

ACCEPTANCE

Vapetasia LLC
Attention: Jon Rose, General Manager
Wages & White Lion Investments LLC dba Triton Distribution
789 North Grove Rd, Suite 111
Richardson, Texas 75081

FDA Submission Tracking Numbers (STNs): PM0003531-PD1 through PM0003531-PD83, see Appendix A

Dear Mr. Rose:

We accept your PMTAs[1] for the tobacco products identified in Appendix A. Note that attributes in Appendix A may display converted values.

Your PMTAs will move forward in the review process. FDA may request to conduct inspections, which may include manufacturing inspections and clinical and nonclinical research inspections, to verify the information submitted in your PMTAs. The results of these inspections may also be used to verify the in-

[1] Premarket Tobacco Product Applications (PMTAs) submitted under section 910 of the Federal Food, Drug, and Cosmetic Act (FD&C Act)

formation submitted in any additional applications that reference the same manufacturing and research information. To ensure that the appropriate records and personnel will be available during the inspections, FDA will notify the point(s) of contact identified prior to the inspection start date.

We will notify you if samples are required for independent testing and verification. If samples are required, you will be notified by letter of the number of samples required and the laboratory address where samples must be received. All requested samples should be received by the laboratory identified in the letter within 14 calendar days of the request.

If you have any questions, please contact Crystal Caesar, Regulatory Health Project Manager, at 240-402-4793 or Crystal.Caesar@fda.hhs.gov.

Sincerely,

Digitally signed by Ryan Nguy -S
Date: 2021.04.12 08:37:35 -04'00'

Ryan Nguy
Team Supervisor, Regulatory Health Project Manager
Division of Regulatory Project Management
Office of Science
Center for Tobacco Products

Enclosure (if provided electronically, the Appendix is not included in physical mail):

Appendix A—New Tobacco Product Subject of This Letter

Appendix A[2,3]
New Tobacco Products Subject of This Letter

Common Attributes	
Submission date	September 09, 2020
Receipt date	September 09, 2020
Applicant	Vapetasia LLC
Product manufacturer	Vapetasia LLC
Product category	ENDS (VAPES)
Product subcategory	ENDS Component
Attributes	New Tobacco Product
STN	PM0003531
Static Product ID	PD1
Product Name	Vapetasia Blackberry Lemonade 0mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Blackberry Lemonade
Additional Property	Nicotine: 0mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, lO0mL
STN	PM0003531

[2] Properties to uniquely identify the new tobacco products were provided by the applicant as of the date of this letter, and not confirmed by FDA. Upon scientific review, the unique identification may be revised.

[3] Brand/sub-brand or other commercial name used in commercial distribution.

Static Product ID	PD2
Product Name	Vapetasia Blackberry Lemonade 3mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Blackberry Lemonade
Additional Property	Nicotine: 3mg/mL, PG/VG Ratio: 70/30, E-liquid Volumes: 60mL, lO0mL
STN	PM0003531
Static Product ID	PD3
Product Name	Vapetasia Blackberry Lemonade 6mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Blackberry Lemonade
Additional Property	Nicotine: 6mg/mL, PG/VG Ratio: 70/30, E-liquid Volumes: 60mL, 100ml
STN	PM0003531
Static Product ID	PD4
Product Name	Vapetasia Blackberry Lemonade Salt 24mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Blackberry Lemonade Salt
Additional Property	Nicotine: 24mg/mL, PG/VG

	Ratio: 60/40, E-Liquid Volume: 30mL
STN	PM0003531
Static Product ID	PD5
Product Name	Vapetasia Blackberry Lemonade Salt 48mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Blackberry Lemonade Salt
Additional Property	Nicotine: 48mg/mL, PG/VG Ratio: 60/40, E-Liquid Volume: 30mL
STN	PM0003531
Static Product ID	PD6
Product Name	Vapetasia Blueberry Parfait 0mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Blueberry Parfait
Additional Property	Nicotine: 0mg/mL, PG/VG Ratio: 70/30, E-liquid Volumes: 60mL, 100mL
STN	PM0003531
Static Product ID	PD7
Product Name	Vapetasia Blueberry Parfait 3mg
Package Type	Bottle

Package Quantity	1 Bottle
Characterizing Flavor	Blueberry Parfait
Additional Property	Nicotine: 3mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 100mL
STN	PM0003531
Static Product ID	PD8
Product Name	Vapetasia Blueberry Parfait 6mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Blueberry Parfait
Additional Property	Nicotine: 6mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 100mL
STN	PM0003531
Static Product ID	PD9
Product Name	Vapetasia Blueberry Parfait Salt 24mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Blueberry Parfait Salt
Additional Property	Nicotine: 24mg/ml, PG/VG Ratio: 60/40, E-Liquid Volume: 30mL
STN	PM0003531
Static Product ID	PD10

Product Name	Vapetasia Blueberry Parfait Salt 48mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Blueberry Parfait Salt
Additional Property	Nicotine: 48mg/mL, PG/VG Ratio: 60/40, E-Liquid Volume: 30mL
STN	PM0003531
Static Product ID	PD11
Product Name	Vapetasia Iced Blackberry Lemonade 0mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Iced Blackberry Lemonade
Additional Property	Nicotine: 0mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 100mL
STN	PM0003531
Static Product ID	PD12
Product Name	Vapetasia Iced Blackberry Lemonade 3mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Iced Blackberry Lemonade
Additional Property	Nicotine: 3mg/mL, PG/VG Ratio: 70/30, E-Liquid Vol-

	umes: 60mL, 100mL
STN	PM0003531
Static Product ID	PD13
Product Name	Vapetasia Iced Blackberry Lemonade 6mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Iced Blackberry Lemonade
Additional Property	Nicotine: 6mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 100mL
STN	PM0003531
Static Product ID	PD14
Product Name	Vapetasia Iced Blackberry Lemonade Salt 24mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Iced Blackberry Lemonade Salt
Additional Property	Nicotine: 24mg/mL, PG/VG Ratio: 60/40, E-Liquid Volume: 30mL
STN	PM0003531
Static Product ID	PD15
Product Name	Vapetasia Iced Blackberry Lemonade Salt 48mg
Package Type	Bottle

Package Quantity	1 Bottle
Characterizing Flavor	Iced Blackberry Lemonade Salt
Additional Property	Nicotine: 48mg/mL, PG/VG Ratio: 60/40, E-Liquid Volume: 30mL
STN	PM0003531
Static Product ID	PD16
Product Name	Vapetasia Iced Milk of The Poppy 0mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Iced Milk of The Poppy
Additional Property	Nicotine: 0mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 100mL
STN	PM0003531
Static Product ID	PD17
Product Name	Vapetasia Iced Milk of The Poppy 3mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Iced Milk of The Poppy
Additional Property	Nicotine: 3mg/mL, PG/VG Ratio: 70/30, E-liquid Volumes: 60mL, 100mL
STN	PM0003531

Static Product ID	PD18
Product Name	Vapetasia Iced Milk of The Poppy 6mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Iced Milk of The Poppy
Additional Property	Nicotine: 6mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 100mL
STN	PM0003531
Static Product ID	PD19
Product Name	Vapetasia Iced Milk of The Poppy Salt 24mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Iced Milk of The Poppy Salt
Additional Property	Nicotine: 24mg/mL, PG/VG Ratio: 60/40, E-Liquid Volume: 30mL
STN	PM0003531
Static Product ID	PD20
Product Name	Vapetasia Iced Milk of The Poppy Salt 48mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Iced Milk of The Poppy Salt
Additional Property	Nicotine: 48mg/mL, PG/VG

	Ratio: 60/40, E-Liquid Volume: 30mL
STN	PM0003531
Static Product ID	PD21
Product Name	Vapetasia Iced Pineapple Express 0mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Iced Pineapple Express
Additional Property	Nicotine: 0mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 100mL
STN	PM0003531
Static Product ID	PD22
Product Name	Vapetasia Iced Pineapple Express 3mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Iced Pineapple Express
Additional Property	Nicotine: 3mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 100mL
STN	PM0003531
Static Product ID	PD23
Product Name	Vapetasia Iced Pineapple Express 6mg
Package Type	Bottle

Package Quantity	1 Bottle
Characterizing Flavor	Iced Pineapple Express
Additional Property	Nicotine: 6mg/mL, PG/VG Ratio: 70/30, E-liquid Volumes: 60mL, 100mL
STN	PM0003531
Static Product ID	PD24
Product Name	Vapetasia Iced Pineapple Express Salt 24mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Iced Pineapple Express Salt
Additional Property	Nicotine: 24mg/mL, PG/VG Ratio: 60/40, E-Liquid Volume: 30mL
STN	PM0003531
Static Product ID	PD25
Product Name	Vapetasia Iced Pineapple Express Salt 48mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Iced Pineapple Express Salt
Additional Property	Nicotine: 48mg/mL, PG/VG Ratio: 60/40, E-Liquid Volume: 30mL
STN	PM0003531
Static Product ID	PD26

Product Name	Vapetasia Killer Kustard Blueberry 0mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Killer Kustard Blueberry
Additional Property	Nicotine: 0mg/mL, PG/VG Ratio: 70/30, E-liquid Volumes: 60mL, 100mL
STN	PM0003531
Static Product ID	PD27
Product Name	Vapetasia Killer Kustard Blueberry 3mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Killer Kustard Blueberry
Additional Property	Nicotine: 3mg/mL, PG/VG Ratio: 70/30, E-liquid Volumes: 60mL, 100mL
STN	PM0003531
Static Product ID	PD28
Product Name	Vapetasia Killer Kustard Blueberry 6mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Killer Kustard Blueberry
Additional Property	Nicotine: 6mg/mL, PG/VG Ratio: 70/30, E-Liquid Vol-

	umes: 60mL, 100mL
STN	PM0003531
Static Product ID	PD29
Product Name	Vapetasia Killer Kustard Blueberry Salt 24mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Killer Kustard Blueberry Salt
Additional Property	Nicotine: 24mg/mL, PG/VG Ratio: 60/40, E-Liquid Volume: 30mL
STN	PM0003531
Static Product ID	PD30
Product Name	Vapetasia Killer Kustard Blueberry Salt 48mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Killer Kustard Blueberry Salt
Additional Property	Nicotine: 48mg/mL, PG/VG Ratio: 60/40, E-Liquid Volume: 30mL
STN	PM0003531
Static Product ID	PD31
Product Name	Vapetasia Killer Kustard 0mg

Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Killer Kustard
Additional Property	Nicotine: 0mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 100mL
STN	PM0003531
Static Product ID	PD32
Product Name	Vapetasia Killer Kustard 3mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Killer Kustard
Additional Property	Nicotine: 3mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 100mL
STN	PM0003531
Static Product ID	PD33
Product Name	Vapetasia Killer Kustard 6mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Killer Kustard
Additional Property	Nicotine: 6mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 100mL
STN	PM0003531

Static Product ID	PD34
Product Name	Vapetasia Killer Kustard 12mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Killer Kustard
Additional Property	Nicotine: 12mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 100mL
STN	PM0003531
Static Product ID	PD35
Product Name	Vapetasia Killer Kustard Honeydew 0mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Killer Kustard Honeydew
Additional Property	Nicotine: 0mg/mL, PG/VG Ratio: 70/30, E-liquid Volume: 100mL
STN	PM0003531
Static Product ID	PD36
Product Name	Vapetasia Killer Kustard Honeydew 3mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Killer Kustard Honeydew
Additional Property	Nicotine: 3mg/mL, PG/VG

	Ratio: 70/30, E-liquid Volume: 100mL
STN	PM0003531
Static Product ID	PD37
Product Name	Vapetasia Killer Kustard Honeydew 6mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Killer Kustard Honeydew
Additional Property	Nicotine: 6mg/mL, PG/VG Ratio: 70/30, E-liquid Volume: l00mL
STN	PM0003531
Static Product ID	PD38
Product Name	Vapetasia Killer Kustard Lemon 0mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Killer Kustard Lemon
Additional Property	Nicotine: 0mg/mL, PG/VG Ratio: 70/30, E-liquid Volume: 10mL
STN	PM0003531
Static Product ID	PD39
Product Name	Vapetasia Killer Kustard Lemon 3mg
Package Type	Bottle

Package Quantity	1 Bottle
Characterizing Flavor	Killer Kustard Lemon
Additional Property	Nicotine: 3mg/mL, PG/VG Ratio: 70/30, E-liquid Volume: 100mL
STN	PM0003531
Static Product ID	PD40
Product Name	Vapetasia Killer Kustard Lemon 6mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Killer Kustard Lemon
Additional Property	Nicotine: 6mg/mL, PG/VG Ratio: 70/30, E-liquid Volume: 100mL
STN	PM0003531
Static Product ID	PD41
Product Name	Vapetasia Killer Kustard Salt 12mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Killer Kustard Salt
Additional Property	Nicotine: 12mg/mL, PG/VG Ratio: 60/40, E-Liquid Volume: 30mL
STN	PM0003531
Static Product ID	PD42

Product Name	Vapetasia Killer Kustard Salt 24mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Killer Kustard Salt
Additional Property	Nicotine: 24mg/mL, PG/VG Ratio: 60/40, E-Liquid Volume: 30mL
STN	PM0003531
Static Product ID	PD43
Product Name	Vapetasia Killer Kustard Salt 48mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Killer Kustard Salt
Additional Property	Nicotine: 48mg/mL, PG/VG Ratio: 60/40, E-Liquid Volume: 30mL
STN	PM0003531
Static Product ID	PD44
Product Name	Vapetasia Killer Kustard Strawberry 0mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Killer Kustard Strawberry
Additional Property	Nicotine: 0mg/mL, PG/VG Ratio: 70/30, E-Liquid Vol-

	umes: 60mL, 100mL
STN	PM0003531
Static Product ID	PD45
Product Name	Vapetasia Killer Kustard Strawberry 3mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Killer Kustard Strawberry
Additional Property	Nicotine: 3mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 100mL
STN	PM0003531
Static Product ID	PD46
Product Name	Vapetasia Killer Kustard Strawberry 6mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Killer Kustard Strawberry
Additional Property	Nicotine: 6mg/mL, PG/VG Ratio: 70/30, E-liquid Volumes: 60mL, 100mL
STN	PM0003531
Static Product ID	PD47
Product Name	Vapetasia Killer Kustard Strawberry Salt 12mg
Package Type	Bottle
Package Quantity	1 Bottle

Characterizing Flavor	Killer Kustard Strawberry Salt
Additional Property	Nicotine: 12mg/mL, PG/VG Ratio: 60/40, E-Liquid Volume: 30mL
STN	PM0003531
Static Product ID	PD48
Product Name	Vapetasia Killer Kustard Strawberry Salt 24mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Killer Kustard Strawberry Salt
Additional Property	Nicotine: 24mg/mL, PG/VG Ratio: 60/40, E-Liquid Volume: 30mL
STN	PM0003531
Static Product ID	PD49
Product Name	Vapetasia Killer Kustard Strawberry Salt 48mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Killer Kustard Strawberry Salt
Additional Property	Nicotine: 48mg/mL, PG/VG Ratio: 60/40, E-Liquid Volume: 30mL
STN	PM0003531

Static Product ID	PD50
Product Name	Vapetasia Milk of The Poppy 0mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Milk of The Poppy
Additional Property	Nicotine: 0mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 100mL
STN	PM0003531
Static Product ID	PD51
Product Name	Vapetasia Milk of The Poppy 3mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Milk of The Poppy
Additional Property	Nicotine: 3mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 100mL
STN	PM0003531
Static Product ID	PD52
Product Name	Vapetasia Milk of The Poppy 6mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Milk of The Poppy
Additional Property	Nicotine: 6mg/mL, PG/VG

	Ratio: 70/30, E-Liquid Volumes: 60mL, 100mL
STN	PM0003531
Static Product ID	PD53
Product Name	Vapetasia Milk of The Poppy 12mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Milk of The Poppy
Additional Property	Nicotine: 12mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 100mL
STN	PM0003531
Static Product ID	PD54
Product Name	Vapetasia Milk of The Poppy Salt 12mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Milk of The Poppy Salt
Additional Property	Nicotine: 12mg/mL, PG/VG Ratio: 60/40, E-Liquid Volume: 30mL
STN	PM0003531
Static Product ID	PD55
Product Name	Vapetasia Milk of The Poppy Salt 24mg
Package Type	Bottle

Package Quantity	1 Bottle
Characterizing Flavor	Milk of The Poppy Salt
Additional Property	Nicotine: 24mg/mL, PG/VG Ratio: 60/40, E-Liquid Volume: 30mL
STN	PM0003531
Static Product ID	PD56
Product Name	Vapetasia Milk of The Poppy Salt 48mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Milk of The Poppy Salt
Additional Property	Nicotine: 48mg/mL, PG/VG Ratio: 60/40, E-Liquid Volume: 30mL
STN	PM0003531
Static Product ID	PD57
Product Name	Vapetasia Pineapple Express 0mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Pineapple Express
Additional Property	Nicotine: 0mg/mL, PG/VG Ratio: 70/30, E-liquid Volumes: 60mL, 100mL
STN	PM0003531
Static Product ID	PD58

Product Name	Vapetasia Pineapple Express 3mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Pineapple Express
Additional Property	Nicotine: 3mg/mL, PG/VG Ratio: 70/30, E-liquid Volumes: 60mL, 100mL
STN	PM0003531
Static Product ID	PD59
Product Name	Vapetasia Pineapple Express 6mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Pineapple Express
Additional Property	Nicotine: 6mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, lO0mL
STN	PM0003531
Static Product ID	PD60
Product Name	Vapetasia Pineapple Express Salt 2.4mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Pineapple Express Salt
Additional Property	Nicotine: 24mg/mL, PG/VG Ratio: 60/40, E-Liquid Vol-

	ume: 30mL
STN	PM0003531
Static Product ID	PD61
Product Name	Vapetasia Pineapple Express Salt 48mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Pineapple Express Salt
Additional Property	Nicotine: 48mg/mL, PG/VG Ratio: 60/40, E-Liquid Volume: 30mL
STN	PM0003531
Static Product ID	PD62
Product Name	Vapetasia Pink Lemonade 0mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Pink Lemonade
Additional Property	Nicotine: 0mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, lO0mL
STN	PM0003531
Static Product ID	PD63
Product Name	Vapetasia Pink Lemonade 3mg
Package Type	Bottle
Package Quantity	1 Bottle

Characterizing Flavor	Pink Lemonade
Additional Property	Nicotine: 3mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 100mL
STN	PM0003531
Static Product ID	PD64
Product Name	Vapetasia Pink Lemonade 6mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Pink Lemonade
Additional Property	Nicotine: 6mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 100mL
STN	PM0003531
Static Product ID	PD65
Product Name	Vapetasia Pink Lemonade Salt 24mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Pink Lemonade Salt
Additional Property	Nicotine: 24mg/mL, PG/VG Ratio: 60/40, E-Liquid Volume: 30mL
STN	PM0003531
Static Product ID	PD66
Product Name	Vapetasia Pink Lemonade

	Salt 48mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Pink Lemonade Salt
Additional Property	Nicotine: 48mg/mL, PG/VG Ratio: 60/40, E-Liquid Volume: 30mL
STN	PM0003531
Static Product ID	PD67
Product Name	Vapetasia Rainbow Road 0mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Rainbow Road
Additional Property	Nicotine: 0mg/mL, PG/VG Ratio: 70/30, E-liquid Volumes: 60mL, 100mL
STN	PM0003531
Static Product ID	PD68
Product Name	Vapetasia Rainbow Road 3mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Rainbow Road
Additional Property	Nicotine: 3mg/mL, PG/VG Ratio: 70/30, E-liquid Vol-

	umes: 60mL, 100mL
STN	PM0003531
Static Product ID	PD69
Product Name	Vapetasia Rainbow Road 6mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Rainbow Road
Additional Property	Nicotine: 6mg/mL, PG/VG Ratio: 70/30, E-liquid Volumes: 60mL, 100mL
STN	PM0003531
Static Product ID	PD70
Product Name	Vapetasia Rainbow Road Salt 24mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Rainbow Road Salt
Additional Property	Nicotine: 24mg/mL, PG/VG Ratio: 60/40, E-Liquid Volume: 30mL
STN	PM0003531
Static Product ID	PD71
Product Name	Vapetasia Rainbow Road Salt 48mg
Package Type	Bottle
Package Quantity	1 Bottle

Characterizing Flavor	Rainbow Road Salt
Additional Property	Nicotine: 48mg/mL, PG/VG Ratio: 60/40, E-Liquid Volume: 30mL
STN	PM0003531
Static Product ID	PD72
Product Name	Vapetasia Royalty Two 0mg
Package Type	Bottle
Package quantity	1 Bottle
Characterizing Flavor	Royalty Two
Additional Property	Nicotine: 0mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 100mL
STN	PM0003531
Static Product ID	PD73
Product Name	Vapetasia Royalty Two 3mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Royalty Two
Additional Property	Nicotine: 3mg/mL, PG/VG Ratio: 70/30, E-liquid Volumes: 60mL, 100mL
STN	PM0003531
Static Product ID	PD74
Product Name	Vapetasia Royalty Two 6mg
Package Type	Bottle

Package Quantity	1 Bottle
Characterizing Flavor	Royalty Two
Additional Property	Nicotine: 6mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 100mL
STN	PM0003531
Static Product ID	PD75
Product Name	Vapetasia Royalty Two 12mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Royalty Two
Additional Property	Nicotine: 12mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 100mL
STN	PM0003531
Static Product ID	PD76
Product Name	Vapetasia Royalty Two Salt 12mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Royalty Two Salt
Additional Property	Nicotine: 12mg/mL, PG/VG Ratio: 60/40, E-Liquid Volume: 30mL
STN	PM0003531
Static Product ID	PD77

Product Name	Vapetasia Royalty Two Salt 24mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Royalty Two Salt
Additional Property	Nicotine: 24mg/mL, PG/VG Ratio: 60/40, E-Liquid Volume: 30mL
STN	PM0003531
Static Product ID	PD78
Product Name	Vapetasia Royalty Two Salt 48mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Royalty Two Salt
Additional Property	Nicotine: 48mg/mL, PG/VG Ratio: 60/40, E-Liquid Volume: 30mL
STN	PM0003531
Static Product ID	PD79
Product Name	Vapetasia Strawberry Parfait 0mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Strawberry Parfait
Additional Property	Nicotine: 0mg/mL, PG/VG Ratio: 70/30, E-Liquid Vol-

	umes: 60mL, 100mL
STN	PM0003531
Static Product ID	PD80
Product Name	Vapetasia Strawberry Parfait 3mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Strawberry Parfait
Additional Property	Nicotine: 3mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 100mL
STN	PM0003531
Static Product ID	PD81
Product Name	Vapetasia Strawberry Parfait 6mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Strawberry Parfait
Additional Property	Nicotine: 6mg/mL, PG/VG Ratio: 70/30, E-Liquid Volumes: 60mL, 100mL
STN	PM0003531
Static Product ID	PD82
Product Name	Vapetasia Strawberry Parfait Salt 24mg
Package Type	Bottle
Package Quantity	1 Bottle

Characterizing Flavor	Strawberry Parfait Salt
Additional Property	Nicotine: 24mg/mL, PG/VG Ratio: 60/40, E-Liquid Volume: 30mL
STN	PM0003531
Static Product ID	PD83
Product Name	Vapetasia Strawberry Parfait Salt 48mg
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Strawberry Parfait Salt
Additional Property	Nicotine: 48mg/mL, PG/VG Ratio: 60/40, E-Liquid Volume: 30mL

U.S. FOOD & DRUG ADMINISTRATION

Review for Flavored[1] ENDS PMTAs

New Products Subject of this Review	
Submission tracking numbers (STNs)	PM0003790, see Appendix A
Common Attributes	
Submission date	September 9, 2020
Receipt date	September 9, 2020
Applicant	Wages & White Lion Investments LLC dba Triton Distribution
Product manufacturer	Wages & White Lion Investments LLC dba Triton Distribution
Application type	Standard
Product category	ENDS (VAPES)
Product subcategory	ENDS Component

[1] Throughout this review, and solely as a matter of shorthand to aid in the drafting of this document, the term *flavored ENDS* refers to any ENDS other than tobacco-flavored and menthol-flavored ENDS.

Conclusion
Evidence is absent in PMTAs

Reviewer: Digitally signed by Sean B. Dolan -S
Date: 2021.09.14 14:22:11 -04'00'

Concurrence: Digitally signed by Alexander I. Persoskie -S
Date: 2021.09.14 15:10:55 -04'00'
For Robert Garica

SCOPE OF REVIEW

This review determines whether the subject PMTAs contain evidence from a randomized controlled trial, longitudinal cohort study, and/or other evidence regarding the impact of the new ENDS on switching or cigarette reduction that could potentially demonstrate the benefit of their flavored ENDS over an appropriate comparator tobacco-flavored ENDS. This review includes a search of the PMTAs to determine whether such evidence is found anywhere within the PMTAs. However, this review does not evaluate whether the evidence, if present, is robust enough to demonstrate that the applicant's flavored ENDS are more beneficial than their tobacco-flavored ENDS. If such evidence is present in the applications, the Technical Project Lead will determine if full scientific review is necessary.

Presence of Evidence for Flavored ENDS Products

Criterion A	Present		Absent
Randomized Controlled Trial (RCT) on a new product use and smoking behavior	☐		☒
Instructions: To select "Present", all of the following boxes must be checked "Yes":	**Yes**	**No**	**N/A[2]**

[2] Not applicable, because no such study was present.

Was the RCT conducted using new products?	☐	☐	☒
Does the RCT include a tobacco-flavored arm and a flavored product arm[3]?	☐	☐	☒
Do the outcomes include users' ENDS and smoking behavior to assess switching and/or cigarette reduction (e.g., measures of cigarettes per day, smoking cessation, ENDS use)?	☐	☐	☒
Comment(s): **N/A**			

[3] Check "yes" if at least one non-tobacco flavored product is compared to a tobacco-flavored product.

Criterion B	Present		Absent
Longitudinal Cohort Study (LCS) on new product use and smoking behavior	☐		☒
Instructions: To select "Present", all of the following boxes must be checked "Yes":	**Yes**	**No**	**N/A[2]**
Was the LCS conducted and does it include users of new products who are followed over time?	☐	☐	☒
Was use of tobacco-flavored products and other flavored products assessed[3]?	☐	☐	☒
Do outcomes include users' ENDS and smoking behavior to assess switching and/or cigarette reduction (e.g., measures of cigarettes per day, smoking cessation, ENDS use)?	☐	☐	☒
Comment(s): **N/A**			

Criterion C
Other evidence in the PTMA(s) related to potential benefit to adults **None**

Review for Flavored[1] ENDS PMTAs

New Products Subject of this Review	
Submission tracking numbers (STNs)	PM0003790, see Appendix A
Common Attributes	
Submission date	September 9, 2020
Receipt date	September 9, 2020
Applicant	Wages & White Lion Investments LLC dba Triton Distribution
Product manufacturer	Wages & White Lion Investments LLC dba Triton Distribution
Application type	Standard
Product category	ENDS (VAPES)
Product subcategory	ENDS Component

[1] Throughout this review, and solely as a matter of shorthand to aid in the drafting of this document, the term *flavored ENDS* refers to any ENDS other than tobacco-flavored and menthol-flavored ENDS.

Conclusion
Evidence is absent in PMTAs

Reviewer: Digitally signed by Alexander I. Persoskie -S
Date: 2021.09.14 15:14:29 -04'00'
For Robert Garica

Concurrence: Digitally signed by Sean B. Dolan -S
Date: 2021.09.14 15:23:05 -04'00'

SCOPE OF REVIEW

This review determines whether the subject PMTAs contain evidence from a randomized controlled trial, longitudinal cohort study, and/or other evidence regarding the impact of the new ENDS on switching or cigarette reduction that could potentially demonstrate the benefit of their flavored ENDS over an appropriate comparator tobacco-flavored ENDS. This review includes a search of the PMTAs to determine whether such evidence is found anywhere within the PMTAs. However, this review does not evaluate whether the evidence, if present, is robust enough to demonstrate that the applicant's flavored ENDS are more beneficial than their tobacco-flavored ENDS. If such evidence is present in the applications, the Technical Project Lead will determine if full scientific review is necessary.

Presence of Evidence for Flavored ENDS Products

Criterion A	Present		Absent
Randomized Controlled Trial (RCT) on a new product use and smoking behavior	☐		☒
Instructions: To select "Present", all of the following boxes must be checked "Yes":	**Yes**	**No**	**N/A[2]**

[2] Not applicable, because no such study was present.

Was the RCT conducted using new products?	☐	☐	☒
Does the RCT include a tobacco-flavored arm and a flavored product arm[3]?	☐	☐	☒
Do the outcomes include users' ENDS and smoking behavior to assess switching and/or cigarette reduction (e.g., measures of cigarettes per day, smoking cessation, ENDS use)?	☐	☐	☒
Comment(s): **N/A**			

[3] Check "yes" if at least one non-tobacco flavored product is compared to a tobacco-flavored product.

Criterion B	Present		Absent
Longitudinal Cohort Study (LCS) on new product use and smoking behavior	☐		☒
Instructions: To select "Present", all of the following boxes must be checked "Yes":	**Yes**	**No**	**N/A[2]**
Was the LCS conducted and does it include users of new products who are followed over time?	☐	☐	☒
Was use of tobacco-flavored products and other flavored products assessed[3]?	☐	☐	☒
Do outcomes include users' ENDS and smoking behavior to assess switching and/or cigarette reduction (e.g., measures of cigarettes per day, smoking cessation, ENDS use)?	☐	☐	☒
Comment(s): **N/A**			

Criterion C
Other evidence in the PTMA(s) related to potential benefit to adults **None**

U.S. FOOD & DRUG ADMINISTRATION

Review for Flavored[1] ENDS PMTAs

New Products Subject of this Review	
Submission tracking numbers (STNs)	PM0003531, see Appendix A
Common Attributes	
Submission date	September 9, 2020
Receipt date	September 9, 2020
Applicant	Vapetasia LLC
Product manufacturer	Vapetasia LLC
Application type	Standard
Product category	ENDS (VAPES)
Product subcategory	ENDS Component
Cross-Referenced Submissions	
All new products	MF0000068, MF0000262, MF0000363, MF0000384, MF0000397, MF0000401, MF0000403, MF0000447

[1] Throughout this review, and solely as a matter of shorthand to aid in the drafting of this document, the term *flavored ENDS* refers to any ENDS other than tobacco-flavored and menthol-flavored ENDS.

Conclusion
Evidence is absent in PMTAs

Reviewer: Digitally signed by Wondimu Teka -S
Date: 2021.09.16 12:51:51 -04'00'

Concurrence: Digitally signed by Willa Dong -S
Date: 2021.09.16 12:53:44 -04'00'

SCOPE OF REVIEW

This review determines whether the subject PMTAs contain evidence from a randomized controlled trial, longitudinal cohort study, and/or other evidence regarding the impact of the new ENDS on switching or cigarette reduction that could potentially demonstrate the benefit of their flavored ENDS over an appropriate comparator tobacco-flavored ENDS. This review includes a search of the PMTAs to determine whether such evidence is found anywhere within the PMTAs. However, this review does not evaluate whether the evidence, if present, is robust enough to demonstrate that the applicant's flavored ENDS are more beneficial than their tobacco-flavored ENDS. If such evidence is present in the applications, the Technical Project Lead will determine if full scientific review is necessary.

Presence of Evidence for Flavored ENDS Products

Criterion A	Present		Absent
Randomized Controlled Trial (RCT) on a new product use and smoking behavior	☐		☒
Instructions: To select "Present", all of the following boxes must be checked "Yes":	**Yes**	**No**	**N/A[2]**

[2] Not applicable, because no such study was present.

Was the RCT conducted using new products?	☐	☐	☒
Does the RCT include a tobacco-flavored arm and a flavored product arm[3]?	☐	☐	☒
Do the outcomes include users' ENDS and smoking behavior to assess switching and/or cigarette reduction (e.g., measures of cigarettes per day, smoking cessation, ENDS use)?	☐	☐	☒
Comment(s): ***N/A***			

[3] Check "yes" if at least one non-tobacco flavored product is compared to a tobacco-flavored product.

Criterion B	Present		Absent
Longitudinal Cohort Study (LCS) on new product use and smoking behavior	☐		☒
Instructions: To select "Present", all of the following boxes must be checked "Yes":	**Yes**	**No**	**N/A[2]**
Was the LCS conducted and does it include users of new products who are followed over time?	☐	☐	☒
Was use of tobacco-flavored products and other flavored products assessed[3]?	☐	☐	☒
Do outcomes include users' ENDS and smoking behavior to assess switching and/or cigarette reduction (e.g., measures of cigarettes per day, smoking cessation, ENDS use)?	☐	☐	☒
Comment(s): ***N/A***			

Criterion C
Other evidence in the PTMA(s) related to potential benefit to adults **None**

U.S. FOOD & DRUG ADMINISTRATION

Review for Flavored[1] ENDS PMTAs

New Products Subject of this Review	
Submission tracking numbers (STNs)	PM0003531, see Appendix A
Common Attributes	
Submission date	September 9, 2020
Receipt date	September 9, 2020
Applicant	Vapetasia LLC
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Application type	Standard
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Product subcategory	ENDS Component
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[1] Throughout this review, and solely as a matter of shorthand to aid in the drafting of this document, the term *flavored ENDS* refers to any ENDS other than tobacco-flavored and menthol-flavored ENDS.

Conclusion
Evidence is absent in PMTAs

Reviewer: Willa Dong -S Digitally signed by Willa Dong -S Date: 2021.09.16 12:47:09 -04'00'

Concurrence: Digitally signed by Wondimu Teka -S
Date: 2021.09.16 12:53:37 -04'00'

SCOPE OF REVIEW

This review determines whether the subject PMTAs contain evidence from a randomized controlled trial, longitudinal cohort study, and/or other evidence regarding the impact of the new ENDS on switching or cigarette reduction that could potentially demonstrate the benefit of their flavored ENDS over an appropriate comparator tobacco-flavored ENDS. This review includes a search of the PMTAs to determine whether such evidence is found anywhere within the PMTAs. However, this review does not evaluate whether the evidence, if present, is robust enough to demonstrate that the applicant's flavored ENDS are more beneficial than their tobacco-flavored ENDS. If such evidence is present in the applications, the Technical Project Lead will determine if full scientific review is necessary.

Presence of Evidence for Flavored ENDS Products

Criterion A	Present		Absent
Randomized Controlled Trial (RCT) on a new product use and smoking behavior	☐		☒
Instructions: To select "Present", all of the following boxes must be checked "Yes":	**Yes**	**No**	**N/A[2]**

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Does the RCT include a tobacco-flavored arm and a flavored product arm[3]?	☐	☐	☒
Do the outcomes include users' ENDS and smoking behavior to assess switching and/or cigarette reduction (e.g., measures of cigarettes per day, smoking cessation, ENDS use)?	☐	☐	☒
Comment(s): **N/A**			

[3] Check "yes" if at least one non-tobacco flavored product is compared to a tobacco-flavored product.

Criterion B	Present		Absent
Longitudinal Cohort Study (LCS) on new product use and smoking behavior	☐		☒
Instructions: To select "Present", all of the following boxes must be checked "Yes":	**Yes**	**No**	**N/A[2]**
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Was use of tobacco-flavored products and other flavored products assessed[3]?	☐	☐	☒
Do outcomes include users' ENDS and smoking behavior to assess switching and/or cigarette reduction (e.g., measures of cigarettes per day, smoking cessation, ENDS use)?	☐	☐	☒
Comment(s): **N/A**			

Criterion C
Other evidence in the PTMA(s) related to potential benefit to adults **None**

UNITED STATES COURT OF APPEALS
FOR THE FIFTH CIRCUIT

Case No.

WAGES AND WHITE LION INVESTMENTS, LLC D/B/A TRITON DISTRIBUTION, PETITIONER

v.

UNITED STATES FOOD AND DRUG ADMINISTRATION, RESPONDENT

DECLARATION OF JONATHAN ROSE

I, Jon Rose, declare and state as follows:

1. I am employed by Wages and White Lion Investments, LLC d/b/a Triton Distribution ("Triton") as the company's General Manager. The company has been in business since 2015 and I have held this position for four years.

2. In my role as the company's General Manager, I was the individual primarily responsible for the management of the company's efforts to prepare and submit a premarket tobacco application for its e-liquid electronic nicotine delivery system (ENDS) products.

3. In my role as the company's General Manager, I am also tasked with ensuring the company's compliance with applicable regulations and regulatory requirements and with monitoring financial performance and, in conjunction with the company's owners, making appropriate adjustments to staffing levels based on demand for our e-liquid products.

4. Among the brands of bottled e-liquids that Triton manufactures are several brands that are owned by Triton, as well as other brands for which Triton acts as a contract manufacturer. In total, the company's revenues in recent years based on both sales of its own branded e-liquids and the e-liquids that it manufactures for third parties have typically been between $15 and $20 million.

5. When it became clear that we would be required to prepare and submit a premarket tobacco application (PMTA) to FDA for all of the e-liquid products that we wished to keep selling in the United States, we embarked on extensive efforts to prepare an appropriate PMTA that would provide the information FDA had indicated it was looking in a PMTA for an ENDS product in both its finalized guidance document on PMTAs for ENDS and in its proposed rule governing PMTAs. We also attended two public meetings put on by staff from the Office of Science in FDA's Center for Tobacco Products in October 2018 and 2019 to learn more about FDA wanted to be included in our PMTA.

6. Based on our reviews of the materials published by FDA, we understood that we would not be required to complete long-term clinical studies, which we understood to mean longitudinal studies of six months or more, as FDA specifically stated that it did not expect that such studies would be required.

7. We also did not understand FDA to have any requirement to conduct a comparative efficacy test whereby we would compare the effectiveness of our non-tobacco-flavored e-liquids in helping existing smokers to stop smoking versus the effectiveness of our tobacco-flavored e-liquids in doing so. Frankly, this idea

never crossed our mind because we and our customers have never been able to market our e-liquids as smoking cessation products. A modified risk tobacco product order from FDA would be required for us or our customers to even explicitly compare our products to combustible cigarettes.

8. All of the e-liquids that were subject to our PMTA have only ever been sold in age-gated vape and tobacco-specialty shops and through age-gated online sales. When I say "age-gated," I mean that customers must prove that they are at least 21, which is the minimum age to buy ENDS products under federal law, in order to have access to or purchase our e-liquid products. None of the e-liquid products manufactured by us have ever been sold in convenience stores or other general retail outlets.

9. In conjunction with submission of our PMTA, we determined not to engage in any marketing for our products outside of the vape and tobacco-specialty shop or online store context. We have not run radio advertisements, magazine advertisements, television spots, or social media posts to attempt to promote our products. Rather, our products are only marketed at the actual point of purchase—whether in-person or online. Part of the reason that we restricted our marketing is to make sure that we are carefully targeting our marketing at our target audience—adult consumers who are cigarette smokers or consumers of vaping products —and not individuals who are non-users of tobacco products.

10. We spent over $500,000 on the product testing and preparation and publishing of our PMTA. We obtained significant reductions in the cost by participating

in a consortium that allowed us to pay only a fraction of what certain aspects of the PMTA would have otherwise cost if we paid for them alone; if we had paid all of the expenses incurred for work that supported our PMTA ourselves, I am confident that we would have paid well in excess of $2 million.

11. In support of our application, we submitted a thorough review of the existing scientific literature on ENDS products, had significant product aerosol testing done on harmful and potentially harmful constituents, prepared marketing and post-market surveillance plans, and had an environmental assessment prepared. We also submitted survey information on the demographics of consumers of our products showing that the majority of consumers of our products were between 25 and 44 years of age. The total size of our packaged PMTA was approximately 9 gigabytes and was composed of hundreds of individual files.

12. Our PMTA was submitted to FDA on September 9, 2021.

13. Our sales of the products presented in the PMTA that is the subject of this appeal totaled approximately 46.6 percent of our overall company revenue in 2020. Virtually all remaining company revenues were derived from manufacturing Vapetasia-branded e-liquids, for which a PMTA was also filed and which received a marketing denial order ("MDO") substantially identical to ours on September 17, 2021.

14. When we first learned about FDA's new requirement for product-specific studies showing the effectiveness of flavored versus tobacco-flavored ENDS through FDA's August 26, 2021 press release associated with the publication of its first set of MDOs for flavored

ENDS products, we immediately consulted with our scientific advisors and legal counsel. On September 1, 2021, through our scientific advisors at Broughton Nicotine Service, we submitted a letter to FDA indicating our intention to conduct additional behavioral studies in support of and to supplement our PMTA, including on adult cessation, particularly in light of the new requirement for comparative efficacy data for tobacco- and non-tobacco-flavored e-liquids.

15. We were surprised then when, almost two weeks later, on September 14, 2021, FDA issued its Marketing Denial Order to us and indicated in Appendix B to the MDO that FDA had not reviewed the Broughton letter because it was "received near the completion of the scientific review."

16. We were even further surprised when, later, in response to a request under the Freedom of Information Act, we learned that FDA's "scientific review" apparently consisted of only two "check-the-box" forms —each of which was only three pages long (without the attached list of our subject products). Copies of these two "check the box" reports are attached hereto as **Exhibits A** and **B**.

17. We also received from FDA in response to a Freedom of Information Act request our "Technical Project Lead" report. A copy of the Technical Project Lead report is attached hereto as **Exhibit C**.

18. Subsequently, FDA has published on its website a sample "Technical Project Lead" report for flavored ENDS products. We have noted that, other than the company and product names, our Technical Project Lead report is essentially identical to the one posted on FDA's website, which leads us to suspect an identical,

cookie-cutter report, has been prepared for every single one of the more than 1 million flavored ENDS products for which FDA has issued an MDO to date.

19. I have reviewed FDA's MDO for our products, as well as the September 9, 2021 press release that FDA has put out regarding its enforcement priorities for ENDS products. As a result of the MDO and FDA's categorizing our products as among the "highest priority" for enforcement, we have stopped manufacturing any of the ENDS products that were subject to the MDO.

20. The ENDS products that were subject to the MDO are 100 percent of the ENDS products that we manufacture for sale in the United States. Since we have been required to stop manufacturing these products by FDA, we now only manufacture a limited number of products for export. The e-liquid products we manufacture for export represented only approximately 10% of our total revenue prior to the issuance of the MDO.

21. If we do not receive relief from the Court in the form of a stay of the MDO in approximately the next two weeks, we will lose approximately 90 percent of our historic revenues and will be forced to lay off most of our employees and potentially shut down our operations if we cannot find an alternative source of revenue.

22. Further, even if we were to receive a stay of the Marketing Denial Order further down the road, because other e-liquid companies have not received marketing denial orders, we would likely lose market share to them and the associated customer goodwill and contractual relationships with distributors of our e-liquid products.

I declare under penalty of perjury under the laws of the United States of America that the foregoing is true, complete, and correct.

Dated: Oct. 5, 2021 /s/ JON ROSE
JON ROSE