No. 21-3855

In the United States Court of Appeals for the Sixth Circuit

TURNING POINT BRANDS, INC. AND TPB INTERNATIONAL, LLC,
PETITIONERS,

v.

UNITED STATES FOOD AND DRUG ADMINISTRATION,
RESPONDENT.

ON PETITION FOR REVIEW OF A FINAL MARKETING DENIAL ORDER BY THE UNITED STATES FOOD AND DRUG ADMINISTRATION

EMERGENCY MOTION FOR A STAY PENDING REVIEW AND FOR EXPEDITED CONSIDERATION

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INTRODUCTION

Pursuant to Federal Rules of Appellate Procedure 18 and 27, petitioners Turning Point Brands, Inc. and TPB International, LLC (collectively, TPB) respectfully request an emergency stay pending this Court's resolution of their petition for review, filed on September 22, 2021, as well as expedited consideration. Respondent, the U.S. Food and Drug Administration (FDA), has indicated its opposition to a stay but consents to expedited consideration. TPB respectfully requests a ruling as soon as practicable.

This is a quintessential case for staying unlawful administrative action pending judicial review. The North Star of administrative law is that agencies cannot induce regulated parties to rely on agency representations about regulatory requirements, then penalize them using unannounced, after-the-fact criteria. But that is precisely what FDA did here.

Petitioners manufacture electronic nicotine delivery system (ENDS) products (*e.g.*, vaping products). To market these products, petitioners need FDA authorization, but FDA lets companies continue selling certain products pending FDA's review. FDA repeatedly instructed the industry that, to obtain marketing authorization, they did *not* need to produce long-term studies. Instead, FDA recommended submitting scientific-literature reviews,

consumer-perception studies, or other alternatives to show that ENDS products are "appropriate for the protection of the public health," 21 U.S.C. § 387j(c)(2)(A).

TPB took FDA at its word, spending two years and $12 million developing an 81,000-page application package. TPB's studies demonstrated that TPB's products help adult smokers transition away from riskier traditional cigarettes. Those studies confirmed that youth users do not currently purchase TPB products and there is virtually zero likelihood that they will in the future.

But on September 14, FDA emailed TPB a terse Marketing Denial Order with one paragraph of reasoning, requiring TPB to immediately withdraw 490 products from the market. FDA's Order was based on criteria FDA never announced beforehand. FDA reasoned that TPB failed to conduct "a randomized controlled trial and/or longitudinal cohort study" or other studies performed "over time" to show that TPB's specific flavored products help adult users stop smoking more than tobacco-flavored products do. A12. Yet FDA previously deemed these studies unnecessary. And FDA rejected TPB's other studies as inherently unreliable, even though FDA previously

encouraged these studies. The Administrative Procedure Act (APA) forbids FDA from engaging in that bait-and-switch.

Further, the APA compels agencies to adequately justify their rulings. But FDA's Order arbitrarily disregarded key evidence. FDA weighed the general risks that youth would use flavored ENDS products against the benefits from adult smokers transitioning to TPB's flavored products. TPB agrees youth usage is concerning. But FDA concluded that the risks outweighed the benefits only by refusing to consider TPB's specific evidence that its products do *not* reach or attract youth. FDA also imposed a heightened evidentiary standard for proving that TPB's ENDS products help adults quit or reduce smoking, yet required less of itself when substantiating risks to youth. And FDA failed to consider the consequences of an across-the-board prohibition on flavored ENDS for millions of adult former smokers who will suddenly lose access to the products they have depended on to quit.

The APA also requires agencies to support their actual actions. FDA's reasoning only asserts purported evidentiary shortcomings affecting ENDS products with flavors *other than* tobacco or menthol. A1-2. But FDA's Order

also prohibits many of TPB's tobacco-, menthol-, and un-flavored products without rhyme or reason.

TPB now faces obvious irreparable harm. FDA's Order forces TPB immediately to stop selling 490 ENDS products nationwide, abruptly wiping out $5 million a year in revenues. A38. TPB cannot recover those massive costs from FDA even if it prevails, given sovereign immunity. Meanwhile, a stay would not harm FDA, which previously set a 2022 deadline for submitting applications for ENDS products. The public interest favors requiring FDA to follow basic APA requirements before forcing millions of products off the market. A mass exodus of TPB's products also risks pushing countless smokers back to traditional cigarettes, which FDA has portrayed as a terrible public-health outcome.

This Court should grant a stay pending its disposition of the petition for review. A stay would restore the status quo ante; like manufacturers awaiting FDA adjudication of other applications, TPB could keep selling its products. At a minimum, the Court should expedite consideration of this petition.

BACKGROUND

A. The Tobacco Control Act

The Family Smoking Prevention and Tobacco Control Act of 2009 (TCA), 21 U.S.C. § 387 *et seq.*, mandated a novel premarket review process for new tobacco products introduced to the market after 2007. *Id.* § 387j(a)-(b). Manufacturers of such products generally must seek FDA pre-clearance by filing a Premarket Tobacco Product Application (PMTA). *Id.* FDA then determines whether marketing that product would be "appropriate for the protection of the public health." *Id.* § 387j(c)(2)(A). If so, FDA must clear the product for sale to consumers. *Id.* § 387j(c)(1)(A), (d). Marketing new products without FDA authorization triggers severe civil and criminal penalties, including possible imprisonment. *Id.* §§ 331(a)-(c), 332-334, 387b(6).

Originally, the TCA applied only to "cigarettes," "smokeless tobacco," and similar listed products. To regulate "other tobacco products," FDA had to issue "regulation[s] deem[ing]" those products "subject to" the TCA. *Id.* § 387a(b). Thus, as of the TCA's 2009 enactment, manufacturers could lawfully market and sell ENDS products without seeking FDA authorization.

Seven years passed. The ENDS industry flourished, fueled by promising signs that ENDS products could help adult smokers transition from traditional cigarettes to lower-risk alternatives. FDA agreed with that aim. *See* FDA Comm'r Gottlieb, *Protecting American Families: Comprehensive Plan for Nicotine and Tobacco* (June 28, 2017), https://tinyurl.com/3k42ye82.

B. FDA's Regulation of ENDS Products

In 2016, FDA issued the "Deeming Rule," defining all ENDS products as new "tobacco products" subject to premarket authorization. 81 Fed. Reg. 28,974 (May 10, 2016). Thus, "[w]hen the Deeming Rule took effect in August 2016, as many as 25,000 products already on the market … would suddenly be in violation of" the TCA's premarket-authorization requirement. *Vapor Tech. Ass'n v. FDA*, 977 F.3d 496, 498 (6th Cir. 2020).

Yet FDA had never announced what evidence ENDS manufacturers needed to provide to file adequate PMTAs. That gap placed manufacturers in a bind. Rigorous studies are time-consuming and cost millions of dollars. But without knowing what kinds of studies FDA would require, manufacturers risked bankrupting themselves if they invested in studies that FDA later dismissed.

To address this Catch-22, FDA's Deeming Rule announced that FDA would exercise its enforcement discretion and allow ENDS products to remain on the market while FDA developed rules for PMTAs. 81 Fed. Reg. at 28,977-78. Again in 2017, FDA announced plans to issue "regulations outlining what information" it expected in PMTAs. *FDA Announces Comprehensive Regulatory Plan to Shift Trajectory of Tobacco-Related Disease, Death* (July 27, 2017), https://tinyurl.com/4e4xutd5. But in 2018, FDA acknowledged it had yet to "delineate key requirements" of the PMTA process. FDA, *Statement from FDA Comm'r Scott Gottlieb* (Mar. 14, 2018), https://tinyurl.com/22zuh3b4. By early 2019, FDA still had not determined the "rules of the road" for PMTAs. *Agriculture, Rural Development, Food and Drug Administration, and Related Agencies Appropriations for 2020: Hearings Before a Subcomm. of the H. Comm. on Appropriations*, 116th Cong. 35 (2019) (statement of FDA Comm'r Gottlieb).

FDA thus repeatedly adjusted PMTA deadlines for ENDS products. In 2016, FDA prescribed a 2018 deadline. 81 Fed. Reg. at 28,978. In 2017, FDA pushed that deadline to 2022. A116-17. In March 2019, FDA pivoted to a 2021 deadline for ENDS products with flavors other than tobacco, menthol, or mint.

A117. FDA explained that tobacco, menthol, and mint flavors should likely be treated differently, and retained the 2022 deadline for those products. A118.

C. FDA's Court-Imposed Application Deadlines

Meanwhile, in the U.S. District Court for the District of Maryland, anti-ENDS advocates challenged FDA's guidance extending application deadlines and sought an injunction compelling FDA to receive all ENDS applications within 4 months. *Vapor Tech.*, 977 F.3d at 499 (summarizing this litigation).

FDA objected to any court-ordered deadlines, but counter-proposed a 10-month deadline for receiving applications and a one-year period for FDA review. A119. FDA considered these deadlines feasible only because FDA expected to receive at most 6,800 PMTAs. A123.

In July 2019, the district court issued an injunction requiring FDA to give ENDS manufacturers ten months (until May 2020) to file all PMTAs, and giving FDA a year to adjudicate applications. *Vapor Tech.*, 977 F.3d at 499-500. The district court later moved the application deadline to September 2020 given the added challenges from COVID. *Id.*

D. FDA's Instructions for ENDS Applications

In June 2019, FDA issued final guidance on ENDS applications. FDA stated: "Given the relatively new entrance of ENDS … FDA understands that limited data may exist from scientific studies and analyses." A68. FDA reassured manufacturers: "[I]n general, FDA does not expect that applicants will need to conduct long-term studies to support an application." A69.

FDA's September 2019 proposed rule governing PMTA requirements again urged the ENDS industry to follow FDA's June 2019 guidance. 84 Fed. Reg. 50,556, 50,619 (Sept. 25, 2019). The preamble reiterated that, while "FDA must be able to determine the likely health risks of the new tobacco product," FDA did "not expect that long-term clinical studies (*i.e.*, those lasting approximately 6 months or longer) will need to be conducted for each PMTA." *Id.* This rule remains pending.

E. TPB's Applications

TPB is a publicly traded company and a leading manufacturer, marketer, and distributor of alternative smoking products and accessories, including e-cigarettes, vaporizers, and e-liquids. Active in the ENDS market for nearly a decade, TPB's portfolio of products are available in nearly 200,000

U.S. retail locations. The products at issue here are 30 and 60 mL bottles of e-liquid, which customers use in refillable "open-system" vaporizers. TPB primarily sells these products in adult-only vape or tobacco shops, or online through age-verified purchasing systems. A35.

In 2018, TPB asked FDA for a meeting about what studies FDA required for a successful application. FDA instead provided a written clarification that data "from a variety of sources" could suffice, and that "it may be possible to support a marketing order for an ENDS product without conducting new nonclinical or clinical studies." A45, A52.

Following FDA's guidance, TPB spent two years and $12 million amassing evidence to show that its products are appropriate for the protection of public health. A36. TPB undertook dozens of clinical, chemistry, stability, microbiology, toxicology, survey, qualitative, and custom commercial market-research studies; population-health modeling; and extensive literature reviews. TPB's original studies included a 500-person survey examining actual use of TPB's products and a 2,000+-person survey examining perceptions and likelihood of use of TPB's products. A165-78. Consistent with FDA's instructions, TPB did not submit long-term studies. A37.

On September 5, 2020, TPB submitted a package of applications spanning some 81,000 pages and covering hundreds of products comprising the vast majority of its proprietary ENDS offerings. A36. The application at issue covered 525 of TPB's e-liquid products, including unflavored, tobacco-flavored, and menthol-flavored varieties, as well as flavors like Latte, Lemon Meringue, and Sea Salt Blueberry. A145-50.

TPB's application featured myriad rigorous studies bearing upon whether TPB's products are "appropriate for the protection of the public health," 21 U.S.C. § 387j(c)(2)(A). Among other studies, TPB submitted:

- A survey study of TPB's adult users, which revealed that 71% of people who regularly smoked cigarettes in the 30 days before using TPB's product had since ceased—making TPB's products about 10 times more effective than FDA-approved nicotine gum or patches. A166-67. TPB's adult users consistently identified flavor variety and quality as the top reasons for using TPB's products to quit smoking. A172-74.
- An original study reviewing over 2.8 million online conversations, which similarly identified flavor-choice as a key cessation tool. A157.
- A live-interview study, which showed that nearly 93% of ENDS users who previously smoked combustible cigarettes no longer did. A168.
- A survey study of over 2,000 never-smokers, former-smokers, current-smokers, and current ENDS users, which suggested virtually "zero risk" that youth would use TPB's products. A177.
- An analysis of TPB's verified sales data, which confirmed the lack of youth usage. A166.

- An analysis of TPB's robust efforts to prevent youth usage at points of sale. A153-56, A158-64.

F. FDA's Form Letter Denying Marketing Authorization

1. FDA expected up to 6,800 product applications. It received *6.5 million*, exceeding its planned-for volume "by orders of magnitude." FDA, *Deemed Product Review: A Conversation with the Office of Science* (June 11, 2021), https://tinyurl.com/ym76bv5s. This "unprecedented number" presented FDA with "challenges," especially "due to the size, complexity and diversity" of applications. Mitch Zeller, *Perspective: FDA's Progress on Review of Tobacco Product Applications Submitted by the Sept. 9, 2020 Deadline*, FDA (Feb. 16, 2021), https://tinyurl.com/ykhfryxn.

FDA's court-ordered deadline elapsed on September 9, 2021. On September 14, 2021, FDA emailed TPB a Marketing Denial Order ordering TPB to pull from the market 490 e-liquid products—virtually all of its offerings. A1-14. FDA's Order covers products that FDA considers "flavored," but also products FDA considers *non*-flavored. A17 n.2.

FDA stated the "key basis" for its decision in one paragraph: "All of your PMTAs lack sufficient evidence demonstrating that your flavored ENDS will provide a benefit to adult users that would be adequate to outweigh the

risks to youth." A1. FDA faulted TPB for not using "a randomized controlled trial and/or longitudinal cohort study" to contrast "your flavored ENDS products" with "an appropriate comparator tobacco-flavored ENDS." *Id.*

FDA acknowledged that TPB *did* submit "clinical studies with abuse liability outcomes and a cross-sectional survey evaluating patterns of use." *Id.* But FDA deemed that evidence inadequate "because it does not evaluate product switching or cigarette reduction resulting from use of these products over time." A1-2. FDA thus reviewed TPB's application only to see what types of studies TPB included; considered TPB's types of studies per se inadequate; and did not "assess other aspects of the applications." *Id.*

FDA issued materially identical denial orders to hundreds of other companies for the same reason. *E.g.*, C.A.2 Dkt. 21-2426, ECF 2 (Marketing Denial Order for Magellan); A127-28.

2. Only on September 27—after TPB sought judicial review of FDA's Order—did FDA's lawyers disclose the Technical Project Lead Review underlying its Order. An FDA Branch Chief issued that technical review on September 14. A15. The Director of FDA's Office of Science concurred and issued the Order an hour later. *Id.*

Very little of FDA's technical review mentions TPB, its studies, or its products. The review instead addressed flavored ENDS products generally. *Compare* A15-33, *with* A125-44 (virtually identical report). FDA balanced the risk of youth usage against the benefits to adult users who rely on flavored ENDS products, and found TPB wanting for reasons that apparently apply to all flavored ENDS products. FDA acknowledged that youth usage is falling, but concluded that health risks remain based on generalized studies. A20-23. FDA did not consider any of TPB's product-specific evidence about why its products do not appeal to youth, or TPB's evidence that its distribution platforms prevent youth access. A25 n.19, A28.

As to adult smoking cessation, FDA concluded that only long-term studies analyzing specific ENDS products and comparing specific flavors of those products against tobacco-flavored comparators would be adequately "rigorous" evidence of health benefits to overcome FDA's general concerns about youth usage. FDA rejected TPB's "clinical studies" and "cross-sectional survey" as "not sufficiently strong," simply because those types of studies do not measure quitting or smoking reduction "over time." A28. FDA thus did not analyze the actual studies.

3. FDA is still reviewing PMTAs for some 100,000 to 200,000 products that TPB's competitors can keep selling in the meantime.[1] Meanwhile, TPB must remove its products from the market to avoid FDA enforcement action "without further notice." A1. FDA has identified "[p]roducts … with a Marketing Denial Order" as "among our highest enforcement priorities," Mitch Zeller, *Perspective: FDA's Progress on Tobacco Product Application Review and Related Enforcement* (Sept. 9, 2021), https://tinyurl.com/2brfm8ce, with civil monetary penalties, seizure, and criminal penalties on the table.

TPB petitioned for review on September 22, 2021, and now seeks an emergency stay of FDA's Order and expedited consideration.

LEGAL STANDARD

This Court has authority to review FDA's Order, *see* 21 U.S.C. § 387*l*(a)(1)(B), and venue is proper because Turning Point Brands, Inc. has its principal place of business in this Circuit, *id.* This Court has discretion to

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[1] David Lim & Lauren Gardner, *Chaos in the Vaping Industry Ensues After FDA's Flavor Bans*, Politico (Sept. 24, 2021), https://tinyurl.com/wsn5aehd; FDA, *Deemed New Tobacco Product Applications List*, https://tinyurl.com/2t2xz5ze (last visited Sept. 30, 2021).

stay FDA's Order pending consideration of TPB's petition for review. *See id.* § 387*l*(b) (authorizing "interim relief"); 5 U.S.C. § 705 (authorizing "postpon[ing] the effective date of an agency action" pending judicial review). Whether to grant a stay depends on (1) whether petitioners have "made a strong showing" that they are "likely to succeed on the merits"; (2) whether they "will be irreparably injured absent a stay"; (3) "whether issuance of the stay will substantially injure the other parties interested in the proceeding"; and (4) "where the public interest lies." *Nken v. Holder*, 556 U.S. 418, 426 (2009) (quotation omitted).

ARGUMENT

TPB satisfies the stay criteria. TPB has a strong likelihood of succeeding on the merits because FDA blatantly violated the APA. Staying the Order pending judicial review would also stave off TPB's immense, impending irreparable harm without prejudicing FDA or the public interest.

I. TPB Is Likely to Succeed on the Merits

Among its most serious APA shortcomings, FDA's Order contradicts FDA's prior recommendations about the types of studies applicants should include—recommendations that TPB diligently followed when investing $12

million in studies that FDA now deems per se inadequate. Further, FDA's analysis is self-contradictory and improperly ignores the highly relevant countervailing evidence TPB submitted. Finally, FDA's reasoning exclusively focuses on evidentiary shortcomings for "flavored products," yet FDA's Order prohibits TPB from selling *non*-flavored products too.

A. FDA's Order Impermissibly Contradicts FDA's Prior Instructions

The APA prohibits agencies from "depart[ing] from a prior policy *sub silentio* or simply disregard[ing] rules that are still on the books." *FCC v. Fox Television Stations, Inc.*, 556 U.S. 502, 515 (2009); *accord Menkes v. Dep't of Homeland Sec.*, 486 F.3d 1307, 1310, 1314 (D.C. Cir. 2007). Due-process principles require agencies to "provide regulated parties fair warning" of what the agency "prohibits or requires" before punishing noncompliance. *Christopher v. SmithKline Beecham Corp.*, 567 U.S. 142, 156 (2012) (quotation omitted). Agencies cannot announce new positions, then create "unfair surprise" by penalizing regulated parties for their "good-faith reliance" on the agency's prior representations. *Id.* at 156-57 (quotation omitted). That fair-warning principle also governs informal guidance. *E.g.*, *Morton v. Ruiz*, 415 U.S. 199, 235 (1974) (agency must comply with internal procedures); *PHH*

Corp. v. CFPB, 839 F.3d 1, 48 (D.C. Cir. 2016) (agency cannot depart without notice from repeated, non-binding letter guidance), *reinstated in relevant part en banc*, 881 F.3d 75, 83 (D.C. Cir. 2018).

1. FDA's Order defies this bedrock rule. FDA's Order faults TPB for failing to conduct long term studies, *i.e.*, a "randomized controlled trial and/or longitudinal cohort study," or similarly "reliabl[e] and robust[]" study "over time" comparing the effectiveness of "flavored" vs. "tobacco-flavored ENDS" products in promoting smoking cessation. A1. And FDA now deems "cross-sectional surveys," "[c]onsumer perception studies," and the "general scientific literature" as categorically unreliable on this score. A26-27.

But FDA's prior instructions induced these purported shortcomings. As FDA's technical report acknowledges, FDA's industry guidance reassured manufacturers that FDA "did not expect that applicants would need to conduct long-term studies." A27 n.23. FDA repeatedly disavowed requiring long-term studies, including "randomized controlled clinical trials." *E.g.*, A45, A51, A69, A93-94, A102-03; 84 Fed. Reg. at 50,619.

Worse, FDA's prior instructions specifically addressed smoking cessation and flavored products by encouraging submission of the very

evidence FDA now rejects. FDA "support[ed] the use of different types of studies, methods, instruments and analyses" from "a variety of sources." A52. As to cessation, FDA offered "[e]xamples of information that FDA recommends" as evidence of "likelihood of … cessation," A94, including the studies FDA now deems unreliable, namely "[p]ublished literature" and "observational studies (perception, actual use, or both) examining cessation behaviors." *Id.*; *accord* A52. As to flavored products, FDA asked manufacturers to "describe consumer perceptions among current ENDS users and other tobacco users for appeal." A98. How? By supplying "published reports and data on consumer perceptions," including "data you collect on consumer perceptions" as to "intentions to use the product." A94; *accord* A44.

2. FDA's about-face creates obvious unfair surprise. FDA issued guidance to "assist persons submitting [PMTAs] for [ENDS]" products, "to improve the efficiency of application submission and review." A57. FDA expressly sought to "enable ENDS manufacturers to consider and strengthen their applications based on the final PMTA for ENDS guidance." A119.

TPB spent $12 million submitting myriad studies that satisfied FDA's guidance. FDA cannot now penalize TPB for following FDA's instructions. FDA's technical review acknowledges that FDA moved the evidentiary goalposts *after* the fact, based on what FDA "learned" from "review[ing] PMTAs for flavored ENDS so far." A17 n.6. But if FDA wanted to change its evidentiary requirements based on its "deepened … understanding of the [appropriate for the protection of public health] evaluation," A25, FDA should have acknowledged that shift *before* the application deadline and offered a "detailed justification." *Encino Motorcars, LLC v. Navarro,* 136 S. Ct. 2117, 2125 (2016) (quotation omitted). The APA forbids FDA from springing new requirements on regulated parties after it is too late to comply.

B. FDA's Reasoning Is Arbitrary

FDA also failed to "articulate a satisfactory explanation for [its] action." *Louisville Gas & Elec. Co. v. FERC*, 988 F.3d 841, 846 (6th Cir. 2021) (quotation omitted). FDA purported to weigh the risks of youth usage against the benefits of flavored ENDS products in promoting adult smoking cessation or reduction, but arbitrarily disregarded key evidence.

1. FDA's conclusions about the risks of youth usage anchor its whole approach. FDA continues to view youth usage as a substantial threat, citing general studies about youth usage of "closed-system" ENDS—*i.e.*, small, highly portable and often disposable devices—and generic scientific literature and consumer studies showing that flavors appeal to youth more than tobacco-flavored or unflavored products. A20-23.

TPB agrees that any youth usage is unacceptable, which is why TPB took pains to prove the many ways its products *mitigate* those risks. A19. But FDA refused to consider evidence that its general risk assessment does not apply to TPB's products. TPB sells bottles of e-liquid products designed for use in things like large tanks. A35. Former FDA Commissioner Gottlieb put it best: "The kids just don't like those big open-tank contraptions." Nicholas Florko, *Former FDA Commissioner Calls for a Full Ban on Pod-Based E-Cigarettes*, Stat (Nov. 12, 2019), https://tinyurl.com/mdrjpyhw. TPB produced studies indicating that youth do *not* use TPB's products, including a 2,000+-person survey suggesting virtually "zero risk" that never-smokers, including younger users, would use TPB's products, A177, plus sales data confirming the

lack of youth usage, A166. FDA's lone response: the agency "did not assess" these "other aspects of the application." A2, A28.

FDA likewise refused to consider evidence of TPB's successful efforts to prevent youth access. TPB's application detailed its thorough auditing and age-verification measures and adults-only marketing strategy. A153-56, A158-64. But FDA acknowledged "not evaluat[ing] any" of this evidence. A25 n.19. Instead, citing *other* applications, FDA claimed to be "[un]aware of access restrictions that, to date, have been successful in sufficiently decreasing the ability of youth to obtain and use ENDS." *Id.* Yet FDA previously confirmed that age-verification protections like TPB's "would protect kids" by "preventing access to flavored" products. FDA, *Statement from Comm'r Gottlieb, M.D., on Proposed New Steps to Protect Youth by Preventing Access to Flavored Tobacco Products and Banning Menthol in Cigarettes* (Nov. 15, 2018), https://tinyurl.com/3na4ec87. Ignoring this contrary evidence was plainly arbitrary and capricious. *See Clark County v. FAA*, 522 F.3d 437, 442-43 (D.C. Cir. 2008).

2. FDA then concluded that, to outweigh what FDA saw as the high risk of youth usage, TPB must produce particularly rigorous evidence of

countervailing benefits to adult smokers. A1-2, A28. Thus, if FDA miscalculated the risks of youth usage, it also mis-calibrated the evidentiary standard for judging benefits to adult smokers.

Regardless, FDA's sky-high evidentiary mandate for showing smoker benefits is arbitrary. FDA demands product-specific studies contrasting the appeal of flavored vs. tobacco-flavored products. A26-27. Yet FDA saw no need for such specifics in asserting risks to youth. A21-23, A26 n.22. Similarly, to show that adult smokers reduce or stop smoking, FDA deemed all "cross-sectional survey[s]," "[c]onsumer perception studies," and "general scientific literature" surveys inherently unreliable. A1-2, A26-27. Yet FDA called these same types of studies "the best available evidence" of youth usage. A26 n.22.

In a footnote (A25 n.20), FDA's technical review speculates that product-specific features drive adult cessation, but not youth initiation. But again, TPB's analyses (which FDA ignored) refute FDA's assertion. It defies credulity that product-specific factors—like the difficulty of obtaining TPB's e-liquids outside age-controlled environments, the cumbersomeness of large e-liquid containers, and particular flavors that lack youth appeal—do not affect youth usage. FDA's "self-contradictory, wandering logic does not constitute

an adequate explanation." *Del. Dep't of Nat. Res. & Env't Control v. EPA*, 785 F.3d 1, 16 (D.C. Cir. 2015) (quotation omitted).

FDA also failed to "adequately consider the impact of" its extraordinarily specific evidentiary standard. *Ackerman v. U.S. Dep't of Agric.*, 995 F.3d 528, 533-34 (6th Cir. 2021). FDA ignores the consequences of employing a rationale that apparently rejects *all* flavored ENDS products for insufficient evidence using cookie-cutter reasoning. *E.g.*, A125-44. Those denials are forcing a mass exodus of products from the market—products that FDA acknowledges former smokers rely upon to stop smoking. A119. FDA previously cautioned that this "public health outcome" was to be "avoided if at all possible" due to the "serious" risk that former adult smokers would switch back to cigarettes. A119-20. FDA likewise failed to consider that its denials could cause ENDS users to turn to the illicit market—another problem FDA previously recognized. *See* 81 Fed. Reg. at 29,007. Now, FDA says nothing about what will happen to millions of former smokers.

C. The Order Contradicts FDA's Stated Reasoning

FDA's Order also violates the cardinal APA rule that the agency's rationale must actually support its decision. *Motor Vehicle Mfrs. Ass'n of U.S.*,

Inc. v. State Farm Mut. Auto. Ins. Co., 463 U.S. 29, 43 (1983). FDA's reasoning exclusively focuses on evidentiary requirements for *flavored* ENDS products, which FDA defines to exclude "tobacco-flavored" and "menthol" products. A17 n.2, A19, A21.

Yet FDA is forcing TPB to pull *non*-flavored products from the market. FDA's Order applies to "Authentic Tobacco" and "Bold Tobacco," yet not "Classic Tobacco" (which FDA is still considering). *Compare* A5 *and* A12, *with* A148. Those are the same flavors with the same formulations; they just use different names across product lines. A147. The same goes for "Ripe Tobacco" (forbidden) and "Smooth Tobacco" (reprieve), and for "Mint" (banned) and "Mighty Menthol" (allowed for now). *Compare* A7 *and* A13, *with* A146 *and* A148.

It is anyone's guess why some of these products must exit the market immediately, yet others might pass muster if FDA actually reviews TPB's studies. FDA has allowed competitors to sell similar non-flavored products while FDA reviews other applications. Lim & Gardner, *Chaos in the Vaping Industry*, *supra*. FDA's arbitrary treatment independently warrants vacatur.

II. Petitioners Face Irreparable Harm Absent a Stay

Unlawful agency orders that impose immense financial burdens on regulated parties present a classic type of irreparable harm. As the Supreme Court recently confirmed, the lack of a "guarantee of eventual recovery" of monetary losses is irreparable harm. *See Al. Ass'n of Realtors v. Dep't of Health & Hum. Servs.*, 2021 WL 3783142, at *4 (U.S. Aug. 26, 2021).

Here, even if TPB prevails, it is guaranteed not to recover the losses FDA's Order inflicts because federal agencies enjoy sovereign immunity. *E.g.*, *E. Bay Sanctuary Covenant v. Biden*, 993 F.3d 640, 677 (9th Cir. 2021). "[A]lmost al[l]" cases involving compliance with later-invalidated agency action thus "produce[] the irreparable harm of nonrecoverable compliance costs." *Texas v. EPA*, 829 F.3d 405, 433 (5th Cir. 2016) (quotation omitted).

TPB's losses from the Order are substantial. FDA declared scores of TPB's products illegal effective immediately and has confirmed that enforcement is imminent, deeming products with Marketing Denial Orders—like TPB's—as among FDA's "highest enforcement priorities." Zeller, *Perspective* (Sept. 9, 2021), *supra*. To comply, TPB has begun dismantling components of its business and pulling thousands of products from shelves

nationwide. A38. TPB will be forced to refund retailers some $1 million for the affected products. *Id.* And TPB projects annual lost revenues of $5 million and annual lost profits of $3 million. *Id.* This textbook irreparable harm warrants a stay.[2]

III. A Stay Will Not Harm FDA and Serves the Public Interest

Staying the Order pending judicial review will not harm FDA or the public interest. FDA originally saw no issue with deferring resolution of ENDS PMTAs until 2022. *Supra* p. 7. FDA is still assessing PMTAs covering more than 100,000 ENDS products, all of which still remain on the market pending FDA's review. FDA cannot credibly argue that a modest delay of this Order pending judicial review would materially harm the agency.

The public interest supports a stay. TPB's specific products are remarkably effective in prompting adult smokers to quit and transitioning them permanently to TPB's alternative products. FDA has long agreed with

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[2] Asking FDA to stay its Order pending judicial review would have been impracticable given the Order's immediate, disruptive effect. *Cf.* Fed. R. App. P. 18(a)(1). FDA can take months to resolve such requests. Further illustrating futility, FDA on September 17 rebuffed TPB's request for enforcement forbearance, instead putting companies like TPB at the top of its enforcement list, *supra* pp. 14-15.

that important public-health goal. *Supra* p. 5. In FDA's own telling, "[d]ramatically and precipitously reducing availability of [ENDS] products could present a serious risk that adults, especially former smokers, who currently use ENDS products … would migrate to combustible tobacco products," thereby potentially reversing public-health gains from declining smoking rates. A120.

Meanwhile, FDA cannot plausibly claim that keeping TPB's products on the market will fuel youth usage of ENDS when FDA refused to engage with TPB's specific evidence showing the opposite. *Supra* pp. 20-21. The public also benefits when courts require agencies to heed statutory limits on their authority before remaking the marketplace. *See Clarke v. Office of Fed. Hous. Enter. Oversight*, 355 F. Supp. 2d 56, 66 (D.D.C. 2004).

IV. At a Minimum, Expedited Consideration Is Warranted

Pursuant to Federal Rules of Appellate Procedure 2, 17, and 27 and Sixth Circuit Rule 27(f), TPB respectfully requests expedited consideration of the petition. "Good cause" for expedited review exists because FDA's Order irreparably harms TPB. FDA has indicated it does not oppose expedited review under the following schedule:

File Administrative Record:	October 11, 2021
Opening Brief:	November 2, 2021
Respondent's Brief:	December 2, 2021
Reply:	December 20, 2021
Oral Argument:	At the earliest opportunity

CONCLUSION

For the foregoing reasons, this Court should stay FDA's Order pending judicial review, which would place TPB on par with companies with pending applications. At a minimum, the Court should expedite review.

Dated: September 30, 2021

Respectfully submitted,

/s/ Sarah M. Harris

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Attorneys for Petitioners Turning Point Brands, Inc. and TPB International, LLC

CERTIFICATE OF COMPLIANCE WITH TYPE-VOLUME LIMIT, TYPEFACE REQUIREMENTS, AND TYPE-STYLE REQUIREMENTS

1. This document complies with the word limit of Fed. R. App. P. 27(d)(2)(A) because, excluding the parts of the document exempted by Fed. R. App. P. 32(f) and Fed. R. App. P. 27(d)(2), this document contains 5,184 words.

2. This document complies with the typeface requirements of Fed. R. App. P. 32(a)(5) and the type-style requirements of Fed. R. App. P. 32(a)(6) because this document has been prepared in a proportionally spaced typeface using Microsoft Word in Century Expanded BT, size 14.

/s/ Sarah M. Harris

Attorney for Petitioners

CERTIFICATE OF CONFERENCE

I hereby certify that counsel for Petitioners Turning Point Brands, Inc. and TPB International, LLC conferred with FDA Counsel Alisa B. Klein on September, 28, 2021, who indicated that FDA i) opposed Petitioners' motion for a stay and ii) consented to Petitioners' request and proposed schedule for expedited consideration.

/s/ Sarah M. Harris

Attorney for Petitioners

CERTIFICATE OF SERVICE

Pursuant to Federal Rules of Appellate Procedure 15(c) and 25(d) and Sixth Circuit Rule 25(b)(1), I hereby certify that on September 30, 2021, true and correct copies of the foregoing **EMERGENCY MOTION FOR A STAY PENDING REVIEW AND FOR EXPEDITED CONSIDERATION** was filed with the Clerk's Office for the United States Court of Appeals for the Sixth Circuit using the CM/ECF system and was served by electronic mail upon the following persons:

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/s/ Sarah M. Harris

Attorney for Petitioners

ADDENDUM

Table of Contents

U.S. FOOD & DRUG ADMINISTRATION

U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov

September 14, 2021

DENIAL

TPB International, LLC
Attention: Brittani Cushman, Senior Vice President External Affairs
5201 Interchange Way
Louisville, KY 40229

FDA Submission Tracking Number (STN): PM0001093, see Appendix A

Dear Ms. Cushman:

We are denying a marketing granted order for the products identified in Appendix A.

Based on our review of your PMTAs[1], we determined that the new products, as described in your applications and specified in Appendix A, lack sufficient evidence to demonstrate that the marketing of these products is appropriate for the protection of the public health (APPH). Therefore, you cannot introduce or deliver for introduction these products into interstate commerce in the United States. Doing so is a prohibited act under section 301(a) of the FD&C Act, the violation of which could result in enforcement action by FDA.

If you choose to submit new applications for these products, you must fulfill all requirements set forth in section 910(b)(1). You may provide information to fulfill some of these requirements by including an authorization for FDA to cross-reference a Tobacco Product Master File.[Error! Bookmark not defined.] You may not cross-reference information submitted in the PMTAs subject to this Denial.

Based on review of your PMTAs, we identified the following key basis for our determination:

1. All of your PMTAs lack sufficient evidence demonstrating that your flavored ENDS will provide a benefit to adult users that would be adequate to outweigh the risks to youth. In light of the known risks to youth of marketing flavored ENDS, robust and reliable evidence is needed regarding the magnitude of the potential benefit to adult smokers. This evidence could have been provided using a randomized controlled trial and/or longitudinal cohort study that demonstrated the benefit of your flavored ENDS products over an appropriate comparator tobacco-flavored ENDS. Alternatively, FDA would consider other evidence but only if it reliably and robustly evaluated the impact of the new flavored vs. tobacco-flavored products on adult smokers' switching or cigarette reduction over time. Although your PMTAs contained clinical studies with abuse liability outcomes and a cross-sectional survey evaluating patterns of use, this evidence is not sufficient to show a benefit to adult smokers of using these flavored ENDS because it does not evaluate product switching or cigarette

[1] Premarket Tobacco Product Applications (PMTAs) submitted under section 910 of the Federal Food, Drug, and Cosmetic Act (FD&C Act)

reduction resulting from use of these products over time. Without this information, FDA concludes that your application is insufficient to demonstrate that these products would provide an added benefit that is adequate to outweigh the risks to youth and, therefore, cannot find that permitting the marketing of your new tobacco products would be appropriate for the protection of the public health.

We cannot find that the marketing of your new tobacco products is APPH. The review concluded that key evidence demonstrating APPH is absent. Therefore, scientific review did not proceed to assess other aspects of the applications. FDA finds that it is not practicable to identify at this time an exhaustive list of all possible deficiencies.

Your PMTAs lack sufficient information to support a finding of APPH; therefore, we are issuing a marketing denial order. Upon issuance of this order, your products are misbranded under section 903(a)(6) of the FD&C Act and adulterated under section 902(6)(A) of the FD&C Act. Failure to comply with the FD&C Act may result in FDA regulatory action without further notice. These actions may include, but are not limited to, civil money penalties, seizure, and/or injunction.

We encourage you to submit all regulatory correspondence electronically via the CTP Portal[2,3] using eSubmitter.[4] Alternatively, submissions may be mailed to:

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

The CTP Portal and FDA's Electronic Submission Gateway (ESG) are generally available 24 hours a day, seven days a week; submissions are considered received by DCC on the day of successful upload. Submissions delivered to DCC by courier or physical mail will be considered timely if received during delivery hours on or before the due date[5]; if the due date falls on a weekend or holiday, the delivery must be received on or before the preceding business day. We are unable to accept regulatory submissions by e-mail.

[2] For more information about CTP Portal, see https://www.fda.gov/tobacco-products/manufacturing/submit-documents-ctp-portal
[3] FDA's Electronic Submission Gateway (ESG) is still available as an alternative to the CTP Portal.
[4] For more information about eSubmitter, see https://www.fda.gov/industry/fda-esubmitter
[5] https://www.fda.gov/tobacco-products/about-center-tobacco-products-ctp/contact-ctp

If you have any questions, please contact Grace Kaiyuan, M.B.A., MT (ASCP), Regulatory Health Project Manager, at (240) 402 - 8240 or Grace.Kaiyuan@fda.hhs.gov.

Sincerely,

Digitally signed by Matthew R. Holman -S
Date: 2021.09.14 10:55:05 -04'00'

Matthew R. Holman, Ph.D.
Director
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[7]

New Tobacco Products Subject of This Letter

Common Attributes of PMTAs	
Date of Submission:	September 5, 2020
Date of Receipt:	September 5, 2020
Applicant:	TPB International, LLC
Product Manufacturer:	TPB International, LLC
Product Category:	ENDS (VAPES)
Product Sub-Category:	ENDS Component

[6] Brand/sub-brand or other commercial name used in commercial distribution.

Appendix A

New Tobacco Products Subject of This Letter

STN	PD Number	Product Name	Category	Subcategory	Package Type	Package Quantity	Characterizing Flavor	Additional Property
PM0001093	PD1	Solace Banana Dragonberry	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Solace Banana Dragonberry	Nicotine: 3mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093	PD2	Solace Banana Dragonberry	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Solace Banana Dragonberry	Nicotine: 6mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093	PD3	Solace Banana Dragonberry	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Solace Banana Dragonberry	Nicotine: 18mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093	PD4	Solace Banana Dragonberry	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Solace Banana Dragonberry	Nicotine: 36mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093	PD5	Solace Banana Dragonberry	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Solace Banana Dragonberry	Nicotine: 48mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093	PD6	Solace Berry Bash	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Berry Bash	Nicotine: 3mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093	PD7	Solace Berry Bash	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Berry Bash	Nicotine: 6mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093	PD8	Solace Berry Bash	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Berry Bash	Nicotine: 18mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093	PD9	Solace Berry Bash	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Berry Bash	Nicotine: 36mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093	PD10	Solace Berry Bash	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Berry Bash	Nicotine: 48mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093	PD11	Solace Blue Raspberry Ice	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Blue Raspberry Ice	Nicotine: 3mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093	PD12	Solace Blue Raspberry Ice	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Blue Raspberry Ice	Nicotine: 6mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093	PD13	Solace Blue Raspberry Ice	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Blue Raspberry Ice	Nicotine: 18mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093	PD14	Solace Blue Raspberry Ice	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Blue Raspberry Ice	Nicotine: 36mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093	PD15	Solace Blue Raspberry Ice	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Blue Raspberry Ice	Nicotine: 48mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093	PD16	Solace Blue Raspberry Lemonade Ice	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Raspberry Lemonade Ice	Nicotine: 3mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093	PD17	Solace Blue Raspberry Lemonade Ice	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Raspberry Lemonade Ice	Nicotine: 6mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093	PD18	Solace Blue Raspberry Lemonade Ice	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Raspberry Lemonade Ice	Nicotine: 18mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093	PD19	Solace Blue Raspberry Lemonade Ice	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Raspberry Lemonade Ice	Nicotine: 36mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093	PD20	Solace Blue Raspberry Lemonade Ice	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Raspberry Lemonade Ice	Nicotine: 48mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093	PD21	Solace Blueberry	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Blueberry	Nicotine: 3mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093	PD22	Solace Blueberry	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Blueberry	Nicotine: 6mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093	PD23	Solace Blueberry	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Blueberry	Nicotine: 18mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093	PD24	Solace Blueberry	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Blueberry	Nicotine: 36mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093	PD25	Solace Blueberry	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Blueberry	Nicotine: 48mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093	PD26	Solace Blue's Lemonade	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Blue's Lemonade	Nicotine: 3mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093	PD27	Solace Blue's Lemonade	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Blue's Lemonade	Nicotine: 6mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093	PD28	Solace Blue's Lemonade	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Blue's Lemonade	Nicotine: 18mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093	PD29	Solace Blue's Lemonade	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Blue's Lemonade	Nicotine: 36mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093	PD30	Solace Blue's Lemonade	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Blue's Lemonade	Nicotine: 48mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093	PD31	Solace Blue's Mango	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Blue's Mango	Nicotine: 3mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093	PD32	Solace Blue's Mango	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Blue's Mango	Nicotine: 6mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093	PD33	Solace Blue's Mango	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Blue's Mango	Nicotine: 18mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093	PD34	Solace Blue's Mango	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Blue's Mango	Nicotine: 36mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093	PD35	Solace Blue's Mango	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Blue's Mango	Nicotine: 48mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093	PD36	Solace Bold Tobacco	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Bold Tobacco	Nicotine: 3mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093	PD37	Solace Bold Tobacco	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Bold Tobacco	Nicotine: 6mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093	PD38	Solace Bold Tobacco	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Bold Tobacco	Nicotine: 18mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093	PD39	Solace Bold Tobacco	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Bold Tobacco	Nicotine: 36mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093	PD40	Solace Bold Tobacco	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Bold Tobacco	Nicotine: 48mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093	PD41	Solace Cherry Vanilla	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Cherry Vanilla	Nicotine: 3mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093	PD42	Solace Cherry Vanilla	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Cherry Vanilla	Nicotine: 6mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093	PD43	Solace Cherry Vanilla	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Cherry Vanilla	Nicotine: 18mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093	PD44	Solace Cherry Vanilla	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Cherry Vanilla	Nicotine: 36mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093	PD45	Solace Cherry Vanilla	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Cherry Vanilla	Nicotine: 48mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093	PD46	Solace Cool Mango	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Cool Mango	Nicotine: 3mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093	PD47	Solace Cool Mango	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Cool Mango	Nicotine: 6mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093	PD48	Solace Cool Mango	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Cool Mango	Nicotine: 18mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093	PD49	Solace Cool Mango	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Cool Mango	Nicotine: 36mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093	PD50	Solace Cool Mango	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Cool Mango	Nicotine: 48mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL

Appendix A

New Tobacco Products Subject of This Letter

PM0001093 PD51	Solace Cool Tobacco	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Cool Tobacco	Nicotine: 3mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093 PD52	Solace Cool Tobacco	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Cool Tobacco	Nicotine: 6mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093 PD53	Solace Cool Tobacco	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Cool Tobacco	Nicotine: 18mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD54	Solace Cool Tobacco	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Cool Tobacco	Nicotine: 36mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD55	Solace Cool Tobacco	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Cool Tobacco	Nicotine: 48mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD56	Solace Crème de Menthe	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Crème de Menthe	Nicotine: 3mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093 PD57	Solace Crème de Menthe	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Crème de Menthe	Nicotine: 6mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093 PD58	Solace Crème de Menthe	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Crème de Menthe	Nicotine: 18mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD59	Solace Crème de Menthe	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Crème de Menthe	Nicotine: 36mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD60	Solace Crème de Menthe	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Crème de Menthe	Nicotine: 48mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD61	Solace Dragon Fruit Menthol	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Dragon Fruit Menthol	Nicotine: 3mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093 PD62	Solace Dragon Fruit Menthol	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Dragon Fruit Menthol	Nicotine: 6mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093 PD63	Solace Dragon Fruit Menthol	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Dragon Fruit Menthol	Nicotine: 18mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD64	Solace Dragon Fruit Menthol	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Dragon Fruit Menthol	Nicotine: 36mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD65	Solace Dragon Fruit Menthol	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Dragon Fruit Menthol	Nicotine: 48mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD66	Solace Flavorless	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	None	Nicotine: 3mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093 PD67	Solace Flavorless	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	None	Nicotine: 6mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093 PD68	Solace Flavorless	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	None	Nicotine: 18mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD69	Solace Flavorless	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	None	Nicotine: 36mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD70	Solace Flavorless	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	None	Nicotine: 48mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD71	Solace Grape	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Grape	Nicotine: 3mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093 PD72	Solace Grape	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Grape	Nicotine: 6mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093 PD73	Solace Grape	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Grape	Nicotine: 18mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD74	Solace Grape	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Grape	Nicotine: 36mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD75	Solace Grape	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Grape	Nicotine: 48mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD76	Solace Juiced Apple	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Juiced Apple	Nicotine: 3mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093 PD77	Solace Juiced Apple	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Juiced Apple	Nicotine: 6mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093 PD78	Solace Juiced Apple	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Juiced Apple	Nicotine: 18mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD79	Solace Juiced Apple	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Juiced Apple	Nicotine: 36mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD80	Solace Juiced Apple	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Juiced Apple	Nicotine: 48mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD81	Solace Latte	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Latte	Nicotine: 3mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093 PD82	Solace Latte	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Latte	Nicotine: 6mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093 PD83	Solace Latte	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Latte	Nicotine: 18mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD84	Solace Latte	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Latte	Nicotine: 36mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD85	Solace Latte	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Latte	Nicotine: 48mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD86	Solace Lemon Lime Fusion	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Lemon Lime Fusion	Nicotine: 3mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093 PD87	Solace Lemon Lime Fusion	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Lemon Lime Fusion	Nicotine: 6mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093 PD88	Solace Lemon Lime Fusion	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Lemon Lime Fusion	Nicotine: 18mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD89	Solace Lemon Lime Fusion	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Lemon Lime Fusion	Nicotine: 36mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD90	Solace Lemon Lime Fusion	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Lemon Lime Fusion	Nicotine: 48mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD91	Solace Lemonade	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Lemonade	Nicotine: 3mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093 PD92	Solace Lemonade	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Lemonade	Nicotine: 6mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093 PD93	Solace Lemonade	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Lemonade	Nicotine: 18mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD94	Solace Lemonade	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Lemonade	Nicotine: 36mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD95	Solace Lemonade	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Lemonade	Nicotine: 48mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD96	Solace Mango	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Mango	Nicotine: 3mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093 PD97	Solace Mango	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Mango	Nicotine: 6mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093 PD98	Solace Mango	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Mango	Nicotine: 18mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD99	Solace Mango	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Mango	Nicotine: 36mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD100	Solace Mango	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Mango	Nicotine: 48mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD101	Solace Mint	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Mint	Nicotine: 3mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL

Appendix A

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PM0001093 PD102	Solace Mint	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Mint	Nicotine: 6mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093 PD103	Solace Mint	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Mint	Nicotine: 18mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD104	Solace Mint	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Mint	Nicotine: 36mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD105	Solace Mint	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Mint	Nicotine: 48mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD106	Solace Peach	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Peach	Nicotine: 3mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093 PD107	Solace Peach	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Peach	Nicotine: 6mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093 PD108	Solace Peach	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Peach	Nicotine: 18mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD109	Solace Peach	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Peach	Nicotine: 36mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD110	Solace Peach	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Peach	Nicotine: 48mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD111	Solace Pineapple	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Pineapple	Nicotine: 3mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093 PD112	Solace Pineapple	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Pineapple	Nicotine: 6mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093 PD113	Solace Pineapple	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Pineapple	Nicotine: 18mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD114	Solace Pineapple	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Pineapple	Nicotine: 36mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD115	Solace Pineapple	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Pineapple	Nicotine: 48mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD116	Solace Sea Salt Blueberry	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Sea Salt Blueberry	Nicotine: 3mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093 PD117	Solace Sea Salt Blueberry	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Sea Salt Blueberry	Nicotine: 6mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093 PD118	Solace Sea Salt Blueberry	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Sea Salt Blueberry	Nicotine: 18mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD119	Solace Sea Salt Blueberry	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Sea Salt Blueberry	Nicotine: 36mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD120	Solace Sea Salt Blueberry	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Sea Salt Blueberry	Nicotine: 48mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD121	Solace Seedless Watermelon	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Seedless Watermelon	Nicotine: 3mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093 PD122	Solace Seedless Watermelon	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Seedless Watermelon	Nicotine: 6mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093 PD123	Solace Seedless Watermelon	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Seedless Watermelon	Nicotine: 18mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD124	Solace Seedless Watermelon	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Seedless Watermelon	Nicotine: 36mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD125	Solace Seedless Watermelon	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Seedless Watermelon	Nicotine: 48mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD131	Solace Strawberry	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Strawberry	Nicotine: 3mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093 PD132	Solace Strawberry	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Strawberry	Nicotine: 6mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093 PD133	Solace Strawberry	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Strawberry	Nicotine: 18mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD134	Solace Strawberry	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Strawberry	Nicotine: 36mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD135	Solace Strawberry	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Strawberry	Nicotine: 48mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD136	Solace Strawberry Danish	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Strawberry Danish	Nicotine: 3mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093 PD137	Solace Strawberry Danish	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Strawberry Danish	Nicotine: 6mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093 PD138	Solace Strawberry Danish	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Strawberry Danish	Nicotine: 18mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD139	Solace Strawberry Danish	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Strawberry Danish	Nicotine: 36mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD140	Solace Strawberry Danish	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Strawberry Danish	Nicotine: 48mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD141	Solace Strawberry Kiwi	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Strawberry Kiwi	Nicotine: 3mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093 PD142	Solace Strawberry Kiwi	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Strawberry Kiwi	Nicotine: 6mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093 PD143	Solace Strawberry Kiwi	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Strawberry Kiwi	Nicotine: 18mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD144	Solace Strawberry Kiwi	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Strawberry Kiwi	Nicotine: 36mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD145	Solace Strawberry Kiwi	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Strawberry Kiwi	Nicotine: 48mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD146	Solace Strawberry Kiwi Ice	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Strawberry Kiwi Ice	Nicotine: 3mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093 PD147	Solace Strawberry Kiwi Ice	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Strawberry Kiwi Ice	Nicotine: 6mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093 PD148	Solace Strawberry Kiwi Ice	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Strawberry Kiwi Ice	Nicotine: 18mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD149	Solace Strawberry Kiwi Ice	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Strawberry Kiwi Ice	Nicotine: 36mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD150	Solace Strawberry Kiwi Ice	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Strawberry Kiwi Ice	Nicotine: 48mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD151	Solace Tangerine	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Tangerine	Nicotine: 3mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093 PD152	Solace Tangerine	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Tangerine	Nicotine: 6mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093 PD153	Solace Tangerine	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Tangerine	Nicotine: 18mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD154	Solace Tangerine	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Tangerine	Nicotine: 36mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD155	Solace Tangerine	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Tangerine	Nicotine: 48mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD156	Solace Tropic Strawberry	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Tropic Strawberry	Nicotine: 3mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093 PD157	Solace Tropic Strawberry	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Tropic Strawberry	Nicotine: 6mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL

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PM0001093 PD158	Solace Tropic Strawberry	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Tropic Strawberry	Nicotine: 18mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD159	Solace Tropic Strawberry	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Tropic Strawberry	Nicotine: 36mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD160	Solace Tropic Strawberry	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Tropic Strawberry	Nicotine: 48mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD161	Solace Tropical Fusion	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Tropical Fusion	Nicotine: 3mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093 PD162	Solace Tropical Fusion	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Tropical Fusion	Nicotine: 6mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093 PD163	Solace Tropical Fusion	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Tropical Fusion	Nicotine: 18mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD164	Solace Tropical Fusion	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Tropical Fusion	Nicotine: 36mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD165	Solace Tropical Fusion	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Tropical Fusion	Nicotine: 48mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD166	Solace Vanilla Bean	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Vamilla Bean	Nicotine: 3mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093 PD167	Solace Vanilla Bean	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Vamilla Bean	Nicotine: 6mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093 PD168	Solace Vanilla Bean	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Vamilla Bean	Nicotine: 18mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD169	Solace Vanilla Bean	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Vamilla Bean	Nicotine: 36mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD170	Solace Vanilla Bean	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Vamilla Bean	Nicotine: 48mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD171	Solace Vanilla Cola	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Vanilla Cola	Nicotine: 3mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093 PD172	Solace Vanilla Cola	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Vanilla Cola	Nicotine: 6mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093 PD173	Solace Vanilla Cola	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Vanilla Cola	Nicotine: 18mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD174	Solace Vanilla Cola	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Vanilla Cola	Nicotine: 36mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD175	Solace Vanilla Cola	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Vanilla Cola	Nicotine: 48mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD176	VaporFi Dragon Banana Berry	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Dragon Banana Berry	Nicotine: 3mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093 PD177	VaporFi Dragon Banana Berry	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Dragon Banana Berry	Nicotine: 6mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093 PD178	VaporFi Dragon Banana Berry	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Dragon Banana Berry	Nicotine: 18mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD179	VaporFi Dragon Banana Berry	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Dragon Banana Berry	Nicotine: 36mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD180	VaporFi Dragon Banana Berry	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Dragon Banana Berry	Nicotine: 48mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD181	VaporFi Berry Bash	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Berry Bash	Nicotine: 3mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093 PD182	VaporFi Berry Bash	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Berry Bash	Nicotine: 6mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093 PD183	VaporFi Berry Bash	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Berry Bash	Nicotine: 18mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD184	VaporFi Berry Bash	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Berry Bash	Nicotine: 36mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD185	VaporFi Berry Bash	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Berry Bash	Nicotine: 48mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD186	VaporFi Blueberry Ice	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Blueberry Ice	Nicotine: 3mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093 PD187	VaporFi Blueberry Ice	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Blueberry Ice	Nicotine: 6mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093 PD188	VaporFi Blueberry Ice	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Blueberry Ice	Nicotine: 18mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD189	VaporFi Blueberry Ice	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Blueberry Ice	Nicotine: 36mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD190	VaporFi Blueberry Ice	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Blueberry Ice	Nicotine: 48mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD191	VaporFi Raspberry Lemonade Ice	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Raspberry Lemonade Ice	Nicotine: 3mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093 PD192	VaporFi Raspberry Lemonade Ice	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Raspberry Lemonade Ice	Nicotine: 6mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093 PD193	VaporFi Raspberry Lemonade Ice	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Raspberry Lemonade Ice	Nicotine: 18mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD194	VaporFi Raspberry Lemonade Ice	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Raspberry Lemonade Ice	Nicotine: 36mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD195	VaporFi Raspberry Lemonade Ice	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Raspberry Lemonade Ice	Nicotine: 48mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD196	VaporFi Blueberry Punch	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Blueberry Punch	Nicotine: 3mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093 PD197	VaporFi Blueberry Punch	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Blueberry Punch	Nicotine: 6mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093 PD198	VaporFi Blueberry Punch	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Blueberry Punch	Nicotine: 18mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD199	VaporFi Blueberry Punch	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Blueberry Punch	Nicotine: 36mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD200	VaporFi Blueberry Punch	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Blueberry Punch	Nicotine: 48mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD201	VaporFi Raspberry Lemonade	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Raspberry Lemonade	Nicotine: 3mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093 PD202	VaporFi Raspberry Lemonade	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Raspberry Lemonade	Nicotine: 6mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093 PD203	VaporFi Raspberry Lemonade	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Raspberry Lemonade	Nicotine: 18mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD204	VaporFi Raspberry Lemonade	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Raspberry Lemonade	Nicotine: 36mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD205	VaporFi Raspberry Lemonade	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Raspberry Lemonade	Nicotine: 48mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD206	VaporFi Mango Raspberry	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Mango Raspberry	Nicotine: 3mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093 PD207	VaporFi Mango Raspberry	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Mango Raspberry	Nicotine: 6mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093 PD208	VaporFi Mango Raspberry	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Mango Raspberry	Nicotine: 18mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL

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PM0001093 PD209	VaporFi Mango Raspberry	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Mango Raspberry	Nicotine: 36mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD210	VaporFi Mango Raspberry	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Mango Raspberry	Nicotine: 48mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD216	VaporFi Cherry Vanilla	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Cherry Vanilla	Nicotine: 3mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093 PD217	VaporFi Cherry Vanilla	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Cherry Vanilla	Nicotine: 6mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093 PD218	VaporFi Cherry Vanilla	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Cherry Vanilla	Nicotine: 18mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD219	VaporFi Cherry Vanilla	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Cherry Vanilla	Nicotine: 36mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD220	VaporFi Cherry Vanilla	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Cherry Vanilla	Nicotine: 48mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD221	VaporFi Berry Mango Ice	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Berry Mango Ice	Nicotine: 3mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093 PD222	VaporFi Berry Mango Ice	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Berry Mango Ice	Nicotine: 6mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093 PD223	VaporFi Berry Mango Ice	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Berry Mango Ice	Nicotine: 18mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD224	VaporFi Berry Mango Ice	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Berry Mango Ice	Nicotine: 36mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD225	VaporFi Berry Mango Ice	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Berry Mango Ice	Nicotine: 48mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD231	VaporFi Mint Crème	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Mint Crème	Nicotine: 3mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093 PD232	VaporFi Mint Crème	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Mint Crème	Nicotine: 6mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093 PD233	VaporFi Mint Crème	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Mint Crème	Nicotine: 18mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD234	VaporFi Mint Crème	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Mint Crème	Nicotine: 36mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD235	VaporFi Mint Crème	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Mint Crème	Nicotine: 48mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD236	VaporFi Fruit Dragonthol	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Fruit Dragonthol	Nicotine: 3mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093 PD237	VaporFi Fruit Dragonthol	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Fruit Dragonthol	Nicotine: 6mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093 PD238	VaporFi Fruit Dragonthol	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Fruit Dragonthol	Nicotine: 18mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD239	VaporFi Fruit Dragonthol	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Fruit Dragonthol	Nicotine: 36mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD240	VaporFi Fruit Dragonthol	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Fruit Dragonthol	Nicotine: 48mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD241	VaporFi Flavorless	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	None	Nicotine: 3mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093 PD242	VaporFi Flavorless	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	None	Nicotine: 6mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093 PD243	VaporFi Flavorless	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	None	Nicotine: 18mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD244	VaporFi Flavorless	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	None	Nicotine: 36mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD245	VaporFi Flavorless	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	None	Nicotine: 48mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD246	VaporFi Pure Grape	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Pure Grape	Nicotine: 3mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093 PD247	VaporFi Pure Grape	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Pure Grape	Nicotine: 6mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093 PD248	VaporFi Pure Grape	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Pure Grape	Nicotine: 18mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD249	VaporFi Pure Grape	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Pure Grape	Nicotine: 36mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD250	VaporFi Pure Grape	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Pure Grape	Nicotine: 48mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD251	VaporFi Ripe Apple	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Ripe Apple	Nicotine: 3mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093 PD252	VaporFi Ripe Apple	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Ripe Apple	Nicotine: 6mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093 PD253	VaporFi Ripe Apple	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Ripe Apple	Nicotine: 18mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD254	VaporFi Ripe Apple	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Ripe Apple	Nicotine: 36mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD255	VaporFi Ripe Apple	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Ripe Apple	Nicotine: 48mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD256	VaporFi Catcha Latte	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Catcha Latter	Nicotine: 3mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093 PD257	VaporFi Catcha Latte	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Catcha Latter	Nicotine: 6mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093 PD258	VaporFi Catcha Latte	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Catcha Latter	Nicotine: 18mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD259	VaporFi Catcha Latte	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Catcha Latter	Nicotine: 36mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD260	VaporFi Catcha Latte	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Catcha Latter	Nicotine: 48mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD261	VaporFi Key Lime Pie	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Key Lime Pie	Nicotine: 3mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093 PD262	VaporFi Key Lime Pie	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Key Lime Pie	Nicotine: 6mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093 PD263	VaporFi Key Lime Pie	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Key Lime Pie	Nicotine: 18mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD264	VaporFi Key Lime Pie	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Key Lime Pie	Nicotine: 36mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD265	VaporFi Key Lime Pie	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Key Lime Pie	Nicotine: 48mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD266	VaporFi Lemon Lime	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Lemon Lime	Nicotine: 3mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093 PD267	VaporFi Lemon Lime	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Lemon Lime	Nicotine: 6mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093 PD268	VaporFi Lemon Lime	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Lemon Lime	Nicotine: 18mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD269	VaporFi Lemon Lime	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Lemon Lime	Nicotine: 36mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL

Appendix A

New Tobacco Products Subject of This Letter

PM0001093 PD270	VaporFi Lemon Lime	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Lemon Lime	Nicotine: 48mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD271	VaporFi Fresh Mango	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Fresh Mango	Nicotine: 3mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093 PD272	VaporFi Fresh Mango	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Fresh Mango	Nicotine: 6mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093 PD273	VaporFi Fresh Mango	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Fresh Mango	Nicotine: 18mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD274	VaporFi Fresh Mango	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Fresh Mango	Nicotine: 36mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD275	VaporFi Fresh Mango	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Fresh Mango	Nicotine: 48mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD281	VaporFi Tropical Twist	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Tropical Twist	Nicotine: 3mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093 PD282	VaporFi Tropical Twist	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Tropical Twist	Nicotine: 6mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093 PD283	VaporFi Tropical Twist	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Tropical Twist	Nicotine: 18mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD284	VaporFi Tropical Twist	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Tropical Twist	Nicotine: 36mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD285	VaporFi Tropical Twist	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Tropical Twist	Nicotine: 48mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD286	VaporFi Fresh Pineapple	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Fresh Pineapple	Nicotine: 3mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093 PD287	VaporFi Fresh Pineapple	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Fresh Pineapple	Nicotine: 6mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093 PD288	VaporFi Fresh Pineapple	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Fresh Pineapple	Nicotine: 18mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD289	VaporFi Fresh Pineapple	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Fresh Pineapple	Nicotine: 36mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD290	VaporFi Fresh Pineapple	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Fresh Pineapple	Nicotine: 48mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD291	VaporFi Berry Blueberry	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Berry Blueberry	Nicotine: 3mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093 PD292	VaporFi Berry Blueberry	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Berry Blueberry	Nicotine: 6mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093 PD293	VaporFi Berry Blueberry	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Berry Blueberry	Nicotine: 18mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD294	VaporFi Berry Blueberry	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Berry Blueberry	Nicotine: 36mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD295	VaporFi Berry Blueberry	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Berry Blueberry	Nicotine: 48mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD296	VaporFi Watermelon Wave	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Watermelon Wave	Nicotine: 3mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093 PD297	VaporFi Watermelon Wave	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Watermelon Wave	Nicotine: 6mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093 PD298	VaporFi Watermelon Wave	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Watermelon Wave	Nicotine: 18mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD299	VaporFi Watermelon Wave	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Watermelon Wave	Nicotine: 36mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD300	VaporFi Watermelon Wave	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Watermelon Wave	Nicotine: 48mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD306	VaporFi Strawberry Watermelon	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Strawberry Watermelon	Nicotine: 3mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093 PD307	VaporFi Strawberry Watermelon	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Strawberry Watermelon	Nicotine: 6mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093 PD308	VaporFi Strawberry Watermelon	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Strawberry Watermelon	Nicotine: 18mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD309	VaporFi Strawberry Watermelon	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Strawberry Watermelon	Nicotine: 36mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD310	VaporFi Strawberry Watermelon	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Strawberry Watermelon	Nicotine: 48mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD311	VaporFi Strawberry Pastry	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Strawberry Pastry	Nicotine: 3mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093 PD312	VaporFi Strawberry Pastry	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Strawberry Pastry	Nicotine: 6mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093 PD313	VaporFi Strawberry Pastry	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Strawberry Pastry	Nicotine: 18mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD314	VaporFi Strawberry Pastry	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Strawberry Pastry	Nicotine: 36mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD315	VaporFi Strawberry Pastry	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Strawberry Pastry	Nicotine: 48mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD316	VaporFi Strawberry Kiwi	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Strawberry Kiwi	Nicotine: 3mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093 PD317	VaporFi Strawberry Kiwi	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Strawberry Kiwi	Nicotine: 6mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093 PD318	VaporFi Strawberry Kiwi	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Strawberry Kiwi	Nicotine: 18mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD319	VaporFi Strawberry Kiwi	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Strawberry Kiwi	Nicotine: 36mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD320	VaporFi Strawberry Kiwi	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Strawberry Kiwi	Nicotine: 48mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD321	VaporFi Island Frost	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Island Frost	Nicotine: 3mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093 PD322	VaporFi Island Frost	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Island Frost	Nicotine: 6mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093 PD323	VaporFi Island Frost	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Island Frost	Nicotine: 18mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD324	VaporFi Island Frost	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Island Frost	Nicotine: 36mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD325	VaporFi Island Frost	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Island Frost	Nicotine: 48mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD326	VaporFi Mandarin Orange	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Mandarin Orange	Nicotine: 3mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093 PD327	VaporFi Mandarin Orange	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Mandarin Orange	Nicotine: 6mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093 PD328	VaporFi Mandarin Orange	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Mandarin Orange	Nicotine: 18mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD329	VaporFi Mandarin Orange	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Mandarin Orange	Nicotine: 36mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD330	VaporFi Mandarin Orange	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Mandarin Orange	Nicotine: 48mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL

Appendix A

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PM0001093	PD331	VaporFi Strawberry Daiquiri	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Strawberry Daiquiri	Nicotine: 3mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093	PD332	VaporFi Strawberry Daiquiri	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Strawberry Daiquiri	Nicotine: 6mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093	PD333	VaporFi Strawberry Daiquiri	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Strawberry Daiquiri	Nicotine: 18mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093	PD334	VaporFi Strawberry Daiquiri	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Strawberry Daiquiri	Nicotine: 36mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093	PD335	VaporFi Strawberry Daiquiri	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Strawberry Daiquiri	Nicotine: 48mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093	PD336	VaporFi Strawberry Pineapple Twist	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Strawberry Pineapple Twist	Nicotine: 3mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093	PD337	VaporFi Strawberry Pineapple Twist	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Strawberry Pineapple Twist	Nicotine: 6mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093	PD338	VaporFi Strawberry Pineapple Twist	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Strawberry Pineapple Twist	Nicotine: 18mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093	PD339	VaporFi Strawberry Pineapple Twist	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Strawberry Pineapple Twist	Nicotine: 36mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093	PD340	VaporFi Strawberry Pineapple Twist	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Strawberry Pineapple Twist	Nicotine: 48mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093	PD341	VaporFi Very Vanilla	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Very Vanilla	Nicotine: 3mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093	PD342	VaporFi Very Vanilla	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Very Vanilla	Nicotine: 6mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093	PD343	VaporFi Very Vanilla	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Very Vanilla	Nicotine: 18mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093	PD344	VaporFi Very Vanilla	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Very Vanilla	Nicotine: 36mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093	PD345	VaporFi Very Vanilla	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Very Vanilla	Nicotine: 48mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093	PD346	VaporFi Vanilla Cola	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Vanilla Cola	Nicotine: 3mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093	PD347	VaporFi Vanilla Cola	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Vanilla Cola	Nicotine: 6mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093	PD348	VaporFi Vanilla Cola	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Vanilla Cola	Nicotine: 18mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093	PD349	VaporFi Vanilla Cola	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Vanilla Cola	Nicotine: 36mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093	PD350	VaporFi Vanilla Cola	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Vanilla Cola	Nicotine: 48mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093	PD351	Vapor Shark Banana Dragon Fruit	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Banana Dragon Fruit	Nicotine: 3mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093	PD352	Vapor Shark Banana Dragon Fruit	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Banana Dragon Fruit	Nicotine: 6mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093	PD353	Vapor Shark Banana Dragon Fruit	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Banana Dragon Fruit	Nicotine: 18mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093	PD354	Vapor Shark Banana Dragon Fruit	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Banana Dragon Fruit	Nicotine: 36mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093	PD355	Vapor Shark Banana Dragon Fruit	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Banana Dragon Fruit	Nicotine: 48mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093	PD356	Vapor Shark Berry Blast	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Berry Blast	Nicotine: 3mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093	PD357	Vapor Shark Berry Blast	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Berry Blast	Nicotine: 6mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093	PD358	Vapor Shark Berry Blast	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Berry Blast	Nicotine: 18mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093	PD359	Vapor Shark Berry Blast	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Berry Blast	Nicotine: 36mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093	PD360	Vapor Shark Berry Blast	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Berry Blast	Nicotine: 48mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093	PD361	Vapor Shark Tropical Blue Ice	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Tropical Blue Ice	Nicotine: 3mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093	PD362	Vapor Shark Tropical Blue Ice	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Tropical Blue Ice	Nicotine: 6mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093	PD363	Vapor Shark Tropical Blue Ice	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Tropical Blue Ice	Nicotine: 18mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093	PD364	Vapor Shark Tropical Blue Ice	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Tropical Blue Ice	Nicotine: 36mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093	PD365	Vapor Shark Tropical Blue Ice	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Tropical Blue Ice	Nicotine: 48mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093	PD366	Vapor Shark Cool Blue Lemonade	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Cool Blue Lemonade	Nicotine: 3mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093	PD367	Vapor Shark Cool Blue Lemonade	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Cool Blue Lemonade	Nicotine: 6mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093	PD368	Vapor Shark Cool Blue Lemonade	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Cool Blue Lemonade	Nicotine: 18mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093	PD369	Vapor Shark Cool Blue Lemonade	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Cool Blue Lemonade	Nicotine: 36mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093	PD370	Vapor Shark Cool Blue Lemonade	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Cool Blue Lemonade	Nicotine: 48mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093	PD371	Vapor Shark Blueberry Citrus	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Blueberry Citrus	Nicotine: 3mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093	PD372	Vapor Shark Blueberry Citrus	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Blueberry Citrus	Nicotine: 6mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093	PD373	Vapor Shark Blueberry Citrus	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Blueberry Citrus	Nicotine: 18mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093	PD374	Vapor Shark Blueberry Citrus	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Blueberry Citrus	Nicotine: 36mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093	PD375	Vapor Shark Blueberry Citrus	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Blueberry Citrus	Nicotine: 48mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093	PD376	Vapor Shark Blue Lemonade	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Blue Lemonade	Nicotine: 3mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093	PD377	Vapor Shark Blue Lemonade	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Blue Lemonade	Nicotine: 6mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093	PD378	Vapor Shark Blue Lemonade	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Blue Lemonade	Nicotine: 18mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093	PD379	Vapor Shark Blue Lemonade	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Blue Lemonade	Nicotine: 36mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093	PD380	Vapor Shark Blue Lemonade	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Blue Lemonade	Nicotine: 48mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093	PD381	Vapor Shark Blue Raspberry Mango	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Blue Raspberry Mango	Nicotine: 3mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL

Appendix A

New Tobacco Products Subject of This Letter

PM0001093 PD382	Vapor Shark Blue Raspberry Mango	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Blue Raspberry Mango	Nicotine: 6mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093 PD383	Vapor Shark Blue Raspberry Mango	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Blue Raspberry Mango	Nicotine: 18mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD384	Vapor Shark Blue Raspberry Mango	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Blue Raspberry Mango	Nicotine: 36mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD385	Vapor Shark Blue Raspberry Mango	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Blue Raspberry Mango	Nicotine: 48mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD386	Vapor Shark Authentic Tobacco	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Authentic Tobacco	Nicotine: 3mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093 PD387	Vapor Shark Authentic Tobacco	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Authentic Tobacco	Nicotine: 6mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093 PD388	Vapor Shark Authentic Tobacco	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Authentic Tobacco	Nicotine: 18mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD389	Vapor Shark Authentic Tobacco	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Authentic Tobacco	Nicotine: 36mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD390	Vapor Shark Authentic Tobacco	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Authentic Tobacco	Nicotine: 48mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD391	Vapor Shark Cherry Cream	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Cherry Cream	Nicotine: 3mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093 PD392	Vapor Shark Cherry Cream	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Cherry Cream	Nicotine: 6mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093 PD393	Vapor Shark Cherry Cream	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Cherry Cream	Nicotine: 18mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD394	Vapor Shark Cherry Cream	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Cherry Cream	Nicotine: 36mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD395	Vapor Shark Cherry Cream	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Cherry Cream	Nicotine: 48mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD396	Vapor Shark Berry Menthol Mango	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Berry Menthol Mango	Nicotine: 3mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093 PD397	Vapor Shark Berry Menthol Mango	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Berry Menthol Mango	Nicotine: 6mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093 PD398	Vapor Shark Berry Menthol Mango	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Berry Menthol Mango	Nicotine: 18mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD399	Vapor Shark Berry Menthol Mango	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Berry Menthol Mango	Nicotine: 36mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD400	Vapor Shark Berry Menthol Mango	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Berry Menthol Mango	Nicotine: 48mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD406	Vapor Shark Vanilla Mint	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Vanilla Mint	Nicotine: 3mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093 PD407	Vapor Shark Vanilla Mint	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Vanilla Mint	Nicotine: 6mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093 PD408	Vapor Shark Vanilla Mint	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Vanilla Mint	Nicotine: 18mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD409	Vapor Shark Vanilla Mint	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Vanilla Mint	Nicotine: 36mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD410	Vapor Shark Vanilla Mint	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Vanilla Mint	Nicotine: 48mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD411	Vapor Shark Dragonberry Ice	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Dragonberry Ice	Nicotine: 3mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093 PD412	Vapor Shark Dragonberry Ice	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Dragonberry Ice	Nicotine: 6mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093 PD413	Vapor Shark Dragonberry Ice	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Dragonberry Ice	Nicotine: 18mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD414	Vapor Shark Dragonberry Ice	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Dragonberry Ice	Nicotine: 36mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD415	Vapor Shark Dragonberry Ice	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Dragonberry Ice	Nicotine: 48mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD416	Vapor Shark Flavorless	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	None	Nicotine: 3mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093 PD417	Vapor Shark Flavorless	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	None	Nicotine: 6mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093 PD418	Vapor Shark Flavorless	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	None	Nicotine: 18mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD419	Vapor Shark Flavorless	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	None	Nicotine: 36mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD420	Vapor Shark Flavorless	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	None	Nicotine: 48mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD421	Vapor Shark Grape	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Grape	Nicotine: 3mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093 PD422	Vapor Shark Grape	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Grape	Nicotine: 6mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093 PD423	Vapor Shark Grape	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Grape	Nicotine: 18mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD424	Vapor Shark Grape	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Grape	Nicotine: 36mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD425	Vapor Shark Grape	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Grape	Nicotine: 48mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD426	Vapor Shark Apple	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Apple	Nicotine: 3mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093 PD427	Vapor Shark Apple	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Apple	Nicotine: 6mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093 PD428	Vapor Shark Apple	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Apple	Nicotine: 18mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD429	Vapor Shark Apple	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Apple	Nicotine: 36mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD430	Vapor Shark Apple	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Apple	Nicotine: 48mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD431	Vapor Shark Coffee Cream	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Coffee Cream	Nicotine: 3mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093 PD432	Vapor Shark Coffee Cream	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Coffee Cream	Nicotine: 6mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093 PD433	Vapor Shark Coffee Cream	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Coffee Cream	Nicotine: 18mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD434	Vapor Shark Coffee Cream	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Coffee Cream	Nicotine: 36mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD435	Vapor Shark Coffee Cream	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Coffee Cream	Nicotine: 48mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD436	Vapor Shark Lemon Meringue	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Lemon Meringue	Nicotine: 3mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093 PD437	Vapor Shark Lemon Meringue	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Lemon Meringue	Nicotine: 6mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL

Appendix A
New Tobacco Products Subject of This Letter

PM0001093 PD438	Vapor Shark Lemon Meringue	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Lemon Meringue	Nicotine: 18mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD439	Vapor Shark Lemon Meringue	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Lemon Meringue	Nicotine: 36mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD440	Vapor Shark Lemon Meringue	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Lemon Meringue	Nicotine: 48mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD441	Vapor Shark Citrus Twist	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Citrus Twist	Nicotine: 3mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093 PD442	Vapor Shark Citrus Twist	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Citrus Twist	Nicotine: 6mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093 PD443	Vapor Shark Citrus Twist	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Citrus Twist	Nicotine: 18mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD444	Vapor Shark Citrus Twist	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Citrus Twist	Nicotine: 36mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD445	Vapor Shark Citrus Twist	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Citrus Twist	Nicotine: 48mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD446	Vapor Shark Mango	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Mango	Nicotine: 3mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093 PD447	Vapor Shark Mango	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Mango	Nicotine: 6mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093 PD448	Vapor Shark Mango	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Mango	Nicotine: 18mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD449	Vapor Shark Mango	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Mango	Nicotine: 36mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD450	Vapor Shark Mango	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Mango	Nicotine: 48mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD456	Vapor Shark Fruit Medley	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Fruit Medley	Nicotine: 3mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093 PD457	Vapor Shark Fruit Medley	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Fruit Medley	Nicotine: 6mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093 PD458	Vapor Shark Fruit Medley	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Fruit Medley	Nicotine: 18mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD459	Vapor Shark Fruit Medley	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Fruit Medley	Nicotine: 36mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD460	Vapor Shark Fruit Medley	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Fruit Medley	Nicotine: 48mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD461	Vapor Shark Pineapple	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Pineapple	Nicotine: 3mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093 PD462	Vapor Shark Pineapple	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Pineapple	Nicotine: 6mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093 PD463	Vapor Shark Pineapple	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Pineapple	Nicotine: 18mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD464	Vapor Shark Pineapple	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Pineapple	Nicotine: 36mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD465	Vapor Shark Pineapple	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Pineapple	Nicotine: 48mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD466	Vapor Shark Very Berry	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Very Berry	Nicotine: 3mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093 PD467	Vapor Shark Very Berry	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Very Berry	Nicotine: 6mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093 PD468	Vapor Shark Very Berry	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Very Berry	Nicotine: 18mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD469	Vapor Shark Very Berry	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Very Berry	Nicotine: 36mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD470	Vapor Shark Very Berry	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Very Berry	Nicotine: 48mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD471	Vapor Shark Ripe Watermelon	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Ripe Watermelon	Nicotine: 3mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093 PD472	Vapor Shark Ripe Watermelon	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Ripe Watermelon	Nicotine: 6mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093 PD473	Vapor Shark Ripe Watermelon	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Ripe Watermelon	Nicotine: 18mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD474	Vapor Shark Ripe Watermelon	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Ripe Watermelon	Nicotine: 36mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD475	Vapor Shark Ripe Watermelon	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Ripe Watermelon	Nicotine: 48mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD476	Vapor Shark Ripe Tobacco	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Ripe Tobacco	Nicotine: 3mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093 PD477	Vapor Shark Ripe Tobacco	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Ripe Tobacco	Nicotine: 6mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093 PD478	Vapor Shark Ripe Tobacco	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Ripe Tobacco	Nicotine: 18mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD479	Vapor Shark Ripe Tobacco	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Ripe Tobacco	Nicotine: 36mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD480	Vapor Shark Ripe Tobacco	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Ripe Tobacco	Nicotine: 48mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD481	Vapor Shark Strawberry Melon	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Strawberry Melon	Nicotine: 3mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093 PD482	Vapor Shark Strawberry Melon	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Strawberry Melon	Nicotine: 6mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093 PD483	Vapor Shark Strawberry Melon	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Strawberry Melon	Nicotine: 18mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD484	Vapor Shark Strawberry Melon	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Strawberry Melon	Nicotine: 36mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD485	Vapor Shark Strawberry Melon	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Strawberry Melon	Nicotine: 48mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD486	Vapor Shark Strawberry Whip	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Strawberry Whip	Nicotine: 3mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093 PD487	Vapor Shark Strawberry Whip	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Strawberry Whip	Nicotine: 6mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093 PD488	Vapor Shark Strawberry Whip	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Strawberry Whip	Nicotine: 18mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD489	Vapor Shark Strawberry Whip	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Strawberry Whip	Nicotine: 36mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD490	Vapor Shark Strawberry Whip	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Strawberry Whip	Nicotine: 48mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093 PD491	Vapor Shark Kiwi Berry	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Kiwi Berry	Nicotine: 3mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093 PD492	Vapor Shark Kiwi Berry	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Kiwi Berry	Nicotine: 6mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093 PD493	Vapor Shark Kiwi Berry	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Kiwi Berry	Nicotine: 18mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL

Appendix A

New Tobacco Products Subject of This Letter

PM0001093	PD494	Vapor Shark Kiwi Berry	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Kiwi Berry	Nicotine: 36mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093	PD495	Vapor Shark Kiwi Berry	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Kiwi Berry	Nicotine: 48mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093	PD496	Vapor Shark Tropic Chill	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Tropic Chill	Nicotine: 3mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093	PD497	Vapor Shark Tropic Chill	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Tropic Chill	Nicotine: 6mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093	PD498	Vapor Shark Tropic Chill	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Tropic Chill	Nicotine: 18mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093	PD499	Vapor Shark Tropic Chill	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Tropic Chill	Nicotine: 36mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093	PD500	Vapor Shark Tropic Chill	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Tropic Chill	Nicotine: 48mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093	PD501	Vapor Shark Tangerine Dream	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Tangerine Dream	Nicotine: 3mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093	PD502	Vapor Shark Tangerine Dream	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Tangerine Dream	Nicotine: 6mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093	PD503	Vapor Shark Tangerine Dream	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Tangerine Dream	Nicotine: 18mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093	PD504	Vapor Shark Tangerine Dream	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Tangerine Dream	Nicotine: 36mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093	PD505	Vapor Shark Tangerine Dream	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Tangerine Dream	Nicotine: 48mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093	PD506	Vapor Shark Pineapple Berry Twist	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Pineapple Berry Twist	Nicotine: 3mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093	PD507	Vapor Shark Pineapple Berry Twist	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Pineapple Berry Twist	Nicotine: 6mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093	PD508	Vapor Shark Pineapple Berry Twist	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Pineapple Berry Twist	Nicotine: 18mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093	PD509	Vapor Shark Pineapple Berry Twist	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Pineapple Berry Twist	Nicotine: 36mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093	PD510	Vapor Shark Pineapple Berry Twist	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Pineapple Berry Twist	Nicotine: 48mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093	PD511	Vapor Shark Tropical Strawberry	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Tropical Strawberry	Nicotine: 3mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093	PD512	Vapor Shark Tropical Strawberry	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Tropical Strawberry	Nicotine: 6mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093	PD513	Vapor Shark Tropical Strawberry	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Tropical Strawberry	Nicotine: 18mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093	PD514	Vapor Shark Tropical Strawberry	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Tropical Strawberry	Nicotine: 36mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093	PD515	Vapor Shark Tropical Strawberry	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Tropical Strawberry	Nicotine: 48mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093	PD516	Vapor Shark Vanilla Cream	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Vanilla Cream	Nicotine: 3mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093	PD517	Vapor Shark Vanilla Cream	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Vanilla Cream	Nicotine: 6mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093	PD518	Vapor Shark Vanilla Cream	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Vanilla Cream	Nicotine: 18mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093	PD519	Vapor Shark Vanilla Cream	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Vanilla Cream	Nicotine: 36mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093	PD520	Vapor Shark Vanilla Cream	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Vanilla Cream	Nicotine: 48mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093	PD521	Vapor Shark Cola Float	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Cola Float	Nicotine: 3mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093	PD522	Vapor Shark Cola Float	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Cola Float	Nicotine: 6mg/mL, PG/VG: 27/73, E-liquid Volume: 60mL
PM0001093	PD523	Vapor Shark Cola Float	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Cola Float	Nicotine: 18mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093	PD524	Vapor Shark Cola Float	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Cola Float	Nicotine: 36mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL
PM0001093I	PD525	Vapor Shark Cola Float	ENDS(VAPES)	ENDS Component	Bottle	1 Bottle	Cola Float	Nicotine: 48mg/mL, PG/VG: 44/56, E-liquid Volume: 30mL

FDA U.S. FOOD & DRUG ADMINISTRATION

Technical Project Lead (TPL) Review of PMTAs

New Products Subject of this Review[i]	
Submission tracking numbers (STNs)	PM0001093, see Appendix A
Common Attributes	
Submission date	September 5, 2020
Receipt date	September 5, 2020
Applicant	TPB International, LLC.
Product manufacturer	TPB International, LLC.
Application type	Standard
Product category	ENDS (VAPES)
Product subcategory	ENDS Component
Cross-Referenced Submissions	
All PMTAs	MF0000276, MF0000384, MF0000474, and MF0000751
Recommendation	
Issue marketing denial orders for the new tobacco products subject of this review.	

Technical Project Lead (TPL):

Digitally signed by Megan J. Schroeder -S
Date: 2021.09.14 09:37:39 -04'00'

Megan Schroeder, Ph.D.
Branch Chief, Behavioral and Clinical Pharmacology
Division of Individual Health Science

Signatory Decision: Concur with TPL recommendation and basis of recommendation

Digitally signed by Matthew R. Holman -S
Date: 2021.09.14 10:54:32 -04'00'

Matthew R. Holman, Ph.D.
Director
Office of Science

[i] Product details, amendments, and dates provided in the Appendix. PMTA means premarket tobacco application. Scientific references are listed at the end of this document and referred to with Arabic numerals; general footnotes are referred to with Roman numerals.

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1. EXECUTIVE SUMMARY

These applications for flavored ENDS[ii] products lack evidence to demonstrate that permitting the marketing of these products would be appropriate for the protection of the public health (APPH). Given the known and substantial risk of flavored ENDS with respect to youth appeal, uptake, and use, applicants would need reliable and robust evidence of a potential benefit to adult smokers[iii] that could justify that risk. Accordingly, in order to show that a flavored ENDS is APPH, the applicant must show that the benefit to adults switching from or reducing cigarettes outweighs the risk to youth.

Based on existing scientific evidence and our experiences in conducting premarket review employing the APPH standard over the last several years, FDA has determined for these applications that, to effectively demonstrate this benefit in terms of product use behavior, only the strongest types of evidence will be sufficiently reliable and robust —most likely product specific evidence from a randomized controlled trial (RCT)[iv] or longitudinal cohort study, although other types of evidence could be adequate, and will be evaluated on a case-by-case basis.[v,vi] Moreover, tobacco-flavored ENDS may offer the same type of public health benefit as flavored 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 demonstrate the potential benefit to current users, FDA has reviewed these applications for any 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 have reviewed the subject applications to determine whether they contain sufficient evidence of the type described above to demonstrate APPH. Our review determined that the applications do <u>not</u> contain evidence from a randomized controlled trial or longitudinal cohort study regarding the impact of the ENDS on switching or cigarette reduction that could potentially demonstrate the benefit of their flavored ENDS over tobacco-flavored ENDS. The PMTAs do contain other evidence

[ii] The term *flavored ENDS* in this review refers to any ENDS other than tobacco-flavored and menthol-flavored ENDS. Tobacco-flavored ENDS are discussed below. Applications for menthol-flavored ENDS will be addressed separately. 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. The term *flavored ENDS* also includes 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.

[iii] 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. This review is focused on the risk to youth nonusers as well as the potential benefit to adult smokers as current users, as they are the group through which the potential benefit to public health is most substantial and could overcome the known risk to youth.

[iv] 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.

[v] 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).

[vi] For example, we would consider evidence from another study design if 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.

regarding the potential benefit to adult users; however, for the reasons explained below, this other evidence is not adequate.

As a result, the applicant has failed to provide evidence to overcome the risk to youth and show a net population health benefit necessary to determine that permitting the marketing of the new tobacco product is APPH.

2. BACKGROUND

2.1. NEW PRODUCTS

The applicant submitted information for the new products listed on the cover page and in Appendix A.

2.2. REGULATORY ACTIVITY

FDA issued an Acceptance letter to the applicant on May 14, 2021.

2.3. BASIS FOR REQUIRING RELIABLE, ROBUST EVIDENCE TO DEMONSTRATE BENEFIT

The rationale for FDA's decision for these flavored ENDS applications is consistent with previous decisions for other flavored ENDS and is set forth below.

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 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.[vii]

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 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" (2020 Enforcement Priorities Guidance). In this guidance,

[vii] This review focuses on risk to youth nonusers and the potential benefit to adult smokers as current tobacco product users, given that these are the subpopulations that raise the most significant public health concerns and therefore are the most relevant in evaluating the impact on the population as a whole. FDA has also considered the APPH standard with respect to the likelihood that an authorization will increase or decrease the number of tobacco users in the overall population. The availability of such products has generally led to greater tobacco use among youth overall, notwithstanding the decrease in cigarette smoking for youth, which reinforces the focus in this review on having sufficiently reliable and robust evidence to justify authorization of these PMTAs. 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.

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.[viii]

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,[ix] 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 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 policy described in the 2020 Enforcement Priorities Guidance because, at that time that policy was developed, those products 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.

2.3.1. 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

[viii] 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.

[ix] 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.

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.

2.3.1.1. 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.

The evidence shows 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[x] users reported using a flavored e-cigarette.[10] By the 2020 NYTS, the proportion of e-cigarette users reporting using a flavored product[xi] 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/menthol[xii], 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]

[x] We use "e-cigarette" here to be consistent with the survey, but we interpret it to have the same meaning as ENDS.
[xi] Flavored product use in these studies means use of flavors other than tobacco.
[xii] 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.

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 users, 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 taking 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.

2.3.1.2. The appeal of flavors across ENDS devices

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] The published literature is sufficient to demonstrate the substantial appeal to youth of flavored ENDS, because it is robust and consistent. As described above, the preference for use of flavored ENDS among youth is consistently demonstrated across large, national surveys and longitudinal cohort studies.

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 flavor 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.[xiii] 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[xiv]--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 flavor options, underscoring the fundamental role of flavor in driving appeal.

2.3.1.3. 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.[xv]

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 psychosocial 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]

2.3.1.4. 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 generally greater health risk. A 2017 systematic review and meta-analysis that summarized nine prospective

[xiii] 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.

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

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

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.

2.3.1.5. 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[xvi] 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 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.

2.3.1.6. 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 demonstrates that flavored ENDS pose a significant risk to youth.

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

2.3.2. 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.

2.3.2.1. 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]

2.3.2.2. 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,[xvii] 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 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

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

demonstrating that permitting the marketing of specific flavored ENDS would be APPH given 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,[xviii] 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 show a net population health benefit, FDA has determined that these applications must demonstrate potential benefits to smokers from marketing such products with robust and reliable 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, FDA is reviewing these applications to determine whether they demonstrate that a benefit of a new product is significant enough to overcome the risk to youth. In particular, FDA's review of these applications has considered the degree of benefit to a flavored ENDS product over a tobacco-flavored variety in facilitating smokers completely switching or significantly reducing their smoking, given the significant increase in risk of youth initiation associated with flavored ENDS compared to tobacco-flavored ENDS. Note that applications with this type of information may still not be APPH: 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.[xix]

We have been using the APPH standard for several years in reviewing previous PMTAs for non-ENDS 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. In these reviews, 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.[xx] In fact, the findings are quite mixed and as a result the literature does not

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

[xix] 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, and we have not evaluated any marketing plans submitted with these applications.

[xx] This discrepancy between the literature for youth initiation and adult switching also likely reflects fundamental differences in the two outcomes being assessed—youth initiation and switching among adult smokers—and their

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, FDA has reviewed these applications for any acceptably strong product-specific evidence.

More specifically, in order to adequately assess whether such an added benefit has been demonstrated, FDA has reviewed these applications for product-specific[xxi] evidence that would enable a comparison between the applications' 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), evidence generated using either an RCT design or longitudinal cohort study design is mostly likely to demonstrate such a benefit, although other types of evidence could be adequate if sufficiently reliable and robust, and will be evaluated on a case-by-case basis. [xxii]

CTP will consider other types of evidence if it is sufficiently robust and direct to demonstrate 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.

In contrast, cross-sectional surveys entail a one-time assessment of self-reported outcomes: although participants can be asked to recall 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

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determinants. For switching among adult smokers, the behavior change is occurring in the context of nicotine dependence. Thus, the specific product's ability to provide adequate reinforcement and continue to satisfy a smoker's cravings over time, which is a function of the design of the specific product itself, are critical factors in determining likelihood of continued use and the product's ability to promote switching. Whereas for youth initiation, experimentation among naïve or novice users is not driven by these factors.

[xxi] 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.

[xxii] Conversely, such longitudinal or product-specific data are not necessarily required to assess experimentation and appeal among youth. The available literature on youth initiation contains valid scientific evidence sufficient to evaluate the risk to youth of ENDS. The literature includes longitudinal cohort studies, such as the PATH study, which have been used to assess uptake of tobacco products, including flavored ENDS, among youth and young adults. These studies have evaluated the impact of flavors on the promotion of established regular use. Additionally, the literature includes large, nationally representative cross-sectional surveys, which are among the best available evidence to understand patterns of youth ENDS use and the key characteristics associated with such use These studies enable observation of youth behavior as it naturally occurs in representative samples of the U.S. population. These data available in the literature provide clear and overwhelming evidence that ENDS are the most widely used products by youth, the majority of youth users use a flavored ENDS, and that youth users are more likely to use flavored ENDS than adult ENDS users. We note that, in assessing the risks to youth from flavored ENDS, RCTs are not possible because it would be unethical to randomize youth never or naive users to try a particular ENDS to examine what impact it would have on initiation, experimentation, or progression to regular use.

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 behavior over time[xxiii]; 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.[xxiv] 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 product use or (2) significant reduction in cigarettes per day (CPD).

2.3.2.3. Conclusion

Given the known and substantial risk to youth posed by flavored ENDS, FDA has reviewed these applications for the presence of particularly reliable product-specific[xxv] evidence to 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

[xxiii] 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. However, it is also possible that studies with a shorter duration would be adequately reliable.

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

[xxv] 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.

switching or reducing their smoking could demonstrate the potential benefit to current users that would outweigh the risk to youth posed by flavored ENDS.

2.4. SCOPE OF REVIEW

The reviews evaluated whether the subject PMTAs contain evidence from a randomized controlled trial, longitudinal cohort study, and/or other evidence regarding the impact of the new products on switching or cigarette reduction that could potentially demonstrate the added benefit to adult users of their flavored ENDS over an appropriate comparator tobacco-flavored ENDS. These reviews included a search of the PMTAs to determine whether the evidence is found anywhere within the PMTAs, and if present, if certain conditions were met (e.g., was the randomized controlled trial conducted using the new products that are the subject of the PMTA). Our review also included a search for other studies that provided product-specific evidence related to the potential benefit to adult users.

3. SCIENTIFIC REVIEW

Reviews were completed by Apostolos Alexandridis and Erin Ellis on September 13, 2021.

The reviews determined that the PMTAs did not contain evidence from a randomized controlled trial and/or longitudinal cohort study examining the benefit to adult users of their flavored ENDS over an appropriate comparator tobacco-flavored ENDS in terms of switching from or reducing cigarettes. The PMTAs contained clinical studies with abuse liability outcomes and a cross-sectional survey identifying patterns of use, but this evidence is not sufficiently strong to support the benefit to adult smokers of using these flavored ENDS because it does not evaluate product switching or cigarette reduction resulting from use of these products over time. Accordingly, this evidence is not adequate and therefore, we did not assess other aspects of the application as part of this scientific review.

4. ENVIRONMENTAL DECISION

Under 21 CFR 25.35(b), issuance of an order under section 910(c) of the Federal Food, Drug, and Cosmetic Act that a new product may not be introduced or delivered for introduction into interstate commerce (i.e., a marketing denial order) falls within a class of actions that are ordinarily categorically excluded from the preparation of an environmental assessment (EA) or environmental impact statement (EIS). To the best of our knowledge, no extraordinary circumstances exist that would preclude application of this categorical exclusion. FDA concludes that categorical exclusion is warranted and no EA or EIS is required.

5. CONCLUSION AND RECOMMENDATION

FDA has reviewed these applications for evidence demonstrating that the new flavored products will provide an added benefit to adult smokers relative to tobacco-flavored products. Based on our review, we determined that the PMTAs for the applicant's new products, as described in the applications and specified in Appendix A, lack sufficient evidence to demonstrate that permitting the marketing of the new products would be APPH. Thus, a Denial letter should be issued to the applicant. The applicant cannot introduce or deliver for introduction these products into interstate commerce in the United States. Doing so is a prohibited act under section 301(a) of the FD&C Act, the violation of which could result in enforcement action by FDA.

The following deficiency should be conveyed to the applicant as the key basis for our determination that marketing of the new products is not APPH:

1. All of your PMTAs lack sufficient evidence demonstrating that your flavored ENDS will provide a benefit to adult users that would be adequate to outweigh the risks to youth. In light of the known risks to youth of marketing flavored ENDS, robust and reliable evidence is needed regarding the magnitude of the potential benefit to adult smokers. This evidence could have been provided using a randomized controlled trial and/or longitudinal cohort study that demonstrated the benefit of your flavored ENDS products over an appropriate comparator tobacco-flavored ENDS.

   Alternatively, FDA would consider other evidence but only if it reliably and robustly evaluated the impact of the new flavored vs. tobacco-flavored products on adult smokers' switching or cigarette reduction over time. Although your PMTAs contained clinical studies with abuse liability outcomes and a cross-sectional survey evaluating patterns of use, this evidence is not sufficient to show a benefit to adult smokers of using these flavored ENDS because it does not evaluate product switching or cigarette reduction resulting from use of these products over time.

   Without this information, FDA concludes that your application is insufficient to demonstrate that these products would provide an added benefit that is adequate to outweigh the risks to youth and, therefore, cannot find that permitting the marketing of your new tobacco products would be appropriate for the protection of the public health.

6. APPENDIX

Appendix A. New Products

Common Attributes [xxvi] [xxvii]	
Submission date	September 5, 2020
Receipt date	September 5, 2020
Applicant	TPB International, LLC
Product manufacturer	TPB International, LLC
Product category	ENDS (VAPES)
Product subcategory	ENDS Component

[xxvi] We interpret package type to mean container closure system and package quantity to mean product quantity within the container closure system, unless otherwise identified.
[xxvii] Brand/sub-brand or other commercial name used in commercial distribution.

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UNITED STATES COURT OF APPEALS
FOR THE SIXTH CIRCUIT

Turning Point Brands, Inc. and TPB International, LLC, Petitioners, v. U.S. Food and Drug Administration, Respondent.	Case No. 21-3855

DECLARATION OF BRIAN WIGGINTON IN SUPPORT OF PETITIONERS' EMERGENCY MOTION FOR A STAY

I, Brian Wigginton, declare and state as follows:

1. I am employed by Turning Point Brands, Inc. (TPB), where I have worked for nearly five years. I am currently Senior Vice President of Finance and Chief Accounting Officer at TPB. I am responsible for ensuring company compliance with SEC reporting requirements and generally accepted accounting standards. My responsibilities require me to track company profits and losses and to understand TPB's inventory. I also stay informed of regulatory decisions and analyze how those decisions impact TPB's financial outlook.

2. I have over two decades of financial accounting and regulatory

compliance experience. I joined TPB in November 2016 from GE Appliances, where I worked as a technical accounting resource for the appliance and lighting businesses, which posted annual revenues exceeding $8.9 billion. Before working at GE Appliances, I was a Senior Manager at Ernst & Young, where I spent over nine years reviewing regulatory filings and overseeing audits of public and private clients. I hold Bachelor degrees in accounting and management from the University of Kentucky.

3. TPB is a publicly owned corporation and a leading manufacturer, marketer, and distributor of branded consumer products, including electronic-nicotine-delivery-system (ENDS) products.

4. Among TPB's leading proprietary ENDS brands are Solace®, VaporFi®, and Vapor Shark® e-liquids. TPB's subsidiary, TPB International, LLC (TPB International), markets and sells these products. These e-liquids are designed to be used with "open system" vapor devices, and principally sold in age-restricted tobacco or vapor shops or through online platforms, which have age-verification systems for consumer sales.

5. These products are among the consumer goods identified in TPB's bundle of Premarket Tobacco Product Applications (PMTA), which TPB International submitted to the United States Food & Drug Administration

(FDA) on September 5, 2020.

6. That package of PMTAs covered a wide range of "unflavored," "flavored," tobacco, and menthol e-liquids marketed and sold by TPB International. None of the products included in the PMTAs are closed pod-based systems.

7. The PMTAs totaled over 81,000 pages and included an array of scientific studies and consumer research. Preparing the PMTAs took over two years and cost approximately $12 million. Outside scientific consultants and outside legal counsel were involved in preparing the PMTAs.

8. TPB requested a meeting with FDA on May 9, 2018, to discuss the design and substance of the PMTAs and obtain clarity on FDA's broadly-drafted guidance. No such meeting occurred. Instead, three months later, on August 3, 2018, FDA provided a written response to questions included in TPB's meeting request, largely repeating guidance already provided by FDA. TPB did not request a follow-up meeting with FDA about its applications, because doing so was impracticable. TPB's prior request for a meeting was rebuffed and there was no prospect that a subsequent request would be treated differently. In addition, TPB faced a sudden 10-month timetable for developing and submitting its PMTAs in light of the court-imposed deadlines

in *American Academy of Pediatrics v. Food & Drug Administration*, 399 F. Supp. 3d 479 (D. Md. 2019), *appeal dismissed sub nom. In re Cigar Association of America*, 812 F. App'x 128 (4th Cir. 2020), and FDA's April 2020 Guidance, *Enforcement Priorities for Electronic Nicotine Delivery Systems (ENDS) and Other Deemed Products on the Market Without Premarket Authorization*. That timetable alone made it impracticable to expend time and resources setting up a meeting with FDA, which usually takes considerable time.

9. TPB developed its PMTAs by relying heavily on FDA's June 2019 Guidance, *Premarket Tobacco Product Applications for Electronic Nicotine Delivery Systems: Guidance for Industry*, and FDA's September 25, 2019 proposed rule, 84 Fed. Reg. 50,556. In particular, TPB relied on FDA's advice that manufacturers need not conduct long-term studies and supplied an array of studies consistent with FDA's guidance.

10. On September 14, 2021, FDA issued a terse marketing denial order (Order) in which it concluded that the marketing of 490 of TPB's ENDS products is not appropriate for the protection of the public health.

11. I have reviewed FDA's Order and understand its contents. This declaration addresses the steps TPB is taking to comply with the Order and

the costs associated with TPB's compliance.

12. FDA's Order requires TPB to cease marketing certain e-liquid products immediately. Relatedly, the Order requires that TPB remove these ENDS products from the market and ensure the products remain off the market. Complying with these requirements imposes significant financial costs on TPB.

13. TPB estimates it will lose $5 million in annual revenue and $3 million in annual gross profits from lost sales. It will be difficult for TPB to offset these lost profits by selling other consumer goods.

14. Pulling ENDS products from the market is a significant endeavor. TPB's ENDS products subject to FDA's Order were distributed in numerous tobacco and vapor shops across the country. Recovering these products will require a significant investment of time and resources that will not be recouped, to say nothing of the time and resources necessary to ensure continued compliance.

15. Additionally, TPB compensates wholesale and retail partners for returned products. The estimated refund price for ENDS products currently on the market that are impacted by FDA's Order is $1 million.

16. TPB also has stored in inventory ENDS products covered by the

Order. The value of these products is approximately $650,000, and because TPB cannot market these products, it will lose additional profits.

17. The removal of these ENDS products may have additional negative consequences for TPB, as consumers may switch to similarly flavored products offered by other brands, tobacco and vapor shop retailers may distribute other products in the place of those offered by TPB, and TPB may lose the benefit of the goodwill it has established in these brands.

I declare under penalty of perjury under the laws of the United States of America that the foregoing is true and correct.

Executed on September 29, 2021

_____

Brian Wigginton

U.S. FOOD & DRUG ADMINISTRATION

U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov

August 03, 2018

WRITTEN RESPONSE

Turning Point Brands, LLC
Attention: Donald R. Becker, Assistant General Counsel
5201 Interchange Way
Louisville, KY 40229

FDA Submission Tracking Number (STN): TC0003730

Dear Mr. Becker:

Please refer to the May 23, 2018 Meeting Granted Letter where FDA notified you of our decision to provide a written response only in lieu of a face-to-face meeting as indicated in your meeting request.

This letter provides our written response to your May 9, 2018, meeting request related to your planned submission of a Premarket Tobacco Product Application (PMTA) under section 910(b) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Miami Vice E-Liquid.

A copy of the official written response is attached for your information. This meeting request is now closed. If you decide to request another meeting on this topic, a new meeting request is required.

If you have any questions please contact Jeffrey Toy, Lead Regulatory Health Project Manager, at (301) 796-6489.

Sincerely,

Iilun C. Murphy -S
2018.08.03 14:13:38 -04'00'

Iilun Murphy, MD
Director, Division of Individual Health Science
Office of Science
Center for Tobacco Products

Enclosure: Written Response

U.S. FOOD & DRUG ADMINISTRATION

U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov

WRITTEN RESPONSE

FDA Submission Tracking Number:	TC0003730
Meeting Category:	PMTA
Applicant Name:	Vapor Shark, LLC.
Meeting Requestor:	Donald Becker
Received Meeting Information Package:	June 22, 2018
SUBJECT:	To discuss the design and conduct of investigations intended to support Premarket Tobacco Product Applications (PMTAs) for e-liquids including the Miami Vice E-Liquid product (nicotine strength 18 mg/ml) for use in electronic nicotine delivery systems (ENDS).

I. BACKGROUND

Turning Point Brands, LLC (TPB) submitted a meeting request on May 9, 2018, received May 11, 2018. The request was for a face-to-face meeting with FDA to discuss the design and conduct of investigations intended to support Premarket Tobacco Product Applications (PMTAs) for e-liquids including the Miami Vice E-Liquid product (nicotine strength 18 mg/ml) for use in ENDS. The product is intended to be sold through Vapor Shark LLC, a subsidiary of TPB. Based on the objectives of the meeting, FDA determined to respond to the questions with written response only in lieu of the face-to-face meeting as indicated in the meeting request.

II. OBJECTIVES

The meeting information package containing objectives, agenda, specific questions, and meeting attendees was received on June 22, 2018 (TC0003825) from Vapor Shark, LLC. As described in the meeting information package, the following objectives and outcomes were expected by Turning Point Brands, LLC:

1. Determine whether TPB may utilize strategic screening of compounds of concern, and omit detailed review of "de minimis" exposures, in order to satisfy FDA's public health questions.

2. Determine whether TPB may bundle ingredients of similarly-prepared e-liquids and rely primarily upon published studies to satisfy FDA's public health questions.

3. Determine whether any customized clinical or non-clinical custom studies will be required by FDA and, if so, determine the scope and nature of those studies and their relevance compared to published literature concerning the product category.

4. Describe TPB's "factory" approach to PMTAs and gain alignment with FDA that such a process is permissible under the current Guidance Document (or any subsequent version published after the date of this letter) and encouraged by FDA in order to expedite FDA's internal review.

III. DISCUSSION

General FDA Response

Presubmission information can provide feedback on the types of studies and data/information sources that could be used in an application. Whether or not the data that is submitted in support of your application is sufficient to support a marketing authorization is always a review issue. This response is not intended to provide the level of detail that your questions appear to be asking for, such as agreeing that the method you are using to answer the questions at hand is sufficient.

Applicant Question 1

Whether utilizing strategic compounds of concern and omitting a detailed review of "de minims" exposures will satisfy FDA's public health questions?

FDA RESPONSE:

It is unclear to FDA what you mean by "utilizing strategic compounds of concern and omitting a detailed review of "de minimis" exposures." At this time, there is no established standard for determining whether the calculated upper bound non-cancer hazard or risk of cancer posed by an ingredient, additive or component in tobacco products is low enough to be considered to pose a "de mimimis" risk. Although the exposure concentration of one chemical compound alone may be too small to elicit an effect, the addition of a multitude of compounds with a similar mode of action may be enough to increase the total user exposure to a level that results in an adverse effect. Also, toxicants may be produced during aerosol generation even from e-liquid ingredients or components added at low concentrations. Thus, a compound added to the e-liquid at a level that may result in user exposures considered below a level of toxicological concern for that specific ingredient or component, does not necessarily equate to a lack of toxicity or potential adverse human health effects from exposure to the chemical mixture of the aerosols generated by your new tobacco products. Therefore, a categorization based on exposure estimates for the individual e-liquid compounds, may not be adequate if used alone as criteria to "omit" compounds in the toxicological evaluation of your new tobacco products.

To determine the adequacy of information used to address the toxicology evaluation of a PMTA submission, a full scientific review of the application would be needed. Consumers of ENDS products have simultaneous exposures to more than one chemical, and therefore, the public health risks associated with product use can vary depending upon the number and type of chemicals (i.e., carcinogenic versus non-carcinogenic) present in the e-liquids or aerosols. In general, toxicity profiles via the inhalation route should be considered for all ingredients and components added to your e-liquid, as well as potential heat degradation by-products that may form during use. In addition, some aerosol constituents may have additive or synergestic effects based on similar mode of action that may be of potential toxicological concern when combined in the aerosols generated by your new tobacco products. The toxicology review of your PMTA considers the total aerosol generated by your new tobacco products and will weigh all the scientific evidence provided in the application, including the potential health risks as a result of exposure to the total aerosol mixture generated by your new tobacco products.

As described in the "Premarket Tobacco Product Applications for Electronic Nicotine Delivery Systems Draft Guidance" (ENDS DG), which is available for public comment and when final will

represent FDA's current thinking on PMTAs for ENDS products, the constituents on the FDA's established harmful and potentially harmful constituents (HPHC) list and other chemicals of interest in e-liquids and vapor (e.g., diacetyl, acetyl propionyl, diethylene glycol, ethylene glycol, glycerol and propylene glycol) are constituents that could potentially cause health hazards. However, these constituents may not include all toxic constituents that are contained in, or generated by your product, and thus, appropriate to measure. FDA recommends inclusion of information and analyses on e-liquids, or aerosols, or both, as appropriate for your products. Consider providing information on levels of toxic chemicals that are generated as reaction products through the heating of the e-liquid during use. For aerosol testing, consider both intense machine vaping conditions (e.g., higher puff volume, puff duration, puff frequency, power) and non-intense conditions (e.g., lower puff volume, puff duration, puff frequency, power) to be included for a quantitative analysis of relevant HPHCs or other toxicants that may be generated.

Applicant Question 2

Whether Vapor Shark may bundle ingredients of similarly-prepared e-liquids and rely primarily upon published studies to satisfy FDA's public health questions?

FDA RESPONSE:

It is unclear what you mean by "bundle ingredients of similarly prepared e-liquids." Tobacco products including ENDS, that meet the definition of a "new tobacco product," are subject to the premarket requirements in sections 910 and 905 (21 U.S.C. 387j and 103 387e) of the FD&C Act; each new e-liquid formulation (even if they are prepared similarly) would constitute a new tobacco product. You may bundle applications for multiple distinct products into a single submission. However, as separate determinations are made for each product, FDA will unbundle these submissions as separate applications. It is your responsibility to provide data to support the regulatory and scientific requirements for marketing authorization of each distinct product.

If you choose to bundle your submission, we recommend that you provide a single, combined cover letter and table of contents across all products. It is important that you clearly identify and delineate what content pertains or does not pertain to each uniquely identified product and show that you have satisfied the requirements of section 910(b)(1) for each product.

In the context of a PMTA review, all ingredients, components and aerosol constituents are evaluated based upon how they contribute, directly and indirectly, to the total health impact of a specific product (see ENDS DG). Because the public health risks associated with product use can vary depending upon the number and type of chemicals present in the different e-liquids or aerosols, ideally, a PMTA would include studies (e.g., analytical chemistry, toxicological assessments) conducted using each new tobacco product; though, bridging of data from one product to another may be feasible for a subset of products or for certain types of toxicity studies. If you choose to bridge data from a previously studied tobacco product to additional new tobacco products (including different e-liquid products containing different flavors, or different concentrations of nicotine), you should provide sound scientific rationale and justification to support bridging (e.g., why the data from one product is applicable to your specific new tobacco product evaluated in the PMTA).

If you choose to use data from published studies on single ingredients, additives, or other components in your new tobacco products or aerosols to support your application, consider the overall toxicity of the mixture, especially when there is evidence that the chemical components could have additive effects. To support that the study data are relevant to your products, we recommend that you use studies completed using a relevant exposure route and compare published exposure levels to those found in your products. Tobacco product characteristics that you may wish to evaluate in the bridged studies include, but are not limited to, the identities and quantities of e-liquid ingredients and constituents, and aerosol constituents, and the apparatus operating features (e.g., heating source, temperature range). Also consider, as appropriate, the manner, duration and frequency of use. Provide the scientific rationale and adequate justification for bridging the data from the published studies to your specific new products to demonstrate that the findings of such studies are applicable and relevant to your new tobacco products.

Research suggests that flavors are associated with initiation and continued use of tobacco products, particularly among youth and young adults, and may impact consumer perceptions and use behavior. Some products, even from the same brand, may have different impacts on population health. Thus, we recommend you provide information on each flavor to demonstrate how consumers perceive the product and its flavor, as well as its impact on intention to use the product and actual use of the product. If it is not feasible or necessary to provide such data for each individual flavor to assess impact on public health, extrapolation (with the appropriate scientific rationale) may be sufficient.

You also asked whether you can 'rely primarily on published studies to address the public health questions' in your application. The determination of whether the evidence included in your application is sufficient to support a marketing authorization for one or all of your ENDS products is a matter of scientific review upon receipt of a PMTA. However, data from the published literature, from government-sponsored databases, or data from other sources may be used to support the finding that authorizing a new tobacco product to enter the market would be appropriate for the protection of public health. Note that FDA's ENDS DG states that "published literature reviews or reports may be acceptable to support a PMTA, but are considered a less robust form of support for a PMTA." Multiple corroborating lines of evidence utilizing a variety of study approaches is likely to be the most valuable in making a marketing authorization determination.

If published literature from similar products is used, we recommend you clearly articulate how the relevant literature was identified and describe how these studies are applicable to your products. Section X.B of the ENDS DG describes the elements that an applicant should provide for literature reviews, and Section VI.H.2 of the ENDS DG provides further detail on the types of information that should be included in PMTAs. If you use a literature review to support your application, we suggest that you conduct a systematic literature review(s) that is relevant to your product. The systematic review should describe in detail the methods used to conduct the literature review(s) and include, at a minimum, the databases searched and the date of searches, search terms, reasons for inclusion/exclusion of documents, the strategy for study quality assessment, and number of articles retrieved and ultimately included in the literature synthesis. When utilizing evidence from the open scientific literature to support a regulatory submission, the methods used to identify and synthesize the evidence should be transparent and reproducible. Standards have been developed for reporting in systematic reviews and meta-analyses to ensure transparency and replicability, such as:

- The Preferred Reporting Items for Systematic Reviews and Meta-Analyses or PRISMA: http://prisma-statement.org/
- Finding What Works in Health Care: Standards for Systematic Reviews: http://www.nationalacademies.org/hmd/Reports/2011/Finding-What-Works-in-Health-Care-Standards-for-Systematic-Reviews.aspx
- Cochrane Collaboration Handbook http://handbook.cochrane.org/

Applicant Question 3

Whether any customized clinical or non-clinical studies will be required by FDA and, if so, determine the scope and nature of those studies and their relevance compared to published literature concerning the product category?

FDA RESPONSE:

In the absence of a complete submission, FDA cannot comment on whether any nonclinical or clinical studies specific to your products will be necessary to fully evaluate your products. However, Section VI.H.2 of the ENDS DG states 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. Due to the 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 you will need to conduct certain investigations yourself and submit your own research findings as part of your PMTA. In cases where a product's potential impact on the public health has not yet been sufficiently studied, new nonclinical and clinical studies may be necessary to fully understand your product's impact on public health.

It is the responsibility of the applicant to provide the scientific evidence to support that a product is appropriate for the protection of public health. Where appropriate for your product, FDA has some additional comments for your consideration for your PMTA:

- Include a detailed list of uniquely identified constituents that are contained within your product or delivered by your product (Note: for an e-liquid, this may include, but is not limited to, degradation or oxidation products of the e-liquid ingredients, leachables from the container, and reaction products that may form from the heating of the product during aerosolization);
- Provide a quantitative assessment of these constituents, as well as other potentially toxic compounds in your product and in the aerosol generated by your product (Note: for aerosol emissions testing, FDA suggests that you consider testing the aerosol under a series of conditions that encompass the anticipated range of consumer use).
    - Direct analytical testing on your product and the aerosol produced by your product is one method of obtaining this data. If you choose to perform such testing, FDA suggests you consider using validated analytical methods that are fit for purpose in your proposed PMTA and providing full reports for all testing performed. You may

refer to CBER and CDER Guidance for Industry, "Process Validation: General Principles and Practices" and "Analytical Procedures and Methods Validation for Drugs and Biologics." FDA suggests that these reports provide the following information:

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

- You state that due to the simplicity of design and operation, Vapor Shark does not intend to perform any human factor and usability engineering studies for this category of products, i.e., e-liquids. From the engineering perspective FDA agrees that neither the e-liquid nor the e-liquid bottle need to undergo human factors or usability studies.
- From a microbiology perspective, FDA recommends including product stability studies to establish the expected storage time and appropriate storage conditions of the final to-be-marketed tobacco product. Stability testing should be conducted on the product packaged in the same container-closure system in which it is to be marketed. Microbiological determinations including water activity (aw), and microbial counts (TAMC, TYMC) over the established shelf-life of the product are recommended. In addition, for nicotine-containing e-liquids, Tobacco-Specific Nitrosamine (total, NNN and NNK) measurements over product shelf-life are recommended. If a parameter is not applicable for the study, state as such and provide a scientific rationale for the exclusion of the parameter in the stability study. Complete stability testing data (i.e., sample size, sample manufacture and test date, test intervals, test methods, data sets, and a summary of results) from samples that are representative of the manufacturing scale of production is recommended.
- FDA will need to understand tobacco product perceptions and intentions, including how consumer populations including youth may perceive, use, or intend to use your products, as youth are a vulnerable population in terms of tobacco use initiation. FDA recommends that Vapor Shark include information on all studies conducted, for all age groups (youth, adolescent, young adults, adults) who may be exposed to your product. FDA also recommends that you clearly explain what information was contained in these studies and how such data can be extrapolated to the product and population(s) of interest, including youth, for the product that is the subject of the PMTA.
- In order to assess the human health impact of your products in your PMTA, it is important that you provide sufficient information so that FDA may understand the potential short and long-term health risks associated with your product. In addition to any potential studies, your PMTA must include "full reports of all information, published or known to, or which should reasonably be known" to you, "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." This is a requirement to support filing your PMTA as described in Section 910(b)(1)(A).

Applicant Question 4

Whether a "factory approach" to developing PMTAs to assist and expedite FDA's internal review is permissible under the current Guidance Document? More specifically:

Vapor Shark conceptualizes its "factory" approach as a drafting method that would result in a modular based PMTA designed to streamline the application and review process, reduce FDA's review burden insomuch as the PMTA would be organized straightforwardly by reviewing disciplines, and to be strategically organized in manner such that subsequent applications could include re-purposed and familiar application elements. Vapor Shark proposes the PMTA be organized by the following disciplines:

1. Chemistry
2. Toxicology
3. Microbiology
4. Engineering
5. Medical/Epidemiology
6. Addiction
7. Clinical/Non-Clinical
8. Social Science
9. Statistics; and
10. Environmental Biology

Vapor Shark anticipates multiple reviewing disciplines will be interested in the same information; thus, the PMTA will be structured such that each discipline will have its material information accessible, even if the information is duplicative of another discipline's material information. Vapor Shark proposes using various electronic capabilities to allow any one individual to easily aggregate the information needed for his or her review. This should substantially reduce the need to search for information and consequently ease and shorten review time. The programming will not prevent any one individual from reviewing the entire document if so desired.

FDA RESPONSE:

Currently, there are no requirements for the format of the table of contents, but a well-organized PMTA that is formatted consistently (with pages numbered sequentially) is helpful to facilitate review of the application. Instead of organizing your PMTA by scientific discipline, to further facilitate review of your PMTA, FDA recommends that you organize the PMTA so that the elements appear in the same order that the elements are discussed in Section VI of the ENDS DG. FDA requests that you ensure hyperlinks work properly, especially when cross-referencing documents. FDA recommends a Cover Letter, a Table of Contents, List of References, List of Appendices, and summary data tables, where appropriate, which help organize and present scientific information and complex data and facilitate navigation of your PMTA.

As stated in the ENDS DG page 19, to facilitate review, each PMTA should:

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

- *Enable the user to print each document page by page as it would have been provided in paper, maintaining fonts, special orientations, table formats, and page numbers.*
- *Allow the user to copy the text , images and data electronically into other common software formats.*

These are examples of acceptable file formats that would help FDA reviewers evaluate your electronic submission:
https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM347471.pdf

In addition, the following are discipline specific comments to consider when preparing your PMTA:

- The product description would benefit from additional information for e-liquids. This information would include e-liquid boiling point (°C) and e-liquid viscosity (at 20°C). In addition, FDA recommends you provide an explanation of the e-cigarette configuration used for the e-liquid testing and why that configuration was chosen and how it compares to those currently on the U.S. market.
- FDA recommends that manufacturers of e-liquids test the constituent delivery in an aerosolizing apparatus that is designed to deliver low levels of aerosol (i.e. open refillable cigarette-like systems), as well as in an aerosolizing apparatus that is designed to deliver higher levels of aerosol with varying temperatures and voltage (such as a tank or mod system).

Applicant Question 5
May [Vapor Shark], in consultation with FDA, establish 'de minimis" vapor exposure loading for minor components, below which extensive testing will not be required?

FDA RESPONSE:

Currently, there are no established standards for determining whether the calculated upper bound non-cancer hazard or risk of cancer posed by a "minor component" in tobacco products is low enough to be considered to pose a "de mimimis" risk. Recommendations and information regarding the toxicological assessment and review of your new tobacco products is provided in the FDA response to question #1.

Applicant Question 6
May [Vapor Shark] normalize e-liquid vapor exposure utilizing the typical operating temperature of a selected device, and similarly, may [Vapor Shark] normalize nicotine exposure to a standard conventional cigarette or 1 mg of nicotine.

FDA RESPONSE:

At this time, FDA does not have requirements regarding specific ENDS operating parameters or normalization processes necessary for PMTA authorization for tobacco products. However, you may want to consider whether and how to conduct testing to span the available operating

conditions of the aerosolizing apparatus proposed in your PMTA (e.g., temperature, voltage, and liquid tank fill status, if applicable). We recommend identifying and evaluating operating conditions most likely to be used by product users.

The temperature at which the e-liquid is aerosolized has a direct effect on nicotine yield; higher temperatures are associated with greater nicotine aerosolisation. In addition, the operating temperature or the coil temperature has an effect on vapor constituents such as carbonyls. With the evolution of e-cigarettes, consumers have the ability to set and control temperatures. Therefore, FDA recommends that manufacturers of e-liquids test the constituent delivery in an ENDS that is designed to deliver low levels of aerosol (i.e. open refillable cigarette-like systems), as well as in an ENDS 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.

While delivery of nicotine is achieved in a similar manner for ENDS products and conventional cigarettes, via inhalation of an aerosol or smoke, the pharmacokinetics of nicotine in users may be dramatically different. It is well known that pharmacokinetic parameters associated with nicotine delivery, such as T_{max} and C_{max} values (calculated using measured blood plasma nicotine and nicotine metabolite levels), may play an important role in use patterns and behaviors for different tobacco products. The nicotine concentration in aerosolized e-liquids may not deliver an equivalent level of nicotine in vivo, compared to conventional cigarette smoke containing the same nicotine concentration. For example, the nicotine form (e.g., freebase nicotine versus different nicotine salt formulations) used in the e-liquid formation may impact nicotine pharmacokinetics in users. As tobacco product use is linked to delivered nicotine, not aerosol or smoke concentrations of nicotine, normalization of nicotine based on aerosol concentrations may lead to underestimations of ENDS exposures and exposures to constituents of toxicological concern. For example, if less nicotine is delivered to the user from ENDS aerosols compared to conventional cigarette smoke, the ENDS user may compensate and increase use of [and exposure to] the product to achieve the same delivered nicotine dose experienced from a conventional cigarette. Therefore, FDA suggests you assess the new tobacco products' pharmacokinetic profile for nicotine and to normalize nicotine exposures based on delivered nicotine levels in vivo.

Nicotine delivery (i.e., the amount of nicotine delivered to the blood) following a given level of nicotine exposure (i.e., the amount of nicotine present in the smoke or aerosol) may be different for conventional cigarettes and e-liquids. As a result, nicotine exposure may not reflect the actual use patterns of the two products being compared. Therefore, comparing aerosol or smoke test results that are normalized to nicotine may not be appropriate. If you wish to normalize your aerosol testing results to the amount of nicotine generated, FDA recommends that you provide justification for why you believe such a comparison is warranted.

Applicant Question 7

Will published studies of potential aldehyde generation from propylene glycol (PG) and glycerol (VG) or flavoring by products be sufficient as references, or will [Vapor Shark] need to undertake specific formulation/device combination studies?

FDA RESPONSE:

To properly evaluate the possible health effects of your product, FDA suggests that you provide detailed and quantitative information about the levels of aldehydes, and other HPHCs that may be in or generated by your product. The constituents currently on the established HPHC list and other chemicals of interest in e-liquids and vapor as stated in the ENDS DG (e.g., diacetyl, acetyl propionyl, diethylene glycol, ethylene glycol, glycerol and propylene glycol) are constituents that could potentially cause health hazards. Aldehydes only represent a single chemical class found on the HPHC list. FDA recommends consideration of all HPHCs and other toxic chemicals potentially generated during use of your new tobacco products. FDA recommends that you consider providing this information for those compounds on the current HPHC list, the potentially toxic chemicals highlighted in the ENDS DG, and any other potentially toxic constituents that are appropriate for your specific product. FDA also recommends that you provide this data for aerosols generated under conditions that represent the range of operational temperatures, flow rates, and power levels expected for consumer use.

FDA does not require that you obtain this information using specific formulation/device combinations. However, since this approach may allow you more closely replicate conditions that are representative of consumer use, it may provide more relevant data for your application.

As stated previously, if you choose to use published studies to provide this information, FDA recommends that you provide clear justification for why these studies are appropriate and a clear explanation of how the data presented in studies may be extrapolated to your product.

Applicant Question 8

Can [Vapor Shark] work with FDA to establish a pre-screened database of flavor, fragrance, or taste enhancement ingredients that can be utilized at minor or trace levels in several formulations without the need for separate PMTA submissions.

FDA RESPONSE:

The PMTA pathway is intended for new tobacco products to be authorized for marketing in the United States. Each new tobacco product submitted under the PMTA pathway, requires a separate marketing authorization. FDA does not authorize individual ingredients that may be utilized in several different new products in absence of a marketing authorization for the individual new products. FDA suggests that you consider submitting a Tobacco Product Master File (TPMF) [see FDA's "Tobacco Product Master Files – Guidance for Industry"]. A TPMF may provide a full listing of materials, ingredients, and composition information for all components in a given tobacco product as well as relevant nonclinical or clinical study information. Although providing information in a TPMF alone does not satisfy the requirement for receiving premarket authorization for a new product, one advantage of the TPMF is that the information contained therein can be referenced by a manufacturer in subsequent new product applications without the need for resubmitting and duplicating information.

Applicant Question 9

May [Vapor Shark] rely upon published literature in lieu of product-specific clinical studies, filling in haps by broad flavor categories (e.g., fruit, tobacco, bakery, cereal, and mint flavors) only to the extent necessary when no published literature is available to address abuse liability and use behavior.

FDA RESPONSE:

See FDA Response #2.

FDA agrees to the inclusion of results from a literature review of additional information, such as demographics and use patterns, abuse liability, biomarkers of exposure, dual-use or poly-use, switching, and cessation/initiation behaviors. FDA suggests that each application contain enough supporting evidence specific to each specific product that is the subject of that application to enable FDA to assess whether marketing of that product is appropriate for the protection of public health. Note that FDA does not expect that applicants will need to conduct clinical studies as part of a PMTA; applicants may demonstrate abuse liability and use behavior, for example, by including existing studies from the public literature or extrapolating from other studies on the proposed products. When using published studies relevant to your products, consider study designs with adequate sample sizes for robust statistical analyses and sufficient sensitivity to evaluate study endpoints. Bioassays and biomarkers should be fit for purpose and appropriate for evaluating the specific e-liquid categories and flavorings in the tobacco product that is the subject of the application. Further, FDA recommends that you include the literature review methods, including databases searched, date of searches, search terms, reasons for inclusion/exclusions of documents, strategy for study quality assessment, and specific questions addressed, in the PMTA. As stated in FDA's reply to Question #2, standards have been developed for reporting in systematic reviews to ensure transparency and replicability, such as: (1) The Preferred Reporting Items for Systematic Reviews and Meta-Analyses or PRISMA; and (2) Finding What Works in Health Care: Standards for Systematic Reviews.

You may also refer to the ENDS DG page 45 describing recommendations for literature reviews. It is important to note that peer-reviewed and published studies of ENDS use are not likely to be specific to each of the products listed in this meeting request. Using such information to extrapolate to your specific products should provide sufficient scientific information to allow for bridging between the products examined in published literature and the ones that are the subject of interest in this meeting request. Additionally, scientific studies published in the peer-reviewed literature often are constrained by journal word limits, which preclude providing the level of detail that would typically be reported for a study conducted by a sponsor to support a regulatory submission. In some cases, this may limit the ability to thoroughly assess the scientific validity of the findings reported.

We suggest that you justify why data on the broad category of fruit flavors might be relevant to each of your strawberry, peach, and coconut flavored e-liquids. However, in considering the impact of your product on health behavior, it is important that you address the impact of your specific product on current non-users, including youth, and current tobacco users, specifically the likelihood that the availability of your product with that specific flavor would promote complete switching among current cigarette smokers, and the likelihood that former tobacco users would initiate use of your product.

Applicant Question 10

May [Vapor Shark] rely solely upon the PATH study and published literature, with bridging as appropriate, to address comparisons of e-liquid use to smoking conventional cigarettes and to address FDA's concerns regarding the possible impact of e-liquid use on cessation?

FDA RESPONSE:

FDA supports the use of different types of studies, methods, instruments and analyses to answer the likely impact of a tobacco product on population health. The data submitted as part of your PMTA could come from a variety of sources. Providing data from PATH and the published literature or other relevant sources in your application with appropriate bridging information germane to your specific product is one possible approach. As stated previously, FDA recommends that Vapor Shark clearly describe how the bridging from data sources address the larger questions, including how such data can be extrapolated to the population or populations of interest, including youth, for the product(s) that is the subject of the PMTA.

To address comparisons of e-liquid use to smoking conventional cigarettes, consider use differences that could impact the user's exposure to constituents of toxicological concern that may result in adverse health effects. Consider the manner of use, duration and frequency of use, and the setting(s) or environment (e.g., indoor space, outdoor space) in which the tobacco products were used in these studies. We also recommend that you consider the demographic characteristics of the exposed users and nonusers (including never users and former users) as well as to explore key user states and transitions that inform the population impact (e.g., likelihood of initiation among never-users and former users, cessation among current tobacco users, complete switching, dual use, likelihood of product use by youth, and the impact of migration to/from the proposed ENDS product and other ENDS products, which may be more or less harmful than the proposed ENDS product) in the bridged studies and how they compare to the users and nonusers of your tobacco products. You may also wish to ensure that findings from the studies are generalizable to the U.S. population in common and worst-case settings of exposure.

Applicant Question 11

May [Vapor Shark] rely upon published literature for PMTA submission of its e-liquid products, supplemented by small-sample (n=30) consumer perception evaluations only if necessary after PMTA submission, to address human health impact of the category of e-liquids which are the subject of the PMTA application?

FDA RESPONSE:

It is not clear what is meant by *"...only if necessary after PMTA submission..."* There is insufficient information provided on intended PMTA content related to perception and appeal of your proposed products as well as to the proposed consumer perception study to be able to fully respond to your question.

Section 910(b)(1) of the FD&C Act states that your PMTA should include 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 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 at the time of submission. FDA recommends that you provide information specific to each product in your PMTA, clearly explain what information was contained in these studies and how such data can be extrapolated to the product and population(s) of interest, including youth, for the product that is the subject of the PMTA. FDA expects PMTAs to be complete at the time they are received; however, applicants may amend their PMTA with additional information either at the request of FDA or via an unsolicited amendment. Because some amendments may require additional FDA review time to complete the PMTA evaluation, the amendment would need to be received in time to be considered as part of FDA's evaluation.

Premarket Tobacco Product Applications for Electronic Nicotine Delivery Systems

Guidance for Industry

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

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

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

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

June 2019

Table of Contents

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.

The guidance explains, among other things:

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

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

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

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

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

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

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

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

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

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

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

II. BACKGROUND

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

G. Finished Tobacco Product

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

H. New Tobacco Product

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

(A) any tobacco product (including those products in test markets) that was not commercially marketed in the United States as of February 15, 2007; or
(B) any modification (including a change in design, any component, any part, or any constituent, including a smoke constituent, or in the content, delivery or form of nicotine, or any other additive or ingredient) of a tobacco product where the modified product was commercially marketed in the United States after February 15, 2007.[11]

I. Tobacco Product

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

IV. DISCUSSION

A. Products to Which This Guidance Applies

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

[11] See note 7.

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

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

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

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

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

1. Considerations for All Applicants

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

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

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

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

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

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

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

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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).

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

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

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

C. General Procedures for ENDS PMTA Review

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

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

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

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

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

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

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

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

D. Public Health Considerations for ENDS Products

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

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

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

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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

[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.

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

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

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

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

2. Valid scientific evidence

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

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

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

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

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

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

3. Comparison Products

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

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

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

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

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

4. Nicotine exposure warnings

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

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

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

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

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

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

5. Warning statement regarding the addictiveness of nicotine

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

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

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

6. Protective packaging

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

V. HOW TO SUBMIT A PMTA

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

A. General Information

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

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

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

B. Table of Contents

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

C. Descriptive Information

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

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

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

FDA recommends that the unique identification of the product include:

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

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

D. Product Samples

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

E. Labeling

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

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

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

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

F. Environmental Assessment

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

G. Summary of All Research Information

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

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

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.

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

b. Properties

[33] See the R&D meetings guidance.
[34] Available on the Internet at https://www.fda.gov/tobacco-products/rules-regulations-and-guidance/guidance.

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

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

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

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

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

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

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

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

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

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

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

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

c. Principles of operation

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

d. Manufacturing

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

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

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

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

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

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

2. Nonclinical and Human Subject Studies

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

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

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

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

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

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

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

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

[40] See the R&D meetings guidance.

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

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

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

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

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

- 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.

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

a. Nonclinical health risk information

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

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

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

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

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

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

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

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

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

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

- If the consumer can change the voltage and/or temperature of the heating element, we recommend that you provide any available data on the subsequent changes in the aerosol ingredients. Please also include any toxicity information relevant to these changes.
- We recommend that you provide aerosolization properties of each of the ingredients (e.g., constituents, humectants, metals, flavors included), particle size of these ingredients in the product, and deposition of these particles through inhalation. We also recommend that you discuss how these properties could affect the product's toxicity profile.
- In vitro assays can be used to evaluate the genotoxic potential of the ENDS in comparison to other tobacco products. We suggest using the ICH S2(R1) guidance[42] and Organization for Economic Cooperation and Development protocols as a guide for genotoxicity assessment. We also recommend that you conduct these assays with multiple concentrations of your final product for validating your results. For appropriate hazard identification comparison, you should include the comparator products (e.g., products in the same category) in your in vitro assay.

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

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

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

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

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

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

[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.

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

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

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

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

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

iv. Labeling comprehension and actual use

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

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

v. Human factors

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

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

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

vi. Abuse liability

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

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

vii. Biomarkers of harm and biomarkers of exposure

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

viii. Health outcomes

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 Inc. (UL) Standard 2054 2nd Edition;[47] (3) UL Standard 1642 5th Edition.[48] Examples of voluntary battery standards for rechargeable batteries include: (1) IEC 62133 Edition 2.0 2012-12;[49] (2) UL 2054 2nd Edition;[50] or (3) UL's

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

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

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

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

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

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

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

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

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

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

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

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

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

D. Master Files

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

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

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

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

E. Bridging

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

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

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

XI. POSTMARKET REQUIREMENTS

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

XII. REQUESTING MEETINGS WITH FDA

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

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

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

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

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

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

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

XIII. OFFICE OF SMALL BUSINESS ASSISTANCE

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

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

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

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF MARYLAND

AMERICAN ACADEMY OF PEDIATRICS, *et al.*, Plaintiffs, v. UNITED STATES FOOD AND DRUG ADMINISTRATION, *et al.*, Defendants.	Civil Action No. 8:18-cv-883-PWG

DECLARATION OF MITCHELL ZELLER

I, Mitchell Zeller, declare as follows:

1. I am the Director of the Center for Tobacco Products ("CTP"), United States Food and Drug Administration ("FDA"), a position I have held since March 2013. In this role, I direct the development and implementation of programs and policies for regulating the manufacture, marketing, and distribution of tobacco products. In my capacity as Director of CTP, I am fully familiar with the instant matter and the facts stated herein.

2. I have dedicated my career to working on FDA issues (nearly 37 years), including the last 25 years focused on tobacco regulation. I am a graduate of Dartmouth College and the American University Washington College of Law. I began my career as a public interest attorney in 1982 at the Center for Science in the Public Interest working on FDA food safety and nutrition issues. In 1988, I served as counsel to the Human Resources and Intergovernmental Relations Subcommittee of the House of Representatives Government Operations Committee, where I conducted oversight of enforcement of federal health and safety laws, including human and animal drugs, dietary supplements, and food policies at FDA. In 1993, I joined the staff of

then-FDA Commissioner, Dr. David Kessler, M.D., on a two-week assignment to examine the practices of the tobacco industry. This assignment led to my serving as associate commissioner and director of FDA's first Office of Tobacco Programs where I led FDA's efforts to craft the agency's 1996 tobacco regulations. In this capacity, I represented FDA before Congress, federal and state agencies, and served as an official United States delegate to the World Health Organization Working Group for the Framework Convention on Tobacco Control. In 2000, I left FDA to continue my work in tobacco control as executive vice president of the American Legacy Foundation, where my responsibilities included marketing, communications, strategic partnerships, and creating the foundation's first Office of Policy and Government Relations. I later joined Pinney Associates as senior vice president in 2002, where I remained until I took my current position as Director of CTP. In that role, I provided strategic planning and communications advice on domestic and global health policy issues involving the treatment of tobacco dependence and the regulation of tobacco products and pharmaceuticals.

3. The Family Smoking Prevention and Tobacco Control Act, Pub. L. No. 111-31, 123 Stat. 1776 (2009) ("TCA") gave FDA authority to "deem" additional tobacco products subject to Chapter IX of the FDCA through notice and comment rulemaking. On May 10, 2016, FDA issued the "deeming rule," which subjected all other tobacco products (except accessories) to the requirements in Chapter IX of the FDCA, including electronic nicotine delivery systems ("ENDS") and cigars. 81 Fed. Reg. 28,974.

4. FDA has used and will continue to use its authority under the TCA and the deeming rule to address serious concerns about tobacco products, including youth use of ENDS and flavored cigars. We are committed to keeping tobacco products out of the hands of youth, and have used our authority and resources forcefully to prevent youth access, curb the marketing

of tobacco products aimed at youth, and educate teens and their families about the health risks of vaping and other tobacco product use. Specifically, since early 2018, these actions have included: (1) in May 2018, issuing 17 warning letters to manufacturers and retailers for selling e-liquids that resembled kid-friendly food products, which prompted all of the recipients to stop selling the violative products;[1] (2) in summer 2018, conducting a nationwide undercover investigation that resulted in over 1,300 warning letters and civil money penalty actions against retailers who illegally sold ENDS products to minors;[2] (3) in January 2019, holding a public hearing to discuss strategies to eliminate youth use of ENDS with a focus on the role of drug therapies to help young people quit using e-cigarettes and other tobacco products;[3] (4) in March and April 2019, publicly admonishing thirteen national chain stores and franchises with high rates of violations for illegal sales of tobacco products to minors, and requesting plans that describe how these retailers will address and mitigate illegal sales to minors;[4] (5) in June 2019, sending four warning letters jointly with the Federal Trade Commission for violations related to online posts by social media influencers;[5] and (6) continuing robust public education efforts to prevent youth use of tobacco, including expanding its tobacco prevention campaign—called "The Real Cost"—to ENDS products with messaging that has been seen by teens nearly 500 million times.[6] Other CTP actions to address youth use are described in a March 2019 draft

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[1] *See* FDA News Release, *available at* https://www.fda.gov/news-events/press-announcements/fda-warns-more-companies-stop-misleading-kids-e-liquids-resemble-kid-friendly-foods-part-youth.
[2] *See* FDA News Release, *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.
[3] *See* Eliminating Youth Electronic Cigarette and Other Tobacco Product Use: The Role for Drug Therapies Public Hearing, Jan. 18, 2019, https://www.fda.gov/news-events/fda-meetings-conferences-and-workshops/eliminating-youth-electronic-cigarette-and-other-tobacco-product-use-role-drug-therapies-public.
[4] *See* https://www.fda.gov/news-events/press-announcements/statement-fda-commissioner-scott-gottlieb-md-forceful-new-actions-focused-retailers-manufacturers.
[5] *See* https://www.fda.gov/news-events/press-announcements/fda-ftc-take-action-protect-kids-citing-four-firms-make-sell-flavored-e-liquids-violations-related.
[6] *See* https://www.fda.gov/tobacco-products/public-health-education-campaigns/real-cost-campaign.

guidance document.[7]

5. This case relates to the premarket review of deemed tobacco products that are new tobacco products as defined in 21 U.S.C. § 387j(a)(1). I describe the various pathways in which tobacco products may be legally marketed below:

a. Grandfathered Tobacco Products. Products that were commercially marketed in the United States as of February 15, 2007, are considered "grandfathered" and do not require prior authorization to be legally marketed. *See* 21 U.S.C. § 387j(a)(1). They also may serve as a predicate tobacco product for a substantial equivalence (SE) report, described below. FDA has made 1,651 grandfathered determinations for deemed products (e.g., cigars, pipe tobacco, and waterpipe tobacco).[8] Seeking an FDA grandfather determination is a voluntary process and there are likely many additional grandfathered products being marketed.

b. Substantial Equivalence (SE). A substantially equivalent tobacco product is a new tobacco product that has been found by FDA either to have the same characteristics as a predicate tobacco product or to have different characteristics than the predicate tobacco product, but, in the latter case, the substantial equivalence report submitted by the manufacturer demonstrates that it is not appropriate to regulate the new tobacco product under the Premarket Tobacco Application (PMTA) pathway because the product does not raise different questions of public health. 21 U.S.C. § 387j(a)(3)(A). A predicate tobacco product that an applicant can use is one that was commercially

[7] *See* Modifications to Compliance Policy for Certain Deemed Tobacco Products, Draft Guidance (Mar. 2019) at 5, *available at* https://www.fda.gov/media/121384/download.
[8] *See* Grandfathered Tobacco Products, *available at* https://www.fda.gov/tobacco-products/market-and-distribute-tobacco-product/grandfathered-tobacco-products (page last viewed June 12, 2019).

marketed in the United States as of February 15, 2007 (a grandfathered tobacco product), or has previously been found to be substantially equivalent by FDA, and is in compliance with the requirements in Chapter IX of the FDCA. FDA has issued guidance documents[9] and a proposed rule on April 2, 2019,[10] which address SE reports. As of April 30, 2019, FDA has authorized 1070 products with SE orders. For deemed products, FDA has received 313 SE reports and issued four orders authorizing SE reports.[11]

c. Substantial Equivalence Exemption. A new product may be exempt from the need to demonstrate substantial equivalence if it is modified by adding or deleting a tobacco additive or by increasing or decreasing the quantity of an existing tobacco additive, and such a modification would be a minor modification of a legally marketed product and an SE report is not necessary for the protection of public health. 21 U.S.C. § 387e(j)(3). As of April 30, 2019, FDA has issued 199 SE exemption orders, including 21 orders for deemed products.[12] FDA issued a final rule establishing procedures for requesting an exemption from the substantial equivalence requirements in 2011. *See* 76 Fed. Reg. 38,961 (Jul. 5, 2011). In addition, information about this pathway is available in the SE guidance documents referred to above.

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[9] *See* Section 905(j) Reports: Demonstrating Substantial Equivalence for Tobacco Products (Jan. 2011), available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/section-905j-reports-demonstrating-substantial-equivalence-tobacco-products. FDA has also issued another Guidance, Demonstrating the Substantial Equivalence of a New Tobacco Product: Responses to Frequently Asked Questions, most recently revised in December 2016 (available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/demonstrating-substantial-equivalence-new-tobacco-product-responses-frequently-asked-questions).

[10] *See Content and Format of Substantial Equivalence Reports; Food and Drug Administration Actions on Substantial Equivalence Reports*, 84 Fed. Reg. 12740 (Apr. 2, 2019).

[11] *See* https://www.fda.gov/tobacco-products/substantial-equivalence/marketing-orders-se (Jan. 29, 2019 order for Black & Mild Shorts). SE orders are generally publicly available at the website above, but commercially confidential information must be redacted before posting. Three of the four SE orders referred to above have not yet been posted.

[12] *See* SE Exemption Order for John Middleton Co., Black & Mild (Sept. 7, 2018), *available at* https://www.fda.gov/tobacco-products/exemption-substantial-equivalence/marketing-orders-exemption-se.

d. Premarket Tobacco Application (PMTA). All other new tobacco products must be authorized through the PMTA pathway, which requires applicants to demonstrate that the new tobacco product is appropriate for the protection of the public health, which is determined with respect to the risks and benefits to the population as a whole, including users and non-users of tobacco products, and taking into account the increased or decreased likelihood that existing users of tobacco products will stop using such products, and those who currently do not use tobacco products will start using such products. 21 U.S.C. § 387j(b), (c). FDA issued a guidance specifically for ENDS products, which are likely to be reviewed through the PMTA pathway, on June 11, 2019 ("PMTAs for ENDS Guidance").[13] The PMTAs for ENDS Guidance is intended to assist applicants to prepare PMTAs for these products and explains, among other things, when a PMTA is required, general procedures for review of an ENDS PMTA, what information the FDCA requires applicants to submit in a PMTA, and what information FDA recommends applicants submit in an ENDS PMTA to show whether permitting such new tobacco product to be marketed is appropriate for the protection of the public health. In addition, FDA intends to issue a proposed rule in the near future to further specify application contents and FDA's review and communication procedures under this pathway.[14] As of April 30, 2019, FDA has received 401 PMTA applications, 373 of which are for deemed products. FDA has authorized the marketing of 12 total products

[13] *See* Premarket Tobacco Product Applications for Electronic Nicotine Delivery Systems 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.
[14] *See* Premarket Tobacco Product Application and Recordkeeping Requirements, RIN: 0910-AH44, *available at* https://www.reginfo.gov/public/do/eAgendaViewRule?pubId=201904&RIN=0910-AH44.

under two different product types (non-combustible cigarettes and smokeless tobacco),[15] and closed out 369 of the 373 applications it has received for deemed products as insufficient to accept or file, primarily for failure to file an adequate environmental assessment, as required by 21 C.F.R. § 25.15. Only four PMTA applications are pending with the agency at this time for deemed products, none of them for an ENDS product. Thus far, FDA has provided information about the PMTA application process through public seminars and workshops,[16] and regularly meets with sponsors to discuss FDA's expectations for these applications.

6. By statute, all deemed products require marketing authorization unless they are grandfathered. No deemed products had authorization when the deeming rule went into effect. Thus, when the deeming rule took effect on August 8, 2016, all deemed products on the market were suddenly noncompliant with the statute. Accordingly, in the preamble to the deeming rule, FDA announced a compliance policy under which, as an exercise of enforcement discretion, it intended to defer enforcement of various provisions for limited periods of time to give manufacturers time to come into compliance. With respect to premarket review, for products that were on the market as of August 8, 2016, FDA provided staggered compliance dates for submission of applications depending on the type and complexity of the application; in addition, if an application was submitted within the compliance period, the preamble further stated that the agency did not intend to initiate enforcement for lack of a marketing order from FDA for one year after submission while FDA reviewed the application. *Id.* at 28,977-78. As explained in the preamble, this policy was based on balancing complex and competing public health and resource

[15] *See* Premarket Tobacco Product Marketing Orders, *available at* https://www.fda.gov/tobacco-products/premarket-tobacco-product-applications/premarket-tobacco-product-marketing-orders.
[16] *See* Useful Links for PMTA, *available at* https://www.fda.gov/media/101179/download (Oct. 17, 2016).

considerations, primarily that products would remain available without having undergone scientific review, concerns regarding the effect that flavors have on use of tobacco products by youth and young adults, the potential for some net public health benefits if flavored ENDS remain available, the different risks posed by different classes of products, the fact that some flavored combusted products are grandfathered, the expected complexity of applications, efficiently managing the flow of incoming applications, and encouraging high-quality applications. *Id.*

7. In July 2017, FDA announced a new comprehensive approach to tobacco and nicotine. The approach included many components, the centerpiece of which was developing a regulation aimed at reducing nicotine in cigarettes to minimally addictive or non-addictive levels. In a world where cigarettes were minimally addictive or non-addictive, access to alternative and less harmful forms of nicotine would be essential. Other components included advancing rules to lay out what needs to be in SE and PMTA applications; determining whether and how FDA should regulate youth-appealing flavors in ENDS and other tobacco products; and seeking new information that may inform consideration of the regulation of so-called premium cigars. As one part of this comprehensive public health package, where each component was intended to work alongside the others in striking an appropriate balance, FDA stated that it would further defer enforcement of the premarket review provision for deemed products to encourage development of innovative tobacco products that had the potential to be less dangerous than cigarettes and to provide manufacturers additional time to develop higher quality applications informed by additional guidance and rules and products standards from the agency.

8. On August 8, 2017, FDA issued a revised guidance extending the compliance dates for the submission of premarket review applications for deemed products until August 8,

2021, for combustible new tobacco products (including cigars) and until August 8, 2022, for noncombustible new tobacco products (including most ENDS products)—but only for products that were on the market as of August 8, 2016. *See* Guidance for Industry: Extension of Certain Tobacco Product Compliance Deadlines Related to the Final Deeming Rule (Aug. 2017) ("Guidance"). The Guidance also indicated that FDA expected that these products would remain on the market while their premarket applications were under review (or were withdrawn).

9. In the summer of 2018, data from the annual National Youth Tobacco Survey showed a significant increase in youth use of ENDS products. This followed two years of a reduction or leveling off in youth ENDS prevalence rates. These data prompted FDA to consider revising the compliance policy for premarket review set forth in the Guidance. On March 13, 2019, FDA issued a draft guidance proposing to modify that compliance policy.[17] This new draft guidance reiterated that all deemed products without a marketing order (except "grandfathered" products on the market as of February 15, 2007) were on the market in violation of the statute and therefore potentially subject to enforcement. It outlined FDA's enforcement priorities to help address youth use, particularly youth use of certain flavored products. The draft guidance reflects a careful rebalancing of public health considerations based on new information. It revises the prior deferred-enforcement policy with respect to broad categories of e-cigarette and cigar products, and proposes prioritizing enforcement of the premarket review provisions against: e-cigarette products targeted to minors or likely to promote use by minors; flavored e-cigarette products (except tobacco, mint, and menthol flavors) offered for sale in ways that pose heightened risks of youth access; flavored e-cigarette products (except tobacco, mint, and menthol flavors) offered for domestic sale after August 8, 2021, for which the manufacturer has

[17] *See* Modifications to Compliance Policy for Certain Deemed Tobacco Products, Draft Guidance (Mar. 2019) at 5, *available at* https://www.fda.gov/media/121384/download.

not submitted a premarket application; and flavored cigars. Evidence shows that tobacco, mint and menthol flavors are preferred more by adults than minors, and in the draft guidance FDA noted it is concerned by the potential that adult former smokers who switched to ENDS could be at risk of migrating back to combustible products if there were an abrupt market exit of ENDS.[18]

Remedies

10. FDA has continued to invest significant resources into addressing the recent surge in youth ENDS use and developing the draft March 2019 guidance, and is committed to finalizing the guidance within 120 days. FDA has thus far received over 15,000 comments on the draft guidance and has reviewed the more substantial comments. FDA expects to complete consideration of the comments, draft the final guidance, and publish it on this highly accelerated 120-day timeframe.

11. The general framework of the March 2019 guidance, when finalized, would allow FDA to strike an appropriate balance of complex and competing public health and agency resource considerations, including addressing the rapid rise in youth use of ENDS versus the availability of potentially less harmful products for currently addicted adult users of combustible products. I believe that finalizing this guidance – which focuses on restricting youth access to flavored ENDS products – is one of the most critical public health steps that FDA can take to curb youth vaping.

12. I understand that plaintiffs seek a remedy that would order FDA "to ensure that no new tobacco product" that was subject to the Guidance's extended compliance dates "may

[18] *See* Schneller, L.M., M. Bansal-Travers, M.L. Goniewicz, et al., "Use of flavored electronic cigarette refill liquids among adults and youth in the US—Results from Wave 2 of the Population Assessment of Tobacco and Health Study (2014-2015)," *PLoS ONE* 13(8): e0202744 (2018), available at: https://doi.org/10.1371/journal.pone.0202744; Harrell, M.B., Weaver, S. R., Loukas, A., et al., "Flavored e-cigarette use: Characterizing youth, young adult, and adult users. *Preventive Medicine Reports*, 5, 33-40, (2017), doi: 10.1016/j.pmedr.2016.11.001.

remain on the market without being subject to FDA enforcement action" unless an application for premarket review has been received within 120 days of a remedial order from the Court. It is my firm belief that plaintiffs' proposed 120-day submission deadline creates a genuine risk of migration from potentially less harmful ENDS products back to combustible tobacco products within the population of addicted adult smokers who have completely switched to ENDS. This is a public health outcome that should be avoided if at all possible, while still achieving the public health benefits of earlier premarket review for deemed products, especially with respect to curtailing youth use.

13. If the Court nevertheless finds it necessary to enter an injunction requiring the submission of premarket applications by a date certain, it should not set a deadline sooner than 10 months from now—a date that I believe would at least make it feasible for more manufacturers to develop and submit complete and high quality applications, and for FDA to publish a proposed PMTA rule and be close to finalizing the SE and PMTA rules. It would also enable ENDS manufacturers to consider and strengthen their applications based on the final PMTA for ENDS guidance. Similarly, if the Court enters an injunction limiting the compliance period for products with timely premarket applications on file to one year, as Plaintiffs also request, it should not disturb the FDA's discretion to defer enforcement on a case-by-case basis with respect to applicants who have provided the needed information and made substantial progress toward completion, as was the case under the original compliance policy. *See* 81 Fed. Reg. at 29,012.

14. This approach, although not as accelerated as Plaintiffs' proposal, would better protect the public health. Products lacking an application after 10 months would be subject to enforcement, as would products lacking an authorization after a one-year review period.

Critically, in the interim, all deemed new products would be subject to enforcement in accordance with the priorities set forth in the March 2019 draft guidance, when finalized, even before the 10-month submission and one-year review time periods elapse.

15. Plaintiffs' proposed remedy, by contrast, would cause significant public health concerns, as well as implementation challenges. First and foremost, from the public health perspective, Plaintiffs seek to clear the market of any new and unauthorized deemed products for which no application is submitted within 120 days. Given the nearness of that deadline and the very limited number of companies (fewer than 10) that have sought pre-submission meetings with FDA to discuss potential premarket applications for ENDS products, I believe that, if plaintiffs' proposed remedy were granted, it is likely that there would be a mass market exit of ENDS products. For cigarette smokers who completely switch to ENDS, these products may be less harmful at an individual level than combustible tobacco products. It is possible some of these products may have a net positive effect on public health at a population level, depending on several factors, including patterns of use. Overall population level impact remains uncertain today, especially given youth uptake of ENDS. We do not yet know the general public health impact of these products, but it is likely that some ENDS products may reduce harm at the individual level and that some addicted adult smokers use these products with a goal to end use of combustible tobacco products. Given this, mass market exit of such products would limit the availability of a potentially less harmful alternative for adult smokers seeking to transition or stay away from combustible tobacco products. Dramatically and precipitously reducing availability of these products could present a serious risk that adults, especially former smokers, who currently use ENDS products and are addicted to nicotine would migrate to combustible tobacco products, even if particular ENDS products ultimately receive marketing authorization and return

to the market later. And, although there has been great recent progress in declining use of cigarettes for all age groups, I am concerned that these declines could be slowed or reversed in the case of very sudden and very dramatic reductions in availability.

16. Second, there are important programmatic and logistical considerations. Of course, manufacturers may submit premarket applications for these products at any time, and there is no legal barrier to filing. Indeed, CTP has accepted, filed and authorized applications through each of the available pathways based on statutory criteria even in the absence of rules or product-specific guidance. However, I am concerned that many ENDS manufacturers will be unlikely to submit quality PMTA applications (*e.g.*, applications that are sufficiently complete and organized to enable CTP to efficiently conduct the required scientific review) for deemed products within a 120-day period. Instead, a longer period of time (10 months) would be appropriate to help ensure that manufacturers are better able to prepare quality submissions. Their efforts will be aided by FDA's publication of the PMTAs for ENDS Guidance, which provides important recommendations to help this newly regulated segment of industry develop their applications. Most significantly, that guidance describes the types of information required by the statute for submission in a PMTA, provides recommendations for how to address specific public health concerns, and suggests ways to demonstrate that a product is appropriate for the protection of public health. I am concerned that 120 days is an insufficient amount of time to permit some manufacturers to consider and implement the recommendations in the guidance.

17. In addition, there will also be logistical impediments for CTP to receive and review large numbers of applications without being able to meaningfully prioritize among them. The Final Regulatory Impact Analysis (RIA) from 2016 estimates that manufacturers will apply for marketing authorization for 5,424 to 6,764 deemed products (of all types) in the initial

compliance period (two years). AR 23,995 (RIA at 84). Of these, an estimated 1,250 to 2,000 would be PMTAs for e-liquids, as well as 360-450 for ENDS delivery devices. *Id.* These numbers are based on estimates in the context of significant uncertainty, and it is possible that manufacturers will seek premarket authorization for many more products, particularly if the products' continued marketing is contingent on the filing of an application. One concern here is that low-quality applications, many of which could be time-consuming to review due to their poor quality, will be submitted merely to prolong marketing.

18. For ENDS PMTAs, these are first-ever applications for a previously novel and unregulated category of products. Thousands of these applications are expected to be submitted very close in time. This expectation is based on the dynamics of the deadline coming earlier than many applicants previously anticipated. It is also informed by our experience with provisional SE applications, as discussed below. Many applicants will be newly regulated entities lacking experience with FDA, and based on our experience to date, the applications are anticipated to be lower in quality and less complete than current-day applications for other FDA regulated products. A large volume of incomplete or haphazard applications in which the information is not clearly presented or is missing data will cause further delay because it will divert valuable agency resources into the painstaking effort of reviewing those submissions and communicating deficiencies. In addition, there may be technological challenges to accepting and processing large applications if they come in all at once, especially if the deadline were as soon as 120 days after a court order, allowing FDA less time to continue preparations.

19. For comparison, in 2011, at a parallel point in time with a submission deadline approaching, approximately 3,000 of 3,600 provisional SE applications were submitted within

the last several days leading up to a March 22, 2011 deadline.[19] While FDA has put many more systems in place since then, and has created a robust application review process within CTP's Office of Science, there is no doubt that the agency will be flooded with applications in the final days leading up to any court-ordered submission deadline. I expect that FDA will receive roughly 5,424 to 6,764 applications for three different authorization pathways. This will undoubtedly put a strain on the agency. Additional time to file applications would provide more planning time for FDA and applicants, more time to build out operational systems, and more time to issue guidance and rules to reduce the volume of low-quality applications.

20. Most ENDS products are relatively novel and are unlikely to be substantially equivalent to a valid predicate and so will need to be authorized through the PMTA pathway. Among other things, a PMTA application must include:

a. Full reports of all information concerning investigations which have been made to show the health risks of the new tobacco product and whether such product presents less risk than other tobacco products;

b. Full statement of the components, ingredients, additives, and properties, and of the principle(s) of operation of the new tobacco product; and

c. Full description of the methods used in, and the facilities and controls used for, the manufacture, processing, packing and installation of the new tobacco product.

21. In addition, some applications may need new nonclinical and clinical studies if the product's potential impact on the public health has not yet been sufficiently reviewed, though in some cases it may be possible to support a marketing order for an ENDS product without

[19] *See* FDA Update on Provisional Substantial Equivalence (SE) Review Process (Apr. 5, 2018), *available at* https://www.fda.gov/tobacco-products/ctp-newsroom/fda-update-provisional-substantial-equivalence-se-review-process.

conducting new nonclinical or clinical studies. For example, if there is an established body of evidence regarding the health impact (individual or population) of a product or a similar product that can be adequately bridged to product that is the subject of the application, such as data from the published literature or government-sponsored databases, these data may be sufficient to support a PMTA.

22. Plaintiffs' proposed 120-day deadline for the submission of premarket applications does not account for the sheer number of expected applications, the complexity of those applications and the scientific review process, or the public health and operational concerns I have described. I believe that a submission deadline at least 10 months away would reflect a much better balancing of the competing concerns and, though still accelerated, would at least reduce the potential for administrative disruption and the risk of a mass market exit that could adversely affect the public health.

I declare under penalty of perjury that the foregoing is true and correct to the best of my information, knowledge, and belief.

Dated: Silver Spring, Maryland

June 12, 2019

Mitchell Zeller -S

Digitally signed by Mitchell Zeller -S
Date: 2019.06.12 23:08:03 -04'00'

Mitchell Zeller
Director, Center for Tobacco Products
United States Food and Drug Administration

FDA U.S. FOOD & DRUG ADMINISTRATION

Technical Project Lead (TPL) Review of PMTAs

New Products Subject of this Review[i]	
Submission tracking number (STNs)	(b) (4) See Appendix A
Common Attributes	
Submission date	September 7, 2020
Receipt date	September 7, 2020
Applicant	(b) (4)
Product manufacturer	(b) (4)
Application type	Standard
Product category	ENDS (VAPES)
Product subcategory	ENDS Component
Cross-Referenced Submission	
All new products	None
Recommendation	
Issue marketing denial orders for the new tobacco products subject of this review.	

Technical Project Lead (TPL):

Digitally signed by David B. Portnoy -S
Date: 2021.09.17 10:42:36 -04'00'

David B. Portnoy, Ph.D., M.P.H.
Branch Chief, Social Science Branch 2
Division of Population Health Science

Signatory Decision: Concur with TPL recommendation and basis of recommendation

Digitally signed by Matthew R. Holman -S
Date: 2021.09.17 10:59:24 -04'00'

Matthew R. Holman, Ph.D.
Director
Office of Science

[i] Product details, amendments, and dates provided in the Appendix. PMTA means premarket tobacco application. Scientific references (if any) are listed at the end of this document and referred to with Arabic numerals; general footnotes are referred to with Roman numerals.

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1. EXECUTIVE SUMMARY

These applications for flavored ENDS[ii] products lack evidence to demonstrate that permitting the marketing of these products would be appropriate for the protection of the public health (APPH). Given the known and substantial risk of flavored ENDS with respect to youth appeal, uptake, and use, applicants would need reliable and robust evidence of a potential benefit to adult smokers[iii] that could justify that risk. Accordingly, in order to show that a flavored ENDS is APPH, the applicant must show that the benefit to adults switching from or reducing cigarettes outweighs the risk to youth.

Based on existing scientific evidence and our experiences in conducting premarket review employing the APPH standard over the last several years, FDA has determined for these applications that, to effectively demonstrate this benefit in terms of product use behavior, only the strongest types of evidence will be sufficiently reliable and robust —most likely product specific evidence from a randomized controlled trial (RCT)[iv] or longitudinal cohort study, although other types of evidence could be adequate, and will be evaluated on a case-by-case basis.[v,vi] Moreover, tobacco-flavored ENDS may offer the same type of public health benefit as flavored 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 demonstrate the potential benefit to current users, FDA has reviewed these applications for any 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 have reviewed the subject applications to determine whether they contain sufficient evidence of the type described above to demonstrate APPH. Our review determined that the applications do <u>not</u> contain evidence from a randomized controlled trial or longitudinal cohort study regarding the impact of the ENDS on switching or cigarette reduction that could potentially demonstrate the benefit of their flavored ENDS over tobacco-flavored ENDS. The PMTAs do contain other evidence regarding the potential benefit to adult users; however, for the reasons explained below, this other evidence is not adequate.

[ii] The term *flavored ENDS* in this review refers to any ENDS other than tobacco-flavored and menthol-flavored ENDS. Tobacco-flavored ENDS are discussed below. Applications for menthol-flavored ENDS will be addressed separately. 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. The term *flavored ENDS* also includes 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.

[iii] 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. This review is focused on the risk to youth nonusers as well as the potential benefit to adult smokers as current users, as they are the group through which the potential benefit to public health is most substantial and could overcome the known risk to youth.

[iv] 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.

[v] 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).

[vi] For example, we would consider evidence from another study design if 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.

As a result, the applicant has failed to provide evidence to overcome the risk to youth and show a net population health benefit necessary to determine that permitting the marketing of the new tobacco product is APPH.

2. BACKGROUND

2.1. NEW PRODUCTS

The applicant submitted information for the new products listed on the cover page and in Appendix A.

2.2. REGULATORY ACTIVITY

FDA issued an Acceptance letter to the applicant on October 8, 2020. FDA issued a Filing letter to the applicant on November 9, 2020.

2.3. BASIS FOR REQUIRING RELIABLE, ROBUST EVIDENCE TO DEMONSTRATE BENEFIT

The rationale for FDA's decision for these flavored ENDS applications is consistent with previous decisions for other flavored ENDS and is set forth below.

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 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.[vii]

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 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" (2020 Enforcement Priorities Guidance). In this guidance, FDA described evidence that shows flavors (other than tobacco and menthol) were a key driver of

[vii] This review focuses on risk to youth nonusers and the potential benefit to adult smokers as current tobacco product users, given that these are the subpopulations that raise the most significant public health concerns and therefore are the most relevant in evaluating the impact on the population as a whole. FDA has also considered the APPH standard with respect to the likelihood that an authorization will increase or decrease the number of tobacco users in the overall population. The availability of such products has generally led to greater tobacco use among youth overall, notwithstanding the decrease in cigarette smoking for youth, which reinforces the focus in this review on having sufficiently reliable and robust evidence to justify authorization of these PMTAs. 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 surge in ENDS use among youth and thus prioritized enforcement against certain flavored ENDS products, with the goal of protecting youth from these products.[viii]

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,[ix] 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 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 policy described in the 2020 Enforcement Priorities Guidance because, at that time that policy was developed, those products 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.

2.3.1. 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

[viii] 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.

[ix] 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.

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.

2.3.1.1. 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.

The evidence shows 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[x] users reported using a flavored e-cigarette.[10] By the 2020 NYTS, the proportion of e-cigarette users reporting using a flavored product[xi] 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/menthol[xii], 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 users, 71% reported using ENDS "because they come in flavors I like."[14]

[x] We use "e-cigarette" here to be consistent with the survey, but we interpret it to have the same meaning as ENDS.
[xi] Flavored product use in these studies means use of flavors other than tobacco.
[xii] 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.

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 taking 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.

2.3.1.2. The appeal of flavors across ENDS devices

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] The published literature is sufficient to demonstrate the substantial appeal to youth of flavored ENDS, because it is robust and consistent. As described above, the preference for use of flavored ENDS among youth is consistently demonstrated across large, national surveys and longitudinal cohort studies.

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 flavor 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.[xiii] 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[xiv]--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 flavor options, underscoring the fundamental role of flavor in driving appeal.

2.3.1.3. 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.[xv]

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 psychosocial 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]

2.3.1.4. 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 generally 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

[xiii] 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.

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

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

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.

2.3.1.5. 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[xvi] 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 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.

2.3.1.6. 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 demonstrates that flavored ENDS pose a significant risk to youth.

2.3.2. 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

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

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.

2.3.2.1. 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]

2.3.2.2. 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,[xvii] 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 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 given 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,[xviii] another well-controlled investigation that could serve as an alternative to conducting an RCT to demonstrate adequate benefit is a longitudinal cohort study.

[xvii] Premarket Tobacco Product Applications for Electronic Nicotine Delivery Systems: Guidance for Industry (p.47); October 2019 Public Meeting on Deemed Tobacco Product Applications
[xviii] Premarket Tobacco Product Applications for Electronic Nicotine Delivery Systems: Guidance for Industry (p.47); October 2019 Public Meeting on Deemed Tobacco Product Applications

For flavored ENDS, the known and substantial risk to youth in particular is high. Therefore, to show a net population health benefit, FDA has determined that these applications must demonstrate potential benefits to smokers from marketing such products with robust and reliable 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, FDA is reviewing these applications to determine whether they demonstrate that a benefit of a new product is significant enough to overcome the risk to youth. In particular, FDA's review of these applications has considered the degree of benefit to a flavored ENDS product over a tobacco-flavored variety in facilitating smokers completely switching or significantly reducing their smoking, given the significant increase in risk of youth initiation associated with flavored ENDS compared to tobacco-flavored ENDS. Note that applications with this type of information may still not be APPH: 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.[xix]

We have been using the APPH standard for several years in reviewing previous PMTAs for non-ENDS 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. In these reviews, 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.[xx] 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, FDA has reviewed these applications for any acceptably strong product-specific evidence.

[xix] 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, and we have not evaluated any marketing plans submitted with these applications.

[xx] This discrepancy between the literature for youth initiation and adult switching also likely reflects fundamental differences in the two outcomes being assessed—youth initiation and switching among adult smokers—and their determinants. For switching among adult smokers, the behavior change is occurring in the context of nicotine dependence. Thus, the specific product's ability to provide adequate reinforcement and continue to satisfy a smoker's cravings over time, which is a function of the design of the specific product itself, are critical factors in determining likelihood of continued use and the product's ability to promote switching. Whereas for youth initiation, experimentation among naïve or novice users is not driven by these factors.

More specifically, in order to adequately assess whether such an added benefit has been demonstrated, FDA has reviewed these applications for product-specific[xxi] evidence that would enable a comparison between the applications' 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), evidence generated using either an RCT design or longitudinal cohort study design is mostly likely to demonstrate such a benefit, although other types of evidence could be adequate if sufficiently reliable and robust, and will be evaluated on a case-by-case basis. [xxii]

CTP will consider other types of evidence if it is sufficiently robust and direct to demonstrate 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.

In contrast, cross-sectional surveys entail a one-time assessment of self-reported outcomes: although participants can be asked to recall 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

[xxi] 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.

[xxii] Conversely, such longitudinal or product-specific data are not necessarily required to assess experimentation and appeal among youth. The available literature on youth initiation contains valid scientific evidence sufficient to evaluate the risk to youth of ENDS. The literature includes longitudinal cohort studies, such as the PATH study, which have been used to assess uptake of tobacco products, including flavored ENDS, among youth and young adults. These studies have evaluated the impact of flavors on the promotion of established regular use. Additionally, the literature includes large, nationally representative cross-sectional surveys, which are among the best available evidence to understand patterns of youth ENDS use and the key characteristics associated with such use These studies enable observation of youth behavior as it naturally occurs in representative samples of the U.S. population. These data available in the literature provide clear and overwhelming evidence that ENDS are the most widely used products by youth, the majority of youth users use a flavored ENDS, and that youth users are more likely to use flavored ENDS than adult ENDS users. We note that, in assessing the risks to youth from flavored ENDS, RCTs are not possible because it would be unethical to randomize youth never or naive users to try a particular ENDS to examine what impact it would have on initiation, experimentation, or progression to regular use.

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 behavior over time[xxiii]; 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.[xxiv] 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 product use or (2) significant reduction in cigarettes per day (CPD).

2.3.2.3. Conclusion

Given the known and substantial risk to youth posed by flavored ENDS, FDA has reviewed these applications for the presence of particularly reliable product-specific[xxv] evidence to 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.

2.4. SCOPE OF REVIEW

The reviews evaluated whether the subject PMTAs contain evidence from a randomized controlled trial, longitudinal cohort study, and/or other evidence regarding the impact of the new products on switching or cigarette reduction that could potentially demonstrate the added benefit to adult users of their flavored ENDS over an appropriate comparator tobacco-flavored ENDS. These reviews included a search of the PMTAs to determine whether the evidence is found anywhere within the PMTAs, and if present, if certain conditions were met (e.g., was the randomized controlled trial conducted using the new products that are the subject of the PMTA). Our review also included a

[xxiii] 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. However, it is also possible that studies with a shorter duration would be adequately reliable.

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

[xxv] 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.

search for other studies that provided product-specific evidence related to the potential benefit to adult users.

3. SCIENTIFIC REVIEW

Reviews were completed by Allison Hoffman and Willa Dong on September 17, 2021.

The reviews determined that, although the PMTAs includes a RCT and longitudinal cohort study, the studies did not include the actual use of the new products or compare tobacco-flavored products to other flavored products. In particular, the data from the RCT did not sufficiently demonstrate the relative effect of the flavored products as compared to a tobacco-flavored product or include outcomes assessing switching or cigarette reduction and the data from the cohort study not sufficiently demonstrate the relative effect of the flavored products as compared to a tobacco-flavored product. Therefore, these are insufficient to evaluate the magnitude of the potential benefit to adult users that is needed to complete our assessment.

The PMTAs referenced studies including those that that assessed exposure biomarkers and physiological response following (b)(4) use, the effects of (b)(4) on health outcomes such as lung function, and surveys on consumer perceptions and intentions to use (b)(4), but this evidence is not sufficiently strong to support the benefit to adult smokers of using these flavored ENDS because it was not clear that the referenced studies included the specific products in the application(s); evaluate product switching or cigarette reduction resulting from use of these products over time; or evaluate these outcomes based on flavor type to enable comparisons between tobacco and other flavors. Accordingly, this evidence is not adequate and therefore, we did not assess other aspects of the application as part of this scientific review.

4. ENVIRONMENTAL DECISION

Under 21 CFR 25.35(b), issuance of an order under section 910(c) of the Federal Food, Drug, and Cosmetic Act that a new product may not be introduced or delivered for introduction into interstate commerce (i.e., a marketing denial order) falls within a class of actions that are ordinarily categorically excluded from the preparation of an environmental assessment (EA) or environmental impact statement (EIS). To the best of our knowledge, no extraordinary circumstances exist that would preclude application of this categorical exclusion. FDA concludes that categorical exclusion is warranted and no EA or EIS is required.

5. CONCLUSION AND RECOMMENDATION

FDA has reviewed these applications for evidence demonstrating that the new flavored products will provide an added benefit to adult smokers relative to tobacco-flavored products. Based on our review, we determined that the PMTAs for the applicant's new products, as described in the applications and specified in Appendix A, lack sufficient evidence to demonstrate that permitting the marketing of the new products would be APPH. Thus, a Denial letter should be issued to the applicant. The applicant cannot introduce or deliver for introduction these products into interstate commerce in the United States. Doing so is a prohibited act under section 301(a) of the FD&C Act, the violation of which could result in enforcement action by FDA.

The following deficiency should be conveyed to the applicant as the key basis for our determination that marketing of the new products is not APPH:

1. All of your PMTAs lack sufficient evidence demonstrating that your flavored ENDS will provide a benefit to adult users that would be adequate to outweigh the risks to youth. In

light of the known risks to youth of marketing flavored ENDS, robust and reliable evidence is needed regarding the magnitude of the potential benefit to adult smokers. This evidence could have been provided using a randomized controlled trial (RCT) and/or longitudinal cohort study that demonstrated the benefit of your flavored ENDS products over an appropriate comparator tobacco-flavored ENDS. Although your PMTA includes a RCT and cohort study, it is unclear if they included the actual use of the new products. Additionally, the RCT and cohort studies did not compare tobacco-flavored products to other flavored products or include outcomes assessing switching or cigarette reduction. In particular, the data from your RCT did not sufficiently demonstrate the relative effect of your flavored products as compared to a tobacco-flavored product or the effects on switching or cigarette reduction and the cohort study did not sufficiently demonstrate the relative effect of your flavored products as compared to a tobacco-flavored product. Therefore, these are insufficient to evaluate the magnitude of the potential benefit to adult users that is needed to complete our assessment.

Alternatively, FDA would consider other evidence but only if it reliably and robustly evaluated the impact of the new flavored vs. tobacco-flavored products on adult smokers' switching or cigarette reduction over time. Although your PMTAs referenced studies including those that that assessed exposure biomarkers and physiological response following (b)(4) use, the effects of (b)(4) on health outcomes such as lung function, and surveys on consumer perceptions and intentions to use (b)(4), this evidence is not sufficient to show a benefit to adult smokers of using these flavored ENDS because it was not clear that the referenced studies included the specific products in the application(s); evaluate product switching or cigarette reduction resulting from use of these products over time; or evaluate these outcomes based on flavor type to enable comparisons between tobacco and other flavors. Without this information, FDA concludes that your application is insufficient to demonstrate that these products would provide an added benefit that is adequate to outweigh the risks to youth and, therefore, cannot find that permitting the marketing of your new tobacco products would be appropriate for the protection of the public health.

6. APPENDIX

Appendix A. New Products

Common Attributes	
Submission date	September 7, 2020
Receipt date	September 7, 2020
Applicant	(b) (4)
Product manufacturer	(b) (4)
Product category	ENDS (VAPES)
Product subcategory	ENDS Component

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August 30, 2020

Center for Tobacco Products
Food and Drug Administration
Document Control Center
10903 New Hampshire Avenue
Building 71, Room G335
Silver Spring, MD 20993-0002
ATTN: Matthew R. Holman, PhD, Director, Office of Science

Re: Premarket Tobacco Product Application for ENDS Products
TPB International, LLC

Dear Dr. Holman:

TPB International, LLC (TPB), submits this bundled premarket tobacco product application (PMTA) pursuant to Section 910(b) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), as amended by the Family Smoking Prevention and Tobacco Control Act, and respectfully requests marketing authorization orders under Section 910(c)(1)(A)(i) for the candidate products. In particular, TPB seeks marketing authorization orders that would permit TPB's continued marketing in interstate commerce of the following TPB products ("candidate products"):

	Solace E-Liquids [1]		Nicotine Formulation	**Freebase Nicotine Products**		**Nicotine Salt Products**			
			Package Volume	**60 mL Bottle**		**30 mL Bottle**			
			Base Formulation	PG:VG 27:73		PG:VG 44:56			
	Brand Name	**Flavor Name**	**Characteristic Flavor**	**Product ID 3mg**	**Product ID 6mg**	**Product ID 18mg**	**Product ID 36mg**	**Product ID 48mg**	**# Products per Flavor**
Flavor Formulations N= 35 Unique	Solace	Banana Dragonberry	Other (Fruit)	840158603841	840158603858	840158603797	840158603803	840158603810	5
	Solace	Berry Bash	Blueberry	840158601632	840158601649	840158601564	840158601571	840158601588	5
	Solace	Blue Raspberry Ice	Other (Blueberry, Menthol)	840158601243	840158601250	840158601199	840158601205	840158601212	5
	Solace	Blue Raspberry Lemonade Ice	Other (Blueberry, Menthol)	840158603636	840158603643	840158603582	840158603599	840158603605	5
	Solace	Blueberry	Other (Blueberry, Menthol)	840158601779	840158601786	840158601724	840158601731	840158601748	5
	Solace	Blue's Lemonade	Raspberry	840158600574	840158600581	840158600529	840158600536	840158600543	5

[1] Products physically identical to the Candidate Products are currently marketed under other brand names, including VaporFi and Vapor Shark. For avoidance of confusion, the Candidate Products referred to throughout this bundled PMTA, however, will be referred to as the Solace branded e-liquids.

Those brands and flavor names currently marketed with physically identical characteristics to the Solace E-Liquids are reflected in the chart; however, additional brands may be introduced. Additional brands will be provided to FDA consistent with any postmarket obligations.

	Solace	Blue's Mango	Raspberry	840158601380	840158601397	840158601335	840158601342	840158601359	5
	Solace	Bold Tobacco	Tobacco	840158603285	840158603292	840158603230	840158603247	840158603254	5
	Solace	Cherry Vanilla	Cherry	840158601465	840158601472	840158601410	840158601427	840158601434	5
	Solace	Cool Mango	Other (Menthol, Fruit)	840158603421	840158603438	840158603377	840158603384	840158603391	5
	Solace	Cool Tobacco	Other (Tobacco, Menthol)	840158601915	840158601922	840158601861	840158601878	840158601885	5
	Solace	Crème de Menthe	Other (Vanilla, Menthol)	840158601984	840158601991	840158601939	840158601946	840158601953	5
	Solace	Dragon Fruit Menthol	Other (Fruit, Menthol)	840158603568	840158603575	840158603513	840158603520	840158603537	5
	Solace	Flavorless	None	840158603971	840158603988	840158603933	840158603940	840158603957	5
	Solace	Grape	Other (Grape)	840158601106	840158601113	840158601052	840158601069	840158601076	5
	Solace	Juiced Apple	Other (Apple)	840158601175	840158601182	840158601120	840158601137	840158601144	5
	Solace	Latte	Coffee	840158603070	840158603087	840158603025	840158603032	840158603049	5
	Solace	Lemon Lime Fusion	Other (Lime, Baked Goods)	840158601700	840158601717	840158601656	840158601663	840158601670	5
	Solace	Lemonade	Citrus	840158603773	840158603780	840158603728	840158603735	840158603742	5
	Solace	Mango	Other (Mango)	840158603353	840158603360	840158603308	840158603315	840158603322	5
	Solace	Mint	Menthol	840158600345	840158600352	840158600291	840158600307	840158600314	5
	Solace	Peach	Other (Peach)	840158600277	840158600284	840158600079	840158600086	840158600109	5
	Solace	Pineapple	Other (Pineapple)	840158600055	840158600062	840158600000	840158600017	840158600024	5
	Solace	Sea Salt Blueberry	Blueberry	840158603704	840158603711	840158603650	840158603667	840158603674	5
	Solace	Seedless Watermelon	Other (Watermelon)	840158603490	840158603506	840158603445	840158603452	840158603469	5
	Solace	Smooth Tobacco	Tobacco	840158603148	840158603155	840158603094	840158603100	840158603117	5
	Solace	Strawberry	Other (Strawberry)	840158601311	840158601328	840158601267	840158601274	840158601281	5
	Solace	Strawberry Danish	Other (Strawberry)	840158602936	840158602943	840158602882	840158602899	840158602905	5
	Solace	Strawberry Kiwi	Other (Kiwi)	840158603216	840158603223	840158603162	840158603179	840158603186	5
	Solace	Strawberry Kiwi Ice	Other (Fruit, Menthol)	840158601038	840158601045	840158600598	840158600604	840158600697	5
	Solace	Tangerine	Citrus	840158603919	840158603926	840158603865	840158603872	840158603889	5
	Solace	Tropic Strawberry	Other (Pineapple)	840158600505	840158600512	840158600369	840158600376	840158600383	5
	Solace	Tropical Fusion	Other (Fruit)	840158601540	840158601557	840158601489	840158601496	840158601519	5
	Solace	Vanilla Bean	Vanilla	840158601847	840158601854	840158601793	840158601809	840158601816	5
	Solace	Vanilla Cola	Cola	840158603001	840158603018	840158602950	840158602967	840158602974	5
			# Products per Nicotine Concentration	**35**	**35**	**35**	**35**	**35**	175
									Total

Solace Product Name	White Label Product Name (VaporFi)	White Label Product Name (Vapor Shark)
Banana Dragonberry	Dragon Banana Berry	Banana Dragon Fruit
Berry Bash	Berry Bash	Berry Blast
Blue Raspberry Ice	Blueberry Ice	Tropical Blue Ice
Blue Raspberry Lemonade Ice	Raspberry Lemonade Ice	Cool Blue Lemonade
Blueberry	Blueberry Punch	Blueberry Citrus
Blue's Lemonade	Raspberry Lemonade	Blue lemonade
Blue's Mango	Mango Raspberry	Blue Raspberry Mango
Bold Tobacco	Classic Tobacco	Authentic Tobacco
Cherry Vanilla	Cherry Vanilla	Cherry Cream
Cool Mango	Berry Mango Ice	Berry Menthol Mango
Cool Tobacco	Tobacco Menthol	Menthol Tobacco
Crème de Menthe	Mint Crème	Vanilla Mint
Dragon Fruit Menthol	Fruit Dragonthol	Dragonberry Ice
Flavorless	Flavorless	Flavorless
Grape	Pure Grape	Grape
Juiced Apple	Ripe Apple	Apple
Latte	Catcha Latte	Coffee Cream
Lemon Lime Fusion	Key Lime Pie	Lemon Meringue
Lemonade	Lemon Lime	Citrus Twist
Mango	Fresh Mango	Mango
Mint	Mighty Menthol	Menthol
Peach	Tropical Twist	Fruit Medley
Pineapple	Fresh Pineapple	Pineapple
Sea Salt Blueberry	Berry Blueberry	Very Berry
Seedless Watermelon	Watermelon Wave	Ripe Watermelon
Smooth Tobacco	Smooth Tobacco	Ripe Tobacco
Strawberry	Strawberry Watermelon	Strawberry Melon
Strawberry Danish	Strawberry Pastry	Strawberry Whip
Strawberry Kiwi	Strawberry Kiwi	Kiwi Berry
Strawberry Kiwi Ice	Island Frost	Tropic Chill
Tangerine	Mandarin Orange	Tangerine Dream
Tropic Strawberry	Strawberry Daiquiri	Pineapple Berry Twist
Tropical Fusion	Strawberry Pineapple Twist	Tropical Strawberry
Vanilla Bean	Very Vanilla	Vanilla Cream
Vanilla Cola	Vanilla Cola	Cola Float

	VaporFi E-Liquids		Nicotine Formulation	Freebase Nicotine Products		Nicotine Salt Products			
			Package Volume	60 mL Bottle		30 mL Bottle			
			Base Formulation	PG:VG 27:73		PG:VG 44:56			
	Brand Name	**Flavor Name**	**Characteristic Flavor**	**Product ID 3mg**	**Product ID 6mg**	**Product ID 18mg**	**Product ID 36mg**	**Product ID 48mg**	**# Products per Flavor**
Flavor Formulations N= 35 Unique	VaporFi	Dragon Banana Berry	Other (Fruit)	840158606729	840158606736	840158606743	840158606750	840158606767	5
	VaporFi	Berry Bash	Blueberry	840158606972	840158606989	840158606996	840158607009	840158607016	5
	VaporFi	Blueberry Ice	Other (Blueberry, Menthol)	840158606576	840158606583	840158606590	840158606606	840158606613	5
	VaporFi	Raspberry Lemonade Ice	Other (Blueberry, Menthol)	840158606477	840158606484	840158606491	840158606507	840158606514	5
	VaporFi	Blueberry Punch	Other (Blueberry, Menthol)	840158606378	840158606385	840158606392	840158606408	840158606415	5
	VaporFi	Raspberry Lemonade	Raspberry	840158605821	840158605838	840158605845	840158605852	840158605869	5
	VaporFi	Mango Raspberry	Raspberry	840158606828	840158606835	840158606842	840158606859	840158606866	5
	VaporFi	Classic Tobacco	Tobacco	840158607122	840158607139	840158607146	840158607153	840158607160	5
	VaporFi	Cherry Vanilla	Cherry	840158606873	840158606880	840158606897	840158606903	840158606910	5
	VaporFi	Berry Mango Ice	Other (Menthol, Fruit)	840158606279	840158606286	840158606293	840158606309	840158606316	5
	VaporFi	Tobacco Menthol	Other (Tobacco, Menthol)	840158607221	840158607238	840158607245	840158607252	840158607269	5
	VaporFi	Mint Crème	Other (Vanilla, Menthol)	840158607023	840158607030	840158607047	840158607054	840158607061	5
	VaporFi	Fruit Dragonthol	Other (Fruit, Menthol)	840158606026	840158606033	840158606040	840158606057	840158606064	5
	VaporFi	Flavorless	None	840158607764	840158607771	840158607788	840158607795	840158607801	5
	VaporFi	Pure Grape	Other (Grape)	840158606675	840158606682	840158606699	840158606705	840158606712	5
	VaporFi	Ripe Apple	Other (Apple)	840158606422	840158606439	840158606446	840158606453	840158606460	5
	VaporFi	Catcha Latte	Coffee	840158607078	840158607085	840158607092	840158607108	840158607115	5
	VaporFi	Key Lime Pie	Other (Lime, Baked Goods)	840158606323	840158606330	840158606347	840158606354	840158606361	5
	VaporFi	Lemon Lime	Citrus	840158605777	840158605784	840158605791	840158605807	840158605814	5
	VaporFi	Fresh Mango	Other (Mango)	840158605920	840158605937	840158605944	840158605951	840158605968	5
	VaporFi	Mighty Menthol	Menthol	840158607375	840158607382	840158607399	840158607405	840158607412	5
	VaporFi	Tropical Twist	Other (Peach)	840158606224	840158606231	840158606248	840158606255	840158606262	5
	VaporFi	Fresh Pineapple	Other (Pineapple)	840158606125	840158606132	840158606149	840158606156	840158606163	5
	VaporFi	Berry Blueberry	Blueberry	840158606521	840158606538	840158606545	840158606552	840158606569	5
	VaporFi	Watermelon Wave	Other (Watermelon)	840158605975	840158605982	840158605999	840158606002	840158606019	5
	VaporFi	Smooth	Tobacco	840158607320	840158607337	840158607344	840158607351	840158607368	5

		Tobacco							
	VaporFi	Strawberry Watermelon	Other (Strawberry)	840158605722	840158605739	840158605746	840158605753	840158605760	5
	VaporFi	Strawberry Pastry	Other (Strawberry)	840158607276	840158607283	840158607290	840158607306	840158607313	5
	VaporFi	Strawberry Kiwi	Other (Kiwi)	840158606170	840158606187	840158606194	840158606200	840158606217	5
	VaporFi	Island Frost	Other (Fruit, Menthol)	840158606620	840158606637	840158606644	840158606651	840158606668	5
	VaporFi	Mandarin Orange	Citrus	840158607177	840158607184	840158607191	840158607207	840158607214	5
	VaporFi	Strawberry Daiquiri	Other (Pineapple)	840158605876	840158605883	840158605890	840158605906	840158605913	5
	VaporFi	Strawberry Pineapple Twist	Other (Fruit)	840158606774	840158606781	840158606798	840158606804	840158606811	5
	VaporFi	Very Vanilla	Vanilla	840158606927	840158606934	840158606941	840158606958	840158606965	5
	VaporFi	Vanilla Cola	Cola	840158606071	840158606088	840158606095	840158606101	840158606118	5
			# Products per Nicotine Concentration	**35**	**35**	**35**	**35**	**35**	175
									Total

	Vapor Shark E-Liquids		Nicotine Formulation	**Freebase Nicotine Products**		**Nicotine Salt Products**			
			Package Volume	**60 mL Bottle**		**30 mL Bottle**			
			Base Formulation	PG:VG 27:73		PG:VG 44:56			
	Brand Name	**Flavor Name**	**Characteristic Flavor**	**Product ID 3mg**	**Product ID 6mg**	**Product ID 18mg**	**Product ID 36mg**	**Product ID 48mg**	**# Products per Flavor**
Flavor Formulations N= 35 Unique	Vapor Shark	Banana Dragon Fruit	Other (Fruit)	840158604992	840158605005	840158605012	840158605029	840158605036	5
	Vapor Shark	Berry Blast	Blueberry	840158605258	840158605265	840158605272	840158605289	840158605296	5
	Vapor Shark	Tropical Blue Ice	Other (Blueberry, Menthol)	840158604848	840158604855	840158604862	840158604879	840158604886	5
	Vapor Shark	Cool Blue Lemonade	Other (Blueberry, Menthol)	840158604749	840158604756	840158604763	840158604770	840158604787	5
	Vapor Shark	Blueberry Citrus	Other (Blueberry, Menthol)	840158604640	840158604657	840158604664	840158604671	840158604688	5
	Vapor Shark	Blue Lemonade	Raspberry	840158604091	840158604107	840158604114	840158604121	840158604138	5
	Vapor Shark	Blue Raspberry Mango	Raspberry	840158605098	840158605104	840158605128	840158605135	840158605142	5
	Vapor Shark	Authentic Tobacco	Tobacco	840158605401	840158605418	840158605425	840158605432	840158605449	5
	Vapor Shark	Cherry Cream	Cherry	840158605159	840158605166	840158605173	840158605180	840158605197	5
	Vapor Shark	Berry Menthol Mango	Other (Menthol, Fruit)	840158604541	840158604558	840158604565	840158604572	840158604589	5
	Vapor Shark	Menthol Tobacco	Other (Tobacco, Menthol)	840158605500	840158605524	840158605531	840158605548	840158605555	5

	Vapor Shark	Vanilla Mint	Other (Vanilla, Menthol)	840158605302	840158605319	840158605326	840158605333	840158605340	5
	Vapor Shark	Dragonberry Ice	Other (Fruit, Menthol)	840158604299	840158604305	840158604312	840158604329	840158604336	5
	Vapor Shark	Flavorless	None	840158607818	840158607825	840158607832	840158607849	840158607856	5
	Vapor Shark	Grape	Other (Grape)	840158604947	840158604954	840158604961	840158604978	840158604985	5
	Vapor Shark	Apple	Other (Apple)	840158604695	840158604701	840158604718	840158604725	840158604732	5
	Vapor Shark	Coffee Cream	Coffee	840158605357	840158605364	840158605371	840158605388	840158605395	5
	Vapor Shark	Lemon Meringue	Other (Lime, Baked Goods)	840158604596	840158604602	840158604619	840158604626	840158604633	5
	Vapor Shark	Citrus Twist	Citrus	840158604046	840158604053	840158604060	840158604077	840158604084	5
	Vapor Shark	Mango	Other (Mango)	840158604190	840158604206	840158604213	840158604220	840158604237	5
	Vapor Shark	Menthol	Menthol	840158605661	840158605678	840158605685	840158605692	840158605715	5
	Vapor Shark	Fruit Medley	Other (Peach)	840158604497	840158604503	840158604510	840158604527	840158604534	5
	Vapor Shark	Pineapple	Other (Pineapple)	840158604398	840158604404	840158604411	840158604428	840158604435	5
	Vapor Shark	Very Berry	Blueberry	840158604794	840158604800	840158604817	840158604824	840158604831	5
	Vapor Shark	Ripe Watermelon	Other (Watermelon)	840158604244	840158604251	840158604268	840158604275	840158604282	5
	Vapor Shark	Ripe Tobacco	Tobacco	840158605616	840158605623	840158605630	840158605647	840158605654	5
	Vapor Shark	Strawberry Melon	Other (Strawberry)	840158603995	840158604008	840158604015	840158604022	840158604039	5
	Vapor Shark	Strawberry Whip	Other (Strawberry)	840158605562	840158605579	840158605586	840158605593	840158605609	5
	Vapor Shark	Kiwi Berry	Other (Kiwi)	840158604442	840158604459	840158604466	840158604473	840158604480	5
	Vapor Shark	Tropic Chill	Other (Fruit, Menthol)	840158604893	840158604909	840158604916	840158604923	840158604930	5
	Vapor Shark	Tangerine Dream	Citrus	840158605456	840158605463	840158605470	840158605487	840158605494	5
	Vapor Shark	Pineapple Berry Twist	Other (Pineapple)	840158604145	840158604152	840158604169	840158604176	840158604183	5
	Vapor Shark	Tropical Strawberry	Other (Fruit)	840158605043	840158605050	840158605067	840158605074	840158605081	5
	Vapor Shark	Vanilla Cream	Vanilla	840158605203	840158605210	840158605227	840158605234	840158605241	5
	Vapor Shark	Cola Float	Cola	840158604343	840158604350	840158604367	840158604374	840158604381	5
			# Products per Nicotine Concentration	**35**	**35**	**35**	**35**	**35**	175
									Total

TPB has prepared this PMTA in accordance with the U.S. Food and Drug Administration (FDA) guidance for industry entitled *Premarket Tobacco Product Applications for Electronic Nicotine Delivery Systems* (June 2019) (ENDS PMTA Guidance) and the Proposed Rule entitled *Proposed Rule: Premarket Tobacco Product Applications and Recordkeeping Requirements* (September 2019) (PMTA Proposed Rule). The information provided in this PMTA satisfies the

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1.12 Product Labels

All free-base nicotine e-liquid labels and boxes can be found within this application:

1. 3 mg/mL labels
2. 3 mg/mL boxes
3. 6 mg/mL labels
4. 6 mg/mL boxes

All salt nicotine e-liquid labels and boxes can be found within this application:

1. 18 mg/mL labels
2. 18 mg/mL boxes
3. 36 mg/mL labels
4. 36 mg/mL boxes
5. 48 mg/mL labels
6. 48 mg/mL boxes

1.13 Marketing Plan

1.13.1 Executive summary

TPB International, LLC (TPB), is dedicated to the responsible marketing of the candidate products and is fully committed to complying with all applicable laws and regulations governing e-liquids. TPB targets its marketing activities to both male and female current combustible cigarette smokers and current vaping consumers that are 21 years of age and older. The Company plans to continue to engage in appropriately targeted marketing activity, consistent with all legal requirements, industry standards, and best practices.

In the sections that follow, TPB lays out in detail the principles, strategies, and marketing activities that the Company will utilize in promoting the candidate products.

1.13.2 Core principles

1. TPB is committed to fully complying with all applicable federal laws and regulations governing e-liquids and ENDS.
2. TPB's e-liquid sales will comply with any additional state and local laws and regulations, including but not limited to those relating to flavor bans, taxation, and packaging.
3. The candidate products are for adults only and should not be marketed to, sold to, or used by those who have not attained the age of 21 years (Minors). Further, TPB markets the candidate products toward current combustible cigarette smokers and/or current vapor product users. TPB will communicate to consumers that the candidate products are not without risks and that nonusers should not start using the candidate products or any other type of tobacco product.
4. TPB endorses the use of only well-designed ENDS (WD ENDS) with the candidate products. Any discussion of ENDS in this document, in relation to the usage of the candidate products, assumes the use of a WD ENDS.
5. TPB strongly supports efforts to prevent Minors' access and exposure to the candidate products and other similar products while also maintaining a variety of products for adult consumers seeking to switch from combustible cigarettes.

1.13.3 Labeling, sales, and marketing guidelines

1.13.3.1 Labeling

The following items appear on candidate product labeling (i.e., labeling on any package that displays a UPC code for the candidate products):

1. Ingredients: List of ingredients appears on the labeling in descending order by weight.
2. Labeling pursuant to Section 903 of the FD&C Act:
   a. The name and full business address of the product distributor, TPB International, LLC.
   b. An accurate statement of the quantity in terms of weight, measure, or numerical count of the product. Specifically, the label contains a statement of the milliliters of liquid in the bottle.
   c. The statement "Sale only allowed in the United States." on labels, packaging, and shipping containers pursuant to Section 920(a) of the FD&C Act.
3. FDA Nicotine Addictiveness Warning (FDA Warning) for tobacco-derived, nicotine-containing products pursuant to 21 C.F.R. § 1143.3(a): "WARNING: This product contains nicotine. Nicotine is an addictive chemical."
   a. The FDA Warning appears directly on the package, defined as the outer carton and/or the e-liquid bottle, and is clearly visible underneath any cellophane or other clear wrapping.
   b. The FDA Warning is conspicuously located and prominently placed on the two principal display panels of the package. The FDA Warning area comprises 30% of each of the principal display panels.
   c. The FDA Warning is printed in 12-point font size and occupies the greatest possible proportion of the Warning area set aside for the required text.
   d. The FDA Warning is printed in conspicuous and legible font type and in white text on a black background (or in black text on a white background, where appropriate) in a manner that contrasts typography, layout, or color, with all other printed material on the package.
   e. The FDA Warning is capitalized and punctuated as indicated above.
   f. The FDA Warning is centered in the FDA Warning area in which the text is required to be printed and positioned such that the text of the required FDA Warning and other information on the principal display panel have the same orientation.
4. California Proposition 65 Warning Language (Prop 65 Warning) disclosing the identity of at least one listed chemical to which a user may be exposed.

1.13.3.2 Advertisements and marketing

1. FDA Warning: All candidate product advertising for tobacco-derived, nicotine-containing products contains the FDA Warning, pursuant to 21 C.F.R. § 1143.3(b): "WARNING: This product contains nicotine. Nicotine is an addictive chemical."
   a. The FDA Warning occupies at least 20% of the upper portion of the advertisement.
   b. The FDA Warning appears in at least 12-point font size and occupies the greatest possible proportion of the warning area set aside for the required text.
   c. The FDA Warning appears in conspicuous and legible font type 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.
   d. The FDA Warning is capitalized and punctuated as indicated above.
   e. The FDA Warning is centered in the FDA 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 panel have the same orientation.
   f. The FDA Warning is surrounded by a rectangular border that is the same color as the text and that is not less than 3 millimeters or more than 4 millimeters.

2. No Appeal to Minors: The marketing of the candidate products does not include content directed toward Minors. Such prohibited marketing content includes childish images, cartoons, characters, mascots, juvenile designs, or other themes or imagery known to resonate with Minors.
3. Intended Audience for Marketing: TPB does not utilize any channel of marketing unless at least 85% of its audience is 21 years of age or older. This restriction includes, but is not limited to, television, internet, direct mail, email, print, and radio advertising, as well as event marketing or sponsorships.
4. No Improper Use of Trademarks or Trade Dress: The candidate products do not utilize names, imagery, or designs that intentionally mimic, play upon, invoke or otherwise infringe upon existing trademarks, trade names, or trade dress, particularly those associated with products that are or were primarily marketed to Minors.
5. No Smoking Cessation of Other Therapeutic Claims: TPB does not portray the candidate products as a smoking cessation product. TPB also does not market the candidate products as providing a therapeutic value or as being "safe" or "healthy" for consumers.
6. No Modified Risk Descriptors or Claims: TPB does not market or sell the candidate products using modified risk descriptors or claims (e.g., "light," "low," and/ or "mild"). By way of example only, the candidate products are 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.
7. No Health Professionals: TPB does not use health professionals to market or otherwise endorse the candidate products, either directly or indirectly.
8. Use Only with WD ENDS. TPB recommends the use of well-designed ENDS (WD ENDS) with the candidate products. The proliferation of devices available for consumers makes it impossible for TPB to specifically recommend any one device. However, TPB web properties will remind consumers of the importance of using a WD ENDS as part of its marketing activity.

1.13.3.3 Preventing minor access to candidate products

Candidate products are intended to be sold to and used by adults 21 years of age and older. To implement this principle, TPB adheres to the following policies and practices:

1. TPB follows all local, state and federal age restrictions applicable to the candidate products.
2. TPB labeling and advertising materials contain all nicotine and other warning requirements as directed by state and federal authorities, including the FDA Warning. Additionally, the candidate product labeling directs adults to keep these products out of reach of children.
3. TPB complies with the child-resistant packaging and flow restriction requirements of the Child Nicotine Poisoning Prevention Act of 2015 for all candidate products.
4. For TPB's own online retail (B2C) sales, TPB utilizes a robust third-party online age verification process for all online purchases by consumers, as discussed in more detail in Section 1.13.3.4. For B2B sales, TPB requires purchasers register as a distributor or retailer and requires documentation that the purchaser is buying candidate products solely for the purpose of reselling, e.g., sales tax license applicable tobacco licenses.
5. For TPB's own online B2C sales, TPB will limit consumers to purchases of 15 bottles per customer per month. The policy is intended to prevent social sourcing of products to Minors. TPB monitors purchase patterns of its consumers for outliers and will revisit its bulk limits if it sees activity indicative of consumer bulk purchasing.
6. On its business-to-business (B2B) website section, TPB offers suggestions of resources for its downstream customers related to prevention of youth access. These resources include information

related to retailer-focused FDA Guidance, third-party age verification software available to both brick-and-mortar and online sellers, and helpful websites that offer compliance tools, e.g., WeCard.

7. TPB monitors the compliance of downstream distributors and retailers by periodically auditing customer entities on the FDA Warning Letter database. TPB provides instructions with all order confirmations that all customers should adhere to the following guidelines when purchasing the candidate products:
   a. For retailers, implement strict age verification policies requiring that their employees verify valid government-issued photo IDs as required by law. TPB additionally offers suggestions of third-party age verification software available to both brick-and-mortar and online sellers.
   b. Comply and take corrective action immediately in response to any enforcement actions by any government entity. TPB further requests that downstream customers notify TPB of any enforcement actions and subsequent corrective actions so that TPB may consider whether and how to proceed with future sales of the candidate products to these customers.
   c. For online retailers, prevent sales of candidate products to Minors either through direct verification of valid government-issued photo identification upon delivery of product (i.e., signature on delivery) or through the use of a robust third-party age verification process, as outlined further below.
   d. For retailers, suggest protocols for implementing bulk sales limits for consumer purchases in order to prevent social sources for Minors.
8. TPB maintains a customer service contact which accepts reports of retailer issues related to the candidate products, e.g., sales to Minors. When TPB receives reports of this nature, it compiles them and reports them to FDA on a quarterly basis.

1.13.3.4 TPB online sales

1. Age to Purchase: TPB sales of candidate products must comply with all local, state, and federal age restriction laws for ENDS product purchases.
2. Online Browsing: TPB web properties include a pop-up window, which requires the users to affirm that they are of the legal age to purchase the candidate products.
3. Age Verification: Online sales of the candidate product through TPB web properties are restricted to adults, 21 years of age or older, and are age-verified by an independent, third-party age- and identity-verification service that compares customer information against third-party data sources or, in the alternative, requires uploading of the customer's valid government identification, which is then reviewed by the third-party service. In circumstances where the third-party service is unable to verify a consumer's government identification, TPB personnel may manually age verify using the steps identified inManual review process for government-issued photo identificationty 1.13.6.4. A step-by-step example of the full process is included 1.13.6.3

1.13.4 SOLACE™ brand

1.13.4.1 Brand overview

TPB's mission is to shift current adult smokers who are unwilling or unable to quit using nicotine to the candidate e-liquids and also provide high-quality e-liquids in a variety of responsibly marketed branded flavored products for current adult e-liquid consumers.

behaviors of e-liquid category users. This study will help validate TPB's e-liquid data and provide insight into category level opinions and behavior.

6. "1,000 Person Study". TPB commissioned a custom, commercial market research study meant to assess demographics, perceptions, and behaviors of e-liquid category users. As the study had a sample size of n=1,000, moving forward we refer to the project as the "1,000 person" study. (Venebio, 2020)
7. "Online Listening Study". TPB commissioned a consumer behavior and attitude online listening study targeting vapers who use open e-liquids (hereinafter referred to as "Online Listening Study"). 2.8 million online conversations were retroactively analyzed to identify authentic voices and, thus, real consumer attitudes and usage behaviors for e-liquids. The study period was February 26, 2019 to February 25, 2020. A third-party company that specializes in online media listening analyzed an array of conversations, blogs, discussion threads, posts, etc., from a large variety of publicly available forums as shown below. The data analyzed were limited to open or publicly available platforms; privacy restrictions did prevent access to certain platforms. Refer to Online Listening Study for full details.

1.13.4.4.2 SOLACE sales data – historical and projected

TPB originally made only freebase nicotine e-liquids, branded as VaporFi and VaporShark. With the acquisition of Solace Vapor in 2019, TPB expanded its e-liquid portfolio. Historically, the Solace brand has offered only nicotine salt products.

The overwhelming majority of TPB freebase nicotine e-liquid units sold directly to consumers since July 2016 have been custom blends. Consumers have been able to specify exactly what flavors, nicotine strengths, and PG/VG ratios they preferred in their orders. **Table 5 5** provides the top-ten selling freebase nicotine e-liquid blends shipped since July 2016.[6] Note that currently and post-PMTA authorization, TPB has ceased sales of freebase nicotine custom blends and, going forward, only sells a specific set of SKUs, which are rebranded under the same brand family as the nicotine salts e-liquids.

Table 5 Top-selling freebase nicotine e-liquids, July 2016-present

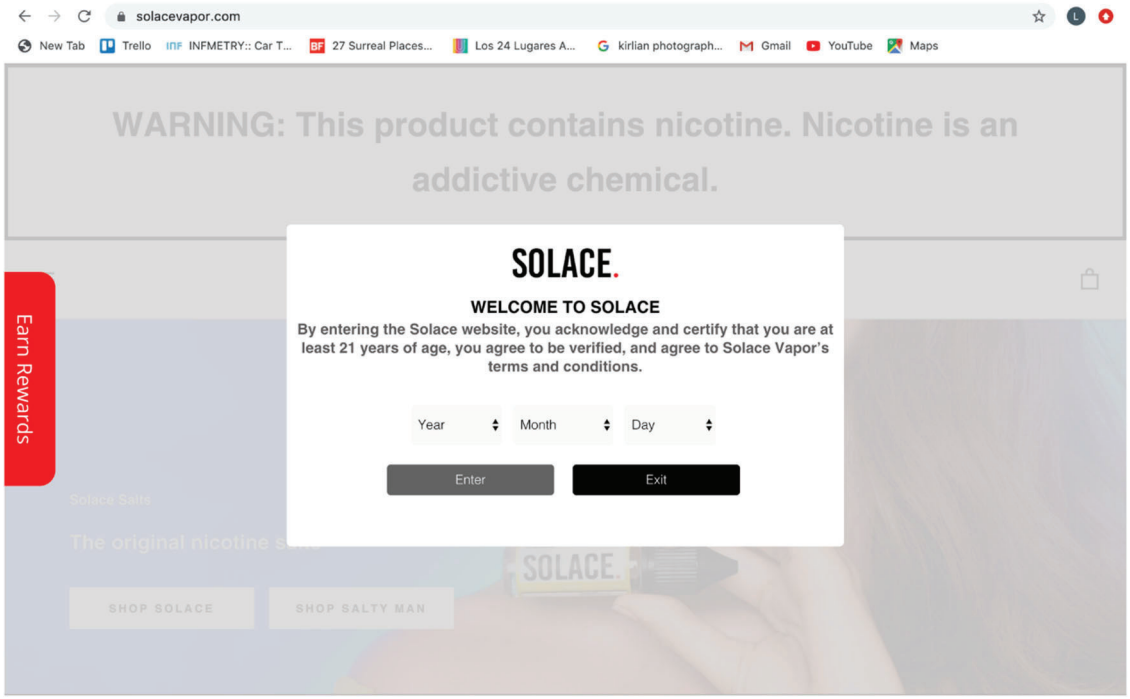
Product	# units shipped
VaporFi E-Liquid (30ML) - 06mg PG 50% / VG 50%	88,464
VaporFi E-Liquid (30ML) - 03mg PG 50% / VG 50%	85,820
VaporFi E-Liquid (30ML) - 12mg PG 50% / VG 50%	85,796
VaporFi E-Liquid (30ML) - 18mg PG 50% / VG 50%	84,049
VaporFi E-Liquid (60ML) - 03mg VG 50%/ PG 50%	44,426
VaporFi E-Liquid (30ML) - 12mg PG 70% / VG 30%	42,048
VaporFi E-Liquid (30ML) - 06mg PG 70% / VG 30%	41,292
VaporFi E-Liquid (30ML) - 18mg PG 70% / VG 30%	37,355
VaporFi E-Liquid (60ML) - 06mg VG 50% / PG 50%	33,949
VaporFi E-Liquid (30ML) - 03mg PG 70% / VG 30%	32,974

[6] *Note that VaporFi custom blend consumers were able to specify up to three different flavors per e-liquid, resulting in many potential flavor combinations. Thus, sales records reflect top-selling freebase nicotine e-liquids by size, flavor variant, nicotine strength, and PG/VG ratio.*

1.13.6.3 SOLACE online store

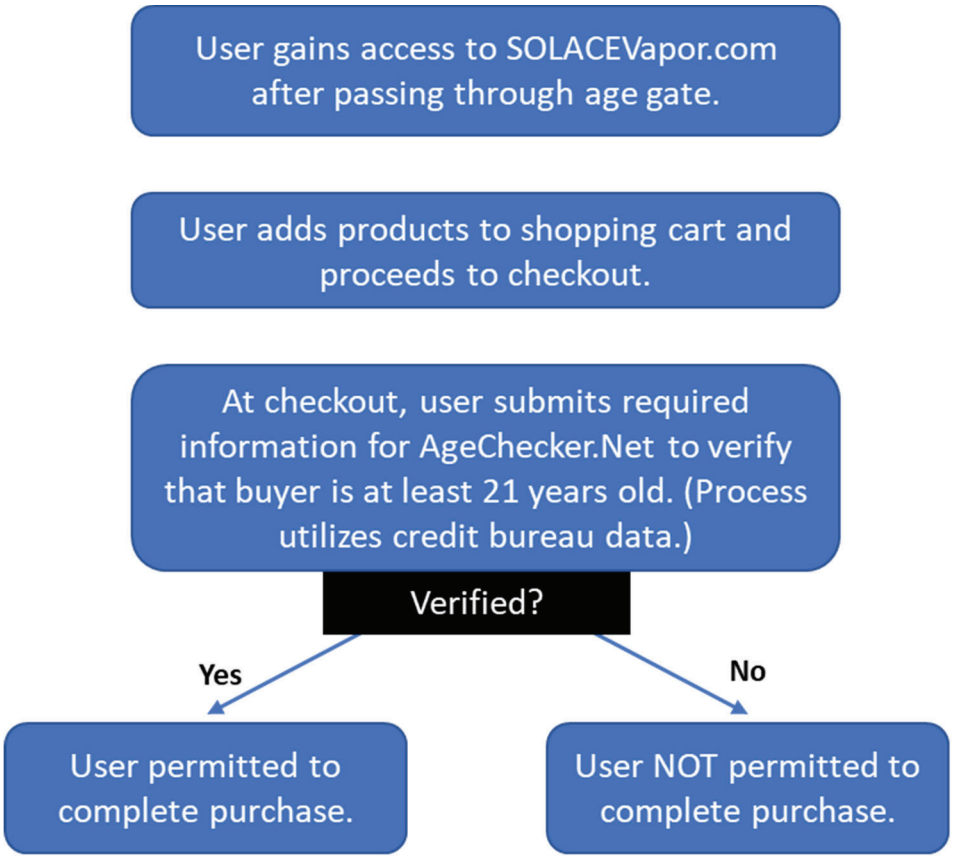
SOLACE products are currently marketed and sold in the SOLACE proprietary B2C online store, https://solacevapor.com/. SOLACE's online platform utilizes a number of security features to prevent the sale of the candidate products to Minors. SOLACE requires all online visitors to input their date of birth via an automatic pop-up prior to being given access to the site, as illustrated in **Figure 10** example.

Figure 10 Website age gate



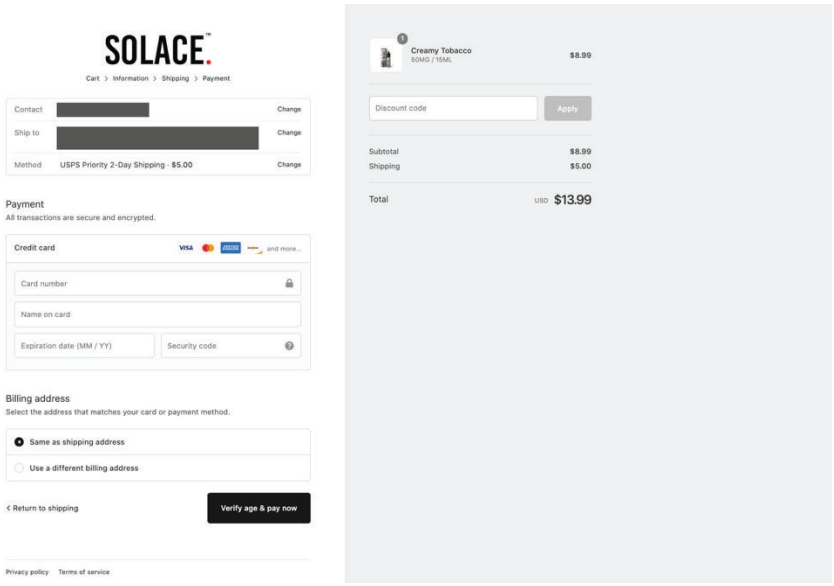
The SOLACE Online Store additionally employs third-party age verification software, as outlined in detail below in **Figure 11** through **Figure 18**. TPB currently uses the agechecker.net (AgeChecker) platform to verify the age of all purchasers on the SOLACE online store.

Figure 11 Flow through of the SOLACE store age verification for purchases



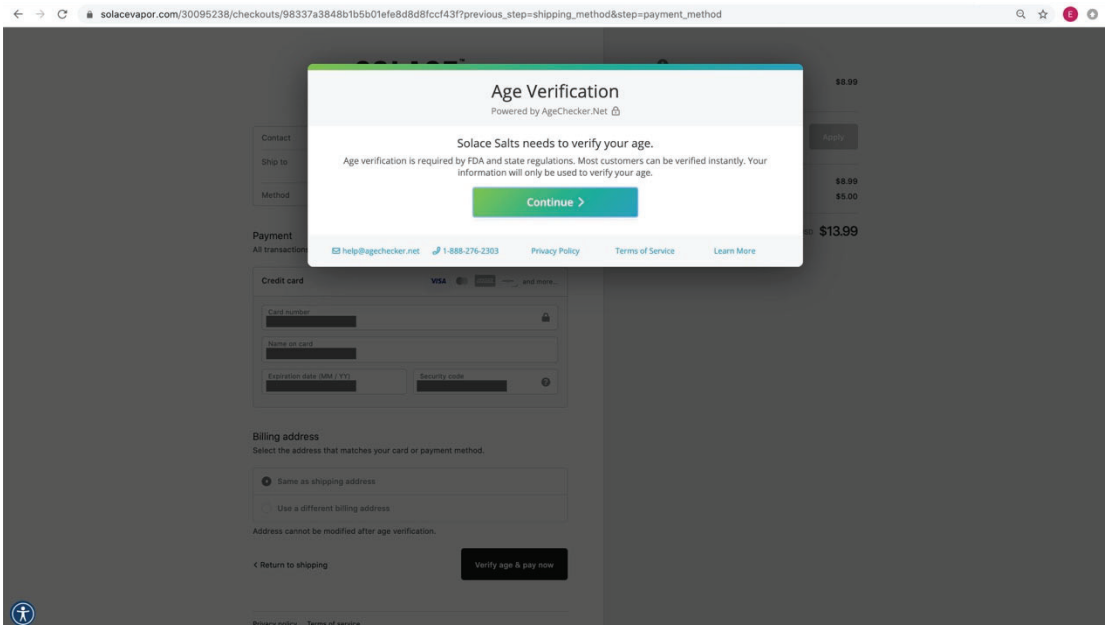
Step 1: Upon entering checkout, customer will be prompted to enter Shipping Information as well as payment information before getting verified and completing purchase.

Figure 12 Step 1 of SOLACE store age verification flow-through



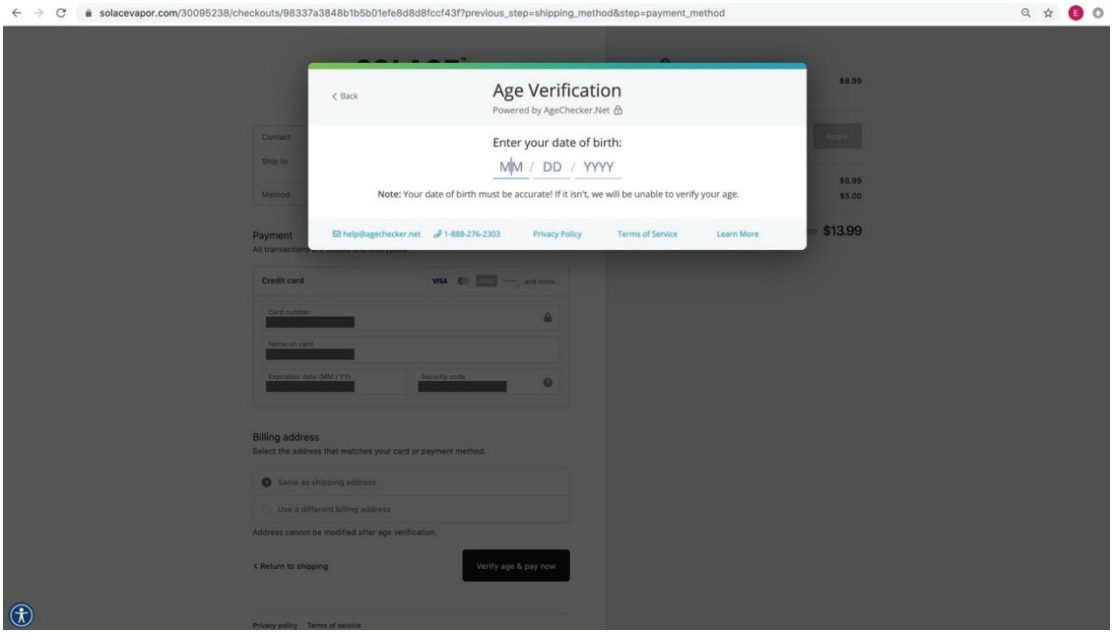
Step 2: After entering in all necessary information, customer will be prompted to Age Verification pop up before finalizing the transaction.

Figure 13 Step 2 of SOLACE store age verification flow-through



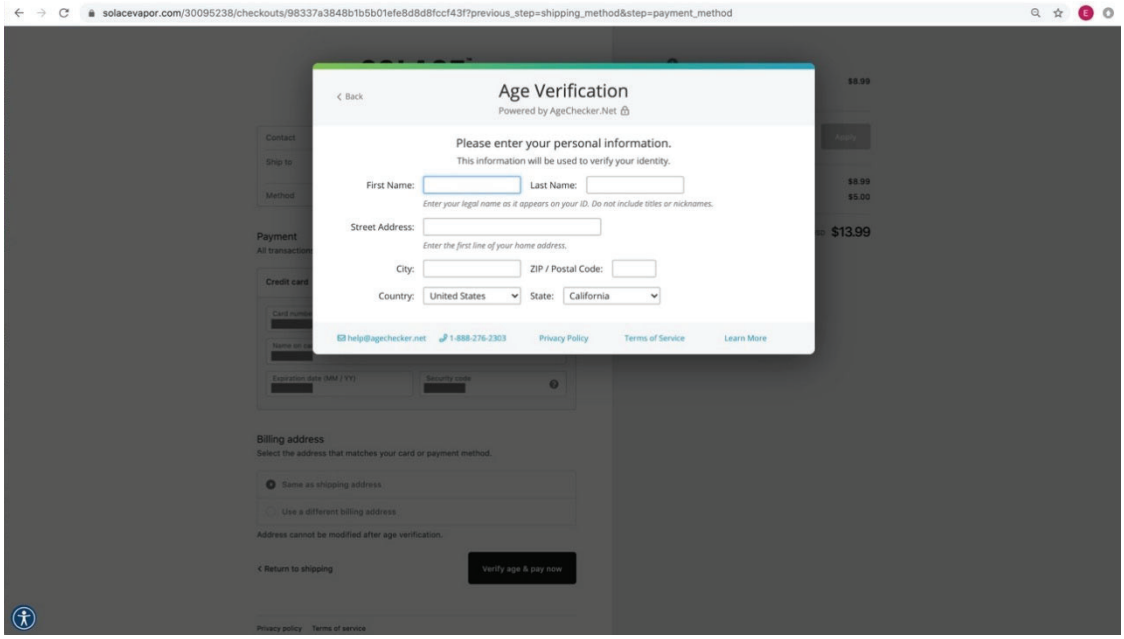
Step 3: Customer is required to enter date of birth to proceed.

Figure 14 Step 3 of SOLACE store age verification flow-through



Step 4: If date of birth is verified and the customer is of legal age to purchase, they must then input additional personal information in order to continue with the verification process.

Figure 15 Step 4 of SOLACE store age verification flow-through



Step 5: If the additional information is validated and the third-party verification company (Agechecker.net) can automatically validate the customer, the customer is then verified and redirected back to the checkout to complete the purchase. If AgeChecker cannot automatically verify the customer using existing databases, the customer will be prompted to submit a photo of their government issued ID to be manually verified.

Figure 16 Step 5a of SOLACE store age verification flow-through

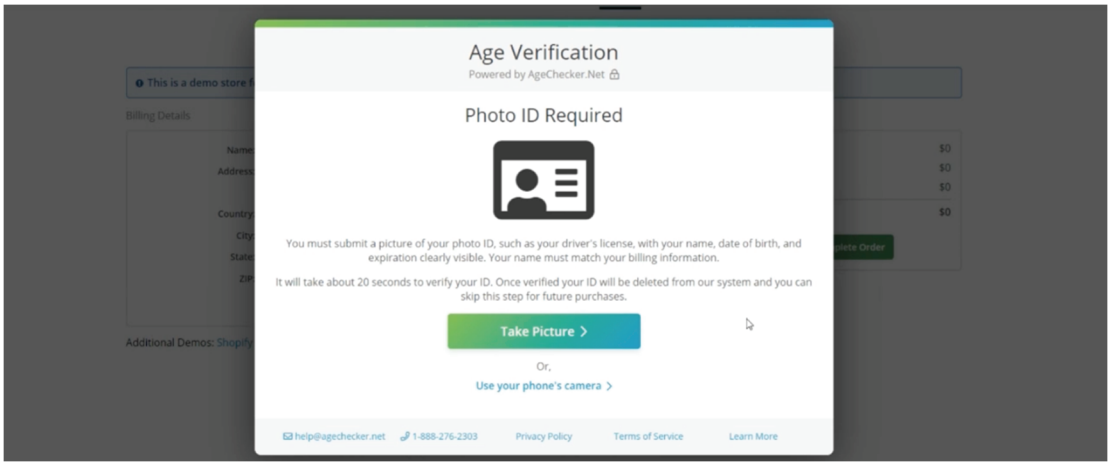


Figure 17 Step 5b of SOLACE store age verification flow-through

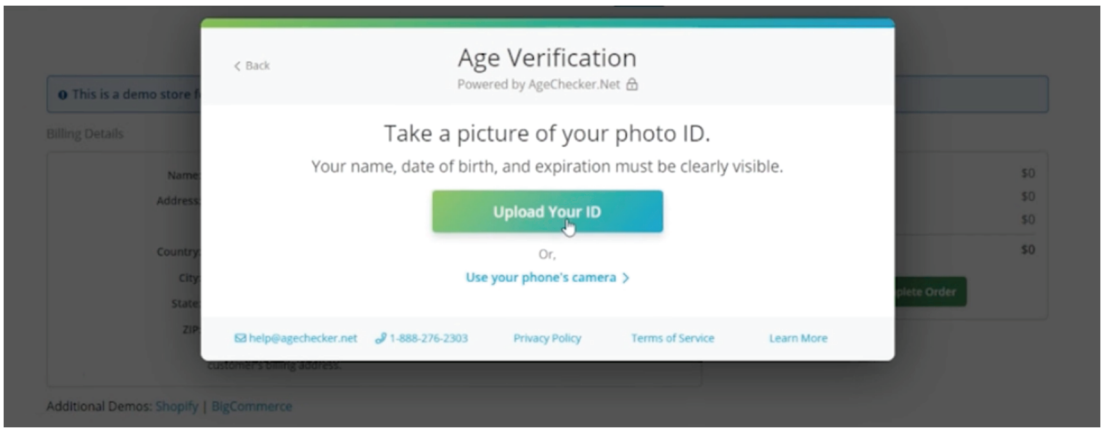
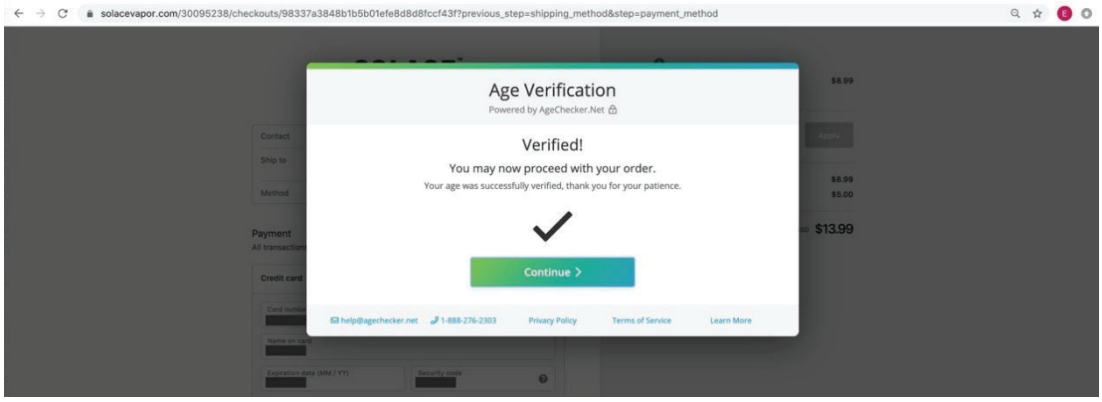


Figure 18 Step 5c of SOLACE store age verification flow-through



Transaction and consumer data for approved purchases are stored by Shopify, the e-commerce platform TPB currently utilizes for the SOLACE online store. AgeChecker protects all confidential consumer data received, including social security numbers and government-issued photo identifications. TPB receives access to the names, dates of birth, and addresses of consumers who purchase through the SOLACE online store, as referenced in Section 1.13.6.3.

Customers are subject to the bulk sales limit, outlined in Section 1.13.3.3.

1.13.6.4 Manual review process for government-issued photo identification

From time to time, third-party age verification software is unable to verify a purchaser's age. This can occur for numerous reasons, e.g., age verification software is unable to read the scanned copy of the purchaser's identification because of a glare. In those circumstances, TPB has an internal process for manually reviewing to verify a purchaser's age. This process is only used if the age verification software is unable to verify the purchaser's age after review of an image of the government-issued identification, and only TPB Customer Service Personnel who have been trained by internal legal personnel may perform this review.

1. TPB Customer Service Personnel receives notice that a customer government-issued identification document is unreadable.
2. TPB Customer Service Personnel reviews the name and date of birth. The name on the government-issued identification must match the name on the order. The date of birth must demonstrate that the consumer is 21 years of age or older.
3. If the government-issued identification is unreadable by manual review, the TPB Customer Service Personnel will contact the purchaser to request a new image of the government-issued identification.
4. If either the name on the order and the name on the government-issued identification do not match or the date of birth does not demonstrate the purchaser is at least 21 years of age or older, TPB Customer Service will terminate the order.

1.13.7 Ensuring compliance - data to demonstrate target audience delivery of advertising

TPB has included plans for monitoring compliance with SOLACE's marketing programs in the Post-Marketing Surveillance section of this PMTA. The Annual Report will provide findings regarding the following topics.

1.13.7.1 Reports regarding retailer compliance with TPB guidelines

If TPB Customer Service receives notice through the Customer Service contact, or otherwise, about a retailer who is not following TPB guidelines for sales of the candidate products, as outlined in Section 1.13.3.3, TPB will record and track these reports for inclusion in the Annual Report. Any follow-up actions taken by TPB will also be provided in the Annual Report.

1.13.7.2 Marketing plan execution compliance verification

To ensure TPB marketing programs were executed in accordance with the Marketing Plan, TPB will maintain records of the following information:

- Demographic information and/or media kits related to radio/podcast or digital media buys, as provided by the seller of the respective media channel.
- Copies of all executed media creative should FDA wish to review the materials.

TPB will review SOLACE marketing materials active in the marketplace for adherence to the Marketing Plan and FDA regulations. If errors or omissions are detected in either audience targeting or FDA Warnings, the Company will take the following actions:

- The erroneous print, radio/podcast, or digital media will be cancelled as soon as feasible and/or replaced with corrected materials, where applicable.
- If after initiation of a marketing execution of the respective medium, the medium is found to skew less than 85% 21 years and older, that campaign will be permanently cancelled as soon as feasible.

1.14 Samples Requested and Provided

TPB is willing to submit samples upon request from the FDA. Additionally, these samples would be provided within the 30-day timeline.

1.15 Health Documents [904(a)(4)]

None to disclose.

1.16 Requested Documents [904(b)]

None at this time.

1.17 Certification Statement

For the signed copy of the Certification Statement, refer to Section 1.19 of this PMTA.

repeatedly stated, fully transitioning smokers to ENDS products like the candidate products can reduce the morbidity and mortality associated with tobacco use.

2.4 The Candidate Products Do Not Appeal to Never Users, Youth, or Young Adults

Likelihood of Use (LOU) studies conducted with the candidate products (Module 6.2) demonstrate that never users and former users, including those in the young adult age group (which is also representative of the youth age group), do not indicate an interest in the candidate products. These studies measured intention to buy the candidate e-liquids using the Juster scale, a validated scale that measures the probability of a given behavior. The scale runs from 0 to 10, and the mean response predicts the proportion of the population that will perform the behavior.

As described in **Table 2.6.1.1**, below, in the LOU study of the Solace freebase nicotine e-liquids, the likelihood of use by never users 21 years of age or older was only 1.8% and by former users was 2.2%. In the young adult age group of 21 to 24 years old, the likelihood of use by never users was 1.5% and by former users 3.4%.

Table 2.6.1.1 Future Intention to Buy Solace Freebase Nicotine E-Liquids Among Tobacco Nicotine Product (TNP) Never/Former Users

	Never TNP users (from participants ≥ 21 years old)	Former TNP users (from participants ≥ 21 years old)	Never TNP users (from participants ≥ 21 to 24 years old)	Former TNP users (from participants ≥ 21 to 24 years old)
N*	451	640	151	213
Mean ± Std Dev	0.18 ± 1.12	0.22 ± 0.92	0.15 ± 1.00	0.34 ± 1.19
(95% CI)	(0.07 - 0.28)	(0.15 - 0.29)	(0.00 - 0.31)	(0.18 - 0.50)

*Number of non-missing responses

CI: Confidence Interval

In contrast, the likelihood of use by current smokers 21 years of age or older was 10.6% and by current ENDS users was 32.3%. In the young adult age group of 21 to 24 years old, the likelihood of use by current smokers was 13.4% and current ENDS users was 25.2%. See **Table 2.6.1.2**, below.

Table 2.6.1.2 Future Intention to Buy Solace Freebase Nicotine E-Liquids Among TNP Users

	Current cigarette smokers (from participants ≥ 21 years old)	Current ENDS users (from participants ≥ 21 years old)	Current cigarette smokers (from participants ≥ 21 to 24 years old)	Current ENDS users (from participants ≥ 21 to 24 years old)
N*	547	539	59	141
Mean ± Std Dev	1.06 ± 2.01	3.23 ± 2.83	1.34 ± 2.37	2.52 ± 2.64
(95% CI)	(0.90 - 1.23)	(2.99 - 3.47)	(0.72 - 1.96)	(2.08 - 2.96)

*Number of non-missing responses

CI: Confidence Interval

The results of the LOU study of the Solace nicotine salt products were similar, see Module 6.2. Thus, the candidate products do not appeal to never users or former users in any age group, indicating a very low likelihood of initiation in those groups with the candidate products.

The Company's third-party age-verification sales data also demonstrate that the candidate products are intended for and appeal to an older demographic (see Module 1.13). The data in **Table 2.6.1.3** and **Table 2.6.1.4** below indicate that the median age of purchasers of the candidate products is 43.6 (freebase) and 35.1 (salt), and the mean age of the purchasers is 44.82 (freebase) and 37.06 (salt). Significantly, for freebase products only 6.07% of purchasers were 21-24 years of age, while only 18.02% of purchasers chose salt products.

The sales breakdown for the freebase products since implementation of Tobacco 21 is listed in **Table 2.6.1.3**.

Table 2.6.1.3 Age distribution of freebase nicotine product consumers based on online sales data (Source: vaporfi.com and vapershark.com).

Time Period	Dataset	N	18-20, n (%)	21-24, n (%)	25-39, n (%)	40-64, n (%)	65+, n (%)	mean (%RSD, Range)	missing, n (%)
Post-January 1, 2020 (1/1/2020 - 6/25/2020)	**Online Sales**	27,153	0 (0%)	1649 (6.07%)	8951 (32.97%)	12966 (47.75%)	2221 (8.18%)	44.82 (30.43, 21.02-83.66)	1366 (5.03%)

%RSD, percent relative standard deviation.

The sales breakdown for the nicotine salt products since implementation of Tobacco 21 is listed in **Table 2.6.1.4**.

Table 2.6.1.4 Age distribution of nicotine salt product consumers based on online sales data (Source: directvapor.com and vaporfi.com).

Time Period	Dataset	N	18-20, n (%)	21-24, n (%)	25-39, n (%)	40-64, n (%)	65+, n (%)	mean (%RSD, Range)	missing, n (%)
Post-January 1, 2020 (1/1/2020 - 5/17/2020)	**Online Sales**	8,747	0 (0%)	1576 (18.02%)	3991 (45.63%)	3005 (34.35%)	172 (1.97%)	37.06 (32.23, 21.01-92.72)	3 (0.03%)

%RSD, percent relative standard deviation.

Thus, this PMTA demonstrates that the candidate products do not appeal to never users, youth, or young adults.

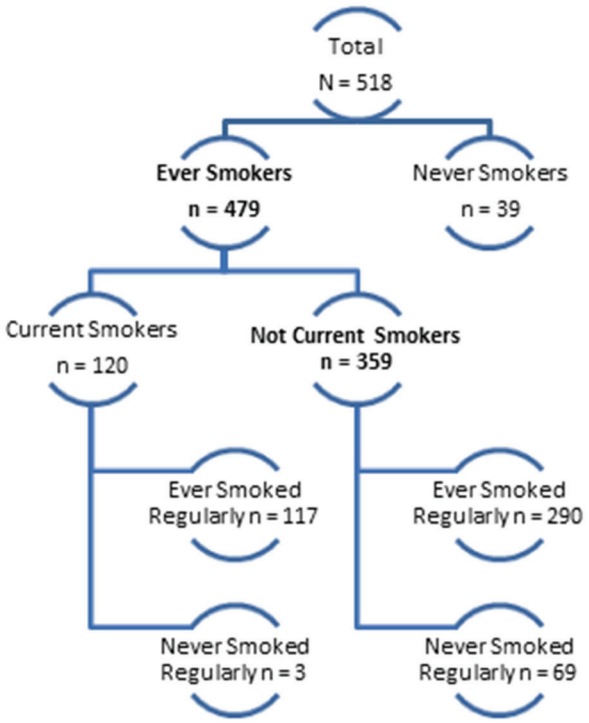
Use of the Candidate Products Leads to Smoking Cessation at a Rate That is Meaningfully Higher Than FDA-Approved Over-the-Counter (OTC) Nicotine Replacement Therapy (NRT) Products and Does Not Lead to Significant Levels of Dual or Poly Use

The data and information in this PMTA demonstrate that smokers that start using the candidate products are very likely to switch completely to the product. In fact, these data indicate that the candidate products are

substantially more effective **(on the order of 10 times more effective)** for smoking cessation than FDA-approved OTC NRT products such as the gum, lozenge and patch. Although the Company has no intention of making any smoking cessation claims for the candidate products, the fact that users of the candidate products overwhelmingly switch completely from smoking to the candidate products strongly indicates that the candidate products have a positive population-level impact and are APPH.

For example, in the Patterns of Use (POU) study conducted with the candidate products (Module 5.4), of 479 ever smokers (92.48% of the 518 total subjects), **75% of the candidate product users do not currently smoke cigarettes at all**. See **Figure 2.6.1.1**, below, for a schematic overview of the use of cigarettes by the POU study respondents.

Figure 2.6.1.1 POU Study Cohort



Among the 39 subjects who had never smoked a cigarette, 15 only used ENDS and the other 24 had used other tobacco/nicotine products. Thus, only 2.9% of subjects were nicotine naïve.

Importantly, of the 518 respondents in the study, only 11.9% reported smoking combustible cigarettes every day over the prior 30 days and 13.2% reported smoking combustible cigarettes on some days over the past 30 days. In other words, only 25% of past 30-day vapers who used the candidate products also smoked any cigarettes at all (i.e., dual use) during that same period. In sum, the POU demonstrates a smoking quit rate of 75% while only 25% of subjects continued to smoke at all while using the candidate products, with only 11.9% smoking every day. See **Table 2.6.1.5** below.

Table 2.6.1.5 Current Smoking Behavior

		TPB e-liquid nicotine product all users	TPB e-liquid freebase nicotine product users	TPB e-liquid nicotine salt product users
Total Subjects	**N**	**518**	**302**	**216**
Reported cigarette use	N*	479	273	206
Every day (%)	n (%)	57 (11.9%)	32 (11.7%)	25 (12.1%)
	(95% CI)	(9.1% - 15.1%)	(8.2% - 16.1%)	(8.0% - 17.4%)
Some days (%)	n (%)	63 (13.2%)	39 (14.3%)	24 (11.7%)
	(95% CI)	(10.3% - 16.5%)	(10.4% - 19.0%)	(7.6% - 16.8%)
Not at all (%)	n (%)	359 (74.9%)	202 (74.0%)	157 (76.2%)
	(95% CI)	(70.8% - 78.8%)	(68.4% - 79.1%)	(69.8% - 81.9%)
Don't know (%)	n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	(95% CI)	NA	NA	NA
Decline to answer (%)	n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	(95% CI)	NA	NA	NA

CI: Confidence Interval
*Number of non-missing responses

The fact that use of the candidate products leads to a very high rate of smoking cessation and a low rate of dual use is also supported by a Company-sponsored IRB-reviewed live interview study with users of box mod (tanks and coils) devices, which are frequently used (25%) with the candidate products (**Table 2.6.1.6**).

Table 2.6.1.6 Vaping devices used most frequently with TPB E-Liquid

		TPB E-Liquid users
Total Subjects		**518**
Vaping devices used most frequently with TPB E-Liquid		
N*		518
E-cigarettes used with TPB E-Liquid (%)	n (%)	14 (2.7%)
	(95% CI)	(1.5% - 4.5%)
Pod vape used with TPB E-Liquid (%)	n (%)	110 (21.2%)
	(95% CI)	(17.8% - 25.0%)
Vape pen used with TPB E-Liquid (%)	n (%)	260 (50.2%)
	(95% CI)	(45.8% - 54.6%)
Box mod used with TPB E-Liquid (%)	n (%)	132 (25.5%)
	(95% CI)	(21.8% - 29.5%)
Don't know (%)	n (%)	0 (0.0%)
	(95% CI)	NA
Decline to answer (%)	n (%)	2 (0.4%)
	(95% CI)	(0.0% - 1.4%)

CI: Confidence Interval
*Number of non-missing responses

In this study of 36 subjects that used box mods (tanks and coils), 28 of the 36 subjects smoked cigarettes before using vape devices. Of the remaining subjects, 5 used other tobacco products and 3 were nicotine naïve. Of those subjects that used cigarettes (28), only 2 continue to smoke cigarettes and the remaining 26 or **92.8% no longer smoke cigarettes**.

Significantly, the smoking cessation rates demonstrated in the studies described above (75% and 92.8%) are substantially higher – **on the order of 10 times more effective** – than any cessation rates demonstrated by FDA-approved NRT products. Indeed, most published studies put the smoking cessation efficacy rate of OTC NRT products in the range of about 7% to 14% (Etter & Stapleton, 2006; Hughes, Shiffman, Callas, & Zhang, 2003; Lindson et al., 2019; Moore et al., 2009).

In summary, this PMTA demonstrates that the candidate products do not appeal to never users, youth, young adults, or former users and a significant majority of the users of the candidate products have completely ceased use of combustible cigarettes **(at a smoking cessation rate that is substantially higher than users of FDA-approved OTC NRT products)**. Although the Company does not intend to make any smoking cessation claims for its products, the statutory standard of APPH, as interpreted by FDA, requires a population health impact assessment taking into account the following factors:

- The likelihood of product use by current cigarette smokers;
- The likelihood of poly-use of tobacco products (i.e., the product(s) under review and other tobacco products);
- The likelihood of product initiation by current nonsmokers (or nontobacco users), specifically former smokers/users, never smokers/users, and youth; and
- The likelihood of the product(s) under review leading to tobacco product cessation (or smoking cessation)

As described above and demonstrated in this PMTA, a significant majority of users of the candidate products are/were cigarette smokers, poly-use of the candidate products with other tobacco products is low, initiation of the candidate products by nonsmokers or youth is very low, and the products are very likely to lead to smoking cessation. In addition, the HPHC testing and other data in this PMTA, as well as the absence of adverse events associated with the candidate products, demonstrate that the candidate products are substantially less harmful than combustible cigarettes and comparable to other products in the ENDS category. Thus, the candidate products, if authorized for sale by FDA, would have a positive individual and population health impact and therefore are APPH.

2.5 Regulatory Compliance

The information provided in this PMTA for TPB satisfies the statutory content requirements set forth in FD&C Act Section 910(b)(1). Specifically, this PMTA includes the following sections:

Table 2.6.1.1 *Section 910(b)(1) Application Content Requirements*

Application Contents	PMTA Location
(A) full reports of all information, published or known to, or which should reasonably be known to, the applicant, concerning investigations which have been made to show the health risks of such tobacco product and whether such tobacco product presents less risk than other tobacco products;	Module 3 Module 4 Module 5 Module 6 Module 7
(B) a full statement of the components, ingredients, additives, and properties, and of the principle or principles of operation, of such tobacco product;	Module 3

moving them to exclusive use of ENDS. Through this strategy, TPB will educate adult tobacco smoker on the importance of purchasing authorized nicotine vaping devices and e-liquids and using those products only as intended.

2.8 Target Market for TPB e-liquids

TPB understands that marketing plans can provide important information regarding whether permitting the marketing of the candidate-liquids would be APPH. Therefore, as suggested in the proposed § 1114.7(f)(2) of the FD&C Act, we include information on the intended target audience(s), media and distribution channels, specific tactics, total dollar amount(s) of media buys and marketing and promotional activities, and timing for the activities in this PMTA. We also describe data sources, tools, technologies, and methodologies to establish, maintain, and monitor highly targeted marketing plans and media buys (Module 1.13).

TPB's vision is that the candidate e-liquids will help significantly reduce U.S. cigarette usage. The candidate e-liquids should not, however, be considered an alternative to quitting all tobacco product use. The best choice for adult smokers concerned about the health risks of tobacco product use is to quit altogether. The candidate products are not risk-free. Therefore, TPB's consumer marketing efforts will focus on the three segments listed below.

- Current users of TPB-branded e-liquids (i.e. marketing to current consumers).
- Current users of competitive nicotine-based e-liquids (i.e. attempts to gain share of the e-liquid market).
- Current smokers (i.e. attempts to convert smokers to users of e-liquids).

Note that these three segments are not necessarily mutually exclusive and targets across all three segments must be age 21 or over. TPB wants to significantly reduce U.S. cigarette usage while limiting reach to unintended audiences (i.e. non-tobacco users and youth).

Based on data collected from a Likelihood of Use (LOU) study (Module 6.2) our marketing efforts have been effective. The population most likely to use TPB e-liquids are current ENDS users followed by cigarette smokers. TPB communications did not reverse the respondents stated intention to quit smoking. Additionally, these smokers understood that the candidate e-liquids are not a substitute for cessation. Lastly, the candidate e-liquids do not appear to be attractive to youth.

Although TPB's e-liquids are not attractive to youth, TPB has taken aggressive measures to prevent youth exposure, access and appeal of the candidate products. TPB monitors consumer use patterns, reviews demographic information, and verifies the purchase age for all consumer sales through age verification software. In addition, TPB will work actively with distributors, brick-and-mortar retail stores, and online retailers to provide resources and guidance to ensure zero-to-minimal exposure of the candidate e-liquids to unintended audiences. TPB closely follows FDA updates on its enforcement policies and activities in order to modify its own policies as needed. Lastly, we will have a robust surveillance program that in part includes monitoring marketing practices (Module 6.3).

In addition to marketing plans, TPB also includes specimens of proposed labeling to be used for the TPB e-liquids in this PMTA. This includes labels, inserts, onserts, instructions, and other accompanying information (Module 1.12) In accordance with federal requirements, all candidate e-liquids and marketing collateral will include the mandatory nicotine warning statement: "WARNING: This product contains nicotine. Nicotine is an addictive chemical."

2.14 Summary

- The candidate products are designed and manufactured with controls for ingredients, formulations, facilities, manufacturing process, packaging, and understanding of product stability (Module 3).
- The candidate products exhibit a relatively low toxicity profile compared to cigarettes. The scientific evidence supports fewer or significantly reduced levels of cigarette smoking-related harmful and potentially harmful constituents (HPHCs). HPHC levels are also comparable to HPHC levels in similar e-liquids on the market (Module 4.2 and Module 4.5).
- The hazard of all ingredients & materials are evaluated, and the scientific evidence supports low absolute health risk of aerosols produced from the candidate e-liquids (Module 4.5).
- Adult smokers who completely switch to ENDS exhibit significant reductions of selected biomarkers of exposure (BOEs) when compared to smokers who continue smoking cigarettes, based on clinical pharmacology literature (Module 5.7).
- The candidate products have nicotine delivery and abuse liability similar to or lower than cigarettes and other inhaled non-combustible tobacco products and use of candidate e-liquid products can facilitate complete switching from cigarettes. In fact, a meaningful proportion of cigarette smokers successfully switch to the candidate products (Module 5.2).
- There is a low likelihood that ENDS will decrease cessation among adult tobacco consumers intending to quit using cigarettes (Module 6.2). In fact, the alternative is true for TPB liquids. We see an increase in cigarette smoking cessation following the use of TPB e-liquids (Module 5.4).
- Labeling of the candidate products is factual and includes nicotine exposure and addictiveness warning statements. Adult smokers and ENDS users understand the packaging materials and can correctly assemble and disassemble the product (Module 6.2).
- The company will continue taking substantive action to reduce youth access and use (Module 6.3).
- Current non-users have minimal interest in initiating or re-initiating tobacco use with the candidate products (Module 6.2).
- The young adult age group (which is also representative of the youth age group), do not indicate an interest in the candidate products (Module 6.2).
- Most young adults (which is also representative of the youth age group) perceive daily and occasional use of the products as harmful and addictive (Module 6).
- A Population Health Impact Model suggests that the candidate products are APPH and that market authorization will significantly reduce a smoker's risk of developing cigarette smoke-induced disease (Module 6.5).
- TPB has proposed a post-market surveillance program to evaluate the effect of continued marketing of the candidate e-liquids on the population over time (Module 6.3).
- Each environmental assessment identified no significant environmental risks associated with market authorization of the Candidate Products. As such, a Finding of No Significant Impact (FONSI) by the FDA is warranted for the environmental assessment of each candidate product. (Module 7).

4. Explore daily TNP patterns of use among TPB e-liquid users, including reasons for use.

Information captured as part of Secondary Objective 4 provides valuable insight into what other products respondents use and why they use them. First, users of TPB e-liquids, much like the broader population of vapers (Soneji, Knutzen, & Villanti, 2019), clearly indicate the importance of flavors in their product choices. (Table 5.4.7 contains information pertaining to most frequently used flavors.) When asked why they (a) use refillable vaping devices and (b) first tried their current TPB brand of e-liquid, flavors rise to the top of the list; results are shown in Table 5.4.15 and Table 5.4.16.

Table 5.4.15 Among Users of Refillable Vaping Devices, Reason(s) for Using Such a Device

Reason for choosing to use a refillable vaping device N*	394
It allows me to choose my flavors	80%
It allows me to control the nicotine level	69%
It satisfies my nicotine cravings	69%
It costs less to use compared to other vaping devices	57%
It's more convenient than other vaping devices	52%
I can use it in places where I cannot smoke cigarettes	44%
It allows me to customize the throat hit	42%
It allows me to choose the PG/VG ratio	41%
It lets me control the amount of visible vapor	26%

Note: Respondents could select more than one answer.

Table 5.4.16 Reason(s) for Trying Current TPB E-Liquid

Reason why first tried current TPB brand N*	518
Better flavor than other e-liquids	40%
Just curious to see what it was like	35%
Comes in several different levels of nicotine strength	34%
Less harmful to my health than cigarettes	33%
To help me quit smoking cigarettes	30%
New and interesting	26%
To add variety to the products I use	25%
Recommended by someone I know	22%
To control the nicotine level	21%
Would not cause me to smell like smoke/tobacco	21%
Less harmful for those around me than cigarettes	21%
Cheaper than other e-liquids	21%
Seemed a more appealing option than other e-liquid(s)	20%
To better satisfy nicotine cravings	20%
More convenient to buy than other e-liquids	18%
To choose the PG/VG ratio I want	17%
Seemed easy to use	17%
To use in places where I could not smoke	12%
The leftover smell is better than other e-liquids	10%
It is a less harmful option than other e-liquid(s)	10%
To help me reduce my cigarette smoking	10%
More acceptable to non-tobacco users	9%
To customize the throat hit	8%
To control the amount of visible vapor	3%

Note: Respondents could select more than one answer.

The common thread with these questions and data appears to be successfully staying away from cigarettes; as already discussed in this section, the majority of TPB e-liquid consumers use the products to stay away from smoking. When looking at flavors used, 55% of respondents selected “fruit” or “candy, desserts, or other sweets.” Only 16% of TPB e-liquid users preferred a tobacco-flavored option, and an additional 8% selected menthol, which one could associate with cigarettes. Flavor variety clearly matters to these users, as only 35.5% of respondents indicated they consistently use only one flavor. On the topic of choosing one’s device, other topics of relevance include controlling nicotine levels and satisfying cravings. When discussing the choice of their current TPB e-liquid brand, respondents cite curiosity, variety in nicotine strengths, and smoking cessation/reduction in addition to flavor preference. Tying this information together, one infers that users who want to stop smoking cigarettes benefit from the variety of available choices of the vaping experience or, in other words, the ability to customize to their personal preference.

Before conducting this POU study, questions existed about what differences, if any, exist when comparing users of freebase nicotine vs. nicotine salt varieties of TPB e-liquids. As noted earlier, the levels of nicotine differ noticeably when comparing freebase nicotine and nicotine salt e-liquids. Responses suggest that users of TPB freebase nicotine e-liquids approach their vaping differently than users of TPB nicotine salt e-liquids and vice versa.

Reasons for using TPB e-liquids show variance by user type, as shown in Table 5.4.17.

Table 5.4.17 Reasons for Use of TPB E-Liquids

Reported reason for TPB e-liquid use	All	Freebase nicotine	Nicotine salt
N*	518	302	216
Better flavor than other e-liquids	56%	47%	69%
Less harmful to my health than cigarettes	43%	45%	40%
To control the nicotine level	39%	44%	32%
To better satisfy nicotine cravings	37%	31%	45%
To help me quit smoking cigarettes	35%	35%	35%
Ease of use	34%	35%	32%
To add variety to the products I use	29%	34%	21%
Less harmful for those around me than cigarettes	26%	28%	25%
To choose the PG/VG ratio I want	26%	37%	12%
Cheaper than other e-liquids	23%	27%	18%
More convenient to buy than other e-liquids	22%	27%	16%
New and interesting	19%	22%	15%
Recommended by someone I know	18%	13%	25%
Less harmful to my health than other e-liquid(s)	17%	20%	12%
The leftover smell is better than other e-liquids	15%	13%	18%
To customize the throat hit	13%	13%	14%
Less harmful for those around me than other e-liquid choices	12%	12%	12%
To help me reduce my cigarette smoking	12%	13%	10%
To control the amount of visible vapor	6%	7%	6%
None of the above	0%	0%	1%
Don't know	0%	0%	0%

Note: Respondents could select more than one answer.

Users of TPB nicotine salt e-liquids were much more likely to select “Better flavor than other e-liquids” and also more likely to select “To better satisfy nicotine cravings.” A product with high nicotine concentration would logically be more likely to satisfy a craving, but no diagnostic data were collected within this study as

to why nicotine salt users cite "better flavor" more frequently. Users of TPB freebase nicotine e-liquids were much more likely to select "To choose the PG/VG ratio I want" and were more likely to select "To control the nicotine level," "To add variety to the products I use," and "More convenient to buy than other e-liquids."

Results from the study revealed variation in device types used. While both users of freebase nicotine and nicotine salt TPB e-liquids cite using vape pens most often, freebase nicotine users are much more apt to also use box mods, while nicotine salt users skew toward pod vapes. Freebase nicotine users also tend to fill their devices more frequently, with 45% saying they refill their devices more than once per day, compared to 21% of nicotine salt users. This study did not inquire as to why refill frequency varies; the difference could be due to usage habits, different device capacities, or other factors.

Results showed that users of nicotine salt TPB e-liquids have some moderately different habits concerning flavor usage. Flavor used most frequently is shown in Table 5.4.18.

Table 5.4.18 Flavor of TPB E-Liquid Used Most Frequently

Flavor of TPB e-liquid most frequently used	All	Freebase nicotine	Nicotine salt
N*	518	302	216
Fruit (%)	33.8%	33.1%	34.7%
Candy, desserts, or other sweets (%)	20.7%	24.2%	15.7%
Tobacco-flavored (%)	15.6%	13.6%	18.5%
Mint (%)	11.4%	6.0%	19.0%
Menthol (%)	8.1%	11.3%	3.7%
Other flavor (%)	4.1%	4.3%	3.7%
A non-alcoholic drink (%)	3.9%	1.3%	0.0%
Chocolate (%)	1.0%	1.0%	0.9%
Clove or spice (%)	0.8%	1.0%	0.5%
An alcoholic drink (%)	0.8%	1.3%	0.0%

Fruit was the most popular option among both user groups. Freebase nicotine e-liquid users displayed a modest tendency toward candy, desserts, and other sweets and menthol vs. nicotine salt; however, nicotine salt e-liquid users displayed a modest tendency toward tobacco-flavored and mint options. Without further information behind flavor choices, these results could simply be a function of flavor availability as well as actual preferences.

1. *Among all respondents, assess whether being exposed to a Solace e-liquid packaging label and product description impacts perceptions and intentions related to the use of TNP.*

    i. *Among never-users of TNP, evaluate:*
        - *current likelihood to initiate TNP based on intention to buy TNP*
        - *future likelihood to initiate TNP based on intention to buy Solace e-liquid after being exposed to a Solace e-liquid packaging label and product description.*

    ii. *Among former users of TNP, evaluate:*
        - *current likelihood to reinitiate TNP based on intention to buy TNP*
        - *future likelihood to reinitiate TNP based on intention to buy Solace e-liquid after being exposed to a Solace e-liquid packaging label and product description.*

    iii. *Among current users of TNP (cigarette smokers, ENDS users, and dual users of cigarettes and ENDS), evaluate:*
        - *current use of TNP*
        - *among current users of TNP ages 21+, evaluate:*
            - *future intention to buy Solace e-liquid after being exposed to a Solace e-liquid packaging label and product description*
            - *future intention to use current TNP after being exposed to a Solace e-liquid packaging label and product description.*

    iv. *Among current users of TNP (cigarette smokers, ENDS users, and dual users of cigarettes and ENDS), evaluate:*
        - *current intention to quit use of TNP*
        - *future intention to quit use of TNP after being exposed to a Solace e-liquid packaging label and product description.*

Intention to buy Solace e-liquids was measured using the Juster scale, a validated scale that measures the probability of a given behavior. The scale runs from 0 to 10, and the mean response predicts the proportion of the population that will perform the behavior. Mean scores for the cohorts of interest in the study are identified in Tables 6.2.1.2 and 6.2.1.3.

Table 6.2.1.2 Future Intention to Buy Solace Freebase Nicotine E-Liquids Among TNP Never/Former Users

	Never TNP users (from participants ≥ 21 years old)	Former TNP users (from participants ≥ 21 years old)	Never TNP users (from participants ≥ 21 to 24 years old)	Former TNP users (from participants ≥ 21 to 24 years old)
N*	451	640	151	213
Mean ± Std Dev	0.18 ± 1.12	0.22 ± 0.92	0.15 ± 1.00	0.34 ± 1.19

(95% CI)	(0.07 - 0.28)	(0.15 - 0.29)	(0.00 - 0.31)	(0.18 - 0.50)

*Number of non-missing responses
CI: Confidence Interval

Table 6.2.1.3 Future Intention to Buy Solace Freebase Nicotine E-Liquids Among TNP Users

	Current cigarette smokers (from participants ≥ 21 years old)	Current ENDS users (from participants ≥ 21 years old)	Current cigarette smokers (from participants ≥ 21 to 24 years old)	Current ENDS users (from participants ≥ 21 to 24 years old)
N*	547	539	59	141
Mean ± Std Dev	1.06 ± 2.01	3.23 ± 2.83	1.34 ± 2.37	2.52 ± 2.64
(95% CI)	(0.90 - 1.23)	(2.99 - 3.47)	(0.72 - 1.96)	(2.08 - 2.96)

*Number of non-missing responses
CI: Confidence Interval

In general, study results provided clear evidence of the lack of interest in Solace freebase nicotine e-liquids among nonusers, former users, and nonusers ages 21 to 24 in general as the mean scores for all of those segments fell below 1.0. Current smokers even displayed minimal interest in buying Solace freebase nicotine e-liquids, with a mean score of 1.1. Only current electronic nicotine delivery systems (ENDS) users displayed measurable interest in perhaps buying Solace freebase nicotine e-liquids, with a mean score of 3.2.

Of utmost importance to establishing Solace as APPH are the low scores for all TNP nonusers. In fact, exposure to the Solace freebase nicotine e-liquid label and stimuli resulted in scores very similar to current intention to purchase other TNP. Among never users, mean intention to buy cigarettes, ENDS, or Solace freebase nicotine e-liquids poststimuli exposure equaled 0.14, 0.09, and 0.18 respectively. Among former users, mean intention to reinitiate on cigarettes, ENDS, or Solace freebase nicotine e-liquids poststimuli exposure equaled 0.24, 0.35, and 0.22 respectively. These scores clearly fall on the low end of the Juster scale and suggest virtually zero risk of uptake among never and former users due to the availability of Solace freebase nicotine e-liquids on the market.

Before seeing any information about Solace freebase nicotine e-liquids, current smokers and ENDS users were asked about their motivation to quit. This metric was captured using a validated scale called Motivation to Stop Smoking (MTSS). The MTSS consists of one question with seven response options ranging from 1 (lowest) to 7 (highest level of motivation to stop smoking), also including “Don’t know.” Mean scores are commonly used to report MTSS results. In this study, mean MTSS scores were 3.2 and 3.1 for smoking

Solace freebase nicotine e-liquids consistently skews higher for people who already use ENDS products; even there, the percentage of ENDS users who find Solace freebase nicotine e-liquids to be “very appealing” or “extremely appealing” (top two choices on a five-point scale) equaled 21.8%, well below a majority of users.

Given the high level of attention placed on youth vaping, it makes sense to compare how all ENDS users view the appeal of Solace freebase nicotine e-liquids in comparison to younger users. In this case, younger users are defined as ages 21 to 24. With the enactment of the law limiting tobacco to ages 21 and over in December 2019 being a factor, this study did not allow respondents under age 21 to rate the appeal of Solace freebase nicotine e-liquids for concern of enticing underage users to try and purchase the product. Looking first at the overall appeal of Solace freebase nicotine e-liquids, 19.6% of all current ENDS users and 12.7% of current ENDS users ages 21 to 24 in the study find the product to be “very appealing” or “extremely appealing” (top two choices on a five-point scale). Clearly, there exists no evidence that Solace freebase nicotine e-liquids are more appealing to younger users. Complete data is shown in Table 6.2.1.5.

Table 6.2.1.5 Overall Appeal of Solace Freebase Nicotine E-Liquids

		Current ENDS users (from participants ≥ 21 years old)	Current ENDS users (from participants ≥ 21 to 24 years old)
N*		539	141
Not at all appealing (%)	n (%)	113 (21.0%)	41 (29.1%)
	95% CI	(17.6% - 24.6%)	(21.7% - 37.3%)
Slightly appealing (%)	n (%)	151 (28.0%)	47 (33.3%)
	95% CI	(24.3% - 32.0%)	(25.6% - 41.8%)
Moderately appealing (%)	n (%)	157 (29.1%)	35 (24.8%)
	95% CI	(25.3% - 33.2%)	(17.9% - 32.8%)
Very appealing (%)	n (%)	67 (12.4%)	13 (9.2%)
	95% CI	(9.8% - 15.5%)	(5.0% - 15.3%)
Extremely appealing (%)	n (%)	39 (7.2%)	5 (3.5%)
	95% CI	(5.2% - 9.8%)	(1.2% - 8.1%)
Don't know (%)	n (%)	11 (2.0%)	0 (0.0%)
	95% CI	(1.0% - 3.6%)	NA
Decline to answer (%)	n (%)	1 (0.2%)	0 (0.0%)
	95% CI	(0.0% - 1.0%)	NA

*Number of non-missing responses
CI: Confidence Interval

Similarly, Table 6.2.1.6 shows the appeal of Solace freebase nicotine e-liquids’ variety of flavors. Years of academic research suggest younger users of TNP prefer flavored products. Yet, the percentage of younger current ENDS users (ages 21 to 24) who find Solace freebase nicotine e-liquids’ flavor variety to be “very

appealing" or "extremely appealing" (35.5%) is directionally lower compared to the ratings among the percentage of all current ENDS users in the study (43.0%).

Table 6.2.1.6 Appeal of Solace Freebase Nicotine E-Liquids' Variety of Flavors

		Current ENDS users (from participants ≥ 21 years old)	Current ENDS users (from participants ≥ 21 to 24 years old)
N*		539	141
Not at all appealing (%)	n (%)	61 (11.3%)	17 (12.1%)
	95% CI	(8.8% - 14.3%)	(7.2% - 18.6%)
Slightly appealing (%)	n (%)	115 (21.3%)	40 (28.4%)
	95% CI	(17.9% - 25.0%)	(21.1% - 36.6%)
Moderately appealing (%)	n (%)	124 (23.0%)	34 (24.1%)
	95% CI	(19.5% - 26.8%)	(17.3% - 32.0%)
Very appealing (%)	n (%)	143 (26.5%)	30 (21.3%)
	95% CI	(22.8% - 30.5%)	(14.8% - 29.0%)
Extremely appealing (%)	n (%)	89 (16.5%)	20 (14.2%)
	95% CI	(13.5% - 19.9%)	(8.9% - 21.1%)
Don't know (%)	n (%)	7 (1.3%)	0 (0.0%)
	95% CI	(0.5% - 2.7%)	NA
Decline to answer (%)	n (%)	0 (0.0%)	0 (0.0%)
	95% CI	NA	NA

*Number of non-missing responses
CI: Confidence Interval

Table 6.2.1.7 highlights the younger users (ages 21 to 24) vs. all users comparison for one more metric, specifically appeal of Solace freebase nicotine e-liquid packaging. Results are similar to the outcome for overall appeal and appeal of flavors in that the percentage of younger users who find Solace freebase nicotine e-liquid packaging to be "very appealing" or "extremely appealing" (23.4%) is statistically equivalent to the ratings among the percentage of all ENDS users in the study (26.2%).

Table 6.2.1.7 Appeal of Solace Freebase Nicotine E-Liquid Packaging

		Current ENDS users (from participants ≥ 21 years old)	Current ENDS users (from participants ≥ 21 to 24 years old)
N*		539	141
Not at all appealing (%)	n (%)	119 (22.1%)	40 (28.4%)
	95% CI	(18.6% - 25.8%)	(21.1% - 36.6%)
Slightly appealing (%)	n (%)	130 (24.1%)	30 (21.3%)
	95% CI	(20.6% - 28.0%)	(14.8% - 29.0%)
Moderately appealing (%)	n (%)	143 (26.5%)	38 (27.0%)

	95% CI	(22.8% - 30.5%)	(19.8% - 35.1%)
Very appealing (%)	n (%)	93 (17.3%)	24 (17.0%)
	95% CI	(14.2% - 20.7%)	(11.2% - 24.3%)
Extremely appealing (%)	n (%)	48 (8.9%)	9 (6.4%)
	95% CI	(6.6% - 11.6%)	(3.0% - 11.8%)
Don't know (%)	n (%)	5 (0.9%)	0 (0.0%)
	95% CI	(0.3% - 2.2%)	NA
Decline to answer (%)	n (%)	1 (0.2%)	0 (0.0%)
	95% CI	(0.0% - 1.0%)	NA

*Number of non-missing responses
CI: Confidence Interval

Results were consistent for nicotine strengths and propylene glycol/vegetable glycerin (PG/VG) ratios. Additionally, nonusers of TNP continued to suggest Solace freebase nicotine e-liquids offer zero to minimal appeal, which is to be expected given their lack of interest in the ENDS space.

Within Primary Objective 3, the definition of the original study cohorts led to a comparison of all users ages 21 and over vs. users ages 21 to 24. Some observers will note that users ages 21 to 24 are actually contained in both cohorts, leading to the question of how a comparison of 21- to 24-year old ENDS users vs. ages 25 and over would look. In that context, the three following tables (Tables 6.2.8, 6.2.9, and 6.2.10) add the appeal scores for ages 25 and over to Tables 6.2.5, 6.2.6, and 6.2.7 respectively. Only point estimate results are displayed.

Table 6.2.1.8 Overall Appeal of Solace Freebase Nicotine E-Liquids, Including Ages 25 and Over

	Current ENDS users (from participants ≥ 21 years old)	Current ENDS users (from participants ≥ 21 to 24 years old)	Current ENDS users (from participants ≥ 25 years old)
N*	539	141	398
Not at all appealing (%)	21.0%	29.1%	18.1%
Slightly appealing (%)	28.0%	33.3%	26.1%
Moderately appealing (%)	29.1%	24.8%	30.7%
Very appealing (%)	12.4%	9.2%	13.6%
Extremely appealing (%)	7.2%	3.5%	8.5%
Don't know (%)	2.0%	0.0%	2.8%
Decline to answer (%)	0.2%	0.0%	0.3%

*Number of non-missing responses

Table 6.2.1 Appeal of Solace Freebase Nicotine E-Liquids' Variety of Flavors, Including Ages 25 and Over

	Current ENDS users (from participants ≥ 21 years old)	Current ENDS users (from participants ≥ 21 to 24 years old)	Current ENDS users (from participants ≥ 25 years old)
N*	539	141	398
Not at all appealing (%)	11.3%	12.1%	11.1%
Slightly appealing (%)	21.3%	28.4%	18.8%
Moderately appealing (%)	23.0%	24.1%	22.6%
Very appealing (%)	26.5%	21.3%	28.4%
Extremely appealing (%)	16.5%	14.2%	17.3%
Don't know (%)	1.3%	0.0%	1.8%
Decline to answer (%)	0.0%	0.0%	0.0%

*Number of non-missing responses

Table 6.2.1.9 Appeal of Solace Freebase Nicotine E-Liquid Packaging, Including Ages 25 and Over

	Current ENDS users (from participants ≥ 21 years old)	Current ENDS users (from participants ≥ 21 to 24 years old)	Current ENDS users (from participants ≥ 25 years old)
N*	539	141	398
Not at all appealing (%)	22.1%	28.4%	19.5%
Slightly appealing (%)	24.1%	21.3%	24.6%
Moderately appealing (%)	26.5%	27.0%	17.0%
Very appealing (%)	17.3%	17.0%	27.8%
Extremely appealing (%)	8.9%	6.4%	9.6%
Don't know (%)	0.9%	0.0%	1.2%
Decline to answer (%)	0.2%	0.0%	0.2%

*Number of non-missing responses

Again, results were consistent for nicotine strengths and PG/VG ratios. By isolating out the ENDS users ages 25 and over, it's easy to conclude that appeal for Solace freebase nicotine e-liquids among younger users was equivalent to appeal among the older group. There exists no evidence of any skew by age group when examining the appeal of Solace freebase nicotine e-liquids.

Secondary Objectives:

1. *Among all respondent cohorts, explore variation in perceptions of absolute risk associated with never having used any TNP, using ENDS, smoking cigarettes, and using an ENDS product containing only Solace e-liquid.*

    i. *Measurement of absolute risk of non-usage, ENDS usage, and smoking to occur prior to showing respondents the Solace e-liquid packaging label and product description*