APPENDICES

APPENDIX A

LOWER COURT OPINION

RECOMMENDED FOR PUBLICATION
Pursuant to Sixth Circuit I.O.P. 32.1(b)

File Name: 21a0260p.06

UNITED STATES COURT OF APPEALS

FOR THE SIXTH CIRCUIT

BREEZE SMOKE, LLC,

Petitioner,

v.

UNITED STATES FOOD AND DRUG ADMINISTRATION,

Respondent.

No. 21-3902

On Emergency Motion for Administrative Stay.

Petition for Review of an Order of the United States Food and Drug Administration; Agency Case No. PM0000983.

Decided and Filed: November 12, 2021

Before: MOORE, GILMAN, and KETHLEDGE, Circuit Judges.

COUNSEL

ON EMERGENCY MOTION FOR ADMINISTRATIVE STAY AND REPLY: Brian T. Burgess, Andrew Kim, GOODWIN PROCTER LLP, Washington, D.C., for Petitioner. **ON RESPONSE:** Kathleen B. Gilchrist, Hilary K. Perkins, UNITED STATES DEPARTMENT OF JUSTICE, Washington, D.C., for Respondent. **ON MOTION TO FILE AMICUS BRIEF AND ON BRIEF:** Jacquelyn A. Klima, KERR, RUSSELL, AND WEBER, PLC, Detroit, Michigan, for Amicus Curiae.

The court delivered an order. KETHLEDGE, J., (pg. 11), delivered a separate dissenting opinion.

ORDER

Breeze Smoke, LLC petitions for review of a Food and Drug Administration ("FDA") order denying its Premarket Tobacco Product Applications for certain of its electronic nicotine

delivery systems ("ENDS"). Breeze Smoke moves for a stay of the FDA's order. In addition, several parties—the American Academy of Pediatrics, American Cancer Society Cancer Action Network, American Heart Association, American Lung Association, Campaign for Tobacco-Free Kids, Parents Against Vaping E-Cigarettes, and Truth Initiative—move to file an amicus brief in support of the FDA's position.

"A petitioner must ordinarily move first before the agency for a stay pending review of its decision or order." Fed. R. App. P. 18(a)(1). Thus, a party first moving for relief in this court must "show that moving first before the agency would be impracticable" or "that, a motion having been made, the agency denied the motion or failed to afford the relief requested . . . ." Fed. R. App. P. 18(a)(2)(A)(i)–(ii). Under the Family Smoking Prevention and Tobacco Control Act ("TCA"), however, "any person adversely affected by" the denial of a Premarket Tobacco Product Application may seek judicial review of the denial, 21 U.S.C. § 387*l*(a)(1)(B), and "the court shall have jurisdiction to review the regulation or order . . . and to grant appropriate relief, including interim relief," *id.* § 387*l*(b). Breeze Smoke contends that seeking a stay from the FDA of its marketing-denial order would have been impracticable because the order takes effect immediately and the FDA can take months to consider an agency-level request for a stay. We agree. *See Wages & White Lion Invs., LLC v. FDA*, — F.4th —, No. 21-60766, 2021 WL 4955257, at *2 n.1 (5th Cir. Oct. 26, 2021).

A stay is "an exercise of judicial discretion" dependent on the case's facts. *Nken v. Holder*, 556 U.S. 418, 433 (2009) (quotation omitted). The party seeking "a stay bears the burden of showing that the circumstances justify an exercise of [our] discretion." *Id.* at 433–34. We consider four factors in determining whether to grant a stay: (1) "whether the stay applicant has made a strong showing that [it] is likely to succeed on the merits"; (2) the likelihood that "the applicant will be irreparably injured absent a stay"; (3) "whether issuance of the stay will substantially injure" other interested parties; and (4) "where the public interest lies." *Hilton v. Braunskill*, 481 U.S. 770, 776 (1987). The first two factors "are the most critical." *Nken*, 556 U.S. at 434.

"The FDA's administrative decisions are subject to review under the Administrative Procedure Act ('APA'), 5 U.S.C. § 706, which requires the reviewing court to set aside an

agency action that is 'arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law.'" *ISTA Pharms. v. FDA*, 898 F. Supp. 2d 227, 230 (D.D.C. 2012) (citation omitted); *see also* 21 U.S.C. § 387*l*(b). We therefore "must consider whether the decision was based on a consideration of the relevant factors and whether there has been a clear error of judgment." *Marsh v. Or. Nat. Res. Council*, 490 U.S. 360, 378 (1989) (quotation omitted). Although "[j]udicial review under [the arbitrary or capricious] standard is deferential, and a court may not substitute its own policy judgment for that of the agency," we must "ensure[] that the agency has acted within a zone of reasonableness and, in particular, has reasonably considered the relevant issues and reasonably explained the decision." *FCC v. Prometheus Radio Project*, 141 S. Ct. 1150, 1158 (2021).

Breeze Smoke has not made a strong showing that it would likely succeed on its claim that the FDA's review of its application was arbitrary or capricious. Nor has Breeze Smoke made a strong showing that the FDA's denial of its application contradicted the FDA's nonbinding 2019 guidance because that guidance contemplated more rigorous scientific data than Breeze Smoke's application contained.

Administrative agencies are generally required to provide "fair notice" of requirements. *See Golden Living Ctr. – Mountain View v. Sec'y of Health & Human Servs.*, 832 F. App'x 967, 975–76 (6th Cir. 2020) (citing the fair-notice doctrine). The fair-notice requirement extends to informal guidance. *PHH Corp. v. Consumer Fin. Prot. Bureau*, 839 F.3d 1, 48 (D.C. Cir. 2016), *reinstated in relevant part*, 881 F.3d 75, 83 (D.C. Cir. 2018) (en banc), *abrogated on other grounds sub nom. Seila Law, LLC v. Consumer Fin. Prot. Bureau*, 140 S. Ct. 2182 (2020). Courts must review agency action based on the justifications given at the time, not post hoc litigation rationales. *Dep't Homeland Sec. v. Regents of Univ. of Cal.*, 140 S. Ct. 1891, 1909 (2020). Finally, although agencies must consider reliance interests when they "change[] course," *id.* at 1913, the fact that a regulated entity has relied on an agency decision does not bar the agency from reconsidering that decision, *Belville Mining Co. v. United States*, 999 F.2d 989, 999 (6th Cir. 1993).

The TCA subjects certain new tobacco products to the FDA's premarketing review. 21 U.S.C. § 387 *et seq.* All parties agree that the TCA applies to Breeze Smoke's flavored

ENDS products. Under the TCA, the FDA "shall deny" applications for new products if, based on the information submitted to the FDA as part of the application "and any other information before [the FDA] with respect to such tobacco product," the FDA finds "a lack of a showing that permitting such tobacco product to be marketed would be appropriate for the protection of the public health ['APPH']." 21 U.S.C. § 387j(c)(2). To determine whether the marketing of the tobacco product is appropriate for the protection of the public health, the FDA evaluates "the risks and benefits to the population as a whole, including users and nonusers of the tobacco product." *Id.* § 387j(c)(4). That requires considering both the "likelihood that existing users of tobacco products will stop using such products," and the "likelihood that those who do not use tobacco products will start using such products." *Id.*

In 2016, the FDA deemed all tobacco products subject to the TCA. 81 Fed. Reg. 28,973 (May 10, 2016). This meant that tens of thousands of products then on the market could not legally be sold without the FDA's approval. The FDA allowed the products to stay on the market while it considered the flood of applications, and after a series of schedule changes implemented by the FDA and federal courts, the deadline fell on September 9, 2020. *Vapor Tech. Ass'n v. FDA*, 977 F.3d 496, 500 (6th Cir. 2020).

In advance of this deadline, the FDA issued nonbinding guidance that sought to help firms comply with this accelerated deadline. Hotly contested here is the FDA's guidance regarding "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 (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. If an application includes, for example, information on other products (e.g., published literature, marketing information) with appropriate bridging studies, FDA intends to review that information to determine whether it is valid scientific evidence sufficient to demonstrate that the marketing of a product would be APPH.** Nonclinical studies alone are generally not sufficient to support a determination that permitting the marketing of a tobacco product would be appropriate for the protection of the public health. **Nonetheless, in general, FDA does not expect that applicants will need to conduct long-term**

> **studies to support an application. 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.** 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[n application], 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.

Premarket Tobacco Product Applications for ENDS: Guidance for Industry, A204–05 (emphasis added) (footnotes omitted). To provide brief context on this language: The FDA acknowledged in 2018 that ENDS products may provide a beneficial alternative to combustible cigarettes because they deliver nicotine without also bombarding the user's lungs with the toxins found in cigarettes. *See Vapor Tech. Ass'n*, 977 F.3d at 499. The FDA has also recognized, however, that ENDS products particularly appeal to children, with high-school-age use of ENDS products increasing by over 75% from 2017 to 2018, and middle-school-age use increasing by almost 50% over that same period. *Am. Acad. of Pediatrics v. FDA*, 379 F. Supp. 3d 461, 467 (D. Md. 2019). Flavored ENDS products especially appeal to children: As of 2020, 84.7% of high school ENDS users and 73.9% of middle school ENDS users reported using flavored products. FDA Review of Breeze Smoke's Application, A12. And according to one study, over 80% of children aged 12-17 said that their first experience with ENDS involved a flavored product. *Id.*

This data brings into focus the problem facing the FDA: e-cigarettes offer potential health benefits, to the extent that they convince combustible-tobacco users to get their nicotine from e-cigarettes instead. But *flavored* e-cigarettes disproportionately appeal to children. The FDA, under a statutory obligation to approve only those products that are "appropriate for the protection of the public health," must determine whether applicants can show that their flavored ENDS product will benefit public health enough to outweigh this public-health detriment to children. *See* FDA Review of Breeze Smoke's Application, A9 (noting the importance of

considering whether "the flavored products have an added benefit relative to that of tobacco-flavored [e-cigarettes] in facilitating smokers completely switching away from or significantly reducing their smoking.").

Turning to this case's facts, Breeze Smoke contends that it followed the FDA's 2019 industry guidelines for submitting its Premarket Tobacco Product Applications. But the FDA denied Breeze Smoke's application, citing the lack of longitudinal cohort studies and randomized controlled trials and the insufficiency of the evidence provided, which included published literature, marketing information on other products, bridging studies, and its marketing plan, all of which Breeze Smoke believed comported with the earlier-issued guidance.

The FDA's denial of Breeze Smoke's application emphasized that the strong appeal of flavored ENDS products to youths required a showing of a "substantial enough" "magnitude of the likely benefit . . . to overcome the significant risk of youth uptake and use posed by the flavored ENDS product." FDA Review of Breeze Smoke's Application, A16; *see also id.*, A18 n.xxii. The FDA suggested that randomized control trials would present the strongest evidence of appropriateness for the public health. *Id.*, A17. The FDA then acknowledged that applicants theoretically could "rely on, and bridge to," data concerning general ENDS category literature. *Id.* But the FDA concluded that, based on the known risks that flavored ENDS products present to youths, Breeze Smoke's application did not demonstrate health benefits to adult smokers sufficient to overcome flavored products' appeal to youths. *Id.*, A21.

Breeze Smoke identifies four buckets of evidence that it submitted: (1) a literature review showing that ENDS use is less harmful than smoking tobacco combustibles, (2) information "bridging" its products to those evaluated in the literature, (3) a survey that Breeze Smoke conducted of its adult users that purported to show a preference for flavored products, and (4) information concerning Breeze Smoke's plan to avoid marketing its products to youth. Pet'r Br. at 7.

The Breeze Smoke literature review offers mixed findings on flavored ENDS products. *See* Breeze Smoke Lit. Review, A52 ("The use of food flavorings in e-liquids . . . need[s] more scientific study."), A69 (citing a study suggesting that adults who vape flavored e-cigarettes are

more likely subsequently to quit smoking than those who vape unflavored e-cigarettes), A70 (citing a separate study saying that users strongly prefer flavored e-cigarettes). Breeze Smoke argues that the literature review was meant to bridge to materials specifically concerning flavored products. Pet'r Br. at 7. But as the FDA noted in its denial of Breeze Smoke's application, the "clear and consistent patterns of real-world use" showing youth initiation of flavored ENDS products rendered this bridging insufficient. FDA Review of Breeze Smoke's Application, A17–18.

On this record, Breeze Smoke's survey presents methodological issues. The FDA's 2019 guidance suggested that applicants include studies "with robust rationale, acute toxicological endpoints or other clinical endpoints that may relate to long-term health impacts." Premarket Tobacco Product Applications for ENDS: Guidance for Industry, A205. Breeze Smoke's study, submitted via Google Form, contained responses from customers "solicited . . . by request in the retail stores." Breeze Smoke Lit. Review, A70. This suggests biased respondents. *See id.*, A73–77.

Considering all of Breeze Smoke's evidence, we disagree with Breeze Smoke, and with our colleagues on the Fifth Circuit, who say that the FDA orchestrated a "surprise switcheroo." *Wages & White Lion Invs., LLC v. FDA*, No. 21-60766, 2021 WL 4955257, at *5 (5th Cir. Oct. 26, 2021). The FDA said that, in light of the accelerated court-ordered deadline for submission of applications for new tobacco products, it *might* accept evidence other than long-term studies, if that evidence had sufficient scientific underpinnings to meet the TCA's statutory mandate of demonstrating that flavored ENDS devices are appropriate for the protection of public health. Premarket Tobacco Product Applications for ENDS: Guidance for Industry, A204 ("FDA intends to review that information"), A205 ("[I]nstead 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.") (emphasis added in this and following), A223 ("[I]t is *likely* that applicants will conduct certain investigations themselves and submit their own research findings as a part of their [application]."), A238 ("[I]f 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[n application]").

The FDA found Breeze Smoke's evidence lacking against this standard. *See* FDA Review of Breeze Smoke's Application, A18 (describing the results from bridging literature studies to flavored ENDS products as "quite mixed"). Breeze Smoke argues that the FDA's willingness to consider some forms of evidence, explicitly phrased as such, required the FDA to accept that evidence as meeting a statutory requirement even where the FDA found the evidence unsatisfactory. We decline to embrace that claim.

On this record, the FDA's 2019 language and its 2021 order likely did not fail to consider reliance interests, *see Regents*, 140 S. Ct. at 1914, and did not introduce a new standard of review in adjudication such that it likely deprived Breeze Smoke of fair warning, *see Christopher v. SmithKline Beecham Corp.*, 567 U.S. 142, 156–57 (2012). Additionally, the FDA correctly notes that Breeze Smoke's reliance on caselaw where an agency was not afforded deference because it acted contrary to longstanding precedent is inapposite because the FDA's 2019 guidance does not qualify as "longstanding."

The FDA's formulaic consideration of Breeze Smoke's youth marketing plan warrants further scrutiny. The FDA acknowledged in its denial of Breeze Smoke's application that the marketing plan, the strategy that a firm uses to avoid marketing flavored ENDS products to those under 21, "is a critical aspect of product regulation." FDA Review of Breeze Smoke's Application, A17 n.xix. The FDA called it "theoretically possible" that "significant" mitigation efforts could reduce flavored products' appeal to youths "such that the risk for youth initiation would be reduced." *Id.* The FDA then said that, because it had not yet seen an application that showed advertising restrictions that would significantly enough decrease youth use, it would not evaluate Breeze Smoke's proposal "at this stage of review" "for the sake of efficiency." *Id.*

The FDA likely should have more thoroughly considered Breeze Smoke's marketing plan. Agency action must consider "the relevant factors" when reaching a decision, and may not

"entirely fail[] to consider an important aspect" of the relevant regulatory task. *Motor Vehicle Mfrs. Ass'n of U.S., Inc. v. State Farm Mut. Auto. Ins. Co.*, 463 U.S. 29, 43 (1983). The FDA argues that it properly declined to consider Breeze Smoke's marketing strategy because "consideration of the specific marketing measures proposed in petitioner's application would not alter its analysis." FDA Br. at 18. It is not clear how the FDA could have known this. The FDA cites *Butte County v. Chaudhuri* for the proposition that an agency need not explicitly mention each piece of evidence, but there the agency's analysis cited countervailing evidence showing why it had rejected the allegedly ignored evidence. 887 F.3d 501, 509 (D.C. Cir. 2018). Here, by contrast, the FDA ignored the marketing plan entirely because prior marketing plans had not satisfied the agency.

Because Breeze Smoke bears the burden of showing a strong likelihood of success on the merits, and because the FDA likely properly concluded that Breeze Smoke failed to show that its products adequately protected the public health, described above, we still deny Breeze Smoke's motion for stay, even in light of the FDA's possibly insufficient consideration of Breeze Smoke's marketing plan. This oversight has not "permeated the entire [adjudication] process." *See Pub. Citizen v. Fed. Motor Carrier Safety Admin.*, 374 F.3d 1209, 1217 (D.C. Cir. 2004).

The FDA reasonably concluded that Breeze Smoke's application did not meet the TCA's requirements that new tobacco products be appropriate for the protection of the public health. The FDA cited well-developed evidence showing that flavored ENDS products' special appeal to youths harms the public health to a degree not outweighed by the (far-less-supported) effects of adult cigarette smokers switches to e-cigarettes. Breeze Smoke argues that the FDA deployed separate standards of review, considering literature that supported the thesis that flavored ENDS products pose special health risks to children and requiring Breeze Smoke present more than literature reviews to justify its products' public health benefits. Pet'r Br. at 18. But the FDA relied on literature concerning flavored ENDS products' appeal to youths because those risks are understood as a matter of scientific consensus. *See* Breeze Smoke Lit. Review, A66 ("There is **substantial evidence** that e-cigarette use increases risk of ever using combustible tobacco cigarettes among youth and young adults."); FDA Comm'r Speech, A171 ("we know" that "kid-appealing flavors in products like . . . ENDS . . . are a leading driver of youth smoking");

Enforcement Priorities for ENDS without Premarket Authorization Guidance for Industry, A272–78 (collecting data showing "substantial and increasing initiation of ENDS products by youth, particularly certain flavored, cartridge-based products" (on A278)). This differs sharply from an agency's "raw assertion that [two concepts] are different." *Cincinnati Bell Tel. Co. v. Fed. Commc'ns Comm'n*, 69 F.3d 752, 768 (6th Cir. 1995).

Because Breeze Smoke has not shown a strong likelihood of success on the merits, we need not consider the other stay factors. *Gonzales v. Nat'l Bd. of Med. Exam'rs*, 225 F.3d 620, 632 (6th Cir. 2000). We also need not consider the FDA's argument that, were we to grant a stay, Breeze Smoke would still lack the necessary authorization to market its products.

Accordingly, the motion for a stay is **DENIED**. The motion for leave to file an amicus brief is **GRANTED**.

DISSENT

KETHLEDGE, Circuit Judge, dissenting. I would grant the motion for a stay for substantially the reasons stated by the Fifth Circuit in *Wages & White Lion Invs., L.L.C. v. United States Food & Drug Admin.*, 2021 WL 4955257 (5th Cir. Oct. 26, 2021). The FDA essentially decided these applications *en masse* rather than individually; that case is thus materially identical to this one.

ENTERED BY ORDER OF THE COURT

Deborah S. Hunt, Clerk

APPENDIX B

U.S. FOOD & DRUG ADMINISTRATION

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

September 16, 2021

DENIAL

Breeze Smoke, LLC
Attention: Marc C. Sanchez, Esq
1717 S. Radcliffe Rd.
Portland, Oregon 97219

FDA Submission Tracking Number (STN): PM0000983, see Appendix A

Dear Mr. Sanchez:

We are denying marketing granted orders for the products identified in Appendix A. Refer to Appendix B for a list of amendments received in support of your applications.

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.[2] You may not cross-reference information submitted in the PMTA 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 survey data, this evidence is not sufficient to show a benefit to adult smokers of using these flavored ENDS because it does not

[1] Premarket Tobacco Product Application (PMTA) submitted under section 910 of the Federal Food, Drug, and Cosmetic Act (FD&C Act)
[2] See guidelines at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/tobacco-product-master-files

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.

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[3,4] using eSubmitter.[5] 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[6]; 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.

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

If you have any questions, please contact Sequoia Bacon, M.H.A, Regulatory Health Project Manager, at (301) 796-0736 or Sequoia.Bacon@fda.hhs.gov.

Sincerely,

Digitally signed by Matthew R. Holman -S
Date: 2021.09.16 19:51:32 -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 B – Amendment Received for These Applications

Appendix A[7]

New Tobacco Products Subject of This Letter

Attributes	
Submission date	September 4, 2020
Receipt date	September 4, 2020
Applicant	Breeze Smoke, LLC
Product manufacturer	Breeze Smoke, LLC
Product category	ENDS (VAPES)
Product subcategory	ENDS Component

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

STN	PD Number	Product Name	Category	Subcategory	Package Type	Package Quantity	Characterizing Flavor	Additional Property
PM0000983	PD1	Breeze Smoke Disposable Pod ENDS Banana Mint	ENDS(VAPES)	ENDS Component	E-CIGARETTE	1 E-Cigarette	BANANA MINT	Length 110 mm, Diameter 14 mm, Vol 3.5 mL, Salt Nicotine Concentration 5%, PG 35%, VG 45%, Battery capacity 650mAh
PM0000983	PD2	Breeze Smoke Disposable Pod ENDS Blueberry Lemon	ENDS(VAPES)	ENDS Component	E-CIGARETTE	1 E-Cigarette	BLUEBERRY LEMON	Length 110 mm, Diameter 14 mm, Vol 3.5mL, Salt Nicotine Concentration 5%, PG 44%, VG 45%, Battery capacity 650mAh
PM0000983	PD3	Breeze Smoke Disposable Pod ENDS Cola Mint	ENDS(VAPES)	ENDS Component	E-CIGARETTE	1 E-Cigarette	COLA MINT	Length 110 mm, Diameter 14 mm, Vol 3.5 mL, Salt Nicotine Concentration 5%, PG 39%, VG 45%, Battery capacity 650mAh
PM0000983	PD4	Breeze Smoke Disposable Pod ENDS Peach Mint	ENDS(VAPES)	ENDS Component	E-CIGARETTE	1 E-Cigarette	PEACH MINT	Length 110 mm, Diameter 14 mm, Vol 3.5 mL, Salt Nicotine Concentration 5%, PG 40%, VG 40%, Battery capacity 650mAh
PM0000983	PD5	Breeze Smoke Disposable Pod ENDS Mint	ENDS(VAPES)	ENDS Component	E-CIGARETTE	1 E-Cigarette	Mint	Length 110 mm, Diameter 14 mm, Vol 3.5 mL, Salt Nicotine Concentration 5%, PG 31%, VG 55%, Battery capacity 650mAh
PM0000983	PD7	Breeze Smoke Disposable Pod ENDS Watermelon Mint	ENDS(VAPES)	ENDS Component	E-CIGARETTE	1 E-Cigarette	WATERMELON MINT	Length 110 mm, Diameter 14 mm, Vol 3.5 mL, Salt Nicotine Concentration 5%, PG 38%, VG 40%, Battery capacity 650mAh
PM0000983	PD8	Breeze Smoke Disposable Pod ENDS Strawberry Cream Mint	ENDS(VAPES)	ENDS Component	E-CIGARETTE	1 E-Cigarette	STRAWBERRY CREAM	Length 110 mm, Diameter 14 mm, Vol 3.5 mL, Salt Nicotine Concentration 5%, PG 44%, VG 45%, Battery capacity 650mAh
PM0000983	PD9	Breeze Smoke Disposable Pod ENDS Pomegranate Berry Mint	ENDS(VAPES)	ENDS Component	E-CIGARETTE	1 E-Cigarette	POMEGRANATE BERRY MINT	Length 110 mm, Diameter 14 mm, Vol 3.5 mL, Salt Nicotine Concentration 5%, PG 36%, VG 45%, Battery capacity 650mAh
PM0000983	PD10	Breeze Smoke Disposable Pod ENDS Strawberry Mint	ENDS(VAPES)	ENDS Component	E-CIGARETTE	1 E-Cigarette	STRAWBERRY MINT	Length 110 mm, Diameter 14 mm, Vol 3.5 mL, Salt Nicotine Concentration 5%, PG 44%, VG 45%, Battery capacity 650mAH

Appendix B
Amendment Received for These Applications

Submission Date	Receipt Date	Applications being amended	Reviewed	Brief Description
July 8, 2021	July 8, 2021	PM0000983-PD-8	Yes	Correction or clarification to product characterizing flavor (Strawberry Cream Mint should be Strawberry Cream)

APPENDIX C

FDA U.S. FOOD & DRUG ADMINISTRATION

Technical Project Lead (TPL) Review of PMTAs

New Products Subject of this Review[i]	
Submission tracking numbers (STNs)	PM0000983, See Appendix A
Common Attributes	
Submission date	September 4, 2020
Receipt date	September 4, 2020
Applicant	Breeze Smoke LLC
Product manufacturer	Breeze Smoke LLC
Application type	Standard
Product category	ENDS (VAPES)
Product subcategory	ENDS Component
Recommendation	
Issue marketing denial orders for the new tobacco products subject of this review.	

Technical Project Lead (TPL):

Digitally signed by Cindy A. Tworek -S
Date: 2021.09.16 18:07:13 -04'00'

FOR: Amber R. Koblitz, PhD, MPH
Supervisory Social Scientist
Division of Population Health Science

Signatory Decision: Concur with TPL recommendation and basis of recommendation

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[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 September 17, 2020. FDA issued a Filing letter to the applicant on October 8, 2020.

Refer to Appendix B for a complete list of amendments received by FDA.

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

[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.

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 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

[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.

addiction. Indeed, almost 90 percent of adult daily smokers started smoking by the age of 18.[6] Adolescent tobacco users who initiated tobacco use at earlier ages were more likely than those initiating at older ages to report symptoms of tobacco dependence, putting them at greater risk for maintaining tobacco product use into adulthood.[7] On the other hand, youth and young adults who reach the age of 26 without ever starting to use cigarettes will most likely never become a daily smoker.[6] Because of the lifelong implications of nicotine dependence that can be established in youth, preventing tobacco use initiation in young people is a central priority for protecting population health.

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,

[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.

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]

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]

[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."

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 as 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

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

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 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.

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

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.

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

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

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.

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

[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.

[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.

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

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

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

[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.

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

3. SCIENTIFIC REVIEW

Reviews were completed by Elyse Moreau and Maria Cooper on September 16, 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 survey data, 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 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 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 survey data, 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 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[xxvi]. New Products

Attributes	
Submission date	September 4, 2020
Receipt date	September 4, 2020
Applicant	Breeze Smoke, LLC
Product manufacturer	Breeze Smoke, LLC
Product category	ENDS (VAPES)
Product subcategory	ENDS Component

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

STN	PD Number	Product Name	Category	Subcategory	Package Type	Package Quantity	Characterizing Flavor	Additional Property
PM0000983	PD1	Breeze Smoke Disposable Pod ENDS Banana Mint	ENDS(VAPES)	ENDS Component	E-CIGARETTE	1 E-Cigarette	BANANA MINT	Length 110 mm, Diameter 14 mm, Vol 3.5 mL, Salt Nicotine Concentration 5%, PG 35%, VG 45%, Battery capacity 650mAh
PM0000983	PD2	Breeze Smoke Disposable Pod ENDS Blueberry Lemon	ENDS(VAPES)	ENDS Component	E-CIGARETTE	1 E-Cigarette	BLUEBERRY LEMON	Length 110 mm, Diameter 14 mm, Vol 3.5mL, Salt Nicotine Concentration 5%, PG 44%, VG 45%, Battery capacity 650mAh
PM0000983	PD3	Breeze Smoke Disposable Pod ENDS Cola Mint	ENDS(VAPES)	ENDS Component	E-CIGARETTE	1 E-Cigarette	COLA MINT	Length 110 mm, Diameter 14 mm, Vol 3.5 mL, Salt Nicotine Concentration 5%, PG 39%, VG 45%, Battery capacity 650mAh
PM0000983	PD4	Breeze Smoke Disposable Pod ENDS Peach Mint	ENDS(VAPES)	ENDS Component	E-CIGARETTE	1 E-Cigarette	PEACH MINT	Length 110 mm, Diameter 14 mm, Vol 3.5 mL, Salt Nicotine Concentration 5%, PG 40%, VG 40%, Battery capacity 650mAh
PM0000983	PD5	Breeze Smoke Disposable Pod ENDS Mint	ENDS(VAPES)	ENDS Component	E-CIGARETTE	1 E-Cigarette	Mint	Length 110 mm, Diameter 14 mm, Vol 3.5 mL, Salt Nicotine Concentration 5%, PG 31%, VG 55%, Battery capacity 650mAh
PM0000983	PD7	Breeze Smoke Disposable Pod ENDS Watermelon Mint	ENDS(VAPES)	ENDS Component	E-CIGARETTE	1 E-Cigarette	WATERMELON MINT	Length 110 mm, Diameter 14 mm, Vol 3.5 mL, Salt Nicotine Concentration 5%, PG 38%, VG 40%, Battery capacity 650mAh
PM0000983	PD8	Breeze Smoke Disposable Pod ENDS Strawberry Cream Mint	ENDS(VAPES)	ENDS Component	E-CIGARETTE	1 E-Cigarette	STRAWBERRY CREAM	Length 110 mm, Diameter 14 mm, Vol 3.5 mL, Salt Nicotine Concentration 5%, PG 44%, VG 45%, Battery capacity 650mAh
PM0000983	PD9	Breeze Smoke Disposable Pod ENDS Pomegranate Berry Mint	ENDS(VAPES)	ENDS Component	E-CIGARETTE	1 E-Cigarette	POMEGRANATE BERRY MINT	Length 110 mm, Diameter 14 mm, Vol 3.5 mL, Salt Nicotine Concentration 5%, PG 36%, VG 45%, Battery capacity 650mAh
PM0000983	PD10	Breeze Smoke Disposable Pod ENDS Strawberry Mint	ENDS(VAPES)	ENDS Component	E-CIGARETTE	1 E-Cigarette	STRAWBERRY MINT	Length 110 mm, Diameter 14 mm, Vol 3.5 mL, Salt Nicotine Concentration 5%, PG 44%, VG 45%, Battery capacity 650mAH

Appendix B. Amendments Received

Submission Date	Receipt Date	Applications being amended	Reviewed	Brief Description
July 8, 2021	July 8, 2021	PM0000983-PD-8	Yes	Correction or clarification to product characterizing flavor (Strawberry Cream Mint should be Strawberry Cream)

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APPENDIX D

DECLARATION OF STEVEN HADDAD IN SUPPORT OF BREEZE SMOKE'S APPLICATION FOR STAY

I, Steven Haddad, declare as follows:

1. I am employed by Breeze Smoke LLC ("Breeze Smoke"), where I have worked since September 2020. I am currently the Managing Member of Breeze Smoke. I am responsible for overseeing the manufacturing and quality control of production, purchasing, sales, accounting, and managing inventory levels. I also must stay informed regarding regulatory decisions and analyze how those decisions impact Breeze Smoke's financial outlook.

2. I am competent to testify regarding the matters set forth in this declaration, which are based on my knowledge and personal experience, as well as information provided to me by others at Breeze Smoke in the course of my employment.

I. THE IMPORTANCE OF ENDS PRODUCTS TO BREEZE SMOKE'S BUSINESS

3. Breeze Smoke is a Limited Liability Corporation and a manufacturer, marketer and distributor of electronic-nicotine-delivery-system ("ENDS") products. Breeze Smoke started selling products in May 2019.

4. Breeze Smoke markets disposable pod-based ENDS devices, which come in multiple different flavors. Breeze Smoke markets its ENDS devices exclusively to adults as providing a convenient way for adult smokers to switch from traditional combustion cigarettes. Breeze Smoke sells its products directly to retail stores and through authorized distributors.

5. Breeze Smoke is committed to preventing the sale and distribution of its ENDS products to underage users. Breeze Smoke works hard to comply with all federal and state regulation to prevent sales to minors. Breeze Smoke offers free print materials to partners at retail stores and Authorized Distributors regarding the rules of sales of ENDS products, including stickers, pamphlets, and educational signs. These free print materials are intended to educate retail stores and Authorized Distributors regarding safety measures they should use in sales of ENDS products, including checking the photo ID of everyone under the age of 27 who attempts to purchase Breeze Smoke products; selling products only to customers who are 21 and older; not selling products in a vending machine unless in an adult-only facility; and not giving away free samples. Breeze Smoke does not use cartoons or other designs in marketing materials that could be seen as attracting minors. Breeze Smoke also does not use social media influencers, celebrities, or other influential persons to promote its products. Furthermore, Breeze Smoke advertises that its products are only intended for adult smokers of legal purchase age, and not appropriate for underage individuals, former smokers, or people who have never smoked.

6. In 2020, Breeze Smoke's annual revenue was $63,228,022 and net profit was $22,514,239. Last year, the gross revenue generated by products covered by the U.S. Food and Drug Administration's ("FDA") September 16, 2021 marketing denial order ("Order") was roughly $36,000,000, making up 57% of Breeze Smoke's

gross revenue for the year. Breeze Smoke's entire business is comprised of its ENDS products.

II. BREEZE SMOKE DEVELOPED ITS PMTAS BASED ON FDA GUIDANCE, BUT FDA ISSUED A MARKETING DENIAL ORDER AFTER IMPOSING NEW REQUIREMENTS FOR APPROVAL

A. Breeze Smoke's Understanding of FDA Requirements

7. When Breeze Smoke began marketing its ENDS products, the FDA had not yet established a process for reviewing PMTAs for this product category. ENDS products were not originally subject to premarketing review when Congress enacted legislation providing the FDA with authority to regulate tobacco products.[1] When the FDA subsequently "deemed" that ENDS products should be regulated as tobacco products, it announced that it would exercise its enforcement discretion to allow ENDS products to remain on the market while FDA developed rules for ENDS product PMTAs and then actually processed those PMTAs.[2]

8. FDA issued final guidance in June 2019 titled, *Premarket Tobacco Product Applications for Electronic Nicotine Delivery Systems: Guidance for Industry*, stating, "[I]n general, FDA does not expect that applicants will need to conduct long-term studies to support an application."[3] FDA reiterated this position in a notice of proposed rulemaking issued on September 25, 2019, explaining that

[1] *The Family Smoking Prevention and Tobacco Control Act of 2009* (TCA), 21 U.S.C. § 387 *et seq*.

[2] 81 Fed. Reg. 28,974, 28,977-78 (May 10, 2016).

[3] FDA, *Premarket Tobacco Product Applications for Electronic Nicotine Delivery Systems: Guidance for Industry* (June 2019), at 12-13.

the agency 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."[4]

9. FDA guidance on the timing for its review of PMTAs for ENDS products has shifted over time. In August 2017, FDA issued guidance providing for a phase-in period of until August 2022 before ENDS products would face potential enforcement of PMTA requirements.[5] The guidance further specified that the FDA did not intend to prioritize enforcement of the PMTA requirements "until the agency renders a decision on [the manufacturer's] application … or the application is withdrawn."[6] In the midst of litigation, and following an adverse order from a district court in Maryland,[7] FDA issued new guidance in January 2020.[8] It set a PMTA compliance deadline for May 2020, and indicated that the agency would prioritize enforcement of any ENDS product offered for sale after that date for which a manufacturer had not submitted a PMTA or had received a negative action from FDA on a timely submitted application.[9] The May 2020 deadline was

[4] *Premarket Tobacco Product Applications and Recordkeeping Requirements*, 84 Fed. Reg. 50,556, 50,619 (Sept. 25, 2019).

[5] FDA, *Extension of Certain Tobacco Product Compliance Deadlines Related to the Final Deeming Rule: Guidance for Industry* (Aug. 2017) at 5, 10.

[6] *Id.* at 3.

[7] *Am. Acad. of Pediatrics v. FDA*, 379 F. Supp. 3d 461 (D. Md. 2019).

[8] FDA, *Enforcement Priorities for Electronic Nicotine Delivery Systems (ENDS) and Other Deemed Products on the Market Without Premarket Authorization* (Revised) (orig. Jan. 2020, rev'd Apr. 2020) at 31.

[9] *Id.* at 5, 27.

subsequently extended until September 9, 2020, in light of the COVID-19 pandemic.[10]

B. Breeze Smoke's PMTAs

10. Breeze Smoke developed its PMTAs by relying 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, Breeze Smoke relied on FDA's advice that each manufacturer was not required to conduct its own product-specific, long-term studies. Instead, consistent with FDA's guidance, Breeze Smoke supplied studies from the background literature along with appropriate bridging information.

11. Breeze Smoke submitted its PMTAs on September 3, 2020, complying with the FDA deadline for submission by September 9, 2020. Breeze Smoke submitted PMTAs to FDA covering ten ENDS products with different flavors, all of which are disposable pod-based devices. Breeze Smoke has separately submitted PMTAs for a separate line of products titled "Breeze Pro." The Breeze Pro line of products is not at issue here.

12. Based on FDA guidance, Breeze Smoke submitted PMTAs that were tens of thousands of pages in length, and which included reports of scientific studies and consumer research. Preparing Breeze Smoke's various PMTAs cost approximately $11.25 million for the company to develop and file, with expenses incurred on outside scientific consultants as well as legal counsel.

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[10] FDA, *Enforcement Priorities for Electronic Nicotine Delivery Systems (ENDS) and Other Deemed Products on the Market Without Premarket Authorization (Revised)* (Apr. 2020) (orig. Jan 2020, rev'd Apr. 2020) at 11, 31-33.

13. Breeze Smoke's PMTAs included a robust review of the literature on the benefits of ENDS products. The literature review included several comprehensive studies that spanned several years.[11] For example, Breeze Smoke included a study from the Journal of American Medical Association's Network Open titled "Associations of Flavored e-Cigarette Uptake With Subsequent Smoking Initiation and Cessation" involving 17,929 participants, which concluded that "[r]elative to vaping tobacco flavors, vaping nontobacco-flavored e-cigarettes was not associated with increased youth smoking initiation but was associated with an increase in the odds of adult smoking cessation."[12] Breeze Smoke also included two surveys from the Consumer Advocates for Smoke-Free Alternatives Association. The first surveyed 8,500 respondents and concluded that "the longer a person vapes, the less likely they are to continue to smoke."[13] The second had over 7,000 respondents and showed the majority of individuals who vaped and smoked cigarettes stopped use of cigarettes within two years of beginning to vape.[14]

14. Breeze Smoke also conducted its own survey in retail stores, receiving 164 customer responses.[15] Respondents overwhelmingly found vaping products helpful in keeping them from smoking cigarettes,[16] and specifically reported that

[11] C.A. App. 179-180.

[12] C.A. App. 187-188.

[13] C.A. App. 189.

[14] *Id.*

[15] *Id.*

[16] C.A. App. 190.

"flavored e-liquids were important to them in choosing to vape instead of smoke cigarettes."[17]

15. Breeze Smoke also provided a Competitive Survey Analysis and Regulatory Review of competitor products, summarizing the FDA Warning Letters related to marketed practices aimed at appealing to minors.[18] Breeze Smoke conducted this analysis to ensure that Breeze Smoke's marketing practices would help to prevent unlawful youth access. Breeze Smoke also described the preemptive steps it was taking to minimize the attractiveness of its products to minors, including with regard to product labeling, product naming, and product marketing.[19]

16. Breeze Smoke included information about the process controls and quality assurance procedures to ensure that Breeze Smoke ENDS are manufactured consistently to specification. Breeze Smoke engaged with Avomeen, LLC, an FDA registered lab performing analytical testing for PMTAs. The Avomeen testing confirmed that the toxicological profile of Breeze Smoke ENDS are essentially identical and indicate a potential benefit compared to combustible cigarettes.

C. FDA Issues a Marketing Denial Order

17. On September 17, 2020, FDA informed Breeze Smoke that it had received the company's application, and on October 8, 2020, FDA further notified Breeze Smoke that its applications satisfied the applicable filing requirements. On

[17] C.A. App. 191.

[18] C.A. App. 157.

[19] C.A. App. 166-167.

January 5, 2021, FDA informed Breeze Smoke that its PMTAs would move forward in the review process. On August 19, 2021, FDA informed Breeze Smoke that its products had entered a scientific review.

18. On September 16, 2021, FDA issued the Order in which it concluded that Breeze Smoke's "new products . . . lack sufficient evidence to demonstrate that the marketing of these products is appropriate for the protection of public health."[20] The Order addressed nine of Breeze Smoke's ten flavored products in its September 3, 2020 submission, with a tobacco-flavored disposal ENDS product remaining under review.

19. The Order faulted Breeze Smoke for failing to include "robust and reliable evidence . . . regarding the magnitude of the potential benefit to adult smokers."[21] The Order stated that such evidence "could have been provided using a randomized controlled trial and/or longitudinal cohort study that demonstrated the benefit of [Breeze Smoke's] flavored ENDS products over an appropriate comparator tobacco-flavored ENDS."[22]

20. Under the FDA's guidance, Breeze Smoke had no reason to believe that randomized controlled trials or longitudinal cohort studies were necessary to secure PMTA approval and thus to avoid adverse enforcement consequences. If FDA had provided Breeze Smoke with notice that such studies were necessary, then Breeze Smoke would have made the additional investment needed to conduct those studies and still stands ready to do so. Breeze Smoke was at all times willing to

[20] Application, Ex. B, at 1.
[21] *Id.* at 2.
[22] *Id.*

work cooperatively with FDA to address any perceived deficiencies with its PMTAs, but FDA did not identify any such deficiencies until it issued the Order denying Breeze Smoke's PMTAs for failure to comply with previously undisclosed requirements.

21. In the Order denying Breeze Smoke's PMTAs, FDA instructed Breeze Smoke that it "cannot introduce or deliver for introduction these products into interstate commerce in the United States."[23] FDA stated that failure to comply "may result in FDA regulatory action ***without further notice***"[24] (emphasis added), including civil money penalties, seizure or injunction.

22. It is my understanding that, since August 2021, FDA has issued several hundred market denial orders ("MDOs") for over a million ENDS products. These MDOs appear to derive from a standard form, as my understanding is that the FDA has generally premised its denial orders on the same new requirements for robust studies such as randomized controlled trial or longitudinal cohort studies to show the benefits of access to flavored ENDS products for adult users.

23. It is my understanding that many PMTAs remain pending before the FDA, including the applications of market leaders, such as Juul. These products remain on the market pending FDA review.

24. It is also my understanding that the MDO issued against Wages & White Lion Investments d/b/a Triton Distribution ("Triton") has been stayed by the Fifth Circuit. Triton is a significant competitor to Breeze Smoke. It is my

[23] *Id.* at 1.
[24] *Id.* at 2.

understanding that as a result of the Fifth Circuit's stay order, Triton's products remain on the market.

III. BREEZE SMOKE IS SUFFERING IMMEDIATE, IRREPARABLE INJURY BY VIRTUE OF THE ORDER

25. The Order is already irreparably harming Breeze Smoke by impairing its relationships with existing distributors, retailers and customers, as well as by preventing Breeze Smoke from obtaining new distributors, retailers and customers. Absent a stay of the Order, Breeze Smoke will continue to suffer injuries that would not be remediated even if it prevails in its challenge to the Order.

26. First, Breeze Smoke is already losing contracts with its existing distributors. For example, Breeze Smoke's largest distributor cancelled $900,000 worth of orders immediately following notice of the Order, and other distributors have followed suit. Furthermore, distributors have not made any additional orders of Breeze Smoke products since the MDO. In my experience, once distributors reach agreement with other ENDS competitors, it will be extremely difficult for Breeze Smoke to regain that business. Furthermore, Breeze Smoke is unable to enter partnerships with any additional distributors.

27. Second, Breeze Smoke is losing business with current retailers. Breeze Smoke's retailer customers have told me that since the Order issued, Breeze Smoke competitors like Juul have tried to persuade the retailers to replace inventory of Breeze Smoke products with their own competing products. Retailers are now hesitant to carry Breeze Smoke Products. In fact, retailers are putting signs in store fronts targeted to Breeze Smoke customers saying they will no longer carry

any Breeze Smoke products.[25] It is my understanding that competitors like Juul remain able to sell their products, including products with flavors other than tobacco, by virtue of the fact that FDA has not issued decisions on all submitted PMTAs. It is also my understanding that competitors like Triton remain able to sell their products, including products with flavors other than tobacco, by virtue of the fact that certain Courts of Appeals have stayed the MDOs issued against their respective products. I have no reason to believe that these competitors are otherwise differently situated from Breeze Smoke.

28. Third, Breeze Smoke's customers are switching to similar products offered by other brands and will continue to do so. Once customers go with a new product, it is difficult to recapture customer loyalty.

29. Breeze Smoke has taken action to cease the manufacturing of all its ENDS products in order to comply with the Order. Breeze Smoke is incurring significant costs from stopping manufacturing and will be unable to recover those costs at the end of litigation.

30. Furthermore, as Breeze Smoke is forced out of the market, competitors such as Juul and Triton are seizing Breeze Smoke's market share, and in my experience, it will be very difficult to convert lost market share back to Breeze Smoke's products.

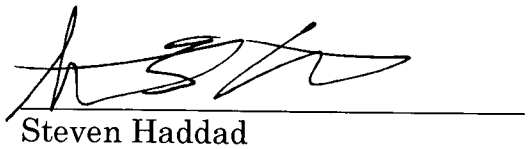
31. Absent a stay, the Order will force Breeze Smoke to lay off employees. Breeze Smoke directly employs three people. Breeze Smoke previously had eight

[25] A true and correct copy of one such sign is attached as Exhibit A to this Declaration.

independent contractors, but due to the Order, they have all had to stop working for Breeze Smoke. The possibility for Breeze Smoke to re-engage these independent contractors diminishes with the passage of time, adding to the urgency of obtaining relief from the Order.

I declare under penalties of perjury that the foregoing is true and correct.

Executed on November 18, 2021



Steven Haddad

APPENDIX E

Exhibit E: Petitions for Review of Marketing Denial Orders for ENDS Devices Before United States Courts of Appeals, By Circuit

Second Circuit

Magellan Tech., Inc. v. FDA, No. 21-2426 (2d Cir. Sept. 24, 2021).

Third Circuit

Liquid Labs LLC v. FDA, No. 21-2883 (3d Cir. Oct. 12, 2021).

Fourth Circuit

Avail Vapor, LLC v. FDA, No. 21-2077 (4th Cir. Sept. 30, 2021).

Bad Modder Fogger, LLC v. FDA, No. 21-2082 (4th Cir. Oct. 4, 2021).

E-Liquid Brands, LLC v. FDA, Nos. 21-2121, -2122, -2123, -2154, -2255, -2256 (4th Cir. Oct. 7, 2021, Oct. 13, 2021).[1]

Fifth Circuit

STW Global Supply, Inc. v. FDA, No. 21-60762 (5th Cir. Oct. 1, 2021).

Wages & White Lion Invs., LLC v. FDA, No. 21-60766 (5th Cir. Oct. 5, 2021) (stay granted on Oct. 26, 2021).

Cloud House LLC v. FDA, No. 21-60777 (5th Cir. Oct. 8, 2021).

Paradigm Distribution v. FDA, No. 21-60778 (5th Cir. Oct. 11, 2021).

Vaporized, Inc. v. FDA, No. 21-60779 (5th Cir. Oct. 11, 2021).

New World Wholesale Inc. v. FDA, No. 21-60780 (5th Cir. Oct. 11, 2021).

SV Packaging v. FDA, No. 21-60801 (5th Cir. Oct. 18, 2021).

Beard Vape Co. v. FDA, No. 21-60803 (5th Cir. Oct. 18, 2021).

Sixth Circuit

Turning Point Brands, Inc., et al v. FDA, No. 21-3855 (6th Cir. Sept. 23, 2021) (voluntary dismissal granted on Oct. 13, 2021).

[1] E-Liquids Brands, LLC has filed six separate petitions for review—one petition on its own behalf and five petitions as successor in interest of various companies that produce ENDS devices and have received a Marketing Denial Order from the FDA.

Breeze Smoke, LLC v. FDA, No. 21-3902 (6th Cir. Oct. 4, 2021) (stay denied on Nov. 12, 2021).

Simple Vapor Co. v. FDA, No. 21-3922 (6th Cir. Oct. 12, 2021).

Seventh Circuit

Gripum LLC v. FDA, No. 21-2840 (7th Cir. Oct. 8, 2021) (stay granted on Nov. 4, 2021).

Ninth Circuit

My Vape Order, Inc. v. FDA, No. 21-71302 (9th Cir. Sept. 30, 2021) (stay denied on Oct. 28, 2021).

7 Daze LLC v. FDA, No. 21-71319 (9th Cir. Oct. 7, 2021).

Nude Nicotine Inc. v. FDA, No. 21-71321 (9th Cir. Oct. 7, 2021).

Fumizer, LLC v. FDA, No. 21-71315 (9th Cir. Oct. 14, 2021).

Humble Juice Co. v. FDA, No. 21-71326 (9th Cir. Oct. 14, 2021) (voluntary dismissal granted on Nov. 22, 2021) .

Lotus Vaping Techs., LLC v. FDA, No. 21-71328 (9th Cir. Oct. 14, 2021).

Tenth Circuit

Electric Clouds v. FDA, No. 21-9577 (10th Cir. Oct. 8, 2021).

Cloud 9 Vapor Products LLC v. FDA, No. 21-9578 (10th Cir. Oct. 8, 2021).

Eleventh Circuit

Bidi Vapor LLC v. FDA, No. 21-13340 (11th Cir. Sept. 29, 2021).

Diamond Vapors, LLC v. FDA, No. 21-13387 (11th Cir. Oct. 1, 2021).

Johnny Cooper LLC v. FDA, No. 21-13438 (11th Cir. Oct. 7, 2021).

Vapor Unlimited LLC v. FDA, No. 21-13454 (11th Cir. Oct. 8, 2021).

Union Street Brands LLC v. FDA, No. 21-13521 (11th Cir. Oct. 15, 2021).

Pop Vapor Co. v. FDA, No. 21-13522 (11th Cir. Oct. 15, 2021).

Vapornine LLC v. FDA, No. 21-13523 (11th Cir. Oct. 15, 2021).

D.C. Circuit

ECS Global LLC v. FDA, No. 21-1200 (D.C. Cir. Oct. 12, 2021).

Prohibition Juice Co. v. FDA, No. 21-1201 (D.C. Cir. Oct. 13, 2021).

ECig Charleston LLC v. FDA, No. 21-1203 (D.C. Cir. Oct. 15, 2021).

Cool Breeze Vapor LLC v. FDA, No. 21-1205 (D.C. Cir. Oct. 15, 2021).

Jay Shore Liquids LLC v. FDA, No. 21-1207 (D.C. Cir. Oct. 18, 2021).

APPENDIX F

STATUTORY PROVISIONS

United States Code Annotated
Title 21. Food and Drugs (Refs & Annos)
Chapter 9. Federal Food, Drug, and Cosmetic Act (Refs & Annos)
Subchapter IX. Tobacco Products (Refs & Annos)

21 U.S.C.A. § 387a

§ 387a. FDA authority over tobacco products

Effective: June 22, 2009
Currentness

(a) In general

Tobacco products, including modified risk tobacco products for which an order has been issued in accordance with section 387k of this title, shall be regulated by the Secretary under this subchapter and shall not be subject to the provisions of subchapter V.

(b) Applicability

This subchapter shall apply to all cigarettes, cigarette tobacco, roll-your-own tobacco, and smokeless tobacco and to any other tobacco products that the Secretary by regulation deems to be subject to this subchapter.

(c) Scope

(1) In general

Nothing in this subchapter, or any policy issued or regulation promulgated thereunder, or in sections 101(a), 102, or 103 of Title I, Title II, or Title III of the Family Smoking Prevention and Tobacco Control Act, shall be construed to affect, expand, or limit the Secretary's authority over (including the authority to determine whether products may be regulated), or the regulation of, products under this chapter that are not tobacco products under subchapter V or any other subchapter.

(2) Limitation of authority

(A) In general

The provisions of this subchapter shall not apply to tobacco leaf that is not in the possession of a manufacturer of tobacco products, or to the producers of tobacco leaf, including tobacco growers, tobacco warehouses, and tobacco grower cooperatives, nor shall any employee of the Food and Drug Administration have any authority to enter onto a farm owned by a producer of tobacco leaf without the written consent of such producer.

(B) Exception

Notwithstanding subparagraph (A), if a producer of tobacco leaf is also a tobacco product manufacturer or controlled by a tobacco product manufacturer, the producer shall be subject to this subchapter in the producer's capacity as a manufacturer. The exception in this subparagraph shall not apply to a producer of tobacco leaf who grows tobacco under a contract with a tobacco product manufacturer and who is not otherwise engaged in the manufacturing process.

(C) Rule of construction

Nothing in this subchapter shall be construed to grant the Secretary authority to promulgate regulations on any matter that involves the production of tobacco leaf or a producer thereof, other than activities by a manufacturer affecting production.

(d) Rulemaking procedures

Each rulemaking under this subchapter shall be in accordance with chapter 5 of Title 5. This subsection shall not be construed to affect the rulemaking provisions of section 102(a) of the Family Smoking Prevention and Tobacco Control Act.

(e) Center for Tobacco Products

Not later than 90 days after June 22, 2009, the Secretary shall establish within the Food and Drug Administration the Center for Tobacco Products, which shall report to the Commissioner of Food and Drugs in the same manner as the other agency centers within the Food and Drug Administration. The Center shall be responsible for the implementation of this subchapter and related matters assigned by the Commissioner.

(f) Office to assist small tobacco product manufacturers

The Secretary shall establish within the Food and Drug Administration an identifiable office to provide technical and other nonfinancial assistance to small tobacco product manufacturers to assist them in complying with the requirements of this chapter.

(g) Consultation prior to rulemaking

Prior to promulgating rules under this subchapter, the Secretary shall endeavor to consult with other Federal agencies as appropriate.

CREDIT(S)

(June 25, 1938, c. 675, § 901, as added Pub.L. 111-31, Div. A, Title I, § 101(b)(3), June 22, 2009, 123 Stat. 1786.)

21 U.S.C.A. § 387a, 21 USCA § 387a
Current through PL 117-57.

End of Document

United States Code Annotated
Title 21. Food and Drugs (Refs & Annos)
Chapter 9. Federal Food, Drug, and Cosmetic Act (Refs & Annos)
Subchapter IX. Tobacco Products (Refs & Annos)

21 U.S.C.A. § 387j

§ 387j. Application for review of certain tobacco products

Effective: June 22, 2009
Currentness

(a) In general

(1) New tobacco product defined

For purposes of this section the term "new tobacco product" means--

(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.

(2) Premarket review required

(A) New products

An order under subsection (c)(1)(A)(i) for a new tobacco product is required unless--

(i) the manufacturer has submitted a report under section 387e(j) of this title; and the Secretary has issued an order that the tobacco product--

(I) is substantially equivalent to a tobacco product commercially marketed (other than for test marketing) in the United States as of February 15, 2007; and

(II) is in compliance with the requirements of this chapter; or

(ii) the tobacco product is exempt from the requirements of section 387e(j) of this title pursuant to a regulation issued under section 387e(j)(3) of this title.

(B) Application to certain post-February 15, 2007, products

Subparagraph (A) shall not apply to a tobacco product--

(i) that was first introduced or delivered for introduction into interstate commerce for commercial distribution in the United States after February 15, 2007, and prior to the date that is 21 months after June 22, 2009; and

(ii) for which a report was submitted under section 387e(j) of this title within such 21-month period,

except that subparagraph (A) shall apply to the tobacco product if the Secretary issues an order that the tobacco product is not substantially equivalent.

(3) Substantially equivalent defined

(A) In general

In this section and section 387e(j) of this title, the term "substantially equivalent" or "substantial equivalence" means, with respect to the tobacco product being compared to the predicate tobacco product, that the Secretary by order has found that the tobacco product--

(i) has the same characteristics as the predicate tobacco product; or

(ii) has different characteristics and the information submitted contains information, including clinical data if deemed necessary by the Secretary, that demonstrates that it is not appropriate to regulate the product under this section because the product does not raise different questions of public health.

(B) Characteristics

In subparagraph (A), the term "characteristics" means the materials, ingredients, design, composition, heating source, or other features of a tobacco product.

(C) Limitation

A tobacco product may not be found to be substantially equivalent to a predicate tobacco product that has been removed from the market at the initiative of the Secretary or that has been determined by a judicial order to be misbranded or adulterated.

(4) Health information

(A) Summary

As part of a submission under section 387e(j) of this title respecting a tobacco product, the person required to file a premarket notification under such section shall provide an adequate summary of any health information related to the tobacco product or state that such information will be made available upon request by any person.

(B) Required information

Any summary under subparagraph (A) respecting a tobacco product shall contain detailed information regarding data concerning adverse health effects and shall be made available to the public by the Secretary within 30 days of the issuance of a determination that such tobacco product is substantially equivalent to another tobacco product.

(b) Application

(1) Contents

An application under this section shall contain--

(A) full reports of all information, published or known to, or which should reasonably be known to, the applicant, concerning investigations which have been made to show the health risks of such tobacco product and whether such tobacco product presents less risk than other tobacco products;

(B) a full statement of the components, ingredients, additives, and properties, and of the principle or principles of operation, of such tobacco product;

(C) a full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and, when relevant, packing and installation of, such tobacco product;

(D) an identifying reference to any tobacco product standard under section 387g of this title 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.

(2) Referral to Tobacco Products Scientific Advisory Committee

Upon receipt of an application meeting the requirements set forth in paragraph (1), the Secretary--

(A) may, on the Secretary's own initiative; or

(B) may, upon the request of an applicant,

refer such application to the Tobacco Products Scientific Advisory Committee for reference and for submission (within such period as the Secretary may establish) of a report and recommendation respecting the application, together with all underlying data and the reasons or basis for the recommendation.

(c) Action on application

(1) Deadline

(A) In general

As promptly as possible, but in no event later than 180 days after the receipt of an application under subsection (b), the Secretary, after considering the report and recommendation submitted under subsection (b)(2), shall--

(i) issue an order that the new product may be introduced or delivered for introduction into interstate commerce if the Secretary finds that none of the grounds specified in paragraph (2) of this subsection applies; or

(ii) issue an order that the new product may not be introduced or delivered for introduction into interstate commerce if the Secretary finds (and sets forth the basis for such finding as part of or accompanying such denial) that 1 or more grounds for denial specified in paragraph (2) of this subsection apply.

(B) Restrictions on sale and distribution

An order under subparagraph (A)(i) 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 387f(d) of this title.

(2) Denial of application

The Secretary shall deny an application submitted under subsection (b) if, upon the basis of the information submitted to the Secretary as part of the application and any other information before the Secretary with respect to such tobacco product, the Secretary finds that--

(A) 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;

(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 387f(e) of this title;

(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 387g of this title, and there is a lack of adequate information to justify the deviation from such standard.

(3) Denial information

Any denial of an application shall, insofar as the Secretary determines to be practicable, be accompanied by a statement informing the applicant of the measures required to remove such application from deniable form (which measures may include further research by the applicant in accordance with 1 or more protocols prescribed by the Secretary).

(4) Basis for finding

For purposes of this section, the finding as to whether the marketing of a tobacco product for which an application has been submitted is appropriate for the protection of the public health shall 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.

(5) Basis for action

(A) Investigations

For purposes of paragraph (2)(A), whether permitting a tobacco product to be marketed would be appropriate for the protection of the public health shall, when appropriate, be determined on the basis of well-controlled investigations, which may include 1 or more clinical investigations by experts qualified by training and experience to evaluate the tobacco product.

(B) Other evidence

If the Secretary determines that there exists valid scientific evidence (other than evidence derived from investigations described in subparagraph (A)) which is sufficient to evaluate the tobacco product, the Secretary may authorize that the determination for purposes of paragraph (2)(A) be made on the basis of such evidence.

(d) Withdrawal and temporary suspension

(1) In general

The Secretary shall, upon obtaining, where appropriate, advice on scientific matters from the Tobacco Products Scientific Advisory Committee, and after due notice and opportunity for informal hearing for a tobacco product for which an order was issued under subsection (c)(1)(A)(i), issue an order withdrawing the order if the Secretary finds--

(A) that the continued marketing of such tobacco product no longer is appropriate for the protection of the public health;

(B) that the application contained or was accompanied by an untrue statement of a material fact;

(C) that the applicant--

(i) has failed to establish a system for maintaining records, or has repeatedly or deliberately failed to maintain records or to make reports, required by an applicable regulation under section 387i of this title;

(ii) has refused to permit access to, or copying or verification of, such records as required by section 374 of this title; or

(iii) has not complied with the requirements of section 387e of this title;

(D) on the basis of new information before the Secretary with respect to such tobacco product, evaluated together with the evidence before the Secretary when the application was reviewed, that the methods used in, or the facilities and controls used for, the manufacture, processing, packing, or installation of such tobacco product do not conform with the requirements of section 387f(e) of this title and were not brought into conformity with such requirements within a reasonable time after receipt of written notice from the Secretary of nonconformity;

(E) on the basis of new information before the Secretary, evaluated together with the evidence before the Secretary when the application was reviewed, that the labeling of such tobacco product, based on a fair evaluation of all material facts, is false or misleading in any particular and was not corrected within a reasonable time after receipt of written notice from the Secretary of such fact; or

(F) on the basis of new information before the Secretary, evaluated together with the evidence before the Secretary when such order was issued, that such tobacco product is not shown to conform in all respects to a tobacco product standard which is in effect under section 387g of this title, compliance with which was a condition to the issuance of an order relating to the application, and that there is a lack of adequate information to justify the deviation from such standard.

(2) Appeal

The holder of an application subject to an order issued under paragraph (1) withdrawing an order issued pursuant to subsection (c)(1)(A)(i) may, by petition filed on or before the 30th day after the date upon which such holder receives notice of such withdrawal, obtain review thereof in accordance with section 387*l* of this title.

(3) Temporary suspension

If, after providing an opportunity for an informal hearing, the Secretary determines there is reasonable probability that the continuation of distribution of a tobacco product under an order would cause serious, adverse health consequences or death, that is greater than ordinarily caused by tobacco products on the market, the Secretary shall by order temporarily suspend the authority of the manufacturer to market the product. If the Secretary issues such an order, the Secretary shall proceed expeditiously under paragraph (1) to withdraw such application.

(e) Service of order

An order issued by the Secretary under this section shall be served--

(1) in person by any officer or employee of the department designated by the Secretary; or

(2) by mailing the order by registered mail or certified mail addressed to the applicant at the applicant's last known address in the records of the Secretary.

(f) Records

(1) Additional information

In the case of any tobacco product for which an order issued pursuant to subsection (c)(1)(A)(i) for an application filed under subsection (b) is in effect, the applicant shall establish and maintain such records, and make such reports to the Secretary, as the Secretary may by regulation, or by order with respect to such application, prescribe on the basis of a finding that such records and reports are necessary in order to enable the Secretary to determine, or facilitate a determination of, whether there is or may be grounds for withdrawing or temporarily suspending such order.

(2) Access to records

Each person required under this section to maintain records, and each person in charge of custody thereof, shall, upon request of an officer or employee designated by the Secretary, permit such officer or employee at all reasonable times to have access to and copy and verify such records.

(g) Investigational tobacco product exemption for investigational use

The Secretary may exempt tobacco products intended for investigational use from the provisions of this subchapter under such conditions as the Secretary may by regulation prescribe.

CREDIT(S)

(June 25, 1938, c. 675, § 910, as added Pub.L. 111-31, Div. A, Title I, § 101(b)(3), June 22, 2009, 123 Stat. 1807.)

21 U.S.C.A. § 387j, 21 USCA § 387j
Current through PL 117-57.

End of Document

United States Code Annotated
Title 21. Food and Drugs (Refs & Annos)
Chapter 9. Federal Food, Drug, and Cosmetic Act (Refs & Annos)
Subchapter IX. Tobacco Products (Refs & Annos)

21 U.S.C.A. § 387*l*

§ 387*l*. Judicial review

Effective: June 22, 2009
Currentness

(a)Right to review

(1)In general

Not later than 30 days after--

(A) the promulgation of a regulation under section 387g of this title establishing, amending, or revoking a tobacco product standard; or

(B) a denial of an application under section 387j(c) of this title,

any person adversely affected by such regulation or denial may file a petition for judicial review of such regulation or denial with the United States Court of Appeals for the District of Columbia or for the circuit in which such person resides or has their principal place of business.

(2)Requirements

(A)Copy of petition

A copy of the petition filed under paragraph (1) shall be transmitted by the clerk of the court involved to the Secretary.

(B)Record of proceedings

On receipt of a petition under subparagraph (A), the Secretary shall file in the court in which such petition was filed--

(i) the record of the proceedings on which the regulation or order was based; and

(ii) a statement of the reasons for the issuance of such a regulation or order.

(C)Definition of record

In this section, the term "record" means--

(i) all notices and other matter published in the Federal Register with respect to the regulation or order reviewed;

(ii) all information submitted to the Secretary with respect to such regulation or order;

(iii) proceedings of any panel or advisory committee with respect to such regulation or order;

(iv) any hearing held with respect to such regulation or order; and

(v) any other information identified by the Secretary, in the administrative proceeding held with respect to such regulation or order, as being relevant to such regulation or order.

(b)Standard of review

Upon the filing of the petition under subsection (a) for judicial review of a regulation or order, the court shall have jurisdiction to review the regulation or order in accordance with chapter 7 of Title 5 and to grant appropriate relief, including interim relief, as provided for in such chapter. A regulation or denial described in subsection (a) shall be reviewed in accordance with section 706(2)(A) of Title 5.

(c)Finality of judgment

The judgment of the court affirming or setting aside, in whole or in part, any regulation or order shall be final, subject to review by the Supreme Court of the United States upon certiorari or certification, as provided in section 1254 of Title 28.

(d)Other remedies

The remedies provided for in this section shall be in addition to, and not in lieu of, any other remedies provided by law.

(e)Regulations and orders must recite basis in record

To facilitate judicial review, a regulation or order issued under section 387f, 387g, 387h, 387i, 387j, or 387p of this title shall contain a statement of the reasons for the issuance of such regulation or order in the record of the proceedings held in connection with its issuance.

CREDIT(S)

(June 25, 1938, c. 675, § 912, as added Pub.L. 111-31, Div. A, Title I, § 101(b)(3), June 22, 2009, 123 Stat. 1819.)

21 U.S.C.A. § 387*l*, 21 USCA § 387l
Current through PL 117-57.