February 2, 2023

Char Owen, President
American Vapor Manufacturers
1201 Iron Springs Road, Suite 3
Prescott, AZ 86305

Re: Docket No. FDA-2022-P-1211

Dear Ms. Owen,

This is a final response regarding your citizen petition received on June 17, 2022, requesting that the Food and Drug Administration (FDA), with respect to synthetic nicotine containing e-liquids used in open-system electronic nicotine delivery systems (ENDS) for which a premarket tobacco product application (PMTA) has been submitted by May 14, 2022, that meet the criteria in 21 CFR § 1105.10 and section 910(b) of the FD&C Act:

1. Exercise enforcement discretion and permit the continued marketing and sale of such synthetic nicotine e-liquids to adults for the duration of the Agency's full scientific review of their respective applications until FDA reaches a final decision on the PMTAs for such products; and
2. Allow manufacturers of these products to continue to submit additional data and amend their applications.

Your petition also specifies that these two requests are limited to manufacturers that have taken certain steps to ensure that their products will not contribute to illegal underage use and that each manufacturer would be required to demonstrate to FDA through documentation and other evidence that it:

1. Has taken steps to prohibit access by and sales to underage (under 21) consumers for brick-and-mortar stores and/or retail websites;
2. Will only market to adults (21+) and not rely on any youth-friendly advertising; and
3. Is otherwise in compliance with Family Smoking Prevention and Tobacco Control Act (Tobacco Control Act or TCA) and Deeming Rule requirements (e.g., facility registration, product listings, warning/labeling requirements, etc.).

FDA has carefully reviewed your petition, and we are denying it for the reasons set forth below.

## I. Background

The Tobacco Control Act, enacted on June 22, 2009, amended the Federal Food, Drug and Cosmetic Act (FD&C Act) and gave FDA the authority to regulate tobacco products (Pub. L.

111-31). The Tobacco Control Act provided FDA authority to regulate cigarettes, cigarette tobacco, roll-your-own tobacco, smokeless tobacco, and any other tobacco products that the Agency by regulation deems to be subject to the law. On May 10, 2016, FDA issued the "Deeming Rule," which extended FDA's tobacco product authority to all tobacco products,[1] other than the accessories of deemed tobacco products, that meet the statutory definition of tobacco product. 81 Fed. Reg. 28974 (May 10, 2016), codified at 21 CFR 1100.1. This includes ENDS, also referred to e-cigarettes (*id*. at 28976).

The Consolidated Appropriations Act of 2022 (the Appropriations Act) (Public Law 117-103), enacted on March 15, 2022, amended the definition of the term "tobacco product" in section 201(rr) of the FD&C Act to include products that contain nicotine from any source. The Appropriations Act also amended section 901(b) of the FD&C Act (21 U.S.C. 387a(b)), which concerns FDA's authority over tobacco products, by adding a sentence stating chapter IX of the FD&C Act shall also apply to any tobacco product containing nicotine that is not made or derived from tobacco (referred to in this document as "non-tobacco nicotine" or "NTN"). As a result, tobacco products that contain NTN, including synthetic nicotine, are subject to the provisions in chapter IX of the FD&C Act, including the requirement in section 910 for premarket review of new tobacco products.

The Appropriations Act also sets forth a number of provisions with respect to the requirements of premarket review for tobacco products containing NTN. Under these provisions, a manufacturer that submits a PMTA for a new tobacco product containing NTN by May 14, 2022, could continue to market such products through July 13, 2022.[2] After July 13, 2022, an NTN tobacco product can only be marketed in the United States if it has received premarket authorization from FDA. An NTN product is in violation of the law if it is marketed without a marketing granted order in effect.[3]

## II. DISCUSSION

As described above, your petition requests FDA exercise enforcement discretion and permit the continued marketing and sale of certain open-system e-liquids containing synthetic nicotine and allow manufacturers to continue to submit data and amend their applications after submission. For the reasons explained below, we deny both requests.

### *A. Your Request for Enforcement Discretion and Permission to Continue Marketing*

In your Petition, you request the Agency "exercise enforcement discretion" and "permit the continued marketing and sale of [certain] synthetic nicotine e-liquids to adults for the duration of

[1] Section 201(rr) of the FD&C Act (21 U.S.C. 321(rr)), as amended by the Tobacco Control Act, defined the term "tobacco product" to mean any product made or derived from tobacco that is intended for human consumption, including any component, part, or accessory of a tobacco product (except for raw materials other than tobacco used in manufacturing a component, part, or accessory of a tobacco product). Pub. L. 111-31, Division A, Title I, Sec. 101(a), 123 Stat. 1776 at 1783.
[2] Consolidated Appropriations Act of 2022, Pub. L. 117-103, Division P, Title I, Subtitle B, Sec. 111(d).
[3] *Id*.

the Agency's full scientific review (*i.e.*, until FDA reaches a final marketing authorization determination) of their respective applications." Petition at 2.

To the extent you are requesting that FDA "permit" manufacturers to market certain synthetic nicotine e-liquid products, the Agency must deny your request as outside of its statutory authority. As the Appropriations Act makes clear, after July 13, 2022, a non-tobacco nicotine product can only be legally marketed in the United States if it has received marketing authorization from FDA.[4] These products have not received marketing authorization from FDA and thus cannot be legally marketed in the United States. Accordingly, FDA cannot authorize or "permit" the marketing of these products and must deny your request. *See*, *Hoffman-LaRoche v. Weinberger*, 425 F. Supp. 890, 894 (D.D.C. 1975) ("FDA's policy of *permitting* new drugs to be marketed without an approved [NDA]" was not a lawful exercise of discretion because it "contravene[d] the clear statutory requirement of preclearance mandated by 21 U.S.C. § 355") (emphasis added).

To the extent that you are requesting that the Agency refrain from taking enforcement action against specific manufacturers of certain NTN-containing open-system e-liquids, your request is not within the scope of FDA's citizen petition procedures. Decisions with respect to such matters are within the discretion of the Agency and are generally made on a case-by-case basis. Specifically, under 21 C.F.R. § 10.30(k), citizen petitions may not be used for "the referral of a matter to a United States attorney for the initiation of court enforcement action and related correspondence." By its terms, § 10.30(k) excludes from the Agency's citizen petition procedures not only requests for referrals to a U.S. Attorney but also "related correspondence." The Department of Justice represents FDA in actions brought to enforce the FD&C Act and other statutes we administer, and FDA typically refers such cases through the local United States Attorney's Office. Therefore, agency decisions to take enforcement actions are decisions related to (and involve correspondence related to) the referral of a matter to a U.S. Attorney for the initiation of a court enforcement action for violations of the FD&C Act.

Further, under 21 C.F.R. § 10.30, the scope of FDA's citizen petition procedures is described as authorizing a person to petition the Agency to issue, amend, or revoke a regulation or order or to take or refrain from taking any other form of "administrative action." FDA regulations at 21 C.F.R. § 10.3 define "administrative action" to include "every act, including the refusal or failure to act, involved in the administration of any law by the Commissioner, except that it does not include the referral of apparent violations to U.S. attorneys for the institution of civil or criminal proceedings or an action in preparation of a referral." Agency decisions to take enforcement action are decisions related to the "referral of apparent violations to U.S. attorneys for the institution of civil or criminal proceedings or acts in preparation of such referrals." [5] Thus, such decisions are excluded from the definition of "administrative action."

[4] Division P, Title I, Subtitle B, Sec. 111(d)(3) of Pub. L. 117-103.

5 *See* Administrative Practices and Procedures, Notice of Proposed Rulemaking, 40 FR 40682, 40683 (Sept. 3, 1975) (preamble to proposed rule establishing FDA's citizen petition procedural regulations, stating that "any activity in preparation or incidental" to the referral of apparent violations to United States attorneys "is specifically excluded" from citizen petition procedures and that "matters related to the agency's law enforcement role are not included" in the definition of "administrative action" under the citizen petition procedural regulations).

Therefore, insofar as the Petition is premised on a request that FDA refrain from taking enforcement action against specific entities, we deny the petition as being outside the scope of the citizen petition process. Such denial is consistent with the agency's regulations and longstanding practice with respect to petitions that ask FDA to refrain from taking enforcement action, because such requests are not the proper subject of citizen petitions.[6]

To the extent you request that FDA issue a statement of policy to exercise enforcement discretion with respect to certain synthetic nicotine e-liquid products, we deny your request. The proposal as described in your petition raises significant issues. One example is the issue discussed above – that you are requesting that FDA "permit" manufacturers to market certain synthetic nicotine e-liquid products. Another example is highlighted by the decision in *Am. Academy of Pediatrics (AAP) v. FDA*, 379 F. Supp. 3d 461, 492 (D. Md. 2019), where the court vacated an enforcement discretion policy contained in an August 2017 guidance, under which FDA would not intend to initiate enforcement of the FD&C Act's premarket review requirements for ENDS and other "non-combustible" products until the Agency rendered a decision on the products' application. The court concluded that the guidance was *ultra vires* and conflicted with the FD&C Act. The Court found that the guidance conflicted with the purpose of the FD&C Act by "allow[ing] unapproved tobacco products to be manufactured, advertised, and sold for five years or longer." *AAP*, 379 F. Supp. 3d at 492. In addition, it found that "FDA's across-the-board suspension of the Tobacco Control Act's premarket approval process . . . amount[ed] to a rule amendment or revocation, as it is inconsistent with the statute." *Id*. According to the court, by delaying enforcement, FDA was "abdicating its statutory duty to review new tobacco products," by implementing what was in effect a *post*market review of such products rather than a *pre*market review as required by the Act, thus exceeding FDA's statutory authority. *Id.*

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6 *See, e.g.*, Letter from Peter Marks, Director, Center for Biologics Evaluation and Research, to George M. Stone, Jr., Patients for Access to Advanced Therapy for Hemophilia (Sept. 25, 2020) ("[T]he definition of administrative action does not include enforcement actions, and requests for FDA to initiate enforcement action are outside the scope of our citizen petition regulations (see 21 CFR 10.30(k))"), *available at* https://www.regulations.gov/document/FDA-2019-P-6099-0005; Letter from Beverly Chernaik, Director for Office of Regulations, Center for Tobacco Products, U.S. Food and Drug Administration, to Joshua Kesselman, BBK Tobacco & Foods, LLP, Jonathan M. Weis and Mitchell S. Chaban, Levin Ginsburg (Aug. 16, 2016) (denying a citizen petition, in part, because the request that FDA refrain from taking any administrative or enforcement action are not within the scope of FDA's citizen petition procedures under 21 CFR 10.30(k)), *available at* https://www.regulations.gov/document/FDA-2010-P-0532-0013; Letter from Janet Woodcock, Director, Center for Drug Evaluation and Research, to William A. Garvin, Buchanan Ingersoll & Rooney PC (Nov. 8, 2016) ("Agency decisions to take, or refrain from taking, enforcement actions are related to referral of a matter to a United States attorney for the initiation of court enforcement action for violations of the Federal, Food, Drug, and Cosmetic Act."), *available at* https://www.regulations.gov/document/FDA-2016-P-2029-0027; Letter from Janet Woodcock, Director, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, to Lenard Thylan (May 22, 2012) (response letter denying citizen petition and citing 21 CFR 10.30 (K) for the proposition that requests for FDA to refrain from taking enforcement action is beyond the scope of the citizen petition process), *available at* https://www.regulations.gov/document/FDA-2011-P-0884-0003; Letter from Janet Woodcock, Director, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, to Edward John Allera, Buchanan Ingersoll & Rooney PC (Mar. 1, 2011) (response letter denying request for the Agency to refrain from taking enforcement action because the relief could not be sought under § 10.30(k)), *available at* https://www.regulations.gov/document/FDA-2008-P-0219-0006.

FDA believes that determinations regarding the risks and benefits of these products are best made in the application review process. FDA has been devoting significant resources to the premarket review of NTN products and has made substantial progress in that review. It received nearly one-million applications for NTN products that were submitted by approximately 250 applicants from April 14 to May 14, 2022. FDA has taken action on 95% of the applications covering over 889,000 products and continues work on the remaining applications that are still pending. At this time, the Agency believes it is preferable to continue to make enforcement decisions regarding the premarket authorization requirement on a case-by-case basis. In making case-by-case enforcement decisions, FDA will consider the relevant facts and circumstances, which may include considerations your request refers to, such as youth access to and use of the product.

Although we are denying your request for the reasons explained above, we would like to take this opportunity to provide additional information with respect to the specific grounds for your request.

You raise several arguments regarding the Agency's reviews of applications for non-tobacco-flavored ENDS products. You assert that FDA has applied a "'fatal flaw' box-checking strategy whereby filed applications for non-tobacco flavored ENDS would receive only a cursory review to determine whether they contained a particular type of study before being allowed to proceed on to the full, statutorily mandated scientific review." Petition at 12. You argue that "[t]his fatal flaw approach[] . . . was unlawful as it was arbitrary, capricious, and ultra vires, or otherwise not in accordance with law." *Id.*

As an initial matter, it is not clear to us how these assertions support your request for enforcement discretion.[7] In any event, these statements regarding FDA's review of non-tobacco-flavored ENDS products are incorrect.

FDA's reviews of applications for non-tobacco-flavored ENDS products apply the standard set forth in the FD&C Act, which, as explained above, directs FDA to deny an application to market a new tobacco product unless the applicant demonstrates that marketing the product would be appropriate for the protection of the public health (APPH). *See* FD&C Act § 910(c)(2), (4). Under this standard, an applicant must show a net benefit to public health based upon the risks and benefits to the population as a whole. In evaluating applications, FDA, among other things, weighs the risk that youth will start using a new product against the product's potential to help adults significantly reduce or cease their use of combustible cigarettes, which are generally considered to be more dangerous than e-cigarettes.

Additionally, in evaluating applications for non-tobacco-flavored ENDS products, FDA has applied the APPH standard on a case-by-case basis. Specifically, FDA has evaluated whether an application contains sufficiently robust or reliable evidence demonstrating that a flavored product provides a net benefit to the public health notwithstanding the significant and well-documented risk to youth—consistent with section 910(c) of the FD&C Act. In the absence of

[7] Because this statement is contained in the "Statement of Grounds" section of your petition, *see* Petition at 12-16, and is not listed in the "Action Requested" section of your petition as required by 21 CFR § 10.30(b)(3), it does not constitute a request to which FDA must furnish a response as described in 21 CFR 10.30(e)(2).

such evidence, FDA has reasonably concluded that the available evidence did not suffice to show that marketing of the applicants' products would be appropriate for the protection of the public health. Notably, five Circuits have upheld these conclusions as reasonable. *See Gripum, LLC v. FDA*, 47 F.4th 553, 559-61 (7th Cir. 2022) ("[FDA]'s determination that Gripum's products lack a clear benefit to current tobacco users was not arbitrary or unreasonable."); *Prohibition Juice Co. v. FDA*, 45 F.4th 8, 21 (D.C. Cir. 2022) (concluding that FDA did not "act arbitrarily and capriciously by finding the manufacturers' evidence insufficiently rigorous."); *Wages & White Lion Invs., LLC v. FDA*, 41 F.4th 427, 442 (5th Cir. 2022) ("[W]e cannot say that FDA acted arbitrarily and capriciously by disagreeing with Petitioners as to the significance of the evidence they presented."); *Liquid Labs LLC v. FDA* No. 21-2883,__ F.4th ___ , 2022 WL 15090594 at *5 (3d Cir. Oct. 27, 2022) ("FDA properly denied the[] [applications] because the other evidence Liquid Labs submitted was insufficient."); *Avail Vapor, LLC v. FDA*, 2022 U.S. App. LEXIS 34084 at *40 (4th Cir. Dec. 12, 2022) (finding "no merit in Avail's remaining arguments that FDA acted arbitrarily and capriciously in reviewing petitioners' PMTAs.").

You are also incorrect that FDA "failed to provide fair notice of [a] long-term study requirement" for these applications. This argument fails because, as the above-mentioned Circuits have recognized, FDA did not apply a new evidentiary standard in reviewing marketing applications for non-tobacco-flavored ENDS. *See Gripum*, 47 F.4th at 559-60; *Prohibition Juice*, 45 F.4th at 21; *Wages & White Lion Invs.*, 41 F.4th at 438-39; *Liquid Labs LLC,* 2022 WL 15090594 at *7 ("FDA did not apply unannounced or changed standards for PMTAs."); *Avail Vapor*, 2022 U.S. App. LEXIS 34084 at *26 (finding "that FDA neither changed the standard nor types of evidence required.").[8] Rather, as explained above, FDA has applied the standard set forth in the FD&C Act and reasonably concluded that the available evidence did not satisfy the statutory standard. As the D.C. Circuit explained, "[t]he agency's finding that the evidence was insufficiently rigorous does not reflect a changed standard, but the manufacturers' failure to meet the standard the agency consistently applied." *Prohibition Juice Co.*, 45 F.4th at 21.

Additionally, you are incorrect that "the Agency repeatedly informed manufacturers . . . that demonstrating APPH would <u>*not*</u> require long-term clinical or cohort studies, or a study going to the specific product comparison described in the MDO." It is not the case that FDA previously made an across-the-board statement that applicants would not need to provide especially robust forms of evidence. Rather, FDA has consistently taken the position that evidence provided in support of a marketing application must be sufficient to demonstrate that a product's benefits to existing users of tobacco products outweigh its risks to nonusers. *See, e.g.*, 2019 Guidance at 11-12; *see also Prohibition Juice*, 45 F.4th at 22 ("FDA consistently required[] studies sufficiently rigorous to show a benefit of flavored e-cigarette products sufficient to overcome their risks"). Consistent with that position, "the FDA said only that 'it *might* accept evidence other than long-term studies, if that evidence had sufficient scientific underpinnings' to meet the statutory standard." *Prohibition Juice Co.*, 45 F.4th at 21 (quoting *Breeze Smoke*, 18 F.4th at 506); *see*

[8] To support your fair notice argument, you rely on the Fifth Circuit motions panel's preliminary order granting an e-cigarette manufacturer's motion for stay. *See Wages & White Lion Invs., LLC v. FDA*, 16 F.4th 1130, 1138-39 (5th Cir. 2021). However, as the subsequent Fifth Circuit merits panel made clear, "a stay panel's determination regarding the likelihood of success on the merits is not itself a determination on the merits." *Wages & White Lion Invs.*, 41 F.4th at 439 n.13. Thus, the Fifth Circuit's subsequent decision controls on the merits of the manufacturer's claims.

*Liquid Labs*, 2022 WL 15090594 at *6 (quoting *Breeze Smoke*, 18 F.4th at 506-07); *Gripum*, 47 F.4th at 559-60; *Wages & White Lion Invs.*, 41 F.4th at 438-39 ("The fact that [P]etitioners presented other scientific evidence does not make that scientific evidence valid, and it is entirely consistent with FDA's prior statements to reject that evidence."); *Breeze Smoke*, 18 F.4th at 506-07.

You further assert that "[t]he PMTAs for non-tobacco flavored synthetic nicotine e-liquids should not be summarily 'knocked out' by FDA based on this fatal flaw review process before being allowed to proceed on to the full, statutorily mandated scientific review required for filed applications." Petition at 16. You additionally assert that, "[o]nce these applications are in scientific review, the Agency must[] . . . fully evaluate the entirety of the[] applications, as well as consider the significant real-world evidence . . . and real-world data . . . that the products present significant benefits for adult cigarette smokers" as part of the APPH evaluation. *Id.* at 18. Because these statements are not listed in the "Action Requested" section of your petition as required by 21 CFR § 10.30(b)(3), they do not constitute requests to which FDA must furnish a response as described in 21 CFR 10.30(e)(2). However, we reiterate that, for the reasons explained above, FDA reviews applications in accordance with the TCA and evaluates the evidence presented in applications on a case-by-case basis.[9]

### *B. **Your Request to Amend PMTAs After Submission***

Your petition requests that FDA allow "certain e-liquid manufacturers who submitted timely PMTAs that meet the Agency's acceptance and filing criteria" "to continue to submit additional data and amend their applications." Petition at 2. To support this request, you appear to rely on the same grounds as those addressed above. You also argue that "Congress failed to provide manufacturers with sufficient time to prepare synthetic nicotine PMTAs, taking into account FDA's own requirements for these applications," *id.* at 18, namely the "require[ment] [that] PMTAs for non-tobacco flavored synthetic nicotine products . . . contain [randomized controlled trials (RCTs)] or [longitudinal cohort studies (LCSs)]," which are "clearly impossible to complete . . . within 60 days," *id.* at 17.

We deny your request as moot because it seeks to allow applicants to submit amendments to PMTAs that are already permitted under 21 C.F.R. § 1114.9. Specifically, § 1114.9(a) provides: "[A]n applicant may submit on its own initiative[] an amendment to a PMTA containing information that is necessary for FDA to complete the review of a pending PMTA." "If an amendment is a major amendment (e.g., an amendment that contains significant new data from a previously unreported study, or substantial new manufacturing information), FDA will restart the 180-day review period after receipt of the amendment." *Id.* § 1114.9(b)(1).

[9] We also note that you state that you "are requesting FDA to *continue* to exercise enforcement discretion and *permit* manufacturers of synthetic nicotine e-liquids to stay on the market without the threat of enforcement beyond July 13, 2022" (emphases added). Petition at 3. To the extent you are suggesting that FDA has previously exercised enforcement discretion with respect to such products, that is incorrect. As explained above, the Appropriations Act permitted certain tobacco products for which an application was submitted to continue to continue to be marketed for a 90-day "transition" period beginning on the effective date of the Act, or April 14, 2022. 21 U.S.C. § 387j note (d)(2)(B). The Act provided that such tobacco products were not in violation of the premarket authorization requirement of section 910 of the FD&C Act until the expiration of that transition period. *Id.* § 387j note (d)(2)(B). Therefore, the statute permitted such products to continue to be marketed prior to July 13, 2022.

To the extent you argue that such a proposal would be justified by alleged defects in the Agency's review process for flavored ENDS products, FDA rejects those justifications for the reasons already explained in paragraph A above. Furthermore, we disagree with your assertion that there is a requirement that PMTAs for non-tobacco flavored products contain RCTs or LCSs. FDA does not have any such requirement for these applications. Rather, in evaluating these applications, FDA has considered whether the evidence submitted in the application demonstrates a sufficient benefit to existing users of tobacco products to make the marketing of the products APPH. Although FDA has observed that evidence generated using an RCT or LCS design is most likely to demonstrate such a benefit, specifically when such studies track participants over a period of time, it has also emphasized that other types of evidence could be adequate if sufficiently reliable and robust and will be evaluated on a case-by-case basis. Thus, FDA has not denied applications because they failed to include a long-term clinical study such as an RCT or LCS but because they have failed to include any evidence robust enough to demonstrate a sufficient benefit. *See, e.g.*, *Liquid Labs*, 2022 WL 15090594 at *6 ("[T]he FDA did not deny Liquid Labs' applications solely because they lacked randomized controlled trials or longitudinal cohort studies. Rather, the record indicates that the FDA properly denied them because the other evidence Liquid Labs submitted was insufficient.").

This denial is issued in accordance with FDA's regulation on citizen petitions (21 CFR 10.30).

Sincerely,

May D. Nelson
Director, Office of Regulations
Center for Tobacco Products
Food and Drug Administration