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VIA ELECTRONIC SUBMISSION ON REGULATIONS.GOV

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FDA-2013-S-0610

Re: Citizen Petition by American Vapor Manufacturers Requesting the Food and Drug Administration Exercise Enforcement Discretion to Manufacturers of Open-System Synthetic Nicotine E-Liquid Products

To Be Filed in Docket Nos.: FDA-2013-S-0610; FDA-2019-N-2854-1147; FDA-2019-D-0661-15418; FDA-2019-D-0661-15434; FDA-2014-N-0189; FDA-2019-D-5324; FDA-2015-D-2496; FDA-2017-D-0120; FDA-2018-D-3244

Dear Secretary Becerra and Commissioner Califf:

On behalf of the American Vapor Manufacturers ("AVM" or the "Petitioners"), a trade association representing small, independent vapor and e-liquid manufacturers across the United States, as well as similarly situated businesses and organizations, the undersigned submits this citizen petition pursuant to 21 C.F.R. § 10.30 and the Food, Drug and Cosmetic Act ("FDCA"), as amended by the Family Smoking Prevention and Tobacco Control Act ("TCA").[1]

[1] This petition is also being submitted per the recommendation of the FDA Ombudsman, Laurie Lenkel, who indicated a citizen petition was the proper vehicle for this request for enforcement discretion. *See* e-mail, dated May 9, 2022, from Laurie Lenkel to Amanda Wheeler.

A. Action Requested

On March 15, 2022, the U.S. Food and Drug Administration ("FDA" or the "Agency") Center for Tobacco Products ("CTP") was given the authority to regulate products containing non-tobacco derived synthetic nicotine after President Biden signed the Omnibus Budget Bill (H.R. 2741). Pursuant to the new legislation, which amended the definition of a "tobacco product" in Section 201(rr) of the FDCA, manufacturers of all currently marketed synthetic nicotine products were required to submit a Premarket Tobacco Product Application ("PMTA") by May 14, 2022 to ensure that their products could remain on the market, without the threat of enforcement, for an additional 60 days (*i.e.*, by July 13, 2022). Synthetic nicotine products that do not receive PMTA authorization (*i.e.*, a Marketing Granted Order or "MGO") by July 13, 2022 and that remain on the market thereafter will be in violation of the statute and subject to FDA enforcement.

Accordingly, the Petitioners request the following:

(1) FDA should exercise enforcement discretion and allow manufacturers of synthetic nicotine e-liquids used in open-system ENDS devices who submitted timely PMTAs that meet FDA's criteria for application acceptance (21 C.F.R. § 1105.10) and filing (FDCA § 910(b)) to keep those products on the market for their adult (21+) customers following the end of the "transition period" on July 13, 2022. Specifically, we request that the CTP Office of Compliance and Enforcement ("OCE") permit the continued marketing and sale of such synthetic nicotine e-liquids to adults for the duration of the Agency's full scientific review (*i.e.*, until FDA reaches a final marketing authorization determination) of their respective applications.

(2) Furthermore, we request the FDA CTP Office of Science ("OS") allow manufacturers of these products to continue to submit additional data and amend their applications, as the time provided (60 days between March 15, 2022 and May 14, 2022) was simply insufficient to prepare all of the product-specific data FDA requires PMTAs contain including, in some cases, long-term (6 months+) clinical or longitudinal evidence.

This request is limited to certain e-liquid manufacturers who submitted timely PMTAs that meet the Agency's acceptance and filing criteria, and otherwise have taken steps to ensure that their products will not contribute to illegal underage use. Each manufacturer would be required to demonstrate to FDA through documentation and other evidence that it:

- Has taken steps to prohibit access by and sales to underage (under 21) consumers for brick-and-mortar stores and/or retail websites;
- Will only market to adults (21+) and not rely on any youth-friendly advertising; and

- Is otherwise in compliance with TCA and Deeming Rule requirements (*e.g.*, facility registration, product listings, warning/labeling requirements, etc.).

As noted, we are requesting enforcement discretion be extended only to bottled synthetic nicotine e-liquids, and not to prefilled closed-system ENDS devices (*e.g.*, disposables or cartridge/pod-based ENDS). If the Agency chooses not to exercise enforcement discretion for these e-liquid products, many small businesses will suffer irreparable damage, be forced to lay-off employees, and may ultimately have to shut down.

B. Statement of Grounds

1. Exercising the Requested Enforcement Discretion for Manufacturers of Synthetic Nicotine E-Liquids is Consistent with Promoting the Public Health

As detailed below, the Petitioners 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, while their applications are permitted to proceed through the full PMTA review process (*i.e.*, application acceptance, filing and a complete scientific review). This enforcement approach is also consistent with FDA's long-standing position that it must strike the "appropriate balance between restricting youth access to [cartridge-based] products, while maintaining availability of potentially less harmful options for current and former adult smokers who have transitioned or wish to transition completely away from combusted tobacco products."[2]

This is not surprising as extensive research shows vaping can be an effective quit aid. A recent one-year clinical trial published in the *New England Journal of Medicine* found vaping is nearly twice as effective as other cessation products (*i.e.*, nicotine replacement therapies) when both are combined with behavioral support.[3] The National Academies of Sciences ("NAS") concluded "[w]hile overall evidence from observational trials is mixed, there is moderate evidence from observational studies that more frequent use of e-cigarettes is associated with an

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[2] *See* U.S. FOOD AND DRUG ADMIN., *supra* note 20, at 20-21 ("Accordingly, FDA has recalibrated its balancing of public health considerations in light of the public health threats and significant new evidence [regarding cartridge-based products]. This policy reflects FDA's balancing of concerns regarding the appeal of certain flavored, cartridge-based ENDS products to youth [and] the potential public health benefit of noncombusted options by which some adult smokers might seek to transition completely away from combusted tobacco products.").

[3] *See* Peter Hajek *et al*., *A Randomized Trial of E-Cigarettes versus Nicotine-Replacement Therapy*, 380 N. ENG. J. MED. 629, 632 (2019).

increased likelihood of cessation."[4] A survey of almost 70,000 U.S. vapers found the vast majority had completely replaced smoking with vaping.[5] Public Health England reported almost all of the over three million adult vapers in England are current or ex-smokers, many of whom are vaping to help transition away from cigarettes.[6]

In fact, former CTP Director Mitch Zeller stated that "some addicted adult smokers use these products with a goal to end" their smoking habits and that a "mass market exit of [vapor] products would limit the availability of a potentially less harmful alternative for adult smokers seeking to transition or stay away from" cigarettes.[7] He maintained that "[d]ramatically and precipitously reducing availability of these products could present a serious risk that adults, especially former smokers, who currently use [vapor] products and are addicted to nicotine would migrate to [cigarettes]."[8] He warned this was a "public health outcome that should be avoided if at all possible."[9]

More recently, the Cochrane Library Tobacco Addiction Group published a systematic review of the evidence regarding the role of e-cigarettes in quitting smoking.[10] By way of background, Cochrane systematic reviews attempt to identify, appraise, and synthesize all the empirical evidence that meets pre-specified eligibility criteria to answer a specific research

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[4] COMMITTEE ON THE REVIEW OF HEALTH EFFECTS OF ELECTRONIC NICOTINE DELIVERY SYSTEMS, PUBLIC HEALTH CONSEQUENCES OF E-CIGARETTES 584 (2018).

[5] *See* Konstantinos Farsalino *et al*., *Patterns of flavored e-cigarette use among adults vapers in the United States: an internet survey*, available at: https://www.dropbox.com/s/b8uwoxay6i2fzb2/Docket%20No.%20FDA-2017-N-6565_FARSALINOS.pdf?dl=0.

[6] *Use of e-Cigarettes (Vapes) among Adults in Great Britain*, ACTION ON SMOKING AND HEALTH 2 (2021).

[7] *See* Mitch Zeller Decl. at ¶ 15, https://www.clivebates.com/documents/MarylandZellerDeclarationJune2019.pdf.

[8] *Id.*

[9] *Id.* at ¶ 12; *see also id.* at ¶ 15 (noting that "these products may be less harmful at an individual level than combustible tobacco products" and "it is likely that some ENDS products may reduce harm at the individual level").

[10] Hartmann-Boyce, J., McRobbie, H., Lindson, N., Bullen, C., Begh, R., Theodoulou, A., Notley, C., Rigotti, N. A., Turner, T., Butler, A. R., & Hajek, P. (2020). Electronic cigarettes for smoking cessation (Full). *Cochrane Database of Systematic Reviews*, *10*. https://doi.org/10.1002/14651858.CD010216.pub4 (hereafter, the "Review").

question. These reviews are used to inform clinical practice guidelines and assist policy and decision makers in making well-informed decisions about health care. Generally, Cochrane reviews are performed independent from commercial interests, and use systematic, rigorous selection criteria to assess a wide range of evidence from numerous databases. Researchers conducting systematic reviews use explicit, systematic methods that are selected with a view aimed at minimizing bias to produce more reliable findings that can be used to inform decision-making. Cochrane Reviews are updated to reflect the findings of new evidence when it becomes available because the results of new studies can change the conclusions of a review. All these factors make Cochrane Reviews valuable sources of information for decision-makers and researchers. Due to these factors, the international research and medical communities generally regard Cochrane reviews as the gold standard for systematic reviews.

The October 2020 Review published in the *Cochrane Library Database of Systematic Reviews* provides further evidence that e-cigarettes and ENDS are more effective than nicotine replacement therapy ("NRT") in helping smokers quit.[11] This is the latest *Cochrane* review update and includes 35 new studies. The authors found support for the effectiveness of e-cigarettes in smoking cessation, finding that:

- Nicotine containing e-cigarettes are 70% more effective in supporting smokers to successfully quit than nicotine replacement therapy (NRT; *e.g.*, patches and gum); and
- Nicotine containing e-cigarettes are 70% more effective in supporting smokers to successfully quit than nicotine-free e-cigarettes.

The research team included studies that assessed the use of e-cigarettes to help people quit smoking, and measured cessation for at least six months and unwanted effects. Studies reporting on smoking habits for a minimum of six months or reporting unwanted side-effects for at least one week were included in the Review. In total, 50 studies covering 12,430 adults who smoked were included in the review.[12] The Review considered randomized controlled trials ("RCTs") in which the treatments people received were decided at random, since RCTs are generally accepted as offering the most reliable evidence about the effects of a treatment. The studies included in the Cochrane Review compared nicotine-free e-cigarettes with NRTs, nicotine e-cigarettes, varenicline (Chantix), behavioral support, and no support on the outcomes of interest.

In discussing the reliability of their results, the researchers stated they were "moderately confident that nicotine e-cigarettes help more people to stop smoking than NRTs or nicotine-free e-cigarettes" and "less confident about how nicotine e-cigarettes compare with behavioral support or no support to stop smoking."[13] Thus, the Review confirms that ENDS are at least as

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[11] *Id.*

[12] *Id.*

[13] Hartmann-Boyce et al. 2020 (SUMMARY).

effective as NRT, and likely more so. This is despite the fact that the Cochrane team noted the lack of specific, high quality studies on newer e-cigarettes and the lack of detail and nuance in existing research (*i.e.*, lack of "hard" clinical research on specific flavors). Although flavors were not a specific focus for the Cochrane review, one of the largest RCT studies (Hajek *et al.* 2019) offered participants a choice of flavors, and the availability of flavors may help explain why ENDS fared so well relative to NRTs.[14]

Significantly, clinical trial data on ENDS safety was reviewed in the Cochrane meta-analysis and found little to no evidence of harm. Based on their review, the Cochrane Library Tobacco Addiction Group concluded that "nicotine e-cigarettes probably do help people to stop smoking for at least six months [...] probably work better than nicotine replacement therapy and nicotine-free e-cigarettes," and "may work better than no support, or behavioral support alone, and they may not be associated with serious unwanted effects."[15] Importantly, the Cochrane review included more recent studies than the NASEM 2018 review, which reviewed literature published through August 2017. The recent Cochrane review contradicted the NASEM review conclusion that there is "insufficient evidence" about the effectiveness of e-cigarettes compared to nicotine replacement therapy or no treatment:

> Our review contradicts this latter point, as we now find moderate-certainty evidence of benefit when comparing nicotine EC (electronic cigarettes) with NRT (nicotine replacement therapy); this is primarily due to a large RCT published after NASEM 2018.[16]

Given the strict standards and rigorous methodologies that guide the production of Cochrane's systematic reviews, which again are widely considered the gold standard of systematic reviews, these results represent strong evidence that ENDS are appropriate for the protection of public health.

Accordingly, exercising enforcement discretion and allowing manufacturers of synthetic nicotine e-liquids to keep their products on the market for the duration of the Agency's review

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[14] Hajek, P., Phillips-Waller, A., Przulj, D., Pesola, F., Smith, K. M., Bisal, N., Li, J., Parrott, S., Sasieni, P., Dawkins, L., Ross, L., Goniewicz, M., Wu, Q., & McRobbie, H. J. (2019). E-cigarettes compared with nicotine replacement therapy within the UK Stop Smoking Services: The TEC RCT. *Health Technology Assessment (Winchester, England)*, *23*(43), 1–82. https://doi.org/10.3310/hta23430.

[15] Hartmann-Boyce et al. 2020 (SUMMARY).

[16] *Id*.

(*i.e.*, until FDA reaches a final marketing authorization determination) of the PMTAs accepted and filed by the Agency, while giving these companies time to continue to supplement their timely submitted applications with new data as it is developed, fits squarely within the TCA's goals of promoting products with a relatively favorable position on the continuum of risk. The TCA "provide[s] new and flexible enforcement authority to ensure there is effective oversight of the tobacco industry's efforts to develop, introduce, and promote less harmful tobacco products."[17] FDA must also "promote cessation to reduce disease risk and the social costs associated with tobacco-related diseases" while "continu[ing] to permit the sale of tobacco products to adults in conjunction with measures to ensure they are not sold or accessible to underage purchasers."[18] The TCA, therefore, advances the interests of adult smokers looking for harm reduction tools, a goal that will not be met if e-liquid manufacturers are forced off the market following the end of the transition period on July 13, 2022.

2. Congressional Expansion of FDA's Authority to Regulate Synthetic Nicotine Was in Response to Escalation of Youth Usage of Closed-System Disposable ENDS Containing High Amounts of Nicotine Salt, not Open-System E-liquids

Congress' intent in extending FDA's tobacco authority to ENDS products utilizing synthetic nicotine was in direct response to the increased youth usage and uptake of disposable closed-system high nicotine salt-based ENDS, like the Puff Bar[19], which are discreet, easy-to-use, and often packaged in kid-friendly packaging and colors:

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17 Tobacco Control Act § 3(4); *see, e.g.,* 111 Pub. L. No. 31, 123 Stat. 1776 (2009).

18 *Id.* at §§ 3(7), (9).

19 *See* Laurie McGinley, *Congress Moves to Give FDA New Powers Over Synthetic Nicotine Products Include a Youth Favorite*, WASH. POST, (Mar. 8, 2022, 6:54 PM), https://www.washingtonpost.com/health/2022/03/08/puff-bar-synthenic-nicotine-fda/.

Indeed, FDA has repeatedly acknowledged that closed-system products, initially cartridge-based ENDS (*i.e.*, JUUL), and now disposables, are what youth who vape are most likely to use.[20] In January 2020, FDA issued its current enforcement policy for vapor products.[21] Based on data from the 2019 National Youth Tobacco Survey ("NYTS"), FDA concluded that "youth overwhelmingly prefer cartridge-based ENDS products" and that "cartridge-based products...[are the] primary driver in youth experimentation with, and continued use of, ENDS products."[22] This is due to design features, such as ease of use and concealability, that are popular with young consumers.[23] The same now holds true for disposable ENDS.[24]

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[20] *See* U.S. FOOD & DRUG ADMIN., ENFORCEMENT PRIORITIES FOR ELECTRONIC NICOTINE DELIVERY SYSTEMS (ENDS) AND OTHER DEEMED PRODUCTS ON THE MARKET WITHOUT PREMARKET AUTHORIZATION (REVISED): GUIDANCE FOR INDUSTRY 21, 23, 24, 42 (2020) https://www.fda.gov/media/133880/download.

[21] *See generally id.*

[22] *See id.* at 15-16, 19, 21.

[23] *Id.* at 16.

[24] *Id.*

Significantly, FDA also noted in the guidance that cartridge-based products "are not the products typically produced in vape shops that mix nicotine with e-liquid flavors."[25] Indeed, as noted, open-system e-liquids and ENDS products sold by small businesses are larger in size (*e.g.*, tanks), must be manually refilled using e-liquid contained in bottles, and involve complicated settings to operate – hardly the type of product that would attract underage (under 21) users. As such, the Agency prioritized enforcement against flavored, cartridge-based vapor products, while not targeting vape shops selling open-system products, provided they otherwise take steps to prevent youth access.[26]

Accordingly, following the end of the transition period for synthetic nicotine ENDS, the Agency's enforcement efforts should similarly be targeted towards the manufacturers and retailers of closed-system disposables and cartridge-based ENDS products, particularly the thousands of Chinese counterfeits that appear readily available in convenience stores and gas stations – and not on responsibly manufactured and marketed open-system synthetic nicotine e-liquids that are primarily sold in adult-only (21+) vape shops or online in age-verified transactions. As confirmed by the latest NYTS, youth use of traditional open-system ENDS and bottled e-liquids, which was always relatively low compared to closed-system ENDS, has continued to decline.

3. Distinctions Between Open-System and Disposable Closed System ENDS; Flavored Open-System E-liquids Not Used by Youth

Open-system synthetic nicotine e-liquids are distinguishable from and do not share the same product attributes or consumer base as those for disposable, closed system, high nicotine salt-based ENDS. Unlike disposable vape products (including Chinese counterfeits), which often appear to be marketed towards kids, open-system e-liquids and ENDS devices are used primarily by adult former smokers and are available for purchase at age-restricted retail locations (*e.g.*, vape shops) and on online platforms with strict age-verification measures – but not in convenience stores and gas stations. Additionally, as noted above, traditional open-system, synthetic nicotine ENDS products are larger in size (*e.g.*, tanks) than disposable ENDS and cartridge/pods systems, must be manually refilled using bottled e-liquids, and involve complicated settings to operate. When responsibly marketed to adult consumers (21+), the open-system synthetic nicotine e-liquids and ENDS products are not nearly as attractive to youth as

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[25] *Id.* at 21.

[26] *Id.* at 18 ("This policy should have minimal impact on small manufacturers (*e.g.*, vape shops) that primarily sell non-cartridge-based ENDS products")

the easy-to-use disposables or cartridge/pod systems that contain high concentrations (>50 mg/mL) of nicotine salt:[27]

Open-System ENDS Device

Closed-System ENDS Device

Images not to scale

4. Youth Vaping Rates Continue to Fall Dramatically

The NYTS monitors trends in youth tobacco use behaviors over time.[28] The most recent NYTS data make two things clear – youth combustible cigarette smoking has declined to an all-time low, and youth vaping has fallen dramatically as well, and is now below 2018 levels.

With respect to vaping, the steep decline in youth vaping is reflected in the results of both the 2020 and 2021 NYTS. These results are encouraging and reflect a significant improvement from 2018-2019. In September 2020, FDA and CDC released preliminary findings from the 2020 NYTS showing that 1.8 million fewer U.S. youth are currently using e-cigarettes compared to 2019.[29] The data show in 2020 that the past 30-day vaping prevalence among high school and

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[27] Jason Artman, *Open vs. Closed Vaping Systems: What's the Difference?*, VAPE HK (Mar. 3, 2021), Open vs. Closed Vaping Systems: What's the Difference? • VAPE HK.

[28] *See Download NYTS 2011-2021 and earlier data*, *National Youth Tobacco Survey*, CDC (Mar. 14, 2022), https://www.cdc.gov/tobacco/data_statistics/surveys/nyts/index.htm - nyts-historical [hereinafter NYTS].

[29] U.S. Food & Drug Admin., *National Survey Shows Encouraging Decline in Overall Youth E-Cigarette Use, Concerning Uptick in Use of Disposable Products* (Sept. 9, 2020), available at: https://www.fda.gov/news-events/press-announcements/national-survey-shows-encouraging-decline-overall-youth-e-cigarette-use-concerning-uptick-use.

middle school students combined decreased 42.61% from the 2019 rates.[30] Past 30-day use decreased by 28.73% among high school students, and 55.24% among middle school students. Use of an e-cigarette on 20 or more days in the past 30 days decreased by 49.46% and 18.68% among middle and high school students, respectively, with a 22.17% decrease overall.[31] Importantly, the data show that daily use of e-cigarettes remains low among youth. Significantly, only 2.7% of students reported using e-cigarettes daily in 2020 (4.4% of high school students and 0.4% of middle school students).[32] Notably, this data was gathered prior to nationwide school shutdowns as a result of the COVID-19 pandemic.

The results of the 2021 NYTS survey continue to show a dramatic decline in underage e-cigarette use, particularly for open-system e-liquids and ENDS products such as those manufactured, marketed, and sold by the small businesses that the Petitioner represents. Specifically, the survey indicated that 1.52 million fewer U.S. youth are currently using e-cigarettes compared to 2020 and 3.2 million fewer compared to 2019.[33] In 2021, more than 90% of high school and middle school students combined reported no e-cigarette use in the past 30 days, with overall past 30-day vaping prevalence declining by 42% between 2020 and 2021 (13.1% to 7.6%), and a 62% decline from the 2019 prevalence rate of 20%.[34]

Use of an e-cigarette on 20 or more days in the past 30 days decreased by 53.8% and 35.77% among middle and high school students, respectively, with a 43.7% decrease overall.[35]

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30 *See* Wang *et al*., *Characteristics of e-Cigarette Use Behaviors Among US Youth,* 2020 JAMA NETW OPEN, July 7, 2021, who reported the high school and middle school past 30-day prevalence along with corresponding population estimates. Using these values, it was possible to calculate the implied population size for each group as well as the implied total population, and calculate an estimated prevalence for the groups combined by using the implied population total as the denominator and the combined estimated number of high school and middle school students who used an e-cigarette in the past 30 days as the numerator.

31 *See id.*

32 *See id.* (calculated based on information in Wang *et al*. 2020).

33 *See NYTS*, *supra* note 28.

34 *Id.*

35 *Id.*

Importantly, the data show that daily use of e-cigarettes remains rare among youth. Significantly, only 1.8% of students reported using e-cigarettes daily in 2021.[36]

It is critical to point out that JUUL, the popular pod-system, in particular played a significant role in increasing youth flavored ENDS usage in 2018.[37] In contrast, the data in NYTS 2019 and NYTS 2020 suggests that open-system ENDS products are decreasing in favor with youth.[38] In 2020, only 2.6% of NYTS participants reported using a mod or tank (an open-system ENDS device compatible with tobacco and flavored synthetic nicotine e-liquid) which marks a 62% decrease in youth usage from the 2019 to 2020 NYTS.[39]

5. FDA's Unlawful "Fatal Flaw" Review Approach Should Not Be Applied to PMTAs Non-Tobacco Flavored Synthetic Nicotine E-Liquids

Manufacturers of tobacco-derived nicotine ENDS products on the market as of August 8, 2016 had until September 9, 2020, following a court-order, to submit PMTAs for their products in order to keep those products on the market until September 9, 2021. After that date, all ENDS products not subject to a MGO would become subject to FDA enforcement, even if their respective PMTAs were still being reviewed.

As the September 9, 2021 "deadline" approached, due to the fact that hundreds of applications for millions of products had been accepted and filed, FDA implemented a new "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.

More specifically, if an application for such a non-tobacco flavored product did not contain a product-specific randomized controlled trial ("RCT"), longitudinal cohort study ("LCS"), or another similar long-term study demonstrating that the product provides an "added benefit" to adult cigarette smokers in terms of long-term smoking cessation compared to a tobacco-flavored ENDS product, and that such benefit outweighs the "known" risk that flavored ENDS pose to youth in general, the PMTA was issued a marketing denial order ("MDO") as a matter of course. This fatal flaw approach, however, was unlawful as it was arbitrary, capricious, and *ultra vires*, or otherwise not in accordance with law, as detailed below. For these reasons,

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[36] *Id.*

[37] Terry Turner, *How JUUL Created a Teen Vaping Epidemic*, DRUGWATCH (Feb. 18, 2022), https://www.drugwatch.com/featured/juul-created-teen-vaping-epidemic/.

[38] *Id.*

[39] *Id.*

FDA should not take such an approach with the applications for non-tobacco flavored synthetic nicotine ENDS.

First, the TCA requires FDA to conduct a complex, science-based evaluation based on all contents in each application to determine whether a product is appropriate for the protection of the public health ("APPH"). The TCA directs FDA to make that determination "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."[40] Accordingly, FDA has repeatedly described APPH as a multi-factored and multi-disciplinary standard.

On the contrary, FDA's "fatal flaw" procedure relied on a mere box-checking exercise: if the particular long-term cessation study was not present, the Agency disregarded *all* of the other evidence contained in an application FDA has otherwise said would be relevant to an APPH determination. For instance, FDA's 2019 PMTA Guidance for ENDS advises manufacturers to submit studies and other data on a broad range of issues, from toxicological and pharmacological testing, consumer perception and use surveys, and public scientific literature reviews, to strict underage prevention measures and warning labels.[41] In the 2021 PMTA Final Rule, FDA highlighted the importance of providing data on potential health risks, youth access prevention measures, sales and marketing restrictions, and consumer behavioral/perception/intention studies to support submissions.[42] Neither of these documents mentions the "fatal flaw" step for filed PMTAs for flavored ENDS prior to scientific review.

Put simply, Congress did not limit the complex APPH determination to only one issue, in stark contrast to the "fatal flaw" procedure's sole focus on potential cessation benefits of non-tobacco flavored ENDS for adult smokers (compared to tobacco-flavored ENDS). In fact, FDA itself acknowledges this in its recently finalized PMTA Final Rule, in which FDA declined "to assign weight to different types of evidence," emphasizing APPH "requires a balancing" of risks

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[40] 21 U.S.C. §387j(c)(4) (emphasis added).

[41] U.S. FOOD & DRUG ADMIN., PREMARKET TOBACCO PRODUCT APPLICATIONS FOR ELECTRONIC NICOTINE DELIVERY SYSTEMS: GUIDANCE FOR INDUSTRY 34-35 (2019), https://www.fda.gov/media/127853/download.

[42] *See* Premarket Tobacco Product Applications and Recordkeeping Requirements, 86 Fed. Reg. 55,320, 55,395, 55,396 (Oct. 5, 2021) (to be codified at 21 C.F.R. Parts 1100, 1107, & 1114) (noting sales and marketing restrictions, including age-gating on social media, not using celebrities or influencers, and other youth access restrictions are all particularly relevant to FDA's APPH determination, and reserving FDA's right to further impose such restrictions to ensure a product is APPH).

and benefits.[43] FDA refused "to create a series of criteria" that all products must meet for APPH and noted it "will be made with respect to…the population as a whole, rather than whether a product meets each item in a series of specific criteria."[44] Whether non-tobacco flavored ENDS provide a certain level of cessation benefits to adult smokers is only one of many issues that are relevant to the APPH determination. Further, FDA has refused to require its APPH evaluation to turn on public health benefits for selected population segments or products.[45]

Second, FDA failed to provide fair notice of the long-term study requirement in the form of an RCT, LCS, or other similar evidence. In fact, FDA did the opposite – the Agency repeatedly informed manufacturers of tobacco-derived nicotine ENDS that demonstrating APPH would *not* require long-term clinical or cohort studies, or a study going to the specific product comparison described in the MDO. In the 2019 PMTA Guidance for ENDS, for example, FDA stated, "in general, FDA does not expect that applicants will need to conduct long-term studies to support an application" and said it considers long term studies to last six months or longer.[46] Rather, FDA suggested ENDS manufacturers could rely on other sources of information, such as "existing longer duration studies in published literature [on similar products]…and extrapolating from short-term studies."[47]

Regarding data showing potential cessation benefits, FDA concluded that "[a]though randomized clinical trials could address cessation behavior of users of tobacco products, FDA believes this would also be true for observational studies (perception, actual use, or both) examining cessation behaviors."[48] FDA's basis for the MDOs, as identified in the sample Technical Project Lead Memo ("TPL"), is wholly inconsistent with these prior FDA statements.

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43 Premarket Tobacco Product Applications and Recordkeeping Requirements, 86 Fed. Reg. at 55,384-85.

44 *Id.* at 55,386.

45 *Id*. at 55,385.

46 U.S. FOOD & DRUG ADMIN., *supra* note 41, at 13.

47 *Id*.

48 *Id*. at 38.

Perhaps this led to the Fifth Circuit's statement that FDA "pull[ed] a surprise switcheroo on regulated entities."[49]

Third, by failing to adequately evaluate a PMTA, FDA engaged in arbitrary and capricious decision-making.[50] Agency action must be overturned where it did not rely on factors Congress said must be evaluated or consider an important aspect of the problem.[51]

In interpreting the TCA, FDA has said it must consider "all" information in a PMTA, consider the application in its "totality," and evaluate the PMTA on a "case-by-case" basis.[52] By relying on a truncated "fatal flaw" review for other applications, FDA by-passed the multi-disciplinary PMTA review process set out by Congress in the TCA and FDA's own, long-standing interpretation of APPH. In fact, by filing those PMTAs (that were subsequently denied), FDA made "a threshold determination of whether the application contains sufficient information to permit a substantive review."[53] After filing, FDA must "begin substantive review of the application."[54] FDA did just the opposite by issuing boilerplate MDOs for applications that failed its "fatal flaw" review.

Fourth, the TCA's plain language provides that a PMTA shall be denied if "*upon the basis of information submitted* to [FDA]…and any other information before [FDA]" the applicant has not demonstrated APPH.[55] As noted above, the statute defines APPH in broad terms with respect to "risks and benefits to the population *as a whole,"* including "users and

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[49] *Wages and White Lion Invs., L.L.C., v. FDA,* 16 F.4th 1130, 1138 (5th Cir. 2021)(citing *Env't Integrity Project v. EPA*, 425 F.3d 992, 996 (D.C. Cir. 2005) (Sentelle, J.); accord *Azar v. Allina Health Servs.*, 139 S. Ct. 1804, 1810 (2019) (citing the "surprise switcheroo" doctrine)).

[50] 5 U.S.C. § 706(2)(A); *Sierra Club v. U.S. Army Corps Of Eng'rs*, 295 F.3d 1209, 1216 (11th Cir. 2002) (concluding agencies must take a "hard look" at the record).

[51] *Sierra Club*, 295 F.3d 1216; *Marquez-Martinez v. U.S. Attorney General,* 752 Fed. Appx. 832, 835 (11th Cir. 2018); *Wages and White Lion Invs.*, L.L.C., 16 F.4th 1136.

[52] Premarket Tobacco Product Applications and Recordkeeping Requirements, 86 Fed. Reg. at 55,320.

[53] Premarket Tobacco Product Applications, 21 C.F.R. § 1114.27(b).

[54] 21 C.F.R. § 1114.27(c).

[55] 21 U.S.C. § 387j(c)(2) (emphasis added).

nonusers of tobacco products."[56] In this context, the statute enumerates numerous forms of evidence that must be in any PMTA, including data on health risks, ingredient and additive information, manufacturing practices, product samples, labeling specimens, and any other information required by FDA.[57]

By issuing boilerplate MDOs, FDA failed to provide reasoned justification for the Agency's action. Again, Congress intended that any APPH determination be based on a multi-disciplinary, multi-factored analysis weighing all data and information in a PMTA. The APPH standard of review requires FDA to consider not only underage nonusers and adult users, but also any other population demographics that might be impacted by an ENDS product. FDA must gauge not only the relative cessation benefits to adults, which is the "fatal flaw" procedure's focus, but also all other benefits and risks of a given product, including health risks. Under the statute, once FDA receives a complete PMTA, it must do more than a cursory evaluation; it must review and evaluate the application's contents in its entirety.[58] FDA's marketing denials also insufficiently addressed alternatives to issuing MDOs and "failed to consider less disruptive alternatives."[59]

For synthetic nicotine ENDS products, Congress only gave manufacturers a mere 60 days to submit PMTAs following enactment of the legislation on March 15, 2022. FDA has not yet indicated whether it would similarly require long-term RCTs or LCSs for non-tobacco flavored synthetic nicotine products. Rather than adopting a "fatal flaw" box-checking strategy for non-tobacco flavored synthetic nicotine e-liquids, FDA should pivot and change course, particularly considering the recent court rulings set out above, and conduct a thorough review of each PMTA on its individual merits, assuming the applications have met the Agency's acceptance and filing criteria. The 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. Rather, FDA should first extend enforcement discretion to allow these products to remain on the market while the PMTAs are reviewed, and then it should avoid engaging in arbitrary and capricious decision making as it reviews those applications.

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[56] 21 U.S.C. § 387j(c)(4) (emphasis added).

[57] 21 U.S.C. § 387j(b)(1)(A)-(F).

[58] *See City of Arlington. v. FCC,* 569 U.S. 290, 297 (2013) (when agency exceeds power delegated by Congress it acts *ultra vires)*.

[59] *Wages and White Lion Invs., L.L.C., v. FDA,* 16 F.4th 1130, 1136 (5th Cir. 2021).

6. Manufacturers of Synthetic Nicotine ENDS Products Were Not Provided Adequate Time to Prepare PMTAs

As described above, manufacturers of all currently marketed synthetic nicotine products were notified on March 15, 2022 that PMTAs for their products would be due in just 60 days, by May 14, 2022, and that products not authorized by FDA by July 13, 2022 would be in automatic violation of the Act and subject to FDA enforcement. The sudden PMTA deadline for products that were just redefined to be legally tobacco products was not only difficult for companies to fully comply – it was impossible. FDA's PMTA requirements (including long-term data) are extensive, time consuming, and expensive. PMTAs require significant effort to prepare and submit. Companies must retain and deploy a wide array of regulatory and scientific consultants who each specialize in different components of the applications. These specialized consultants were inundated with requests and did not have the capacity to help more than a handful of companies in the 60-day timeframe for submission.

There are approximately a dozen laboratories around the world that are qualified, accredited, and experienced at carrying out required FDA analytical aerosol testing on vapor products. Aerosol testing is a statutory requirement of the Tobacco Control Act and must be included in applications. Those accredited labs have wait times of 6 months to one year to even begin testing products. A very limited number of companies who were first in line for lab space might have had the ability to have their products go through aerosol testing in 60 days.

FDA also requires stability testing to provide data on how the products degrade and react with packaging materials over time. This again entails interacting with a few specialized laboratories that have limited capacity. Once a lab has capacity, products must be stored at specific humidity and temperature conditions for 12 to 24 months, and those products are pulled out of storage at regular 3-month intervals to have analyses run on them. Even under accelerated stability testing protocols, the fastest any meaningful stability testing data can be provided to FDA is 6 months.

PMTAs must also contain environmental assessments which explore how manufacturing by-products and waste from discarded packaging and vaping items impact the environment.

Although we do not agree that the fatal flaw review process is lawful, as detailed above, if FDA still requires PMTAs for non-tobacco flavored synthetic nicotine products to contain RCTs or LCSs, it was clearly impossible to complete these within 60 days. The requirements for these types of long-term studies include:

- Protocols which must be individually designed for each product/company;
- Meetings with FDA to discuss these proposed studies and their design;
- Institutional Review Board ("IRB") approval;
- Recruitment of study participants;

- At least 6 months of data colletion; and
- Analysis of data and preparation of reports.

It is impossible to collect, analyze and report 6 months of data in 60 days. Further, RCTs and LCSs require a minimum of one year to complete after factoring in the time necessary to prepare study protocols, obtain IRB approvals, conduct the studies, assess the results and report the data. Quite simply, the time frames provided were unrealistic and unfeasible.

Accordingly, because Congress failed to provide manufacturers with sufficient time to prepare synthetic nicotine PMTAs, taking into account FDA's own requirements for these applications, it is critical that the Agency not only extend enforcement discretion to these manufacturers as described above, but that the CTP Office of Science allow these manufacturers to continue to submit data and amend their timely applications as new data and evidence is generated.

7. PMTAs for Synthetic Nicotine E-Liquids Should Be Fully Evaluated by FDA and Real-World Evidence and Real-World Data Should Be Considered as Part of the APPH Evaluation

The recently submitted PMTAs for synthetic nicotine e-liquids should be allowed to proceed through FDA's acceptance and filing review phases while the subject products remain on the market. Once these applications are in scientific review, the Agency must, as noted above, fully evaluate the entirety of the applications, as well as consider the significant real-world evidence ("RWE") and real-world data ("RWD") that the products present significant benefits for adult cigarette smokers. Pursuant to Section 910(c)(5) of the FDCA, FDA may consider other "valid scientific evidence" in evaluating whether permitting a tobacco product to be marketed would be APPH.[60] In general, FDA's stance has been that nonclinical studies alone are insufficient to support a determination that permitting the marketing of a tobacco product is APPH.[61] However, given the established benefits that RWD and RWE have provided in streamlining the drug approval process, it follows that RWD and RWE can and should be considered in the authorization process for marketing of non-combustible tobacco products as well, particularly in the context of open-system synthetic nicotine ENDS products and e-liquids.

By way of background, signed into law on December 13, 2016, the 21st Century Cures Act ("Cures Act")[62] amended the FDCA to add, among other provisions, a framework for

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60 21 U.S.C. § 387j(c)(5)(A), FD&C § 910(c)(5)(B).

61 U.S. FOOD AND DRUG ADMIN., *supra* note 41, at 34.

62 21st Century Cures Act, Pub. L. 114–255, 130 Stat. 1033 (2016).

evaluating the potential use of RWE in support of drug approvals.[63] In its guidance document for the framework, FDA distinguishes between RWE and RWD, in which it defines RWD as data relating to patient health status and/or the delivery of health care, collected from a variety of sources, such as electronic health records, and which forms the basis of RWE.[64] FDA further defines RWE as evidence derived from the analysis of RWD about the usage and potential benefits or risks of a medical product.[65]

FDA has encouraged the use of RWD to improve the efficiency of drug development programs that otherwise rely primarily on traditional clinical trials, and it has long relied on RWE to monitor and evaluate the safety of drug products after approval.[66] FDA has issued a series of guidance documents on using RWD and RWE in regulatory decision-making, covering data sources, data standards, and regulatory considerations.[67] FDA has indicated that the issuance of such guidance is expected to provide the public at large with a greater understanding of how RWD and RWE can fit into the regulatory process, and that it will "continue to consider how to optimally incorporate RWD and RWE to provide trustworthy information about the safety and effectiveness of drug therapies."[68] During his nomination process, FDA Commissioner Dr. Robert Califf also indicated his commitment to promoting the use of RWD and RWE that is fit-for-purpose.[69]

FDA has specifically noted that "the premarket review process for ENDS products will provide an opportunity for FDA to further examine the potential of an ENDS product to meet the

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[63] 21 U.S.C. § 355(g), FD&C § 505F.

[64] U.S FOOD &DRUG ADMIN., FRAMEWORK FOR FDA'S REAL WORLD EVIDENCE PROGRAM, 4 (2018).

[65] *Id.*

[66] *See id.* at 7-8.

[67] U.S. Food and Drug Admin., *Real-World Evidence*, *Publications and Guidance* (May 20, 2022), https://www.fda.gov/science-research/science-and-research-special-topics/real-world-evidence#:~:text=Publications%20and%20Guidance.

[68] U.S. Food and Drug Admin., *FDA Issues Draft Guidance on Real World Evidence, Prepares to Publish More in Future* (Jan. 31, 2022), https://www.fda.gov/drugs/news-events-human-drugs/fda-issues-draft-guidances-real-world-evidence-prepares-publish-more-future.

[69] Michael Mezher, *Califf Previews Priorities if Confirmed as FDA Commissioner*, REGULATORY AFFAIRS PROFESSIONALS SOCIETY (Jan. 18, 2022), https://www.raps.org/news-and-articles/news-articles/2022/1/califf-previews-priorities-if-confirmed-as-fda-com.

tobacco product premarket authorization standard of "appropriate for the protection of public health," including adult decisions to completely transition away from use of combustible products to potentially less harmful ENDS products or other non-combustible forms of nicotine delivery."[70] This is supported by RWD that FDA itself has cited to, that, as of 2018, approximately 9 million adults have transitioned to using ENDS from combustible cigarettes,[71] which FDA has found to be less harmful alternative.[72] When FDA issued its first authorization of an ENDS product, former CTP Director Mitch Zeller acknowledged that the data submitted demonstrated how the products benefitted addicted adult smokers by completely or significantly reducing combustible cigarette consumption and exposure to harmful chemicals.[73]

In line with Commissioner Califf's stated commitment to promoting FDA's use of RWE and RWD that is fit-for-purpose, there is a significant amount of RWD available that cannot be ignored when evaluating whether permitting an ENDS product to be marketed would be APPH, particularly, as more data comes to light about the adverse impact of bans on ENDS are having in the form of increasing cigarette sales.[74]

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[70] U.S. FOOD AND DRUG ADMIN., *supra* note 20, at 24.

[71] *Id.*; MeLisa R. Creamer *et al*., *Tobacco Product Use and Cessation Indicators Among Adults – United States, 2018*, MORBIDITY AND MORTALITY WKLY. REP., (Nov. 15, 2019), https://www.cdc.gov/mmwr/volumes/68/wr/pdfs/mm6845a2-H.pdf.

[72] U.S. Food and Drug Admin., *E-Cigarettes, Vapes, and other Electronic Nicotine Delivery Systems (ENDS)* (Mar. 8, 2022), https://www.fda.gov/tobacco-products/products-ingredients-components/e-cigarettes-vapes-and-other-electronic-nicotine-delivery-systems-ends.

[73] U.S. Food and Drug Admin., *FDA Permits Marketing of E-Cigarette Products, Marking First Authorization of Its Kind by the Agency* (Oct. 12, 2021), https://www.fda.gov/news-events/press-announcements/fda-permits-marketing-e-cigarette-products-marking-first-authorization-its-kind-agency.

[74] *See generally* Yingying Xu *et al*. *The Impact of Banning Electronic Nicotine Delivery Systems on Combustible Cigarette Sales: Evidence From US State-Level Policies*, VALUE IN HEALTH (2022), https://www.sciencedirect.com/science/article/pii/S1098301522000080. Results from this study show that cigarette sales in states where ENDS have been banned were higher than would have been observed otherwise in the post-ban period. *Id.* at 5. A full ban on ENDS was associated with increased cigarette sales of 7.5% in Massachusetts ($P < .01$); banning non-tobacco flavored ENDS was associated with 4.6% ($P < .1$) higher-than-expected cigarette sales. *Id.* This study provides evidence that banning ENDS is associated with increased cigarette sales. *Id.*

As detailed in the PMTAs submitted by synthetic nicotine e-liquid manufacturers, there is significant RWD and RWE demonstrating that open-system synthetic nicotine e-liquids and ENDS products are potentially less harmful than combustible cigarettes, and that millions of adult smokers in the United States have been able to transition away from combustible cigarettes with the assistance of ENDS. FDA should consider this RWD and RWE as a basis for taking the actions requested in this petition.

8. Thousands of Small Businesses Will Face A Substantial Risk Of Closing And Extensive Layoffs if FDA Does Not Exercise Enforcement Discretion

The open-system e-liquid industry should not be considered a priority for enforcement by FDA. Destroying the robust open-system e-liquid industry which is dominated by small businesses and, by in large, produces and responsibly markets and sells products designed to assist adult smokers move away from more dangerous combustible cigarettes, would not be APPH.

It is worth noting that this part of the ENDS industry has created a substantial number of jobs and generates a significant amount of excise tax revenue. In 2021, the vapor industry in the United States provided 66,364 direct jobs, and an additional 67,209 jobs through suppliers and ancillary services for a total of 133,573 jobs that are dependent on sales of vapor products. These jobs result in over $7B in annual wages paid from the vapor industry. There are approximately 10,000 independent specialty retailers in the United States devoted to the sale of these products. The total economic impact of the vapor industry in 2021 was over $22B and contributed a total of over $4.7B in federal and state taxes in 2021.

C. Environmental Impact

This action, to the extent that the National Environmental Policy Act ("NEPA") even applies (note that Petitioners are asking FDA to exercise enforcement discretion), would be subject to a categorical exclusion.[75]

D. Economic Impact

Not applicable.[76]

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[75] *See* 21 C.F.R. § 25.30(h) (exempting guidance regarding the submission of applications for product approval).

[76] *See* 21 U.S.C. § 10.30(b)(3). No economic information has been requested by the FDA Commissioner at this time.

E. Certification

The undersigned certifies that, to the best of her knowledge and belief, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

F. Conclusion

The Petitioners and synthetic nicotine e-liquid manufacturers like them have in good faith strived to complete and submit PMTAs prior to the May 14, 2022 deadline, despite having a mere 60 days. They have done so because they believe that their efforts will ultimately help addicted smokers transition to non-combustible ENDS, all while protecting against sales to youth.

In short, the Petitioners request FDA to extend enforcement discretion and allow timely submitted PMTAs submitted by manufacturers of open-system synthetic nicotine e-liquids, who are marketing their products responsibly to adults, to proceed through the acceptance and filing PMTA review phases, while permitting the subject e-liquid products to remain on the market following the end of the "transition period" on July 13, 2022. Specifically, we request that OCE extend enforcement discretion and permit the continued marketing and sale of such synthetic nicotine e-liquids to adults (21+) for the duration of the Agency's full scientific review (*i.e.*, until FDA reaches a final marketing authorization determination) of the respective applications. Furthermore, we request that the FDA CTP Office of Science allow manufacturers of these products to continue to submit additional data as it is developed and amend their timely applications, as 60 days was simply not enough time to prepare all of the product-specific data FDA requires PMTAs contain, including long-term data.

Failure to exercise such discretion will irreparably harm small e-liquid manufacturers who rely on the sale of these products, and will force many such businesses to close, while also depriving millions of adult smokers and tobacco users of a non-combustible alternative to cigarettes – an end result that would be inconsistent with the TCA's goals and would not be APPH.

Respectfully submitted,

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