REAGAN-UDALL FOUNDATION'S
OPERATIONAL EVALUATION OF FDA'S TOBACCO PROGRAM

Comments of the Vapor Technology Association
November 22, 2022

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I. INTRODUCTION

VTA greatly appreciates the opportunity to present its thoughts to the Reagan-Udall Foundation ("Foundation") on the topics which the Independent Tobacco Expert Panel (ITEP) is considering as part of its Operational Evaluation of FDA's Tobacco Program housed in the FDA Center for Tobacco Products (CTP). In advance, we want to thank both the Foundation and the ITEP for the considerable time and attention you are committing to this important process and for the time you will spend considering the issues and recommendations that we raise herein.[1]

The issues confronting FDA's Tobacco Program are exceptionally challenging and the stakes are high as the proper resolution of the issues discussed herein will have a dramatic impact on public health in the U.S. In these comments, we have endeavored not just to make recommendations, but to put them in the broader context with the benefit of our extensive background and experience working on these issues for almost a decade.

The critical process discussed herein issues are interrelated with the broader mission of CTP and, while some comments may skew toward policy (which is outside your purview), the manner in which CTP comports itself going forward and the processes it implements will have a dramatic impact on policy. As we see it, an unapologetic commitment to the scientific process will lead to a dramatic change in the number and diversity of ENDS products authorized for sale in the U.S. and that will lead to a discernable advancement for the Agency and the country.

The past five years have been extremely challenging for all stakeholders in this important industry but particularly for the small vape shop owners in the independent distribution chain who are doing everything they can to comply with FDA regulation so they can continue to interact with the smokers, former smokers, and quitting smokers who enter their shops on a daily basis looking for a meaningful alternative to cigarettes. That said, we must remember that with all the agitation about vaping by regulators, no one is talking about banning cigarettes (Congress won't consider it and Congress barred the FDA from doing so). Since that is the case, the most critical question is what choices adults will have in deciding how to satisfy their nicotine desires. The process implemented by CTP with respect to less harmful ENDS products has arguably done more to ensure the continued ubiquitous dominance of cigarettes in the U.S. than any cigarette marketing campaign. If that process changes materially through the recommendations made by the Foundation and the ITEP there is a real chance that we can accelerate the decline in smoking and reap tangible public health benefits.

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[1] For convenience, we have cited materials with hyperlinks, wherever possible, so that they may be easily accessed. In addition, we have provided an Appendix which includes particularly relevant materials or materials that are not available online. Also, to assist you in navigating the document each section in the Table of Contents has been hyperlinked to allow the reader to jump directly to the relevant section in the document and, when there, jump back to the Table of Contents.

That is why we at VTA are focused on addressing both youth vaping concerns and preserving adult choices. We have always said and still believe that we can and must do both.

II. BACKGROUND ON THE VAPOR TECHNOLOGY ASSOCIATION

The Vapor Technology Association (VTA) is a national trade association, founded in 2015, comprised of leading manufacturers of devices, e-liquids, distributors, suppliers and retailers in the electronic nicotine delivery systems industry and has been engaged on critical issues related to the regulation of less harmful nicotine products. Bucking common stereotypes that industry "opposes all regulation" (which ironically was the first argument made by the first presenter to ITEP on October 21), VTA was founded on the core principles of advocating for science-based regulations and a well-regulated marketplace for vaping and lower risk nicotine products as alternatives to cigarettes and we have consistently put those principles into practice.

In late 2017, VTA adopted strict industry market standards,[2] and then presented them to FDA Commissioner Gottlieb when we met with him in January 2018 underscoring that marketing restrictions, not flavor restrictions, were key to limiting youth appeal. Also, we publicly applauded Commissioner Gottlieb for announcing his Comprehensive Plan for tobacco and nicotine products. In 2018, VTA filed substantial comments regarding the FDA's proposed rule pertaining to the regulatory and information collection requirements for the filing of premarket tobacco applications (PMTAs).[3] In 2019, VTA put forth its own comprehensive plan to address the substantial rise in youth vaping which included support for raising the minimum purchase age to 21 (which the Administration endorsed and Congressed passed in December 2019), as well as implementing strict marketing standards and access limitations to protect youth (items which we continue to push for in Congress, but which Congress has not yet addressed).[4] At the January 2, 2020, announcement of the FDA's partial flavor ban, which applied only to "closed-system" pod and cartridge products, VTA questioned why the Agency also created a loophole exemption for disposable products arguing that such products are the ultimate closed system and noting that disposable products shared all of the same product characteristics which the Agency used to justify the pod/cartridge flavor ban in the first instance.

Most recently, VTA was the only trade group to file comments in *support* of FDA's proposed tobacco product standard to ban menthol in cigarettes.[5] VTA took this pro-regulation position in part because this was the first time in years that the Agency has taken direct action to attempt to reduce the prevalence of combustible cigarettes, and in part based on the expectation that, because FDA's science justifying its proposed menthol standard is dependent upon the

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[2] VTA, *Marketing Standards for Membership*, December 2017 (See VTA Appendix (App.) 1A-5A) .

[3] VTA, *Comment on Existing CTP Regulatory and Information Collection Requirements*, Docket No. FDA-2017-N-5095, February 5, 2018 (App. 6A-30A).

[4] VTA, *21 & Done. A Comprehensive Plan to Address Underage Use of E-Cigarettes*, Vapor Technology Association, October 21, 2019, available at https://vaportechnology.org/wp-content/uploads/2019/10/21-and-done-final-combined.pdf (App. 31A-34A).

[5] VTA, *Comment in Response to FDA's Proposed Tobacco Product Standard for Menthol in Cigarettes*, Docket No. FDA-2021-N-0001, August 2, 2022, available at https://vaportechnology.org/wp-content/uploads/2022/08/VTA-Comment-on-Menthol-Cigarette-Tobacco-Product-Standard-8-2-22.pdf

existence of a robust set of menthol vaping products, the Agency will see fit to authorize such products (something it has failed to do to date).

VTA has a history of constructive engagement with the FDA, having met with past and present Commissioners, past and present CTP Directors, and with the various offices within CTP responsible for the electronic nicotine delivery system (ENDS) category. VTA has been fully engaged both formally and informally in the PMTA process, has participated in the FDA rulemaking and guidance processes, has participated in FDA workshops on PMTA, has provided CTP recommendations for administering and managing the application process, has presented scientific information through, recognized Ph.Ds with appropriate education, expertise and experience, to CTP, and has offered enforcement strategies to CTP to remove bad actors from the market, including with respect to the most recent authority given FDA over non-tobacco nicotine (i.e., synthetic nicotine) products. It is with this background and our historic commitment to science-based regulatory processes that we offer these written comments.

III. BACKGROUND ON THE INDEPENDENT VAPOR INDUSTRY

Contrary the public narrative that has surrounded vaping, neither the products offered nor the industry is monolithic "Big Tobacco" – a term that nicotine and vaping opponents regularly use in a pejorative sense to denigrate all things vaping. Rather, separate and apart from the traditional combustible tobacco products industry, the vaping sector of the industry comprises an entire network of companies, independent of tobacco that did not exist when the Family Smoking Prevention and Tobacco Control Act of 2009, 21 U.S.C. §§ 387-387s ("Tobacco Control Act") was passed.

To fully understand the industry, VTA commissioned economists at John Dunham & Associates (JDA) to first determine the scope of the independent vaping industry and assess its true economic impact on the U.S. economy. According to JDA's economic impact study, "the vapor industry reaches into all corners of the United States, employing 66,364 and generating $2.74 billion in wages" and also that its "businesses directly generate $8.09 billion in economic activity nationally." JDA, at 3 (App. 37A). However, applying its model to assess the full economic impact of such industries when direct, indirect and induced job creation is calculated, JDA found that "the nicotine vapor industry is a dynamic part of the U.S. economy, accounting for about $22.09 billion in output or about 0.10 percent of GDP" and "employs approximately 133,573 Americans who earned wages and benefits of about $7.00 billion." JDA at 2 (App. 36A)

Importantly, the small business component of the vapor industry is also very significant but is often overlooked as regulators and lawmakers focus their attention on the largest companies. Of the 10,527 vapor companies JDA identified, 9,847 of them are small retail vape shops and small vape shop manufacturers. JDA at 6 (App. 40A, Table 3) JDA also found that small shops generate a significant number of the overall industry's 133,000 jobs, as they explained, "about 53,212 jobs are held by people working for the 9,847 independent retail and blending vape shops located across the country." JDA at 7 (App. 41A, Table 4)

Finally, JDA found that, in addition to sales and consumption taxes, of the myriad business taxes paid by firms and their employees, the vapor industry provides, "$1.48 billion to the federal government and $3.23 billion to state and local governments including income taxes, property

taxes, profits taxes, etc." *See* JDA Table 2 of JDA 2021 Study for a complete breakdown of all the taxes generated by industry both at the federal and state/local levels) (App. 39A).

IV. UNDERSTANDING THIS CROSSROADS MOMENT

The Reagan-Udall Foundation's mission of "modernization,… accelerating innovation and enhancing product safety" could not be better applied to any other product category within the FDA's ambit of authority than less harmful nicotine products. This review couldn't have come at a more important time and Commissioner Califf should be applauded for calling for it and Director King should be applauded for embracing it.

FDA's new leaders have an historic opportunity to dramatically change public health in the U.S. by boldly breaking the shackles of the past, eliminating political interference in the scientific process, providing a clear roadmap for the approval of less harmful ENDS and modern oral nicotine products, and accelerating innovation away from the deadliest product on the market – the combustible cigarette. But FDA will not be able to do so, if at all, at a fast enough pace to save the lives of millions of Americans who still smoke cigarettes unless serious process changes are made that will ensure the authorization of myriad desirable alternative nicotine products.

A. Leading Tobacco-Control Scientists Call for a Rebalancing of U.S. Policy on E-Cigarettes.

The most poignant summary of the benefits of vaping, and criticism of the approach taken by U.S. regulators regarding ENDS products, ironically comes from leading tobacco-control scientists. In September 2021, fifteen of the past presidents of the Society for Research on Nicotine and Tobacco (SRNT), the world's most esteemed scientific group on tobacco and nicotine, published a seminal analytical essay in which they directly challenge U.S. policies regarding vaping and the popularized misconceptions regarding vaping and harm to youth and adults. The significance of their essay is its clarion call for a balancing of e-cigarette policy and its summation of the current science demonstrating the importance of recognizing and embracing the harm reduction potential of vaping products.[6]

1. A renewed focus must be placed on helping adult smokers quit smoking through ENDS.

First, the 15 past presidents of SRNT frame their concerns about the imbalanced U.S. policy in striking terms: "We agree with former Surgeon General C. Everett Koop who, in 1998, urged that '[A]s we take every action to save our children from the ravages of tobacco, we should demonstrate that our commitment to those who are already addicted . . . will never expire.' *The latter appears at risk today.*" *Balfour, et al.* at 1662 (App. 45A) (emphasis supplied). Moreover,

[6] David J. K. Balfour, Neal L. Benowitz, Suzanne M. Colby, Dorothy K. Hatsukami, Harry A. Lando, Scott J. Leischow, Caryn Le man, Robin J. Mermelstein, Raymond Niaura, Kenneth A. Perkins, Ovide F. Pomerleau, Nancy A. Rigotti, Gary E. Swan, Kenneth E. Warner, and Robert West: *Balancing Consideration of the Risks and Benefits of E-Cigarettes*, AM. JRNL. PUB. HLTH., 2021, 111(9):1661-1672, available at https://doi.org/10.2105/AJPH.2021.306416 (App. 44A)

these scientists starkly explain how smoking disproportionately affects vulnerable smoking populations:

> "The need to pay attention to adult smokers is particularly important from a social justice perspective. African Americans suffer disproportionately from smoking-related deaths, a disparity that, a new clinical trial shows, vaping could reduce. Today's smokers come disproportionately from lower education and income groups, the LGBTQ (lesbian, gay, bisexual, transgender, and queer or questioning) community, and populations suffering from mental health conditions and from other drug addictions. […] Smoking accounts for a significant proportion of the large life expectancy difference between affluent and poorer Americans. For smokers with serious psychological distress, two thirds of their 15-year loss of life expectancy compared with nonsmokers without serious psychological distress may be attributable to their smoking. Vaping might assist more of these smokers to quit."

Id. at 1667 (App. 50A).

The 15 past presidents of SRNT explain why adult smokers have been forgotten: "To the more privileged members of society, today's smokers may be nearly invisible. Indeed, many affluent, educated U.S. persons may believe the problem of smoking has been largely 'solved.' They do not smoke. Their friends and colleagues do not smoke. There is no smoking in their workplaces, nor in the restaurants and bars they frequent. Yet 1 of every 7 U.S. adults remains a smoker today. Smoking will claim the lives of 480,000 of our fellow citizens this year alone." *Id.* This is a COVID-style event every two years.

Second, these staunchly anti-tobacco scientists warn that U.S. regulators are not taking seriously the significant impact which ENDS products could have on reducing adult smoking:

> "Many, including this article's authors, believe that vaping can benefit public health, given substantial evidence supporting the potential of vaping to reduce smoking's toll. […] While evidence suggests that *vaping is currently increasing smoking cessation*, the impact could be much larger if the public health community paid serious attention to vaping's potential to help adult smokers, smokers received accurate information about the relative risks of vaping and smoking, and policies were designed with the potential effects on smokers in mind. *That is not happening*."

Id. at 1662 (emphasis supplied).

2. Leading tobacco-control scientists challenge the "singular focus" on youth vaping and put youth concerns in perspective.

The 15 past presidents of SRNT directly warn that U.S. regulators' myopic focus on youth vaping has hindered smoking cessation: "To date, the singular focus of U.S. policies on decreasing youth vaping may well have reduced vaping's potential contribution to reducing adult smoking." *Id.* at 1666 (App. 49A) What follows are direct quotes from the 15 past presidents of SRNT on why the singular focus on youth is misplaced based on the robust body of existing science cited in their essay.

a. Putting concerns regarding youth vaping in context.

"Several considerations raise the question of whether, for youth as a whole, vaping creates dangerous levels of nicotine exposure that would not have occurred in the absence of vaping.

- The large majority of nontobacco product–using young people do not vape and, thus, have no nicotine exposure.
- Among those who vape, most do so infrequently; many are short-term experimenters.
- Frequent vaping is most common among current or former smokers, individuals already exposed to nicotine.
- The most dangerous form of youth exposure to nicotine, cigarette smoking, has declined at an unprecedented rate during the era of youth vaping. Use of other tobacco products has declined as well."

Id. at 1665 (App. 48A). Further they explain that compared to the acute and real harms being suffered by addicted adult smokers, "Young people will not experience smoking-related (and conceivably vaping-related) chronic diseases for three decades, and likely not at all if they quit within a decade or two. Social pressures to quit smoking will probably remain strong, and quitting aids may improve. Furthermore, as noted previously, the rate of smoking among young people has declined while vaping has increased." *Id.*

b. Dispelling myths about youth vaping & addiction

"Vaping likely addicts some young people to nicotine. However, the evidence does not suggest it is addicting very large numbers. Jarvis et al. concluded that 'Data ... do not provide support for claims of a new epidemic of nicotine addiction stemming from use of e-cigarettes.' Jackson et al. recently reported that the e-cigarette–driven increase in nicotine product use among high-school students is not associated with an increase in population-level dependence. Among tobacco-naïve youths, in addition to low vaping prevalence (9.1% in the past 30 days in 2020) and frequency (2.3% vaping 20 days in the past 30 days), small percentages exhibited signs of nicotine dependence." *Id. at* 1664 (App. 47A).

"Frequent use is much more common among current or former smoking youths than among never-smokers. Many former smokers were already addicted to nicotine before initiating vaping. With high-school students' smoking declining at an increasing rate since youths began using e-cigarettes, some may vape to reduce or quit smoking. Nonetheless, to the extent that vaping creates nicotine addiction among otherwise tobacco-naïve youths, concerted efforts are needed to reduce youth vaping." *Id.*

"Vaping may addict some youths to nicotine, but many fewer than popularly believed."

c. Dispelling myths about youth vaping & harm to the developing brain

"[S]tudies lead some researchers to suspect that adolescent nicotine use in any form may lead to long-term structural and functional brain changes with associated negative implications for cognition or impulse control. However, given species differences and questions about the relevance of experimental animal nicotine dosing paradigms to human use patterns, the validity of extrapolation to humans is speculative. Whether impaired brain development with behavioral

consequences occurs in young nicotine consumers is difficult to determine because of potential confounding of genetic and socioeconomic factors, the influence of other substance abuse, and the role of preexisting neuropsychiatric problems associated with youth smoking. Research has yet to isolate nicotine use in the adolescent years and then examine later sequelae." *Id.* at 1665 (App. 48A).

d. Dispelling myths about youth vaping & smoking initiation

On the surface level, the mere fact that youth smoking is at an all-time low, despite an increase in vaping, makes any gateway claim suspect. But the 15 past presidents explain why such often repeated claims are tenuous noting that in studies used to assert a gateway, the "numbers of cigarettes smoked at follow-up are frequently very low, only one or two in the past 12 months in one study." *Id.* They go on to note that, "*Shahab et al.* reported that less than 1% of U.S. students who initiated nicotine or tobacco use with e-cigarettes were established cigarette smokers." *Id.* After reviewing the various studies on both sides, they explain that the actual risk to youth is small, "If vaping causes some young people to try cigarettes, the aggregate impact must be small. A recent study estimated that if vaping increases non-smoking youths' odds of trying cigarettes by 3.5 (as reported by *Soneji et al.*), smoking initiation among young adults would increase less than 1 percentage point. Furthermore, U.S. survey data demonstrate that smoking among young people has declined at its fastest rate ever during vaping's ascendancy. If vaping increases smoking initiation, other unknown factors more than compensate." *Id.*

However, those other factors are not considered in the studies: "Obvious plausible correlates are often not considered, however. Importantly, few studies include youths' use of other psychoactive substances, including marijuana and alcohol. In one study, inclusion of marijuana and three other variables eliminated the otherwise statistically significant link between vaping and subsequent smoking. Most studies do not even consider previous use of tobacco products other than cigarettes. Adjustment for confounders substantially reduces the relationship between vaping and subsequently trying cigarettes." *Id.*

B. In Addition to the Scientific Justifications, the Continuing Decline in Youth Vaping Justifies Changes in CTP Process to Accelerate ENDS Authorizations.

Last month, CDC released the latest results of the annual National Youth Tobacco Survey (NYTS).[7] This survey is a good directional benchmark and tracks self-reported habits around the frequency of smoking and vaping among middle and high school students. When youth vaping peaked in 2019, 27.5 percent of young people reported vaping. Since then, according to the CDC, the number of high school students who vape (i.e., tried it once in the last 30 days) has dropped by 50 percent and the number of middle school students who vape has plummeted by 70 percent. During that same period of time, the number of high-school students who 'frequently' vape has dropped by 37 percent and the number of middle school students has dropped by 65 percent. (App.

[7] Cooper, Maria, PhD, et al., *Notes from the Field: E-cigarette Use Among Middle and High School Students — United States, 2022*, Morbidity and Mortality Weekly Report, 71(40);1283 – 1285, October 7, 2022, https://www.cdc.gov/mmwr/volumes/71/wr/mm7140a3.htm?s_cid=mm7140a3_w. (App. 56A)

56A). As a result, youth vaping has returned to 2014 levels as can be seen in the following graphic which plots historic youth vaping rates.

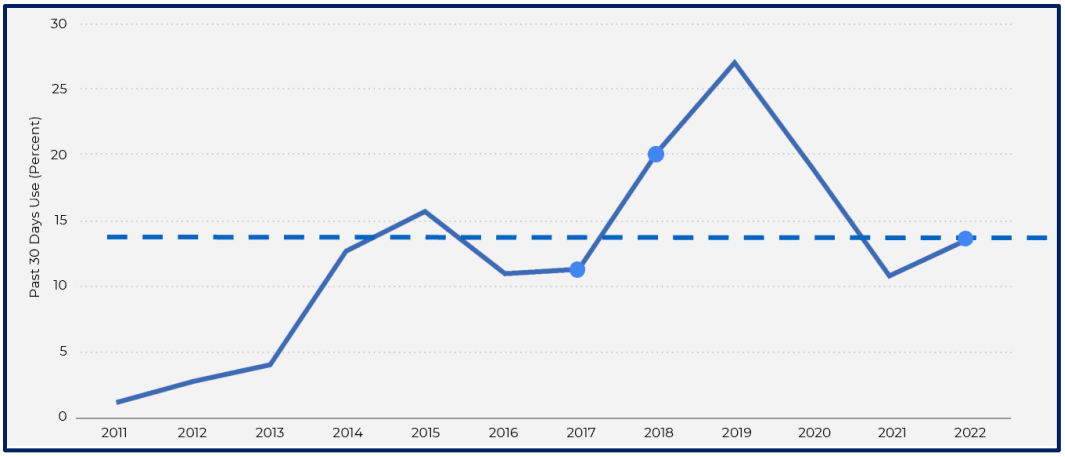

Figure 1: Historic Rates of Youth E-Cig Use (NYTS)

The importance of this moment cannot be overstated yet, instead of heralding the dramatic reduction in youth vaping, regulators have used the most recent NYTS data to alert that youth vaping "remains high", that "2.5 million U.S. youth currently use e-cigarettes," and that flavors are popular.[8] (App. 59A) But a closer look at the numbers demonstrates enormous progress as youth vaping has continuously and dramatically declined for the past three years from its 2019 peak.[9] This decline demonstrates the impact of raising the age to purchase tobacco products in December 2019. In fact, overall U.S. youth nicotine use is lower today than any time in the last 50 years. FDA's near single-minded focus on youth who experiment with vaping without even referencing the data showing the lowest youth smoking rates in history ignores the clear and consistent trend of our kids away from vaping products and nicotine altogether. By presenting the data in this way – it creates confusion among policymakers and consumers that will lead to the dangerous policy outcomes identified above.

The fact that fewer teens vape today than even smoked in 2012 should be treated as a public health victory rather than a continuing crisis. Moreover, this progress is occurring despite the wide availability of flavored products chosen by adults is a preferred smoking reduction, if not cessation, tool. If regulators are willing to recognize that flavors play an important role in helping adult smokers quit and that we can still reduce youth vaping further despite their availability – the next steps will become self-evident.

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[8] FDA, *New Data Show More Than 2.5 Million U.S. Youth Currently Use E-Cigarettes*, October 6, 2022, https://www.fda.gov/news-events/press-announcements/new-data-show-more-25-million-us-youth-currently-use-e-cigarettes (App. 56A).

[9] FDA and CDC note that the 2021 data is likely underreported since the NYTS survey was taken only online due to COVID. Hence, the expectation is that the 2021 was slightly higher than reported.

C. FDA and CTP Leadership Must Pick a Path.

FDA is at a crossroads where it must decide whether it is going to move aggressively to help the 30+ million Americans who remain addicted to cigarettes and the nearly half a million Americans who will die in this year, and the next, and the next, ad infinitum. Or will the Agency remain trapped in its heretofore myopic youth paradigm. The leadership of FDA's Center for Tobacco Products recently acknowledged, once again, that "e-cigarettes – as a general class – have markedly less risk than a combustible tobacco product." This is a positive sign that FDA recognizes its dual mandate – that they must reduce youth vaping/tobacco use while continuing to reduce adult smoking – even if they are not willing to say it that way. However, these words must be converted into authorization actions which have been stymied by a PMTA process that has been perverted by external influences.

To be sure, eight years after the Deeming Rule was first published and six years after it took effect, the Agency has approved only a handful of ENDS products. Included in these small number of approvals are antiquated products some of which are not even on the market at all. In that same period of time, in the United Kingdom, public health authorities (with an admittedly different regulatory process) have approved nearly a million less harmful nicotine products based on the enormously robust science which unequivocally demonstrates the dramatically reduced risk they offer and the actual positive impact of reducing cigarette smoking – a goal that we share but which, to date, the FDA has been unable to achieve.

But the fact that this review is necessary suggests that something has gone decidedly wrong with how FDA and CTP have historically handled the regulation of tobacco products, particularly less harmful ENDS products. For perspective, the events immediately preceding the convening of this independent review are emblematic of numerous questionable actions taken by FDA. On June 22, 2022, the denial of JUUL Labs, Inc.'s premarket tobacco applications was leaked to the national press.[10] On June 23, 2022, FDA issued its marketing denial orders (MDOs) to JUUL,[11] and on the following day a federal court stayed enforcement of the MDOs.[12] Then, on July 5, 2022, on his first day on the job and to his credit, CTP Director King issued an administrative stay of the JUUL MDOs explaining, "The Agency has determined that there are scientific issues unique to the JUUL application that warrant additional review."[13] The fact that after reviewing the JUUL applications for two years CTP issued a denial without having fully reviewed the science submitted sounded alarms within the industry and in the scientific community. Whatever had happened, it was only two weeks later than Commissioner Califf boldly called for this independent review by the Reagan-Udall Foundation.

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[10] Paramasivam, Praveen, *Juul e-cigarettes to be ordered off U.S. shelves*, Wall Street Journal, 6/22/22, https://www.reuters.com/world/us/us-fda-order-juul-e-cigarettes-off-market-wsj-2022-06-22/.

[11] FDA, *FDA Denies Authorization to Market JUUL Products*, 6/23/22, https://www.fda.gov/news-events/press-announcements/fda-denies-authorization-market-juul-products.

[12] Suliman, Adela, *Court temporarily halts FDA ban on Juul e-cigarettes*, Washington Post, 6/25/22, https://www.washingtonpost.com/business/2022/06/25/juul-vaping-cigarettes-fda-ban-appeal/.

[13] Jewett, Christina, *FDA Lets Juul Appeal Ban and Stay on the Market During a Review*, 7/6/22, https://www.nytimes.com/2022/07/06/health/juul-fda-ecigarettes.html.

Hence, while the Reagan-Udall Foundation's charge for this review is limited to process, make no mistake that your recommendations can and will directly impact a policy inasmuch as it appears that past process changes have, either intentionally or unintentionally, had significant policy. We are at moment where FDA must pick a path – either the Agency can continue to make decisions that will push smokers back to cigarettes, or it can incentivize access to innovative, non-combustible nicotine technologies that provably reduce harm for smokers. It is our sincere hope that in years hence, with the Reagan-Udall Foundation and the ITEP's guidance and recommendations, the Agency will be able to recite the words of the poet Robert Frost, "Two roads diverged in a wood; I took the one less traveled by, and that has made all the difference."

V. VTA COMMENTS ON THE APPLICATION PROCESS

A. What the Agency has done well.

There is no question that the Agency has done some things well in managing the tobacco product application process. First, in 2017, Commissioner Gottlieb announced a Comprehensive Plan for addressing tobacco and nicotine issues. Foreseeing the challenges of PMTA compliance, Gottlieb extended the deadline for filing from 2018 to 2022 since the Agency still needed to "issue foundational rules to make the product review process more efficient, predictable, and transparent for manufacturers." See, Comprehensive Plan (App. 63A). Second, Commissioner Gottlieb's Comprehensive Plan[14] also expressly acknowledged the continuum of risk of all tobacco products and explained that ENDS products fall at the lower end of the risk continuum when compared to cigarettes. *Id.* (App. 62A). Third, CTP issued an Advance Notice of Proposed Rulemaking (ANPRM) on the important issue of flavors to examine their impact on initiation and on smoking cessation.[15] Fourth, CTP has effectively administered its Substantial Equivalence (SE) application process for reviewing new tobacco products, efficiently reviewing and authorizing myriad products.

Unfortunately, these positive steps have not led to the successful execution of CTP's mission which is to "make cigarettes part of America's past and not America's future." VTA analyzed all of FDA reports of authorizations issued by CTP under the Substantial Equivalence and Substantial Equivalence Exemption processes and found that, since January 2020, CTP's efficient management of the SE process has bizarrely resulted in the authorization of 600 new combustible tobacco products, *250 of which are new cigarettes*.[16] In stark contrast, FDA's management of the PMTA process has resulted in the authorization only 6 less harmful ENDS devices (some of which are antiquated technologies and/or are not even on the market anymore),

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[14] FDA, Press Release: *FDA Announces Comprehensive Regulatory Plan to Shift Trajectory of Tobacco-Related Disease, Death* (July 28, 2017) (quoting Commissioner Gottlieb: "Envisioning a world where cigarettes would no longer create or sustain addiction, and where adults who still need or want nicotine could get it from alternative and less harmful sources, needs to be the cornerstone of our efforts – and we believe it's vital that we pursue this common ground"), https://www.fda.gov/news-events/press-announcements/fda-announces-comprehensive-regulatory-plan-shift-trajectory-tobacco-related-disease-death ("Comprehensive Plan").

[15] FDA, Regulation of Flavors in Tobacco Products, Docket No. FDA-2017-N-6565 (March 2018), https://www.regulations.gov/document/FDA-2017-N-6565-0001.

[16] FDA, Marketing Orders for SE, available at https://www.fda.gov/tobacco-products/substantial-equivalence/marketing-orders-se (May 31, 2022).

and the questionable denials of thousands of applications covering hundreds of thousands of ENDS products.

B. What the Agency has not done well.

First, the FDA abandoned its Comprehensive Plan and did everything but create the "efficient, predictable, and transparent" process Gottlieb said was necessary. (App. 63A). CTP never finalized the "foundational rule" for PMTAs before applications were filed and it acquiesced to a 2-year acceleration of the filing deadline notwithstanding the unavailability of that final rule. This forced companies to rely on non-binding guidance, rush scientific research and data collection, submit redundant applications, and conduct unnecessary testing.

Second, CTP failed to apply the continuum of risk in its comparative assessment of ENDS to cigarettes, failed to distinguish between open and closed ENDS products, and perpetuated a narrative that all flavored products are attractive to youth.

Third, CTP abandoned its ANPRM on flavors after 2018, never issued a proposed rule on ENDS flavors, and ignored the enormous body of science presented by all stakeholders, including VTA which spent considerable resources to provide CTP a highly substantive and balanced review of every flavor study that had been conducted.[17]

Fourth, CTP altered its review process and standards *after* applications had been accepted for substantive review and has acknowledged issuing marketing denial orders (MDOs) ***without*** conducting a full balancing of all APPH requirements and without a full substantive review of all flavored ENDS applications, as set forth in more detail below. CTP also recently used this same approach to deny Logic's menthol ENDS applications *after* already authorizing sale of Logic's tobacco-flavored ENDS products.[18] Similarly, JUUL's denial in July 2022 is an excellent example of where CTP claimed that concerns regarding one subset of data (genotoxicity) justified the issuance of a MDO. As JUUL pointed out in its legal filing, not only did the company actually present 6000 pages of data which CTP claimed was missing, the Agency's singling out of one set of data on which to based the MDO means that it failed to complete a holistic review of the applications balancing all of the factors required in making an APPH determination.[19]

Fifth, CTP has allowed external forces, including Members of Congress and vocal special interest groups, to invade and alter its scientific review process, particularly as it relates to flavored ENDS.

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[17] VTA, *Comment on Regulation of Flavors in Tobacco Products*, Docket No. FDA-2017-N-6565 (July 19, 2018) (App. 65A).

[18] FDA, Press Release: *FDA Denies Marketing of Logic's Menthol E-Cigarette Products Following Determination They Do Not Meet Public Health Standard*, at https://www.fda.gov/news-events/press-announcements/fda-denies-marketing-logics-menthol-e-cigarette-products-following-determination-they-do-not-meet#:~:text=Today%2C%20the%20U.S.%20Food%20and,Power%20Menthol%20e%2DLiquid%20Package (October 26, 2022).

[19] Article, *FDA Suspends Juul Market Ban Pending Court Appeal*, Vapor Voice, July 6, 2022, at https://vaporvoice.net/2022/07/06/fda-suspends-juul-ban-pending-appeal/.

1. CTP's *En Masse* Rejection of Flavored ENDS PMTAs

The most significant example of how the Agency's *prior* interim leadership allowed outside influences to subvert the PMTA scientific process must be fully understood. In August 2020, CTP's Office of Science documented its process for reviewing applications for flavored ENDS products and explained that it anticipated approving such products as APPH.

On June 11, 2021, the Director of the Office of Science convened a two and a half hour public meeting and transparently described CTP's PMTA review process.[20] During this meeting, CTP announced it had "created a separate queue for the manufacturers with the largest market share" (e.g., JUUL and large tobacco companies) and triaged their PMTAs over all others explaining that resolving those PMTAs would have "the greatest public health impact." (App. 145A). CTP also explained that it "randomized" the review of PMTAs covering millions of products made by smaller, open system manufacturers. *Id.* Further, CTP admitted it wouldn't be able to review all PMTAs by September 9, 2021, but would decide the triaged PMTAs and then continue to review the remaining PMTAs thereafter using enforcement discretion on a case-by-case basis for those companies whose applications have not yet been reviewed after September 9, 2021.

In response to the specific question, "If there is no long-term health data about how a product will effect public health, will that product receive a deficiency letter," CTP's Director of the Office of Science responded: "I think in that scenario, we would like to send a deficiency letter. … I think once we get a substantial scientific review, as we've said a couple of times this afternoon, our intent is to issue a single deficiency letter. And as I explained with the new language we put in the PMTA deficiency letter, specifically, the intent of those letters is to identify information that we think is necessary to complete our review and make it and make our final determination on whether to issue marketing brand [sic: granted] or marketing denying [sic: denial] order. **So if there is missing information like no long term health data about the product, we would likely put a deficiency, likely send the deficiency letter."** (App. 173A).

Little did the CTP know, all that was about to change. On June 23, 2021, FDA's Acting Commissioner Janet Woodcock was summoned to testify before Congress.[21] Before she testified, Woodcock was confronted with a video in which kids and parents directly targeted her by name, imploring her to remove all flavored e-cigarettes from the market. Then, some committee members demanded that Woodcock deny JUUL's PMTAs and deny any flavored e-cigarette PMTAs claiming it was her responsibility to protect kids regardless of the science.[22] The hearing was a

[20] FDA, "Deemed Product Review: A Conversation with the Office of Science," June 11, 2021, https://www.fda.gov/tobacco-products/ctp-newsroom/deemed-product-review-conversation-center-tobacco-products-office-science-06112021-06112021#4 (See Transcript of Meeting, App. 139A-215A).

[21] Hearing, *An Epidemic Continues: Youth Vaping in America*, House Subcommittee on Economic and Consumer Policy, Committee on Oversight and Reform, 117th Congress, June 23, 2021 (App. 179A-215A).

[22] For example, Congresswoman Porter: "The only way to protect our kids is to deny premarket tobacco product applications for every flavored e-cigarette other than tobacco flavor. Will you commit to doing that?" (App. 200A).; Congresswoman Bush: "The FDA must take drastic steps to ban the uses of—usage of JUUL products and minimize the negative impact on our youth…. The FDA has an obligation to intervene and protect our children."

disaster. Woodcock did little to defend the FDA's process or its dedicated employees, did little to defend the rule of science in FDA's decision-making process, and when asked if she trusted FDA's "Tobacco Products Scientific Advisory Committee [sic]" she clumsily admitted "I am not familiar with this committee." (App. 213A)

Immediately after the hearing, we learned from those inside the FDA that Acting Commissioner Woodcock injected herself on the flavor issue. Two weeks thereafter, on July 9, 2021, in an internal memorandum from Anne Radway and co-signed by CTP's Director of the Office of Science, CTP documented the Acting Commissioner Woodcock's interjection:

> "*To date, OS has implemented its plan to review a subset of these [flavored ENDS] applications*…using a plan described in the Premarket Application Review Prioritization Plan memorandum signed August 31, 2020. *Office of Science has been tasked with developing a new plan* to effectively manage the remaining non-tobacco flavored ENDS PMTAs not in Phase III, substantive scientific review. *This task has been assigned by the acting commissioner* … in order to take final action on as many applications as possible by September 10, 2021. The objective is to address these applications by applying a standard for evidence necessary to demonstrate an incremental benefit to adult smokers of non-tobacco flavored ENDS products." [23]

Of course, this drastic change in process reflected a complete reversal of both the process and priorities that the Office of Science announced less than one month earlier when it stated that it was prioritizing JUUL's and other large companies PMTAs for decisions by September 9, 2021, something that the Acting Commissioner also told Congress on June 11, 2021.

All who understand government, understand that the Office of Science wanted to make clear to the world that it had been implementing a specific process for reviewing applications and was instructed by an Acting Commissioner to change that process which they knew would ensure an alternative outcome than may have otherwise been reached.

In addition, the July 9, 2021 Memo is significant for the new standards it created 11 months *after* applications had been filed. First, CTP established, for the first time, a new evidentiary prerequisite: applicants were required to have submitted long term studies (i.e., randomized control trials (RCT) or longitudinal cohort studies. Second, CTP decided that the "absence of these types of studies is considered a fatal flaw, meaning any application lacking this evidence will likely receive a marketing denial order (MDO)." Third, CTP pulled "a selected list of applications out of their respective place in the PMTA priority list." See, July 9, 2021 Memo (App. 216A-217A).

(App. 206A, 207A); Congresswoman Wasserman Schultz: "To be clear, you should reject all of JUUL's products, all of them…" (App. 211A).

[23] FDA, Memorandum from Radway / Holman, ENDS Containing Non-Tobacco Flavored E-Liquid: Approach to PMTAs not in Substantive Scientific Review (Phase III), July 9, 2021 (the "July 9, 2021 Memo") (App. .216A).

Then, on August 17, 2021, CTP more fully explained its changed process and new standard.[24] First, CTP claimed that all flavored ENDS are attractive to youth – a scientifically flawed position that FDA had never before taken. (App. 232A-233A). Second, to overcome "this high burden" of youth risk, applicants would have to already have submitted long-term RCTs demonstrating the benefit of their flavored ENDS for creating smoking cessation. Third, applicants were to already have submitted similar studies which also proved that their flavored ENDS products "had an added benefit relative to that of tobacco-flavored ENDS in facilitating smokers completely switching away from or significantly reducing their smoking." (App. 228A-229A). Most importantly, CTP said, "We intend to conduct a streamlined scientific review of PMTAs for flavored ENDS to determine whether the applications contain evidence of this type….In the absence of this evidence, we generally intend to issue a marketing denial order." (App. 229A).

Less than one month after the Office of Science laid out its process and priorities on June 11, at the direction of the Acting Commissioner everything changed: flavored ENDS, not JUUL, became the priority; product-specific long-term studies on smoking cessation became a prerequisite though CTP had said they were not a requirement; a streamlined fatal flaw process was implemented to issue marketing denial orders, rather than deficiency letters the Office of Science said would be issued on June 11, 2021; and decisions were made without a good faith review of any other parts of the applications, including any of the other science submitted.

Remarkably, less than one month later, FDA used its "Fatal Flaw" analysis to reject thousands of open-system flavored ENDS PMTAs filed by hundreds of companies covering millions of products.

[24] FDA, Memorandum from Apelberg / Holman, PMTA Review: Evidence to Demonstrate Benefit for Flavored ENDS to Adult Smokers, August 17, 2021 (the "August 17, 2021 Memo").

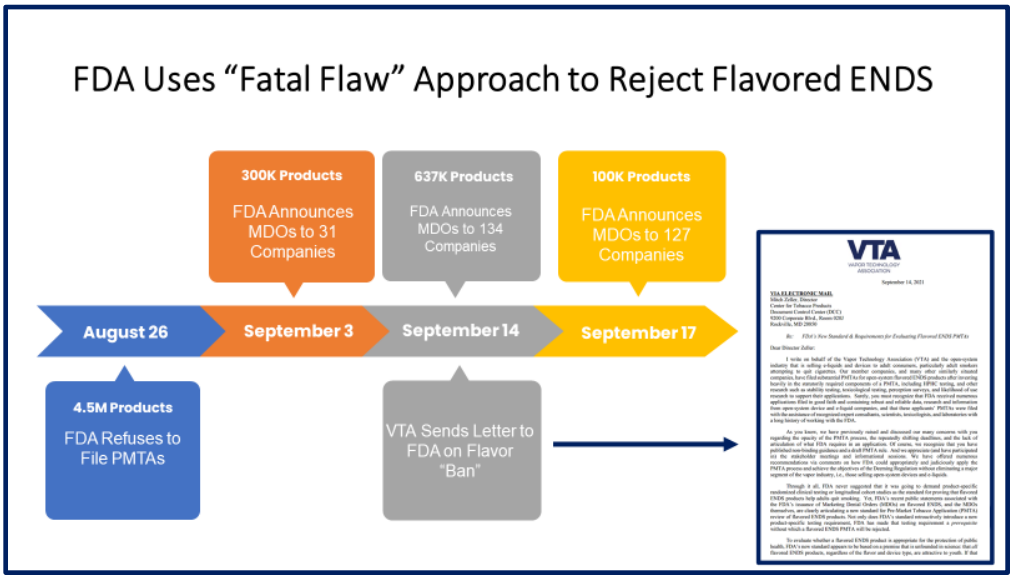

Figure 2: FDA's 2021 Fatal Flaw MDOs

This dramatic process change implemented a de facto policy change and as it was unfolding in September 2021, we heard from people inside FDA who were stunned that the Agency had changed its position on flavors "without any scientific support." As a result, on September 14, 2021, VTA wrote to Director Zeller to raise serious concerns about the implications of the sudden and dramatic change of process in how flavored ENDS applications were being handled. In our letter, we raised numerous concerns. First, the product specific long-term study requirements were revealed for the first time eleven months after the PMTA deadline giving flavored ENDS applicants no chance to comply. Second, FDA's claim that that all flavored ENDS are attractive to youth is "unfounded in science." Third, the category-wide denial of flavors appears to be politically motivated after the Acting Commissioner's haranguing by Congress. Moreover, FDA's rationale for quickly resolving as many ENDS PMTAs by September 10, 2021, was a fiction since FDA repeatedly stated that there was no such deadline and since, as of that writing, FDA still had not announced any decision on JUUL or the majority of PMTAs from the largest manufacturers – the decisions FDA stated would have "the greatest public health impact."[25]

Thus, we were not surprised by the fact that, recently, FDA staff participating in this Reagan-Udall Foundation review so unequivocally articulated our worst fears: that the process had in fact been perverted to accomplish other objectives not based in science. Some of the most alarming staff comments are quoted here:

- "In cases where reviews are finished and scientific decisions are made they are also overruled by political agendas and *pushed to change* decisions."

[25] VTA, Letter to Director Mitch Zeller re: Changing PMTA Standards, September 14, 2021 July 9, 2021 Memo (App. 243A-245A).

- "Politics are being permitted to drive the science and even limit or *alter science-based decisions*."
- "Reviewers in the…Office of Science…lack autonomy to exercise best scientific practices in their application reviews or express differing scientific opinions."
- "Scientific disagreement is frowned upon, if not entirely suppressed and punished…"
- "In some divisions … a 'gotta get em' mentality …, which is unsupportive of a reviewer's fundamental duty to provide an unbiased review…"
- Need "extra barrier of isolation to prevent such *influence* with the scientists..."
- Need "a culture shift to promote that the scientists follow the science and not be *influenced by non-scientists* especially in terms of application review."

2. Leading Tobacco-Control Scientists Warn Against FDA's Efforts to Eliminate Flavored ENDS.

The 15 past presidents of SRNT specifically raise the striking concern that efforts to restrict adult access to flavored vaping products is hampering public health objectives of reducing adult smoking:

> "To date, the singular focus of U.S. policies on decreasing youth vaping may well have reduced vaping's potential contribution to reducing adult smoking. Those policies include … decreasing adult access to flavored e-cigarettes that may facilitate smoking cessation and convincing the public—including smokers—that vaping is as dangerous as smoking."

Balfour et al., at 1666 (App. 44A). Instead of flavor bans, these scientists explain the need for balanced policies: "Policies regarding flavors reflect the more general issue considered in this article: the need to create a balance between the sometimes-conflicting goals of preventing youth vaping and supporting adults' smoking cessation attempts, particularly for smokers unable or unwilling to quit otherwise." *Id.* at 1664 (App. 47A). Yet, FDA's fatal flaw approach failed to include any balancing whatsoever, as described in more detail below.

Based on all the foregoing, VTA offers the following recommendations.

C. VTA Recommendations for Changes to the Application Review Process.

1. FDA must implement safeguards at CTP to ensure that the review process is insulated from external pressures and that CTP scientists are allowed to unapologetically follow the science.

Unless the process is insulated from external pressures, whether they be from interest groups or Members of Congress, CTP will be unable to execute its mission and public confidence in FDA decisions will be undermined. While FDA cannot stop pressure from being exerted on it, it must impose firewalls and processes that prevent, for example, what occurred in the summer and fall of 2021 when the Acting Commissioner of the Agency interjected herself into the deliberations

of the Office of Science, something so significant that the Office of Science leadership felt compelled to document in writing in the July 9, 2021 fatal flaw memo and which FDA staff felt compelled to raise with you.

The Office of Science must be allowed to:

- complete its reviews of applications without interference or changes in review protocols/standards which were not in place *prior to* applications being filed;
- review applications in a timely manner, and not be rushed to issue decisions to achieve external messaging priorities;
- engage directly with companies or, at least, issue multiple deficiency letters to companies, giving them the opportunity to address and cure deficiencies, or explain why they are not deficiencies;
- communicate its decisions to companies *before* the Agency issues a press release to the public; and
- communicate its decisions to companies, and then the marketplace, when they are made rather than having those decisions held until such time as the Agency chooses to announce them.[26]

2. Immediately rescind the July 9, 2021 and August 17, 2021 processes and restore the holistic review process and the primacy of the APPH balancing test.

CTP acknowledges that it is required by statute to conduct a full review of all three prongs of the APPH balancing test,[27] but the examples cited above demonstrate that it hasn't done so, instead adopting a process for flavored ENDS that prevents true balancing and which improperly permits CTP to *not* review all the scientific evidence submitted by applicants. In 2021, *after* applications were filed in 2020, CTP established a new standard for flavored ENDS applications that imposed a new, non-product-specific *presumption* regarding initiation (finding, without scientific support, that that ALL flavored products are attractive to youth) while demanding long-term "product specific" randomized control studies regarding cessation. Specifically, despite the fact that on June 11, 2021, CTP's Office of Science held a public meeting reiterating and clarifying that product-specific long-term studies were *not* a requirement, less than a month later, at the

[26] We have heard that the Office of Science has made decisions on product applications but CTP has not announced those decisions. This is not farfetched given the fact that, after two and a half years, CTP has only issued one decision regarding a menthol product despite the fact that CTP has reviewed thousands of applications covering innumerable menthol products.

[27] There are three prongs to the statutorily required "appropriate for the protection of public health" balancing test which requires FDA to consider scientific evidence concerning:

(i) the risks and benefits to the population as a whole, including users and nonusers of tobacco products;
(ii) the increased or decreased likelihood that existing users of tobacco products will stop using such products; and
(iii) the increased or decreased likelihood that those who do not use tobacco products will start using such products.

Acting Commissioner's direction, the Office of Science changed its review process to demand such studies and, in their absence, denied applications rather than issuing a deficiency letter. This is double standard that drives four related recommendations.

First, CTP should return to the review process the Office of Science outlined in 2019 –and that it was following until the Acting Commissioner interjected herself into the flavored ENDS issue in June-July of 2021 – and fully review the flavored ENDS applications previously filed. Materially changing the testing requirements for proving APPH by establishing a new testing prerequisite *after* the application filing deadline has passed undermines the review process. This is precisely what happened with the *en masse* flavored ENDS application denials in 2021 in which CTP specifically explained that, once it determined the absence of product-specific long term studies demonstrating cessation, it suspended its review of the application.

Second, CTP must eliminate the double standard it has imposed for flavored ENDS by reviewing both "product-specific" evidence regarding cessation as well as "product-specific" evidence regarding youth initiation, including the applicants' real-world youth market experience, perception and use intention studies regarding initiation, and the applicants' marketing plans designed to prevent appeal to and access by youth. Alternatively, if non-product-specific initiation data can be relied upon by CTP with respect to one prong of the APPH test, then non-product-specific smoking cessation data should be equally relevant for CTP's consideration. To this end, the substantial science summarized in the 15 past presidents' essay offers more reason for CTP to rely more broadly on publicly available science.

Third, CTP must eliminate its new standard for flavored ENDS which, after the fact, required that applicants prove that their other-flavored ENDS products were more impactful on the issue of smoking cessation than their tobacco-flavored ENDS products. This is particularly inappropriate since the regulated products are not nicotine-replacement therapies subject smoking cessation effectiveness claims.

Fourth, CTP should publicly disclose and adhere to the process which it uses to address APPH and must conduct holistic reviews of applicants' data. This means that it cannot single out one set of data (i.e., JUUL's genotoxicity data) on which it justifies denials and instead must decide whether to authorize products based on a holistic review of all the data presented.

3. Build the off-ramp from smoking by accelerating the authorization of ENDS products and using the full scope of CTP's post-marketing order authority to monitor and control.

While FDA has used its authority to authorize 600 new combustible products (250 new cigarettes) for sale in the market, its refusal to use its significant regulatory authority to authorize ENDS in any meaningful way threatens public health. CTP is currently reviewing PMTAs that were filed over 2 ½ years ago covering thousands of products. To date, CTP has failed to issue decisions on entire categories of ENDS products. For example, CTP has failed to issue decisions on JUUL, all menthol ENDS products with one exception, all open system devices, and all modern oral nicotine pouch products. The 15 past presidents of SRNT couldn't have framed their concerns any more clearly: the continued failure to authorize ENDS products is jeopardizing the chances that adult smokers have to quit and stay quit. In the meantime, nearly half a million Americans

will die each year from smoking related illnesses. CTP needs to move aggressively to build the off-ramp from smoking with ENDS and modern oral nicotine products.

FDA can authorize products has both extensive pre-market and post-market authority to regulate tobacco products. In balancing the APPH, CTP can and should authorize more products and rely on its post-market authority to address actual (as opposed to feared) concerns about youth initiation. For example, CTP can use post-market consumer studies to monitor its authorizations and evaluate real-world impacts of authorized products and, in the event of adverse findings, CTP has the statutory authority to suspend or withdraw a marketing order if it finds new evidence would so justify it. Similarly, CTP can hold applicants' to the marketing plans that are submitted and approved along with any authorized product and, if real-world circumstances demonstrate an authorized product is the subject of heightened concerns regarding youth use and sales violations, CTP can again suspend or withdraw its marketing granted order. What is inappropriate is continued blanket denials which do not serve the public health interest and, again, lead only to protracted litigation which delays the time we achieve an orderly and regulated market.

4. Clearly articulate CTP's use of enforcement discretion to work companies through the PMTA process, particularly for NTN applications.

CTP needs to clearly articulate that all tobacco products, which already are on the market and are subject to a PMTA under review by FDA, can be marketed, subject to FDA's enforcement discretion, while CTP is evaluating the applications. FDA generally, and CTP specifically, has a long history of using enforcement discretion to allow products in various categories to remain on the market as they go through the Agency's review process. Despite a long history of CTP's statements on the use of enforcement discretion[28] recent statements by CTP are becoming more strident and are confusing to the marketplace.

As a result, stakeholders inside industry have suggested that CTP is applying a different standard for products subject to PMTAs submitted in 2020 with tobacco-derived nicotine (TDN) and products subject to PMTAs submitted in 2022 with non-tobacco nicotine (NTN). Specifically, they are saying CTP is not using enforcement discretion to allow NTN products to remain on the market pending PMTA review, as they are doing for TDN products, in a naked attempt to gain a market advantage by driving NTN products from store shelves.

Enforcement discretion, of course, has always been a necessity since under Section 910 of the Tobacco Control Act FDA is required to review all submitted PMTAs within 180 days but that has never happened and CTP has consistently claimed that products under review are allowed to remain on the market subject to FDA's enforcement discretion. Even after the Court order imposing a transition period of "lawful marketing" for TDN products until September 9, 2021, CTP noted that it still "*retains enforcement discretion*" to allow products to remain on the market while it reviews TDN PMTAs. (App. 246A). In March 2022, Congress passed a law, without any public hearing or input, which for the first time regulated products containing "non-tobacco nicotine" (i.e., synthetic nicotine pharmaceutically manufactured and not derived from the tobacco

[28] Collected CTP Statements on Its Use of Enforcement Discretion (App. 246A).

plant) as tobacco products, and then required companies to submit PMTAs for NTN products within 60 days. The new law also required FDA to review all submitted PMTAs within 60 days which obviously could never happen under a diligent science-based review process.

In so doing, Congress simultaneously demanded and barred companies from properly preparing and submitting science to FDA. Thus, CTP must continue to allow NTN products to remain on the market subject to FDA's enforcement discretion while CTP reviews NTN product applications, just as it has done with tobacco-derived nicotine products over the past 2 ½ years and make clear statements to this effect to avoid confusion in the marketplace and to prevent certain stakeholders from attempting to misrepresent current statements by the Agency.

Ultimately, enforcement discretion is important since working with companies that can comply with the PMTA requirements and providing them the time necessary to complete the required science ensures a stronger process and strong product decisions informed by complete science. This applies to smaller manufacturers who don't have large scientific staff or resources.

This also particularly important for NTN products given the fact that NTN is the cleanest and purest form of nicotine on the market, devoid of nitrosamines, carcinogens, heavy metals and pesticides found in tobacco derived nicotine. In April and May of this year, VTA, along with four Ph.Ds in organic chemistry and inhalation toxicology met with multiple offices in CTP, including the Office of Science, to share the science and public health significance of NTN products and underscore the need for CTP's use of enforcement discretion to work companies which filed NTN PTMAs through the process.

5. Communicate with companies to avoid rejections based on administrative or technical failings and needless litigation.

RUF and the ITEP has received information regarding how CTP used to engage with companies in pre-application review meetings and through the use of deficiency letters during application review. That engagement has essentially ended. Not only did CTP routinely reject requests for pre-application meetings in 2019 and 2020, it implemented a one and done deficiency letter process for certain applicants while allowing other applicants to respond to numerous deficiency letters.

Recently, CTP has refused to accept certain otherwise robust applications because of technicalities. For example, CTP recently "refused to accept" a VTA member's applications because the Agency noted that an improper form had been submitted and that it needed a certification as to the authenticity of "translated" documents. Regarding the form issue, CTP had required use of a specific form and, then only a few weeks before the new application deadline for non-tobacco nicotine products in 2022, CTP altered the form but did not announce the change broadly. Regarding the translated document issue, CTP assumed that documents were translated from another language into English when, in fact, the documents were both originally created in both languages, thus eliminating the need for a translation certification. In these and similar cases, CTP should be allowed to pick up the phone and get those technicalities addressed and cured, rather than simply reject those applications plunging the Agency into more wasteful litigation.

6. Establish defined testing methods.

The testing of harmful and potentially harmful constituents (HPHCs) is a significant regulatory burden and should be standardized and validated to ensure that the data are consistent and accurate. Under current regulation, companies can test for HPHCs as they see fit. That said, if companies don't present the volume of data (in terms of batches tested and replications of the test) that FDA wants, their submissions may be deemed insufficient. Moreover, there are no required testing protocols which means that FDA is receiving non-standard HPHC testing results from company to company. For these reasons, FDA should implement standard testing protocols on which companies can rely to make sure they provide the Agency with exactly what it requires.

These methods require time to validate but most importantly should be based on what is within the realm of realistic (i.e., human) use. As most of these methods are based on machine generated data the testing parameters should be clearly defined so that relative comparisons of the data can be made. The reference for the testing is a combustible cigarette as this is both the most harmful product in the market and the product that would be replaced by ENDS products.

Standards on vaping topography and profiles for aerosol should be developed by referencing and reviewing existing standardized methods for aerosol generation, such as that developed by CORESTA in its recommended method No. 81, *Routine Analytical Machine for E-Cigarette Aerosol Generation and Collection - Definitions and Standard Conditions* (which is of limited utility in studying intense vaping conditions) and those developed by other Centers within FDA, such as CDRH's *Reviewer Guidance for Nebulizers, Metered Dose Inhalers, Spacers, Actuators.*

It would be advisable to use topographical data from human use patterns to establish both the normative and potential misuse of the product as designed. The use of unrealistic conditions for the machine testing could result in the elimination of a potentially beneficial product, for example, the use pattern of an ENDS product can impact the temperatures achieved in the microenvironment of the heating and will significantly affect the production of compounds such as formaldehyde. Excessively long activation times, i.e., those that cannot be achieved by a person using the device, improperly create higher levels of some HPHCs that are a theoretical but not realistic factor in the safety of the product. The temperature is impacted by many factors including, heating coil design, resistance, and activation time. Thus, using the cigarette as a comparator, the standard and intense use could be defined.

The same requirements for repeatability and reproducibility that exist for analytical methods in general should be applied to these testing regimes. The preferred analytical method should be defined and alternative methods should be scientifically justified. Also, only HPHCs with validated methods should be required for the CTP review process. The use of unvalidated methods has the potential to introduce bias in the analysis of the data. The HPHC content of ENDS vapor should be compared to cigarette smoke values to properly assess the potential public health impact. In the absence of such defined testing protocols, the HPHC data that industry will provide FDA will be of limited utility, as a wide variety of testing protocols will be used by different stakeholders and for different products.

7. Eliminate redundant and unnecessary testing.

PMTA requirements are difficult enough, time consuming enough and costly enough to complete without also having to conduct redundant and unnecessary testing. For example, biomarker studies and inhalation studies are irrelevant when companies have presented data showing a dramatic reduction (or absence) of toxins. While biomarker and inhalation data are relevant in some cases, the general approach is to determine the No Observable Adverse Effect Level (NOAEL) for compounds and this is consistent with the studies done for drugs and other products and contaminants. The analytical method may be able to detect the presence of the compound but its mere presence is not an indicator of harm. In toxicology, the dose makes the poison and thus the amount, duration, and route of exposure are all factors that must be considered. For this reason, the evaluation of the need for biomarker or inhalation studies should be triggered by data and not an arbitrary decision.

It is the absence or dramatic reduction of chemicals that a user or non-user are exposed which should be evaluated for toxicological significance, not simply the mere presence of a particular chemical. Inhalation studies take time and create costs, which when not scientifically relevant to the question, divert time and resources from testing that may be more meaningful. The absence of significant reduction in the presence of a chemical will definitely result in a reduction of biomarkers of exposure and/or harm assuming that the only source of this exposure is the product in question. The inhalation risk is also concentration dependent. Therefore, there should be a process that uses the comparative HPHC data to determine the need for these studies, the results of which, can be reasonably inferred from data that exist from the literature or prior studies. Each application should rely on the current state of the science and not be required to recreate well-established data. For example, in the case of nicotine and many flavor compounds there is a significant amount of toxicological data that can be used to determine the need for additional studies based on composition and/or concentration.

8. Develop and publish an PMTA proposed regulation with a finite checklist of required information

One of the greatest difficulties currently facing industry is the lack of specificity in FDA's PMTA rule and guidance and the uncertainty surrounding the types and quantity of testing and survey results needed to support the issuance of a marketing order. VTA thus respectfully submits that FDA should develop and publish a proposed regulation, or issue detailed guidance, that contains a finite checklist of information required to support a PMTA and which states that if such information is provided, it will be sufficient for CTP's evaluation and possible issuance of a marketing order. The standard or guidance could also include additional information that FDA is interested in reviewing but which is not a requirement for proper consideration. Notwithstanding the existing PMTA Rule and guidance, the information articulated is far too indefinite to provide a clear roadmap for the development of a successful PMTA. As things stand now, the PMTA rule articulates all of the information in which FDA is interested but it is unclear, with a few statutory exceptions, what FDA considers as essential components of an application. As noted by one of the presenters, companies often learn through denials of applications what else they needed to provide in order to secure an authorization.

9. Equally fund research proposals.

FDA funded research is critical to the review process today and in the future. To date, the Agency has only funded research purporting to identify problems, i.e., youth initiation. However, given the enormous body of research demonstrating that ENDS and other less harmful nicotine products would promote public health by substantially reducing smokers' exposure to toxins, by assisting smokers in the number of quit attempts, by helping smokers quit at a rate that doubles the quit rate achieved through the approved nicotine-reduction therapies, CTP should equally fund research that focuses on this essential solution.

For example, FDA spent $120 million funding studies on the effect that very low nicotine (VLN) cigarettes would have on smoking reduction and cessation. That research ultimately lead to the FDA's authorization of a VLN (combustible) cigarette and the approval of a modified risk tobacco product designation for that VLN cigarette. While this is another example of CTP authorizing a combustible product, with presumably the same exposure to toxins inherent in combusting and inhaling tobacco, one has to wonder what would happen if FDA aggressively funded science that addressed its key concerns regarding ENDS on MON products.

D. Conclusion

In conclusion, today, CTP is stuck, trapped if you will, managing a monstrous rule of its own creation. It needs direction from the Foundation and the ITEP to impose to restructure its processes, to set and abide by a clear set of requirements, and to ensure strict and fair adherence to science-based decisions. It is our hope that the Reagan-Udall Foundation's review will ultimately lead to the creation of an "efficient, predictable, and transparent" process first promised by Commissioner Gottliebe and, in so doing, make real the promise of less harmful nicotine products.

VI. VTA COMMENTS ON COMPLIANCE AND ENFORCEMENT

A. Background on Enforcement Issues

There is, perhaps, no more important issue to consumers, the industry, and the continued relevance of CTP's regulatory authority and, specifically, the PMTA process, than that of enforcement. To date, CTP has done little to stem the flow into the U.S. of products (particularly disposable ENDS products) that flaunt the PMTA process and FDA regulation altogether. CTP has used its resources primarily on local enforcement efforts focused on youth sales and other potential violations at retail. The effectiveness of CTP's enforcement efforts should be examined to determine whether the extensive resources spent focused on these entities is worth the expenditure.

While we applaud CTP for its recent actions to remove products from the market from companies which have never filed PMTAs,[29] and we encourage continued focus in this area, these actions were directed at small players and will have little impact in the market. As set forth herein, CTP needs to refocus its enforcement efforts where it will have the greatest impact and resonance in the market – at U.S. ports where illicit products are flowing into the country unabated.

B. CTP's Current Retail Enforcement Emphasis is Misfocused.

There are more than 350,000 convenience stores, gas stations, grocers, tobacco shops, vape shops, and other retailers at which tobacco products are sold in the U.S. The majority of CTP's enforcement activity in the past four years has been focused on retail inspections at these stores specifically with the goal of identifying those illegally selling tobacco products to minors. VTA conducted an analysis of FDA's publicly available Compliance Check of Retailers Database and found some interesting results. First, of the more than 300,000 retail inspections conducted by the FDA since January 1, 2019, 86% of them resulted in "no violations"[30] at all (See Table 1), demonstrating a good compliance rate.[31] Second, the overwhelming majority (96%) of all FDA retail inspections are focused on minor sales and the overwhelming majority of the inspections that took place *with* minors involved resulted in "no violations" at all (85.4%), also a good compliance rate.

Table 1: FDA Retail Inspection & Violation Rates (with and without minors involved)

Year Ending	Total No. of Inspections	Inspections w/No Violations	% Inspection with No Violations	% of Inspections w/Minors	% Inspections w/Minors & No Violations
12/31/2019	145,688	126,959	87.1%	99.0%	87.0%
12/31/2020	34,990	31,140	89.0%	90.7%	88.3%
12/31/2021	46,769	40,697	87.0%	84.8%	84.7%
9/30/2022	73,407	59,649	81.3%	99.8%	81.2%
Totals	**300,854**	**258,445**	**85.9%**	**96.0%**	**85.4%**

Importantly, while FDA's public narrative regarding youth has been virtually exclusively focused on youth vaping, and particularly the sales of ENDS to youth, FDA's database reveals that

[29] Florko, Nicholas, *FDA, DOJ sue 6 vape shops for ignoring warnings about selling illegal products*, STAT News, 10/18/22, https://www.statnews.com/2022/10/18/fda-doj-sue-6-vape-shops-for-ignoring-warnings-about-selling-illegal-products/.

[30] Violations include the issuance of either a warning letter, a civil monetary penalty, or a "no tobacco sales order" (NTSO).

[31] VTA Analysis of FDA data housed on FDA's Compliance Check of Retailers Database available at https://www.accessdata.fda.gov/scripts/oce/inspections/oce_insp_searching.cfm.

of all retail inspections conducted since January 1, 2019, only a small fraction (3.7%) of inspections resulted in a warning letter for youth sales violations involving ENDS products. By comparison, since 2019, the number of warning letters issued for youth sales violations for combustible products (e.g., cigarette packs, loose cigarettes, cigarette tobacco, cigars, and hookah tobacco) were two times higher (205%) than for ENDS violations. In fact, in 2022 (through September 30, 2022), the rate of combustible violations is two and a half times (251%) that of ENDS violations. For this reason, one must question why CTP continues its narrative that more youth today are using ENDS products as opposed to combustible tobacco products without simultaneously highlighting it own enforcement data that shows youth are purchasing combustible products at a higher rate or with greater ease than they are purchasing ENDS products.

Table 2: Retail Warning Letters Issued for Tobacco Products

Year Ending	Combustible Warning Letters	ENDS Warning Letters	Combustible v. ENDS Violations	% of Combustible Violations To Inspections	% of ENDS Violations To Inspections
12/31/2019	8877	4515	196.61%	6.09%	3.10%
12/31/2020	1870	592	315.88%	5.34%	1.69%
12/31/2021	3366	2578	130.57%	7.20%	5.51%
9/30/2022	8766	3491	251.10%	11.94%	4.76%
TOTALS	**22879**	**11176**	**204.72%**	**7.60%**	**3.71%**

Ultimately, enforcement is only as strong as how aggressively it is pursued and CTP acknowledges that its warning letters are not a formal initiation of enforcement actions. Since 2019, CTP has only issued 60 "no tobacco sales orders" for repeat violators and only 3 (5%) have been issued for sale of ENDS products to youth. Moreover, the rate of civil monetary penalties issued for youth sales violations of combustible tobacco products is 3.5 times higher than for ENDS products.

One reason the number of NTSOs is so low, is that CTP generally will not pursue NTSOs unless a retailer is cited for youth violations seven times in three years. VTA has advocated for more aggressive use of youth enforcement tools at CTP's disposal and has recommended including a "three-strikes-and-you're-out process" in which tobacco product retailers are issued NTSOs if they are subject to three youth violations in three years.

Moreover, FDA knows that the overwhelming majority of youth illegally gain access to tobacco products (and for that matter other products such as beer and alcohol) through social sources. This is why VTA has proposed other regulations to reduce the incidence of such social sources by limiting the number of products that can be purchased in a single transaction. Given this background, it is clear that retail inspections do not lead to significant enforcement action

which is why attempting to enforce at the point of sale will continue to have little impact on the illicit marketing of products to youth.

C. CTP's Exclusive Focus on Removing Flavored ENDS is Misguided, Based on its own Data, and is Opposed by Leading Tobacco Control Scientists.

To date, CTP entire focus on youth use of tobacco products has routinely stressed that flavors are attractive to youth and, therefore, flavored ENDS must be restricted as aggressively as possible. However, FDA data reveal that the focus on flavors is overstated.

Despite CTP's narrative about youth and flavors, between January 1, 2019 and September 30, 2022, the majority of youth sales violations of vaping products have involved traditional tobacco and menthol flavors (55%), while fruit, sweet or other flavors are involved in violations only 39% of the time.

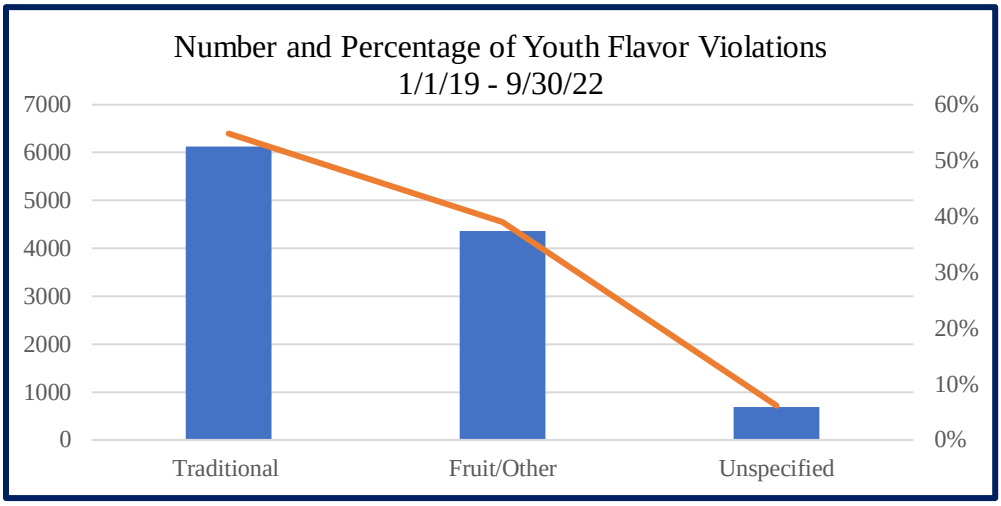

Figure 3: FDA Youth Flavor Violations

D. VTA Recommendations on Enforcement and Compliance

1. CTP Must Ramp Up Border Interdiction of Illicit Products.

While preventing youth sales is of critical importance, much more could be done to restrict the availability of product flowing into the U.S. To this end, CTP must leverage all resources at its disposal to interdict products at the border. Virtually all ENDS devices are imported into the U.S. Therefore, the most efficient and effective way for CTP to limit entry to the U.S. of illicit product is in the few ports of entry that the FDA monitors as compared to the tens of thousands of retail outlets scattered across the 50 states. According to the FDA, "All imported shipments of FDA-regulated products are reviewed by the FDA and must comply with the same standards as domestic products. The FDA determines whether products are admissible into U.S. commerce

and may refuse entry to any that violate or appear to violate any provisions of the Federal Food, Drug, and Cosmetic Act (FD&C Act)."[32]

CTP has recognized the enormous rise of disposable vaping products in the U.S. since 2020 (when FDA banned flavored closed-system products) but inexplicably exempted from its ban flavored disposable products. (See discussion above at Section II.) Only strong enforcement coupled with public announcements demonstrating CTP's actions will stem the flow of illicit product into the U.S. This is a priority for VTA's members and all companies that have invested heavily in the PMTA process since bad actors are successfully competing at a significant advantage in the marketplace – by introducing new and unregulated products – while the good actors are punished for complying with FDA regulations and laws. VTA has asked to meet with CTP's Office of Compliance and Enforcement (OCE) on a number of occasions to discuss specific strategies and tools that would dramatically jumpstart CTP's ability to enforce against illicit products. To date, OCE has not agreed to meet. During its meeting a few months ago with Commissioner Califf, VTA emphasized the need for enforcement at the border and reiterated our willingness to assist CTP in said efforts.

2. CTP Needs to Streamline Its Enforcement Efforts.

In addition to the foregoing, CTP could assist itself in addressing the influx of products, and make material steps to protect youth, by issuing guidance that would restrict sales of flavored ENDS products to adult-only stores. As noted above, the fifteen of the past presidents have warned against U.S. regulators' efforts to restrict flavored ENDS. Most importantly, to correct the wrongfooted priorities on the issue of flavored vapor products, these tobacco-control leaders endorse limiting the "retail sale of flavored e-cigarettes to adult-only outlets such as vape shops." *Balfour, et al.*, at 1666 (App. 49A). Such restrictions they say would protect youth and preserve adult access to flavored ENDS products. *Id.* VTA strongly supports this recommendation made by staunchly anti-tobacco scientists.

Even better, VTA's analysis of FDA data supports the experts' recommendation of limiting sales of flavored vaping products to adult-only stores. Between January 2019 and June 2022, 78% of all youth vaping sales violations have occurred in non-age-restricted facilities such as convenience stores, gas stations, and grocers. Importantly, adult-only tobacco store and vape shop channels preferred by experts account for only 21% of such violations.

[32] FDA, *Import Basics*, https://www.fda.gov/industry/import-program-food-and-drug-administration-fda/import-basics, (current as of April 7, 2022).

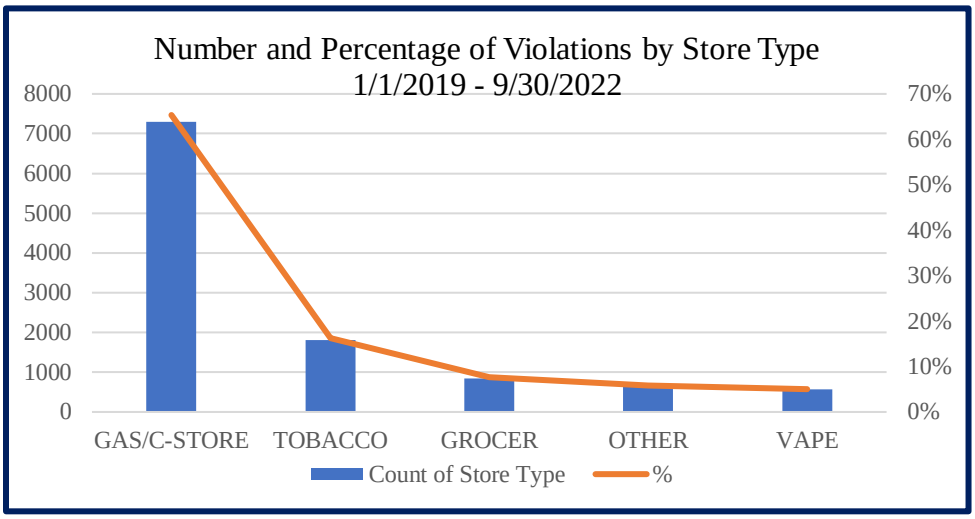

Figure 4: FDA Store Type Violations

Since decisions regarding pending flavored ENDS applications are likely to take years, as will the myriad pending lawsuits challenging CTP's *en masse* denials of flavored ENDS PMTAs, requiring flavored ENDS products to be sold in adult-only stores will be a more meaningful step towards preventing youth access and will aid CTP in focusing its enforcement efforts related to flavored products to far fewer retail locations.

3. CTP Should Publish List of NTN Products Currently Under PMTA Review.

On July 7, 2020, VTA presented CTP with our White Paper that set forth our proposal for a voluntary FDA database that would include the names of all deemed ENDS products that were covered by a timely-filed and pending PMTA the disclosure of which would be authorized by the applicant. We were pleased that CTP took the steps necessary to publish such a list or those products containing TDN.[33]

On June 10, 2022, VTA reiterated the same request regarding the publication of a list of products containing NTN for which PMTAs were undergoing PMTA review in a letter to then Acting CTP Director Mital. VTA explained that, "since the Agency now has authority over all nicotine-containing products, this list will address the significant needs for all stakeholders to know precisely which companies and products are participating in FDA's PMTA process and, more importantly, which specific products are not subject to the FDA's PMTA review process."[34] VTA also noted that, "Now that FDA knows every product on the market for which a pre-market tobacco application has been filed, the publication of such a list will eliminate any question as to which products have no standing under existing laws and regulations to be sold in the United

[33] VTA, Letter to Director Zeller with White Paper on Pending ENDS PMTA Database, July 7, 2020 (App. 247A).

[34] VTA, Letter to Acting Director Mital re: Pending Synthetic Nicotine PMTA Database, June 10, 2022 (App. 250A).

States. This information is essential for the responsible businesses who must decide which products to carry as well as for CTP's enforcement allies charged with removing non-compliant products from the market." To date, CTP has not published any such list or committed to doing so. On November 3, 2022, VTA reiterated this request to Director King and is awaiting a response.

VII. PUBLIC EDUCATION AND COMMUNICATION

The importance of accurate and truthful communication regarding the continuum of risk and the reduced harm offered by ENDS products cannot be overstated. Due to years of hyperbolic rhetoric, funded by tens of millions of dollars of private money spent with the sole purpose of denigrating the industry and the vaping category in general (and flavored ENDS specifically) it is no surprise that the majority of Americans believe that vaping is as or more dangerous than smoking cigarettes and that U.S. doctors wrongly believe nicotine causes cancer.

To its credit, during the EVALI crisis in 2019, which was a serious and real epidemic that was limited to black market THC vaping products, FDA (in contrast to CDC) correctly and properly warned the public against using black market THC products. However, since then FDA has done little to nothing to encourage people who can't or won't quit smoking to even give e-cigarettes a try, much less has FDA attempted to publicize known science regarding the lower risks associated with e-cigarettes.

FDA has made other statements that are accurate. For example, in its proposed product standard to restrict levels of nicotine in combustible products FDA stated, "While nicotine is not what makes smoking cigarettes so toxic, it's the ingredient that makes it very hard to quit." The 15 past presidents of SRNT confirm this fact: "Nicotine is the chemical in tobacco that fosters addiction. However, toxic constituents other than nicotine, pre-dominantly in smoked tobacco, produce the disease resulting from chronic tobacco use." *Balfour, et al.*, at 1667 (App. 50A).

Notwithstanding these facts, the public terribly misinformed about nicotine and the lower risks and harms associated with ENDS products:

> "Unfortunately, the public has a distorted view of the dangers associated with nicotine per se. In a recent survey, 57% of respondents incorrectly agreed that 'nicotine in cigarettes is the substance that causes most of the cancer caused by smoking.' Only 18.9% disagreed. (The rest answered 'Don't know.') In a recent survey of physicians, 80% strongly, but incorrectly, agreed that nicotine causes cancer, cardiovascular disease, and chronic obstructive pulmonary disease."

Id. These facts explain why these tobacco-control scientists have raised the concern that smokers are not receiving "accurate information about the relative risks of vaping and smoking," that current policies are not "designed with the potential effects on smokers in mind," and that policies are "convincing the public—including smokers—that vaping is as dangerous as smoking." *Id.* at 1662, 1666 (App. 45A, 49A).

In a recent interview, Director King clearly recognized the public's misperceptions: "I'm fully aware of the misperceptions that are out there and aren't consistent with the known science. We do know that e-cigarettes — as a general class — have markedly less risk than a combustible

cigarette product. That said, I think it's very critical that we inform any communication campaigns using science and evidence. It has to be very carefully thought out to ensure that we're maximizing impact and avoiding unintended consequences."[35]

So, while certain statements by CTP on nicotine and harm reduction are accurate they are few and far between and they do not fill the vast knowledge gap on nicotine and harm reduction. To complicate matters, instead of clear and direct statements about the relative risks of vaping, CTP has spent millions of taxpayer dollars in its anti-youth vaping campaigns which send the opposite message. In its zeal to dissuade youth (presumably youth that have never used a tobacco product and youth who have tried vaping), the anti-youth vaping campaigns funded by FDA have included extreme and bizarre statements about the dangers of e-cigarettes. Some ads go so far as to repeat antiquated claims of "inhaling metals" and conditions such as "popcorn lung" and worms in the brain that simply bear no resemblance to any proven science regarding how humans actually use vaping products.

Given the dramatic 50% reduction in youth vaping since it peaked in 2019, FDA must now loudly and repeatedly address its commitment to the continuum of risk. FDA must commit equal resources to conducting an aggressive public education campaign, targeted to the adult consuming public, on the dangers of smoking and the lower risks of ENDS and modern oral nicotine products, explaining the continuum of risk, and encouraging adult smokers who have been unable or unwilling to quit to try e-cigarettes. In light of the dangerously distorted narrative, only FDA has the ability to correct the record.

VIII. RECOMMENDATIONS ON REGULATIONS AND GUIDANCE

CTP can and should use guidance to bring order and clarity to the review of tobacco products. Although all guidance documents boldly declare that they are "not binding," they can provide critical insights into the information that CTP is seeking, information that CTP will accept, and issues that CTP is prioritizing. What follows are VTA's recommendations for CTP's use of its regulation and guidance processes.

A. Need for a Comprehensive Plan that Outlines CTP's Posture Regarding ENDS.

Regulations and guidance issued by CTP should be pursuant to an overall vision and comprehensive plan through which the Agency articulates its priorities for implementing its enormous regulatory authority. As noted earlier, Commissioner Gottlieb laid out a Comprehensive Plan in 2017[36] and, after that plan was essentially abandoned, the Agency has struggled to

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[35] Perrone, Matthew, *Insider Q&A: FDA official on vaping's "promise or peril",* Associated Press, 9/26/22, https://www.seattletimes.com/business/insider-qa-fda-official-on-vapings-promise-or-peril/.

[36] FDA, Press Release: *FDA Announces Comprehensive Regulatory Plan to Shift Trajectory of Tobacco-Related Disease, Death* (July 28, 2017) (quoting Commissioner Gottlieb: "Envisioning a world where cigarettes would no longer create or sustain addiction, and where adults who still need or want nicotine could get it from alternative and less harmful sources, needs to be the cornerstone of our efforts – and we believe it's vital that we pursue this common ground"), https://www.fda.gov/news-events/press-announcements/fda-announces-comprehensive-regulatory-plan-shift-trajectory-tobacco-related-disease-death.

articulate a clear message for harm reduction particularly as it relates to ENDS products. FDA should adopt again and announce a Comprehensive Plan to address tobacco and nicotine that adheres to the main tenants of the 2017 plan. Such a plan should include a clear acknowledgment of the Agency's commitment to:

- the continuum of risk related to tobacco products and a recognition that ENDS and modern oral nicotine products sit at the lower end of the risk continuum,
- promoting innovation of those products at the lower end of the risk continuum, particularly ENDS and modern oral nicotine products,
- promoting innovation in nicotine, particularly synthetic nicotine,
- a pure scientific review process,
- funding science to evaluate the benefits of ENDS and modern oral nicotine products,
- working with companies to facilitate the application review process,
- aggressively educating adult smokers on the benefits of trying ENDS products if they are otherwise unwilling or unable to quit smoking using other methods,
- using its enforcement discretion to allow products under review to remain on the market pending authorization reviews, and
- a streamlined process which will ensure prompt review of product applications.

B. CTP Should Engage Industry and Other Stakeholders in the Guidance and Regulation Processes.

CTP's critical guidance and regulatory processes would be dramatically improved if CTP engages with the companies it regulates as much as it does with public interest groups with which FDA has historically believed it is "aligned." As noted at the outset, VTA's members, and many other thoughtful regulated companies in the industry, are aligned with the Agency on the need for regulation of tobacco products and with FDA's mission to make cigarettes part of America's past, not future. Realizing that goal is complicated and can best be achieved through regular and meaningful communication with industry. However, such communication over the past few years has been truncated or stifled.

1. CTP should convert its listening sessions to engagement sessions.

When companies are granted meetings with CTP, they are most often treated as "listening sessions." At the outset of these listening sessions, CTP staff in attendance are admonished that they are only allowed to ask "clarifying questions." Also, though companies may ask questions, CTP staff are prevented from offering direct answers. Oftentimes, these "listening sessions" are one-way engagements where industry presents a detailed and thoughtful presentation and there is little to no meaningful conversation that takes place. As a result, meeting participants leave such

listening sessions trying to divine what CTP is thinking about the issues, information or questions presented based, quite literally, on body language, level of attentiveness, amount of notetaking, or in the case a clarifying question is asked. VTA suggests that this is an inefficient and ineffective way for any parties seeking common answers to engage. Discussions in which knowledgeable and experienced CTP staff are allowed to engage with presenters, to challenge statements made, and raise new questions that come to mind would obviously result in a more productive dialogue that would materially move issues under consideration forward and allow the regulator and the regulated to actually develop sound approaches on what needs to be done *prior to* applications being filed.

2. CTP should reinstitute its workshops.

CTP must start again workshops in which industry participates to address critical questions regarding the creation and implementation of rules, regulations and guidance documents. The last such workshop, entitled Tobacco Product Application Review, took place more than six years ago, on October 22, 2018, in Rockville, MD. VTA participated in that workshop along with numerous other stakeholders. These workshops bring together all stakeholders and allow the presentation and sharing of ideas for consideration, allow for audience members to ask questions, and allow industry to understand the issues that are of importance to CTP. Specifically, CTP is long overdue in holding a workshop that brings together scientists from academia and industry to engage in a dialogue on the most critical scientific issues involving, for example, less harmful nicotine products and public health. Moreover, fully participating CTP staff would be afforded the opportunity to inquire of these scientists the basis for their statements and conclusions, including the limitations thereof.

3. CTP should establish an additional technical advisory committee dedicated to newly deemed alternative nicotine products.

FDA can reduce the regulatory burden associated with the PMTA process by establishing an additional technical advisory committee dedicated to ENDS and other alternative nicotine products that can advise the FDA with respect to the development of standards and technical aspects of the evaluation of premarket applications for these products. While there is no doubt that Section 917 of the FDCA calls for the Tobacco Products Scientific Advisory Committee ("TPSAC") to serve as the principal scientific advisory committee with respect to tobacco products, current TPSAC members might have a conflict of interest and thus not be impartial due to the fact that their research teams or universities might have either received grants from FDA or might currently receive grants or research from pharmaceutical companies engaged in sales or research on smoking cessation products that could be construed as *de facto* competitors of the vapor industry for the same consumers (i.e., adult smokers).[37] Thus, the Commissioner, through

[37] *See Lorillard, Inc. v. United States FDA*, 56 F. Supp. 3d 37, 54, 56 (D.D.C. 2014) (holding that "[s]ince manufacturers of . . . smoking-cessation drugs compete with manufacturers of [dissolvable tobacco products], and since [a member of TPSAC who consulted for NRT manufacturers] stood to profit from the sale of NRT drugs, he faced a conflict with regard to providing advice in the TPSAC's report on [dissolvable tobacco products]" and that "[i]f Congress deemed that past remuneration from tobacco companies constituted a conflict of interest, it stands to

the exercise of his discretion,[38] should establish a standing technical advisory committee that includes scientists and industry representatives with specific expertise in alternative nicotine products to advise the FDA and TPSAC with respect to the development of standards and technical aspects of the evaluation of premarket applications for such products.

The stated purpose of the proposed Technical Advisory Committee (TAC) can be to advise TPSAC and the CTP with respect to technical issues unique to ENDS and alternative nicotine products, including testing regimens, the evaluation of flavorings, and the development of good manufacturing practices and product standards. By way of example, the TAC could assist in the development of product standards on issues such as (i) acceptable and unacceptable ingredients; (ii) aerosolizing device components and protections (i.e., protections against short circuits, battery voltage limits, and charger specifications); and (iii) HPHC testing methodology. Extensive expertise with the manufacturing, testing, and health effects of ENDS and other alternative nicotine products exists in this scientific community and industry; the TAC would create the proper forum for that expertise to advise the decisions of the CTP and its Office of Science. VTA respectfully suggests the establishment of a ten member TAC consisting of five scientists with established expertise in ENDS and other alternative nicotine products, one CTP representative, and four industry representatives, with voting rights reserved only for the five scientists. The establishment of a TAC could assist FDA move away from the current "one size fits all" approach to tobacco products and lessen the regulatory burden associated with premarket applications by helping to suggest and define standards for products and their testing and evaluation.

C. CTP Should Issue Proposed Regulation or Guidance on Product Standards.

FDA has significant product standard authority covering a wide range of issues. Specifically for ENDS products, CTP is long overdue in establishing standards for the manufacture of e-liquids and the manufacture of ENDS devices. Such standards would clearly articulate what CTP would require for the manufacture and performance of the products in question. Merely because the tobacco product standard process is a lengthy multi-year process is not a reason it should not be pursued.

In the interim, however, CTP could issue guidance that lays out its expectations on a host of issues pertaining to product manufacturing and performance. Here are some specific examples:

1. CTP should issue a rule or guidance which explicitly allows widely accepted statistical design methods of research, aggregate testing, and extrapolation for ENDS product stability testing.

The regulatory burden associated with testing e-liquid products and aerosols to determine the effects of variations in temperature and the passage on time on chemistry profile is substantial.

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reason that past remuneration from direct competitors of those companies, such as manufacturers of smoking-cessation drugs, would also constitute a conflict of interest.").

[38] 21 C.F.R. § 14.1(a)(1) allows the Commissioner, in his discretion, to establish a "standing or ad hoc policy or technical public advisory committee" to hold public hearings and to review and make recommendations on any matter before FDA.

In the absence of FDA-published chemical compound stability guidance, VTA refers to ICH Q1A, *Stability Testing of New Drug Substances and Products*, which specifies that a stability study typically requires testing over a period from 12 to 24 months to adequately use regression analysis models to determine compound testing results trends. We also refer to FDA's draft guidance document regarding premarket applications for ENDS products, which contemplates that each e-liquid product containing a unique combination of nicotine concentration, flavorings, and propylene glycol / vegetable glycerin must be independently tested.[39] To lessen this regulatory burden without compromising public health, the VTA respectfully submits that FDA should insert by rule or guidance language that explicitly allows widely accepted statistical design methods of research, aggregate testing, and extrapolation in lieu of the independent testing of each unique product.

Widely accepted statistical design methods of research, such as DOEs and biostatistics, can ensure a targeted analysis and set definite conclusions for a worst-case scenario among a range of e-liquid products while substantially reducing the burden of independently testing each unique product. By way of example, for an applicant that manufactures ten flavors of e-liquids at three nicotine concentration levels, a full factorial analysis would require longitudinal testing of each unique product over a 12- to 24-month period. A methodology that would allow that applicant to combine all ten flavors at the same nicotine concentration level into a single aggregate "product" for purposes of longitudinal testing, however, may reduce the total number of "products" that would need to be tested from thirty (30) to three (3), depending on the selected DOE study. By analyzing the testing results under such an approach and extrapolating the results using statistically sound methods, the applicant can assure FDA that each of the ten flavors sold at the specific nicotine concentration tested will be evaluated under its statistically based worst-case scenario.

This type of testing methodology has been widely accepted by FDA in applications for the approval of drugs, medical devices, and biologics for a wide range of products under different sets of specifications treating different diseases. CDRH, for example, encourages the use of such statistical methodologies in its regulations regarding premarket notifications for medical devices:

> 21 C.F.R. § 820.250 - Statistical techniques; (a) Where appropriate, each manufacturer shall establish and maintain procedures for identifying valid statistical techniques required for establishing, controlling, and verifying the acceptability of process capability and product characteristics. (b) Sampling plans, when used, shall be written and based on a valid statistical rationale. Each manufacturer shall establish and maintain procedures to ensure that sampling methods are adequate for their intended use and to ensure that when changes occur the sampling plans are reviewed. These activities shall be documented.

21 C.F.R. § 820.250. Explicitly authorizing widely accepted statistical design methods of research, aggregate testing, and extrapolation for stability testing would substantially reduce the regulatory

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[39] FDA, Guidance for Industry, *Premarket Tobacco Product Applications for Electronic Nicotine Delivery Systems*, June 2019, at 28, available at https://www.fda.gov/media/127853/download.

burden of chemistry stability testing without compromising either data integrity or the scientific conclusions that can be reached regarding the covered products.

2. CTP should issue guidance permitting manufacturers to market safety and/or quality enhancements with 60-Day notice to FDA.

Under current regulation, virtually any change to a product requires the filing of a new product PMTA, even if such change is made for material safety or quality improvements. By defining such products as "new" tobacco products, they are forbidden from being sold until the multi-year PMTA process plays out. For obvious reasons, this completely stifles innovation. Accordingly, CTP should issue guidance that would allow manufacturers and importers to provide a 60-day advance notification of changes to products that are intended to improve the products' safety and/or quality. Any changes so "notified" to FDA would then need to be referenced in any later-filed PMTAs for the products. Such a measure would allow for continued product innovation and improvements that would likely be beneficial to the public health and safety, instead of having a "frozen" market for ENDS products, as currently exists.

Commissioner Gottlieb spoke frequently about the importance of fostering product innovation and fostering innovation is central to the mission of the Reagan-Udall Foundation. In 2018, the FDA announced its *Healthy Innovation, Safer Families: FDA's 2018 Strategic Policy Roadmap* ("2018 Strategic Plan") in which it declared, "With appropriate product regulation, **new technology, and product innovation** – including new medicinal nicotine products and electronic nicotine delivery systems (ENDS) – could present an opportunity for more smokers to quit combustible tobacco and stay quit. Our plan takes new steps to foster innovation in nicotine delivery, where such innovation could truly make a positive public health impact" (emphasis supplied).[40]

However, without an exemption that allows for manufacturers to introduce modified products to the market that improve upon or enhance the safety, the Agency and the marketplace will be stuck in an innovation paradox and will not be able to embrace or realize the true benefits of innovation in the rapidly evolving vapor technology space. ENDS products are not unlike the myriad technology products on the market in that ENDS companies can innovate their technologies in a matter of months, not years. These advancements, including advancements designed to protect youth, are in place in other parts of the world but FDA has frozen out of the U.S. market the safety enhancements that the rest of the world enjoys.

To be sure, until the introduction of innovative synthetic nicotine, all products for which PMTAs were submitted in 2020 were first designed in 2014 or 2015 and first manufactured in 2015 or 2016. That is because the Deeming Regulation forbade any new product to be introduced into the U.S. market after August 8, 2016. Hence, all design improvements for those products were also forbidden. So, when FDA finishes reviewing the 2020 PMTAs sometime between 2023 (or 2025 as they have told some companies) the designs and engineering of the products they may be

[40] FDA, *Healthy Innovation, Safer Families: FDA's 2018 Strategic Policy Roadmap*, January 2018, at https://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/UCM592001.pdf.

authorizing will be 7-8 years old. Such a scheme is no different than permitting only the sale of an iPhone 5 today when the market could be enjoying the iPhone XX.

D. CTP Should Issue Guidance on Enforcement Priorities.

As noted in the Enforcement discussion, without CTP enforcement against bad actor companies, the relevance of the entire regulatory process is in jeopardy. CTP needs to issue new enforcement guidance that declares unequivocally that it will remove from the market products that violate CTP's regulations in the following priority:

- all disposables in the market for which no PMTA has been filed;
- other ENDS products for which no PMTA has been filed, first prioritizing TDN products and then NTN products, since they are fraction of the market;
- counterfeit and illicit products which grossly violate marketing standards, trademark laws, or otherwise have marketing campaigns directed at youth; and
- products for which CTP has issued MDOs after a full scientific review consistent with requirements of the Tobacco Control Act, except of course, those subject to an FDA administrative stay or a court-ordered stay of enforcement.

Thank you for your consideration.

Respectfully submitted,

On behalf of the
VAPOR TECHNOLOGY ASSOCIATION

Tony Abboud
Executive Director